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IDENTIFICATION OF INDONESIAN ETHNOMEDICINAL PLANTS AS POTENTIAL DRUG CANDIDATES FOR ACUTE RESPIRATORY INFECTION USING COMPUTER-AIDED DRUG DESIGN AND SIMRS MODEL

Identifikasi Tanaman Etnomedis Indonesia sebagai Kandidat Obat Potensial Infeksi Saluran Pernapasan Akut Menggunakan Computer-Aided Drug Design dan Model SIMRS

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ABSTRACT

In 2023, Indonesia's air quality deteriorated, with its Air Quality Index (AQI) tripling clean air standards, causing health sector losses, including a surge in Acute Respiratory Infection (ARI) cases. One of the ARI treatments is the consumption of cefuroxime, yet it can cause side effects. Indonesia's floral biodiversity in ethnomedicinal plants can be utilized as a more natural drug candidate for ARI drugs. To determine this, an *in silico* approach is performed through molecular docking, and Pre-ADMET prediction. Based on the compound selection's results, lanosterol is the most promising compound, with a binding energy value of -8.11 kcal/mol and an efficiency of 78.81%, while cefuroxime as a reference ligand has a binding energy value of -5.92 kcal/mol with an efficiency of 67.87%. After undergoing compound selection, a time series analysis through the Susceptible Infected Medicine Recovered Susceptible (SIMRS) model is conducted. In this analysis, it is found that cefuroxime and lanosterol require the same amount of time, which is 33 days to restore Indonesia to its pre-ARI outbreak condition, indicating that lanosterol can be used as an alternative drug candidate.

Keywords: *Acute Respiratory Infection, cefuroxime, ethnomedicinal plants, in silico, time series, SIMRS model*

ABSTRAK

Pada tahun 2023, kualitas udara Indonesia memburuk, dengan Indeks Kualitas Udara (AQI) yang mencapai tiga kali lipat standar udara bersih, sehingga menyebabkan kerugian di sektor kesehatan, termasuk lonjakan kasus Infeksi Saluran Pernafasan Akut (ISPA). Salah satu pengobatan ISPA adalah dengan konsumsi cefuroxime, namun dapat menimbulkan efek samping. Keanekaragaman hayati flora Indonesia pada tanaman etnomedisinal dapat dimanfaatkan sebagai kandidat obat ISPA yang lebih alami. Untuk menentukan hal tersebut, dilakukan pendekatan in silico melalui molekuler docking, dan prediksi Pra-ADMET. Berdasarkan hasil seleksi senyawa, lanosterol merupakan senyawa yang paling menjanjikan, dengan nilai energi ikat sebesar -8,11 kkal/mol dan efisiensi sebesar 78,81%, sedangkan cefuroxime sebagai ligan pembanding memiliki nilai energi ikat sebesar -5,92 kkal/mol dengan efisiensi sebesar 67,87%. Setelah melalui seleksi senyawa, dilakukan analisis time series melalui model Susceptible Infected Medicine Recovered Susceptible (SIMRS). Pada analisis ini ditemukan bahwa cefuroxime dan lanosterol memerlukan waktu yang sama yaitu 33 hari untuk

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mengembalikan Indonesia ke kondisi sebelum terjadinya wabah ISPA, hal ini menunjukkan bahwa lanosterol dapat digunakan sebagai kandidat obat alternatif.

Kata kunci: Infeksi Saluran Pernafasan Akut, cefuroxime, tanaman etnomedis, in silico, time series, model SIMRS

INTRODUCTION

In 2023, Indonesia's air quality deteriorated, with its Air Quality Index (AQI) tripling clean air standards. There are detrimental effects of poor air quality on both human health and the environment, as evidenced by the sharp rise in Acute Respiratory Infections (ARI). Acute Respiratory Infections (ARI), are infections that affect the respiratory tract of humans. The common symptoms of ARI are coughing, fever, nasal congestion, shortness of breath, headache, and sore throat. ARI is commonly caused by air pollution, viruses, and bacteria including *Streptococcus pneumoniae*, which can cause severe cases of ARI. Over the course of eight months (January–August 2023), 838.291 individuals in DKI Jakarta have been infected by ARI [1]. If Indonesia can attain adequate air quality, locals' average life expectancy may rise by 2.5 years [2]. The antibiotic cefuroxime is one treatment for ARI, yet if taken in excess, it causes negative effects, such as nausea, diarrhea, headaches, and stomachaches. Inhibiting *Streptococcus pneumoniae* with natural chemical compounds from Indonesia's ethnomedicinal plants may serve as an alternative.

As indicated by its second-highest biodiversity ranking behind Brazil, Indonesia is recognized as a nation rich in biodiversity. Up to 19,871 Indonesian ethnomedicinal plants of which 16,218 have been identified and can be utilized as traditional herbs. Based on the findings of this identification, 9,600 species have been identified as having therapeutic potential and 200 more species have served as sources of raw materials for the traditional medicine sector. In order to improve the health of the global society, herbal medicines are currently being regulated by the World Health Organization.

The entire cost of the drug discovery process, which takes ten to fifteen years, is between $500 and $800 million USD, where 90% of new chemical compounds have failed in the clinical trial stage [3]. New developments are therefore required to reduce these shortcomings, which is through the Computer-Aided Drug Design (CADD) simulations. Once a viable drug candidate is obtained, a time series graph will be constructed from a modified SIR model called SIMRS, where 'S' represents susceptible, 'I' infected, 'M' medicine, and 'R' recovered. Overall, this paper aims to determine the potential application of compounds from Indonesian ethnomedicinal plants for the usage of ARI drug candidates.

MATERIAL AND METHODS

3D Structure Preparation

The three-dimensional structure of Penicillin Binding Protein 2X from *Streptococcus pneumoniae* was obtained from the RCSB Protein Data Bank (www.rcsb.org) using the PDB code 1QMF[4]. This structure was then prepared for molecular docking simulations using Autodock Tools (https://autodock.scripps.edu/). Specifically, water molecules were removed from the structure, and the reference ligand, KEF (cefuroxime), was extracted from the 1QMF complex. The target protein structure was first subjected to the addition of polar hydrogens, followed by the merging of nonpolar hydrogens. Next, Gasteiger charges were assigned to the modified structure. The reference ligand was then converted into the PDBQT format, which is a format compatible with the Autodock software. Subsequently, secondary metabolite derivatives from plants exhibiting geometrical structures resembling that of the reference ligand were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) for further exploration as potential drug candidates.

Table 1. PubChem Database

Chemical Compound	CID
Cefuroxime (reference ligand)	5479529
Lanosterol	246983
Campesterol	173183
Triterpenoid	451674
Ergosterol	444679
Stigmasterol	5280794
Flavanon	147806
Laurifolin	44257868
Quercetin	5280343
Flavone	10680
Flavanone	10251
Elatin	44257938
Catechin	9064
Epicatechin	72276
Flavanonol	129819557
Corilagin	73568

Molecular Docking

Molecular docking simulations were conducted using AutoDock 4.2 software on a laptop equipped with an Intel® Core™ i7-1065G7 CPU running at 1.30 GHz, 16.0 GB RAM, Windows 11 64-bit operating system, and Intel® Iris® Plus Graphics as the GPU. To validate the molecular docking result, the reference ligand, KEF (cefuroxime), was superimposed onto the target protein before conducting further molecular docking on secondary metabolites derivatives from Indonesian ethnomedicinal plants. Subsequently, all prepared secondary metabolites derivatives were subjected to molecular docking on the target protein using the same parameters as those employed for the reference ligand. The molecular docking parameters were as follows: central grid point coordinates x = 103.826, y = 61.308, z = 49.685, grid box size 36 × 36 × 36, grid point spacing 0.375 Å, and default docking parameters using the Lamarckian Genetic Algorithm. The resulting intermolecular forces were then analyzed using BIOVIA Discovery Studio 2021 Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download).

Drug-likeness and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Prediction

The drug-likeness of the secondary metabolites derivatives was evaluated using Lipinski's rule of five [8], which was implemented in the pkCSM online tools (https://biosig.lab.uq.edu.au/pkcsm/). To be considered drug-like, a compound must meet the following criteria: a molecular mass below 500 daltons (Da), a log P value less than 5, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, no more than 10 rotatable bonds, and no more than one violation of the previous five rules [7]. After evaluating the drug-likeness, the pharmacokinetic properties (ADMET), including absorption, distribution, metabolism, excretion, and toxicity, were also predicted using the pkCSM online tools.

SIMRS Model

Figure 1 shows the block diagram of a modified SIR model, which is SIMRS model with compartments consisting of susceptible (S), infected (I), medicine (M), and recovered (R) individuals from the total population 1.

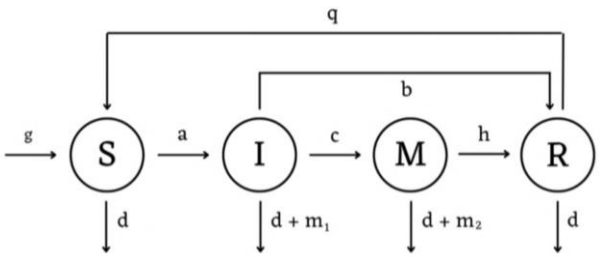


Figure 1. SIMRS Model

Table 2. Classes

Parameter	Name	Unit	Meaning
S	Susceptible	No unit	Proportion of susceptible individuals to be infected (without exception) by ARI
I	Infected	No unit	Proportion of individuals infected by ARI
M	Medicine	No unit	Proportion of individuals who take medicine for ARI
R	Recovered	No unit	Proportion of individuals who recovered from ARI

Table 3. Description of Model Parameters

Parameter	Name	Unit	Meaning
a	Infection rate	$days^{-1}$	The rate in which susceptible individuals become infected individuals
b	Recovery rate	$days^{-1}$	The rate in which infected individuals become recovered individuals
c	Proportion individuals taking medicine	$days^{-1}$	Proportion of individuals who take medicine for ARI
d	Natural mortality rate	$days^{-1}$	The natural daily mortality rate of susceptible, infected, take medicine, and recovered individuals
m_1	ARI mortality rate (infected)	$days^{-1}$	Death rate at which infected individuals die from ARI
m_2	ARI mortality rate (medicine)	$days^{-1}$	Death rate at which take medicine individuals die from ARI
g	Birth rate	$days^{-1}$	Infant birth rate for each day
h	Medicine effective-ness	$days^{-1}$	The level of effectiveness of the medicine so that it affects immunity against infection
q	Recurrence rate	$days^{-1}$	The rate at which individuals get re-infected by ARI due to new variants

Mathematically, the SIMRS model is expressed as a system of ordinary differential equations given as:

$$\frac{dS}{dt} = + g - dS - aSI + qR$$

$$\frac{dI}{dt} = + aSI - (d + m1)I - bI - cI$$

$$\frac{dM}{dt} = + cI - (d + m2)M - hM$$

$$\frac{dR}{dt} = hM - dR + bI - qR$$

where,

$$q = 1 - a$$

because it is assumed that people who get infected by Acute Respiratory Infection (ARI) can get re-infected if they got infected by other

with total population,

$$S(t) + I(t) + M(t) + R(t) = 1$$

Time Series

The construction of a time series graph is obtained through the substitution of the variable and parameter's value into the differential equation through an application namely Excel. Variable and parameter's value are all calculated according to the actual Indonesia's Acute Respiratory Infection condition. As each of the values are obtained, drag the values until it reaches 50 days. Plot the graph from the values obtained and analyze its result to determine whether the drug candidate suits to be an alternative drug candidate for Acute Respiratory Infection (ARI).

RESULTS AND DISCUSSION

1. Docking of Reference Ligand

Through the Protein Data Bank (PDB) database, a protein with the code 1QMF was obtained that has cefuroxime as the reference ligand. This protein is obtained through the X-ray diffraction (XRD) structure between *Streptococcus pneumoniae* and cefuroxime antibiotic. *Streptococcus pneumoniae* was chosen as a representative in the discovery of Acute Respiratory Infection (ARI) drug candidates because it is categorized as a deadly respiratory infection-causing bacterium[4].

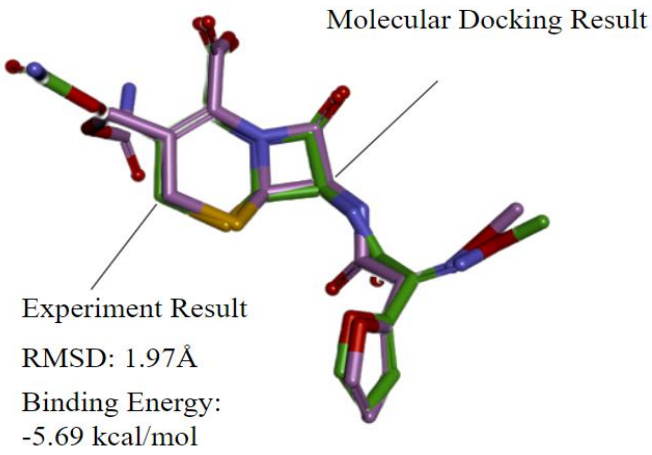


Figure 2. Superimposition of Reference Ligand

According to the molecular docking result, the binding energy of cefuroxime as a reference ligand is -5.69 kcal/mol with a root mean squared deviation (RMSD) value of 1.97Å. The RMSD value is required for the validation process through the re-docking method, where the structure of the reference ligand from molecular docking will be superimposed with the results obtained from the X-ray diffraction (XRD) data from the PDB. The molecular docking is considered valid if the RMSD ≤ 2 Å [9]. This data is used as a control variable for the docking of the chemical compounds.

2. Molecular Docking of Chemical Compounds

Molecular docking is carried out to predict the chemical compounds that have greater potential as drug candidates. This value is determined based on the binding energy value, where theoretically, the chemical compounds with a more negative binding energy compared to the positive control result show that the chemical compounds have the potential to become an alternative drug candidate. This is because the more negative the binding energy, the bond formed between the receptor and the ligand

will be stronger and more stable. In the context of protein code 1QMF, the more negative the binding energy, the more the chemical compounds can inhibit the growth of *Streptococcus pneumoniae*.

Table 4. Molecular Docking Result

Chemical Compound Name	Binding Energy (kcal/mol)	Plant's Scientific Name
Value of Quartile 3 (Q3) = 7.29		
Cefuroxime (reference ligand)	-5.92	-
Lanosterol	-8.11	*Clitoria ternatea*
Campesterol	-8.04	*Haplophyllum bucharicum*
Triterpenoid	-7.83	*Syzygium aqueum*
Ergosterol	-7.29	*Gladiolus italicus*
Stigmasterol	-7.29	*Ficus septica*
Flavanon	-6.80	*Compositae*
Laurifolin	-6.71	*Rollinia laurifolia*
Quercetin	-6.62	*Malus domestica*
Flavone	-6.46	*Acalypha indica*
Flavanone	-6.45	*Citrus paradisi*
Elatin	-6.30	*Lactuca sativa*
Catechin	-6.24	*Camellia sinensis*
Epicatechin	-6.17	*Phyllocladus hypophyllus*
Flavanonol	-6.05	*Vitis vinifera*
Corilagin	-3.70	*Terminalia catappa*

According to the molecular docking results, there are 5 chemical compounds that have a binding energy value ≥ Q3, namely stigmasterol (-7.29 kcal/mol), laurifolin (-8.11 kcal/mol), ergosterol (-7.29 kcal/mol), campesterol (-8.04 kcal/mol), and triterpenoid (-7.83 kcal/mol). These 5 chemical compounds will be further analyzed through Pre-ADMET simulations.

3. Pre-ADMET Analysis

The calculation of drug compound efficiency can be reviewed through Pre-ADMET simulation, which includes aspects of Lipinski's Rule of Five, absorption, distribution, metabolism, excretion, and toxicity [5].

3.1. Lipinski's Rule of Five Analysis

Lipinski's Rule of Five is a general parameter used to test the potential of drug candidates as oral drugs. In this parameter, if the drug candidate does not violate more than one rule, it is considered to have the potential as an oral drug.

Table 5. Lipinski's Rule of Five

Chemical Compounds	Molecular Mass (Dalton)	Hydrogen Bond Donors	Hydrogen Bond Acceptors	Octanol Water Partition Coefficient (log P)	Rotatable Bonds	Number of Violation
Parameter	≤ 500 (Da)	≤ 5	≤ 10	0 ≤ log P ≤ 5	≤ 10	≯ 1
Cefuroxime	424.391	3	9	-0.536	7	1
Triterpenoid	552.774	3	5	6.0331	4	2
Campesterol	400.691	1	1	7.6347	5	1
Ergosterol	396.659	1	1	7.3308	4	1
Lanosterol	426.729	1	1	8.4791	4	1
Stigmasterol	412.702	1	1	7.8008	5	1

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

Molecular mass is related to the distribution process of drugs inside the body. Drugs with molecular mass greater than 500 Dalton tend to have difficulty penetrating biological membranes. The log P value is related to the hydrophobicity of a drug. Drugs with log P values greater than 5 tend to have high toxicity levels because they are too hydrophobic, thus they tend to stay in the lipid bilayer. On the other hand, a log P value less than -0.4 indicates that the drug molecule cannot pass through the lipid. The number of hydrogen donors is the total number of hydrogen-nitrogen and hydrogen-oxygen bonds. The number of hydrogen acceptors is the total number of nitrogen and oxygen atoms. In general, drugs should not have more than 5 hydrogen donors and 10 hydrogen acceptors because the hydrogen bonds that are formed have the potential to form hydrogen bonds with water, which can reduce the ability of the molecule to be absorbed into the bloodstream bilayer membrane. Rotatable bonds are related to the molecular flexibility of a drug molecule. Drugs with high molecular flexibility values can reduce the ability of the drug to be absorbed into the bloodstream. A drug molecule is considered to have good rotatable bonds if the value is less than 10 [6].

Overall, it can be concluded that all chemical compounds, except triterpenoids, have the potential to be used as oral drugs because they do not violate more than one of Lipinski's Rule of Five. To further analyze the absorption, distribution, metabolism, excretion, and toxicity of the chemical compounds, Pre-ADMET simulation is required.

3.2. Absorption Analysis

Drug absorption is the process of the drug entering the bloodstream. This process is the initial stage for the drug's journey through the human body, where drug absorption will allow a drug to reach its biological target, such as the organ or tissue that needs the drug's effect.

Table 6. Pre-ADMET Test (Absorption)

Chemical Compounds	Water Solubility	$Caco_2$ Permeability	Skin Permeability	Intestinal Absorption (%)	P-glycoprotein substrate	P-glycoprotein I inhibitor	P-glycoprotein II inhibitor	Total (%)
Parameter	>-4	>0.9	<-2.5	>80%	Negative	Negative	Negative	
Cefuroxime	-2.900	-0.450	-2.735	32.704	Positive	Negative	Negative	57.14
Triterpenoid	-2.856	0.315	-2.735	27.812	Positive	Negative	Positive	42.86
Campesterol	-7.068	1.223	-2.860	94.543	Negative	Positive	Positive	57.14
Ergosterol	-6.947	1.236	-2.864	95.197	Negative	Positive	Positive	57.14
Lanosterol	-7.498	1.203	-2.926	93.119	Negative	Positive	Positive	57.14
Stigmasterol	-6.682	1.213	-2.783	94.970	Negative	Positive	Positive	57.14

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

The log water solubility is considered to be good if the value is greater than -4, meanwhile if the log water solubility value is less than -4, this indicates that the drug molecule is likely to be poorly soluble in gastrointestinal fluid. Log $Caco_2$ permeability is related to drug absorption. If the number is less than 0.9, this indicates that the drug molecule is difficult to absorb as it has difficulties penetrating the intestinal epithelium to reach the systemic circulation. The log skin permeability discusses the potential of a drug molecule to be a transdermal drug. A drug molecule with a log skin permeability value less than -2.5 indicates that the drug has the potential to be a transdermal drug [7]. A compound is said to have good absorption if it has an intestinal absorption value greater than 80% because it can penetrate the intestinal epithelium to reach the systemic circulation [8]. In the human body, there is a transport protein called P-glycoprotein. This protein is important in the pharmacokinetic steps of drugs, including the drug absorption process. In general, drug molecules should not inhibit or be a substrate of this protein because it has the potential to affect its performance.

According to the results above, campesterol, ergosterol, lanosterol, and stigmasterol have the potential to be poorly soluble in gastrointestinal fluid. Cefuroxime and triterpenoid have difficulties in penetrating the intestinal epithelium. All drug compounds have the potential to be transdermal drugs and have the potential to affect P-glycoprotein as either substrates or inhibitors. Based on the violations, triterpenoids have the poorest absorption value.

3.3. Distribution Analysis

Table 7. Pre-ADMET Test (Distribution)

Chemical Compounds	log VDss	Fraction Unbound	log BBB Permeability	log CNS Permeability	Total (%)
Parameter	≥ 0.15	< 0.15	> -1	> -3	
Cefuroxime	-1.467	0.687	-1.287	-3.466	0
Triterpenoid	-1.170	0.255	-0.902	-2.845	50
Campesterol	0.427	0	0.744	-1.758	100
Ergosterol	0.406	0	0.767	-1.705	100
Lanosterol	0.660	0	0.683	-2.254	100
Stigmasterol	0.178	0	0.771	-1.652	100

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

Drug distribution is the second step in the pharmacokinetic process, where this stage refers to the distribution of drugs throughout the body after the drug enters the bloodstream through the absorption process. Log volume of distribution (VDss) is a theoretical volume where the total dose of a drug is distributed evenly to give a concentration similar to that in the blood plasma. A log VDss value greater than 0.15 indicates that the drug can be distributed well. Fraction unbound is the portion of the drug that is not bound to plasma proteins, so the drug is free to spread to tissues and can provide its pharmacological effects. A fraction unbound value is considered good if it has a value less than 0.15. A drug molecule is considered good if it can penetrate the blood-brain barrier (BBB), which will improve its efficacy. Drug molecules with log BBB permeability values greater than -1 and log CNS permeability values greater than -3 indicate that the drug molecules can penetrate the blood-brain barrier [7].

Based on the table above, it can be concluded that cefuroxime and triterpenoid cannot be distributed well and according to the fraction unbound values, they cannot spread to tissues effectively. All chemical compounds, except cefuroxime, can penetrate the blood-brain barrier. Based on the number of violations, cefuroxime has the worst distribution value.

3.4. Metabolism Analysis

Table 8. Pre-ADMET Test (Metabolism)

Chemical Compounds	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Total (%)
Parameter	Negative	Negative	Negative	Negative	Negative	Negative	Negative	
Cefuroxime	Negative	Negative	Negaitve	Negaitve	Negaitve	Negaitve	Negaitve	100
Triterpenoid	Negative	Positive	Negative	Negative	Negative	Negative	Negative	85.7
Campesterol	Negative	Positive	Negative	Negative	Negative	Negative	Negative	85.7
Ergosterol	Negative	Positive	Negative	Negative	Negative	Negative	Negative	85.7
Lanosterol	Negative	Positive	Negative	Negative	Negative	Negative	Negative	85.7
Stigmasterol	Negative	Positive	Negative	Negative	Negative	Negative	Negative	85.7

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

Metabolism of drugs is a biochemical process that occurs in the body, where the process will change the chemical structure of the drug into a form that is easier to excrete. The cytochrome P450 subfamily, namely CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, are the main enzymes that play a role in the metabolism of most drugs. Therefore, a drug molecule generally does not inhibit or become a substrate of these enzymes because it can affect the performance of the cytochrome[5].

Based on the results above, all chemical compounds, except cefuroxime, have the potential to affect the performance of the cytochrome P450 subfamily because they are substrates of CYP3A4. Therefore, cefuroxime is predicted to be well metabolized in the body.

3.5. Excretion Analysis

Excretion of drugs is the process of removing drugs from the body. This process is considered important because it can help to remove drugs from the body after the drug has reached its therapeutic effect, or in other words, is no longer active.

Table 9. Pre-ADMET (Excretion)

Chemical Compounds	Total Clearance (log ml/min/kg)	Renal OCT2 Substrate	Total (%)
Parameter		Negative	
Cefuroxime	0.164	Negative	100
Triterpenoid	-0.130	Negative	100
Campesterol	0.572	Negative	100
Ergosterol	0.564	Negative	100
Lanosterol	0.403	Negative	100
Stigmasterol	0.618	Negative	100

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

After the metabolism process, drug molecules are excreted, where the excretion rate can be measured through the log total clearance value. A higher value shows that the drug molecule can be excreted the fastest. OCT2 is a protein that plays an important role in the disposition and clearance of drugs. A negative renal OCT 2 substrate value indicates that the drug molecule does not affect the OCT2 substrate[5].

Based on the results, it can be concluded that all of the chemical compounds do not affect the OCT2 substrate. In addition, based on the log total clearance values, it can be concluded that excretion occurs the fastest in stigmasterol and the slowest in triterpenoids.

3.6. Toxicity Analysis

Table 10. Pre-ADMET (Toxicity)

Chemical Compounds	AMES Toxicity	Human Max Tolerated Dose (log mg/kg/day)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity LD50 (mg/kg)
Parameter	Negative	> 0.477	Negative	Negative	> 5000 mg/kg
Cefuroxime	Negative	1.643	Negative	Negative	10000
Triterpenoid	Negative	0.407	Negative	Negative	6000
Campesterol	Negative	-0.458	Negative	Positive	890
Ergosterol	Negative	-0.511	Negative	Positive	10
Lanosterol	Negative	-0.568	Negative	Positive	2000
Stigmasterol	Negative	-0.664	Negative	Positive	890

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

Table 11. Pre-ADMET (Toxicity)

Chemical Compounds	Oral Rat Chronic Toxicity (log LOAEL)	Hepatotoxicity	SkinSensitisation	log *T.pyriformis* Toxicity	log Minnow Toxicity	Total (%)
Parameter	> 3.7	Negative	Negative	> 0.5	> -0.3	
Cefuroxime	1.971	Positive	Negative	0.285	4.239	70
Triterpenoid	2.362	Negative	Negative	0.285	-1.335	60
Campesterol	0.892	Negative	Negative	0.631	-1.940	50
Ergosterol	0.909	Negative	Negative	0.639	-1.770	50
Lanosterol	0.788	Negative	Negative	0.736	-1.757	50
Stigmasterol	0.872	Negative	Negative	0.433	-1.675	40

*The red colour indicates that the chemical compound does not meet the criteria of the corresponding parameter

After analyzing the pharmacokinetic and pharmacodynamic properties of a drug, the toxicity of a drug must also be analyzed. Positive AMES toxicity values indicate that the drug molecule has the potential to be carcinogenic, while negative values show otherwise. The log human maximum tolerated dose (MTD) is the highest dose of the drug molecule that humans can tolerate without causing high toxicity. The log human MTD is considered good if the value is greater than 0.477. hERG I and hERG II represent potassium channels in the human body, whose function is to regulate cardiac repolarization. If hERG I or hERG II is inhibited, it has the potential to cause fatal arrhythmia. The oral rat acute toxicity (ORAT) and oral rat chronic toxicity (ORCT) values explain the dose of the drug that is needed to kill 50% of rats (test animals) in the *in vivo* stage. According to the globally harmonized system (GHS) assessment, the drug molecule is considered non-toxic if the LD_{50} value is greater than 5,000 mg/kg and the log ORCT value is greater than 3.7. A positive hepatotoxicity value indicates that the drug molecule has the potential to cause liver damage. A positive skin sensitization value indicates that the drug molecule has the potential to cause allergic effects on the skin if used as a transdermal drug. The log *T.pyriformis* toxicity and log minnow toxicity values explain the effects of the drug molecule on the environment, especially on marine life. The drug molecule is considered non-toxic to marine life if the log *T.pyriformis* toxicity and the log minnow toxicity value is greater than 0.5 and -0.3 respectively[5].

Based on the results, it is concluded that all chemical compounds are not carcinogenic and do not have the potential to cause skin allergies. Then, based on the hepatotoxicity value, cefuroxime has the potential to cause damage to the human liver. Cefuroxime can be consumed at the highest dose because it has the largest log Human MTD value. Campesterol, ergosterol, lanosterol, and stigmasterol have the potential to cause fatal arrhythmia by inhibiting hERG II. Overall, all chemical compounds have the potential to harm marine life based on the log *T.pyriformis* toxicity and log minnow toxicity values obtained.

3.7. Pre-ADMET Overall Analysis

Table 12. Pre-ADMET (Overall)

Chemical Compounds	Tota Lipinski's Rule of 5 (%)	TotalAbsorption (%)	Total Distribution (%)	Total Metabolism (%)	Total Excretion (%)	Total Toxicity (%)	Overall Efficiency (%)
Cefuroxime	80	57.14	0	100	100	70	67.86
Triterpenoid	60	42.86	50	85.7	100	60	66.43
Campesterol	80	57.14	100	85.7	100	50	78.81
Ergosterol	80	57.14	100	85.7	100	50	78.81
Lanosterol	80	57.14	100	85.7	100	50	78.81
Stigmasterol	80	57.14	100	85.7	100	40	77.14

By considering all Pre-ADMET parameters, namely Lipinski's rule of 5, absorption, distribution, metabolism, excretion, and toxicity, the total drug efficiency value can be obtained. Through this calculation, campesterol, ergosterol, and lanosterol have the highest efficiency, which is 78.81%. Since lanosterol has the most negative binding energy value among the three compounds, it can be concluded that lanosterol is the compound with the most potential based on molecular docking and Pre-ADMET. Lanosterol can boost the human's immune system, especially when it strengthens the body's ability to fight off germs and infections. This suggests that it may be useful for treating lung infections. To further analyze its potential, a time series analysis is conducted according to the constructed SIMRS model.

4. Time Series Analysis

In the SIMRS model simulation, the initial values for each variable and parameters are:

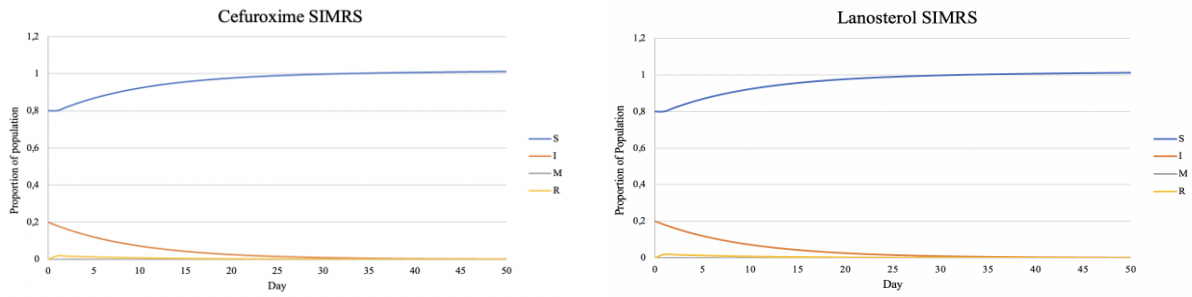
Table 13. Initial Variable Value

Variables	Value
S (Susceptible)	0.8
I (Infected)	0.2
M (Medicine)	0
R (Recovered)	0

Table 14. Initial Parameter Value

Parameters	Value
a	0.00204
b	0.094967844
c	0.00223
d	0.000184
m_1	0.000425
m_2	0.0000712
g	0.000461
h	Cefuroxime: 0.6785714286 Lanosterol: 0.7880952381
q	0.999796

As the variable and parameter's value is substituted into the differential equations, the time series graph obtained is as follows:



Graph 1. Cefuroxime and Lanosterol SIMRS Time Series

The two graphs above show the time series data towards the proportion of Indonesia's population over time, namely for 50 days. In the time series data, it can be seen that for lanosterol, along with the positive control (cefuroxime), people who were infected, took medicine, and recovered tend to reach zero after approximately 33 days, while susceptible people continue to increase over the period of 50 days. This trend illustrates that as time goes by, the proportion of the population infected by ARI will disappear. Since the positive control requires the same time for the state's condition to return to its original condition, this proves that the drug candidate has the potential to be used as an alternative drug.

CONCLUSION

According to the results, lanosterol is the best drug candidate for Acute Respiratory Infection. Based on a time series that is constructed from the SIMRS model, lanosterol and cefuroxime require the same amount of time, which is 33 days to restore Indonesia to its pre-ARI outbreak condition, indicating that it can be used as an alternative. These results indicate that lanosterol, a natural compound abundant in *Clitorea ternatea*, holds promise as a potential ARI drug candidate and merits further exploration.

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