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Analysis of Schleicheraoleosa as bioactive potential compounds using in silico method

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Abstract
.Schleicheraoleosa is a traditional medicinal plant in Indonesia. The properties of bioactive compounds such as caomarin, flavonoid, terpenoid, steroid, and phytosterol found in these plants indicate that they have the potential for medicinal plants. Moreover, this study aim is to investigate the potential bioactive compound of Schleicheraoleosa that can function as antimicrobial using the methods of approach in silico. In this research a pharmacological effect test involving absorption, distribution, metabolism, and excretion (ADME) and toxicity of a bioactive compound from Schleicheraoleosa was conducted. ADME effect and toxicity analysis came with a web method based on aplication FAF-Drug4 and ligan's interaction with receptors in analysis use the docking method. The bioactive flavonoid and the terpenoid compound of Schleicheraoleosahas the potential as new antimicrobial drug compound. The flavonoid and terpenoid compound both have MW: 3600.31, 336.47; LogP: 2.79, 3.4; tPSA: 118.59, 80.59; HBD: 3, 3; HBA: 8, 4; Solubility: reduce solubility and good solubility; Veber rule: good, good, egan rule: good, good; 4/400: good, good; 3/75: good, warning; And both have no deviation from the five Lipinski rules. While the affinity energy of the flavonoid and the terpenoid is as big as -9.3 kcal/mol and -14.1 kcal/mol.

1. Introduction

Schleicheraoleosa or as known as Kesambi is a wooden plant of the sapindaceae family[1] (picture 1): it has been used in the hills and has since ancient times been used extensively in traditional medicine by mussels, East Nusa, Indonesia. The *Schleicheraoleosa* plant is commonly used as an analgesic, antibiotic and dysentery[1]. *Schleicheraoleosa* leaves can be used as fodder[2], while the skin is used for treatments of malaria and dysentery. In the Himalayas of Nepal, the *Schleicheraoleosa* berry is used in the traditional fashion as the anthelmintic[3], while oil from *Schleicheraoleosa* seeds is used for acne, itch, hair growth, and burns. Additionally, the entire part of the plant is also traditionally used as antidiabetic[4] (picture 2). *Schleicheraoleosa* plants have various contents of bioactive compounds such as caomarin, flavonoids, terpenoids, steroids, and phytosterols[5]. This shows that the plant has potential as a medicinal plant. This is confirmed by a number of reports on the results of research conducted both in vitro and in vitro. *Schleicheraoleosa* plants have medicinal effects on anthelmintic[6], anticancer, antioxidant, and antimicrobial[7]. However, reports from some of these researchers are limited to clinical aspects, whereas aspects of biomolecules such as interactions between drug receptors and the bioactive compounds *Schleicheraoleosa* and the pharmacological effects of *Schleicheraoleosa* plants have not been reported. Therefore, further research is needed to examine the molecular interactions of these plants

In line with the problems above, the insilico approach has been widely applied to aspects of molecular biology and medical research. Structural-based methods, such as protein docking with ligands, are efficient and reliable methods for the discovery and design of new drugs. The docking simulation method can explain

the interaction and binding mechanism between the target protein and the corresponding ligand[8]. In addition, the database system also provides pharmacological properties related to absorption, distribution, metabolism, and excretion (ADME) and toxicity[9]. The combination of docking and screening methods for pharmacological properties is an excellent method for finding potential drug compounds.

The purpose of this research is to investigate the potential of *Schleicheraoleosa* bioactive compounds that can function as antimicrobials using the in silico method. Until now, there is no research on interactions between the *DNA gyrase* enzyme receptors from *E. Coli* with the active compound from *Schleicheraoleosa*. In addition, the effects of ADME and toxicity of the active compound *Schleicheraoleosa* have also not widely reported. Therefore research is needed to examine the molecular interactions of the *DNA gyrase* receptor from *E.Coli* with the active compound of the *Schleicheraoleosa* plant, and also the ADME-Tox properties of the bioative compounds from this plantIn this study, the pharmacological effects of bioactive compounds from *Schleicheraoleosa* were also tested. Pharmacological tests were analyzed in silico using the web based application FAF-Drugs4. Docking simulations were then performed between *Schleicheraoleosa* bioactive compounds and various antimicrobial receptors.

Figure 1*Schleichera oleosa* is a wooden plant of the sapindaceae family. Fruit: Round, blackish brown; leaves: single, green, alternating, height = 11-25 cm, width = 2-6 cm, sharp edges, fin bones, round stems ± 1 cm[1].

Figure 2.Part of the *Schleicheraoleosa* plant used as medicine[4]

2. Methodology

Literature review

Awareness about the importance of predicting and optimizing absorption, distribution, metabolism, excretion and toxicity (ADME-Tox) properties of biocative compounds has increased. This is due to the many drug compounds that are developed that have many pharmacokinetic and ADME-Tox properties that are bad, so that it fails in the development stage. In addition, another reason is an error in determining the target of a drug receptor[10]. Recent analysis shows that more than 90% of failures now are caused by toxicity, which causes drugs to be withdrawn in the market[11]. To assist this process, several in vitro and in silico approaches have been designed to predict some key properties of ADME-Tox[12] in silico with the help of computers. The five Lipinski rules are rules for predicting whether a molecule of bioactive compounds can be given orally [13;14]. According to the five Lipinksi rules, drug criteria are compounds that have a molecular mass of less than 500 Dalton; high lipophilicity (expressed as logP less than 5), total donor hydrogen bonds less than 5; the number of recipients of hydrogen bonds is less than 10; and molar endurance between 40-130.

Some research shows that there has been a paradigm shift in drug discovery. Screening the exact nature of ADME-Tox in silico is very important to find new drugs. The work of the in silico method is to predict and

optimize affinity / selectivity bonds, pharmacokinetic properties and avoid toxicity. Screening in silico of the nature of ADME-Tox can use the FAF-Drugs4 web base application resulting from the improvement of FAF-Drugs3[9]managed by the Mobyle Portal, with the primary aim of assisting researchers in designing drugs and chemists before experimental medicine.

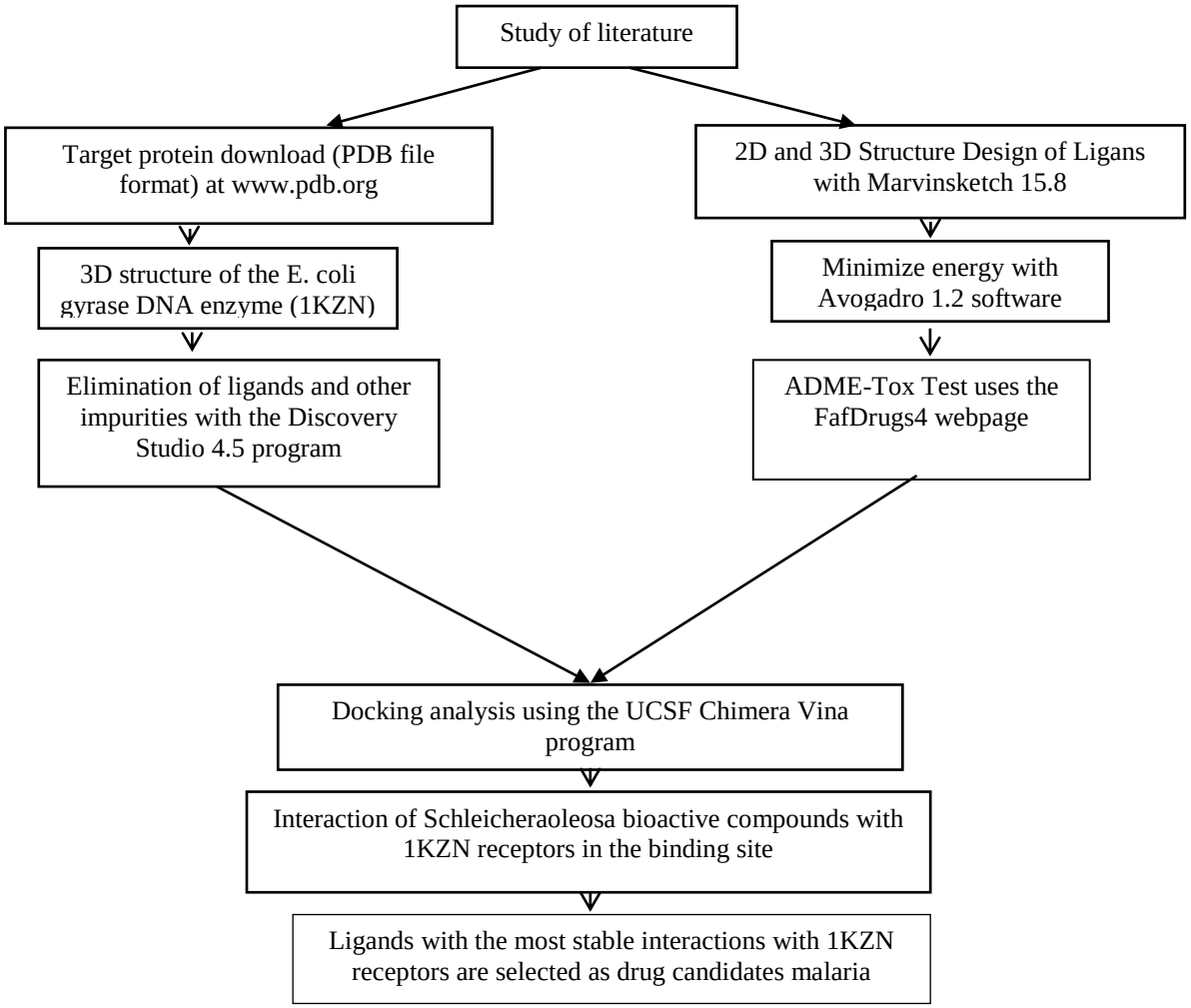
An effective research approach combined with in silico screening is the docking method. Docking can provide the best conformational pose at the protein-ligand complex binding site. The docking procedure consists of the following two steps: The first stage is identifying and selecting the protein region as the active site for docking. And the second stage of the docking process is for the best ligand candidate to the chosen site[15].

Tools and materials

A set of personal computers with a Quad Core Processor (Intel Core I7), 8 gigabyte RAM, NVIDIA Ge Force GTS 9400 32 core GPU and an Ubuntu LINUX operating system version 18.04 LTS. Two-dimensional (2D) and three-dimensional (3D) structures of *Schleicheraoleosa* bioactive compounds and drug compounds were created using MarvinSketch V15.8 software[16]. The antimicrobial receptor used is the *DNA gyrase* enzyme from *E. Coli*[17] (GDP: 1KZN)[18] downloaded from the GDP database[19]. The 3D structure of the *Schleicheraoleosa* bioactive compounds tested consisted of caomarin, flavonoids, terpenoids, steroids, and phytosterols[5] while the antimicrobial drug compounds that function as positive control were chlorobiocin. Furthermore, minimization of the 3D structure of bioactive compounds and drugs by software Avogadro version 1.2[20] and tested the pharmacological effects using the web based application FAF-Drugs4[9]. The chemical structure format was changed by OpenBabelG UI software version 2.3.2[21] and visualization of molecular shapes using Discovery Studio Client V4.5. While the docking method is done using the UCSF Chimera program[22]Autodock Vina[23].

ADME and toxicity analysis (adme-tox)

Screening bioactive compounds and drug compounds using the web based application FAF-DRUGS4. The screening results are then evaluated by five Lipinski rules (RO5)[24] and ADME-TOX predictions using FAF-DRUGS4. According to the five Lipinksi rules, drug criteria are compounds that have a molecular mass of less than 500 Dalton; high lipophilicity (expressed as logP less than 5), total donor hydrogen bonds less than 5; the number of hydrogen bond acceptors is less than 10 and the molar resistance is between 40-130. While the nature of ADME-Tox is predicted in silico by FAF-DRUGS4[9]. The nature of ADME tox in analysts is based on physicochemical properties of molar mass (MW), coefficient of logarithmic partitioning between n-octanol and water, characterizing lipophilicity (LogP), topological polar surface area (tPSA), hydrogen bonding donor (HBD), hydrogen bond acceptor (HBA), solubility estimates index[9], Veberbiovability rules[9], Egan biovailability rules[9], LogP's relationship with MW (4/400)[9], LogP's relationship with tPSA (3/75)[9] and Lipinski rule[9]. Pharmacological effects testing is very necessary because the effects of ADME and poor toxicity are the causes of failure in the process of drug development. ADME and Toxicity values were predicted using the FAF-Drugs4 web-based application, whereas the energy affinity of antimkroba receptors with ligands can be calculated using the docking approach, so as to accelerate the process of drug discovery.



Docking analysis

The docking process using the UCSF Chimera program and screening for pharmacological effects is predicted using the FAF-DRUGS4 web based application. The docking approach using the Chimera UCSF program can provide the best conformational poses at the protein-ligand complex binding site. The docking procedure consists of the following two steps: The first stage is identifying and selecting the protein region as the active site for docking. The Gridbox coordinates used have been validated and have a root mean square deviation (RMSD) value ≤2 [7]. Gridbox coordinates that are used as active sites in docking simulations are x = 19,259, y = 29,159, z = 42,461. while the gridboxdimensions used for the x, y and z axes are 40 Å. The second stage of the docking process is for the best ligand candidate to the chosen site. This confirmed binding site is used to calculate interactions between all potential bioactive compounds and drug compounds with the 1KZN enzyme. Then UCSF Chimera AutodockVina calculates the affinity energy between the conformation of the protein and the ligand. Furthermore the affinity energy is compared with the energy from positive control compounds. The smaller the value of its affinity, the bioactive compound is more stable and has the potential to become a drug compound.The overall research design can be seen in Figure 3.

3. Result and Discussion

ADME and toxicity

Web based application FAF-DRUGS4 calculates ADME value and toxicity of a compound based on molecular properties, namely molar mass (MW), coefficient of logarithmic partitioning between n-octanol and water, characterizing lipophilicity (LogP), topological polar surface area (tPSA), donor hydrogen bonding (HBD), Hydrogen bond acceptor (HBA), solubility estimate index, Veber rule (Veber rule), Egan rule (Egan

rule), LogP relationship with MW (4/400), LogP relationship with tPSA (3) / 75), and Lipinski rule. The results of ADME and toxicity of bioactive compounds and positive control compounds are shown in Table 1.

·The physics of chemistry	· The Compound name					
	Caomarin	Flavonoid	Terpenoid	Steroid	Phytosterol	Clorobiocin*
ID	323	5317287	442023	439761	222284	54706138
MW	146.14	360.31	336.47	336.45	414.71	697.13
AlogP	1.39	2.79	3.40	5.02	9.34	5.33
HBD	0	3	3	1	1	5
HBA	2	8	4	4	1	13
tPSA	30.21	118.59	80.59	74.81	20.23	189.45
Solubility	Good solubility	Reduced Solubility	Good solubility	Good solubility	Reduced Solubility	Reduced Solubility
3/75	Warning	Good	Warning	Bad	Bad	warning
4/400	Good	Good	Good	Good	Bad	Bad
Egan rule	Good	Good	Goog	Good	Good	good
Veber rule	Good	Good	Good	Good	Good	Low
Lipinski rule	0	0	0	1	1	3

*: positive control compound

Table 1.Properties of ADME-Tox*Schleicheraoleosa*bioactive compounds

Based on observations from Table 1, the bioactive compounds caomarin, flavonoids and terpenoids meet the five Lipinski rules. The three bioactive compounds meet the drug criteria because they have a molecular mass of less than 500 Dalton; high lipophilicity (expressed as logP less than 5), total donor hydrogen bonds less than 5; and the number of hydrogen bond acceptors is less than 10. While the nature of ADME-Tox can be seen from the solubility, Veber rule, Egan rule, 4/400 and 3/75. From the observations of the solubility, the bioactive compounds caomarin and terpenoids have goodsolubility, while the flavonoids have little solubility when metabolized in the body. Furthermore, based on the properties of the Veber rule, Egen rule and the 4/400 properties of the three compounds have good properties. According to the Veber rule, good oral biovability is if it has a rotatable bond ≤10 and tPSA ≤ 140 Å or HBA + HBD Acceptors ≤ 12), whereas according to Egen rule, good biovability is $0 \geq$ tPSA ≤ 132 and $-1 \geq \log P \leq 6$, and a good trait of 4/400 is to have a logP value of less than 4 and MW of less than 400 Dalton because it will have a more favorable ADMET trait. Finally, only flavonoids have good 3/75 properties, while caomarin and terpenoids have properties to look out for when entering the body. Good 3/75 properties are compounds that have a high P log (> 3) and a low TPSA (<75). A bad 3/75 has toxicity in the body. Caomarin compounds, flavonoids and terpnoids have the potential as antimicrobial drugs substitute for clorobiocin drugs that have a less good ADMET value than caomarin, flavonoids and terpnoids. This is because clorobiocin has a large molar mass (more than 500 Dalton), also has a poor lipophilicity value because it has a logP value of more than 5.

Docking analysis

Docking simulation using the UCSF Chimera AutodockVina program. The docking simulation process takes place in two stages: the first stage of determining the active side (Figure 4). The active site is the site of the reaction between the 1KZN receptor and the ligand. Whereas the second stage is calculating the affinity energy from the results of 1KZN receptor interaction with the ligand at the active site (Table 2). For visualization of the 1KZN receptor shown in Figure 4.

Table 2. Energy affinity of ligands with 1KZNreceptors

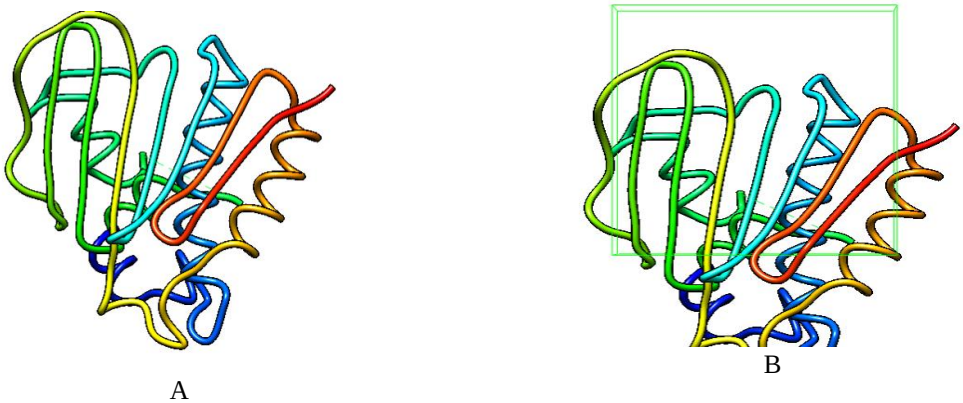
Bioctive compound name	**Afinista energy (Kcal/mol)**
Caomarin	-6.9
Flavonoid	-9.3

Terpenoid	-14.1
Steroid	-12.4
Phytosterol	-11.9
Clorobiocin*	-9.3

*positive control compound

Figure 4 shows that there is no conformational difference between the 1KZN receptor before docking and after the determination of the active-side receptors gridbox. The gridbox is indicated by a green cube. Gridbox that is used as an active site in simulating docking is x = 19,259, y = 29,159, z = 42,461. while the gridbox dimensions used for the x, y and z axes are 30 Å. The gridbox coordinates have been validated to have an RMSD value ≤2 (Nasab et al., 2018). Determination of the coordinates of the gridbox is very important because this gridbox is the place of interaction between ligands and receptors. If the gridbox used is inappropriate, the resulting interaction will not be accurate. Based on the analysis results from table 2, flavonoid compounds, terpenoids, steroids, phytosterol have energy affinity lower or equal to positive control compounds (chlorobiocin). Flavonoid, terpenoid and phytosterol compounds have energy affinity successively is -9.3 kcal / mol; -14.1 kcal / mol; -12.4 kcal / mol; and -11.9 kcal / mol. While the positive control compound chlorobiocin only has an energy affinity of -9.3 kcal / mol. The small affinity energy value indicates that the interaction of the four compounds has the most stable energy and potential as an antimicrobial drug candidate.

Based on the analysis of Tables 1 and 2, flavonoids and terpenoids are the most potentially used as herbal medicines. This is due to the fact that flavonoid and terpenoid compounds possess lower affinitis energy and are equal to positive control compounds (-9.3 kcal / mol) which are -9.3 Kcal / mol and -14.1 kcal / mol (Table 2). In addition, flavonoids and terpenoids also have better ADME and toxicity properties than the chlorobiocin drug compounds (Table 1).



A B

Figure 4. KZN receptor : A (Before docking), B (Determination of theactive side gridbox of the ligand)

4. Conclusion

Based on the results of pharmacological tests and molecular docking simulations, the bioactive compounds of flavonoids and terpenoids from *Schleicheraoleosa*have potential as new antimicrobial drug compounds. Flavonoid and terpenoid compounds have MW: 360.31, 336.47; LogP: 2.79, 3.4; *tPSA*: 118.59, 80.59; HBD: 3, 3; HBA: 8, 4; Solubility: reduced solubility and good solubility; Veber rule: good, good, Egan rule: good, good; 4/400: Good, good; 3/75: good, warning; and neither has a deviation from the five Lipinski rules. While the energy affinity of flavonoids and terpenoids is -9.3 kcal / mol and -14.1 kcal / mol. This research requires further in vitro and in vivo test stages as an antimicrobial validation step of flavonoid and terpenoid bioactive compounds.

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