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ADMET Screening of *Sambucus nigra* as Antiviral Agent Through Computational Simulation

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Ahmad Affan Ali Murtadlo[1,2]*, Sin War Naw[3], Md. Emdad Ullah[4], Muhammad Badrut Tamam[2,5], Dora Dayu Rahma Turista[2,6]

[1]Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia
[2]Generasi Biologi Indonesia Foundation, Gresik, Indonesia
[3]Department of Chemistry, Myitkyina University, Myitkyina, Myanmar
[4]Department of Chemistry, Mississippi State University, Mississippi State, United States
[5]Department of Biology, Faculty of Sciences and Technology, Universitas Muhammadiyah Lamongan, Lamongan, Indonesia
[6]Biology Education Department, Faculty of Teacher Training and Education, Mulawarman University, Samarinda, Indonesia

* Corresponding Author: ahmadaffan171@gmail.com

ABSTRACT

Sambucus nigra L. (Elderberry) can be used as a source of antiviral compounds. Previously this medicinal plant was commonly used to fight influenza virus infections that cause flu and cough. Some preliminary research studies showed antiviral activity in *Sambucus nigra* L. extracts. *Sambucus nigra* L are used as antiviral agents that work effectively, it is important to do absorption, distribution, metabolism, excretion, and toxicity (ADMET) screening, the analysis aims to evaluate and predict the pharmacokinetic and toxicological properties of query compounds. ADMET screening method refers to a way of evaluating the pharmacokinetic and toxicological properties of query compounds in an early stage of drug molecule development. ADMET method can be performed through three research approaches consisting of *in silico*, *in vitro*, and *in vivo* to obtain the pharmacokinetic and toxicological profile of a drug for further testing. The objective in this study is the identification of compounds from *Sambucus nigra* L. with ADMET properties to be effective antiviral agent candidates. The in silico method used in this study consists of retrieving compounds from the database, molecular visualization, druglikeness prediction, and toxicity assessment. Compounds from *Sambucus nigra* L. that can be used as antiviral drug candidates consist of catechin, epicatechin, narigenin, and quercetin. The four compounds act as drug-like molecule and have low toxicity. This can be recommended for further tests in identifying molecular mechanisms as antivirals through an *in silico* and *in vitro* approach

Keywords: Antiviral, ADMET, Druglikeness, *In Silico*, *Sambucus nigra*

INTRODUCTION

The development of drug research is important for effective treatment of viral infections that trigger cases of deadly diseases[1,2,3]. So it is necessary to conduct a study to screen compounds from natural materials that have the potential to inhibit viral replication or antiviral agents[4,5,6]. Medicinal plants such as *Sambucus nigra* L. (Elderberry) can be used as a source of antiviral compounds[7]. Previously this medicinal plant was commonly used to fight influenza virus infections that cause flu and cough. Some preliminary research studies showed antiviral activity in *Sambucus nigra* L. extracts[8]. Before compounds from *Sambucus nigra* L are used as antiviral agents that work effectively, it is important to do absorption, distribution, metabolism, excretion, and

† Footnotes relating to the title and/or authors should appear here.
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toxicity (ADMET) screening, the analysis aims to evaluate and predict the pharmacokinetic and toxicological properties of query compounds[9,10]. The information obtained can be used to understand the performance of drug molecules when they enter the human body.

ADMET screening method refers to a way of evaluating the pharmacokinetic and toxicological properties of query compounds in an early stage of drug molecule development[11,12]. The abbreviation ADMET refers to absorption, distribution, metabolism, excretion, and toxicity, which are parameters that must be used for drug candidate discovery research[13,14]. ADMET is used to identify and predict how a compound is distributed in the body, metabolic processes, excretion mechanisms, and toxicity levels[15,16]. ADMET method can be performed through three research approaches consisting of in silico, in vitro, and in vivo to obtain the pharmacokinetic and toxicological profile of a drug for further testing[17,18]. ADMET analysis through *in silico* approach can be done through SWISS ADME server (http://www.swissadme.ch/), SCFBIO (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp), and ADMETlab (https://admetmesh.scbdd.com/)[19,20].

This study used an *in silico* simulation approach to perform ADMET screening on compounds from *Sambucus nigra* L., *in silico* or computational methods can be used for rapid and efficient analysis on most compounds in the evaluation of potential as antiviral agents. The objective in this study is the identification of compounds from *Sambucus nigra* L. with ADMET properties to be effective antiviral agent candidates. This study is expected to provide an initial understanding of the potential of *Sambucus nigra* L. as a source of antiviral compounds and can be used in efforts to discover new antiviral drugs.

METHOD

Compound Retrieval

Previous research revealed the bioactivity of *Sambucus nigra* L. consisting of Cyanidin-3-sambubioside, Cyanidin-3,5-diglucoside, Catechin, Epicatechin, Naringenin, and Quercetin. Information on ligands consisting of name, CID, molecular weight (g/mol), formula, 3D structure, and SMILE Canonical was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem database serves to store information such as chemical compounds from natural, synthetic, and bioassay materials, this database can be used for depiction and similarity testing of query compounds[21,22,23].

Molecular Visualization

Visualization of the three-dimensional structure of the query compounds from *Sambucus nigra* L. was done through PyMol v2.5. Type sticks with colors based on C, H, and O atoms were used on the query ligands. Structural and color selection aims to visualize the structure with publication standards. PyMol is a molecular visual software that works based on Python algorithm and can be used to generate a representative view with three-dimensional structure[24,25,26].

Druglikeness Prediction

Druglikeness aims to assess the ability of a query compound as a drug-like molecule by referring to several rules such as the Lipinski Rule of Five (Ro5). The physicochemical parameters in Ro5 consist of molecular mass, high lipophilicity, hydrogen bond donor, hydrogen bond acceptor, and molar refractivity. The prediction of druglikeness in this study was done through the SCFBIO server (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp)[27,28,29].

Toxicity Assesment

Toxicity probabilities of the query compounds were identified through the ProTox-II server (https://tox-new.charite.de/protox_II/). The toxicity type consists of liver damage-inducing effects (hepatotoxicity), cancer (carcinogenicity), and mutation agents (mutagenicity), the prediction probability should be inactive so that the side effects of the query compound are not detected[30].

RESULTS AND DISCUSSION

Sambucus nigra L. is known to be used in traditional medicine which has historical value, this plant has been identified to inhibit influenza virus replication in extract form, however, scientific evidence must still be strengthened and the process of dose standardization is currently still under research[31]. Previous research revealed that *Sambucus nigra* L can have potential as an antiviral, antibacterial, antitumor, and antidiabetic, the plant has polyphenol and lectins compounds that are strongly suspected to act as antivirals[32]. However, some specific compounds from *Sambucus nigra* L. have not been well identified and the mechanism triggering the antiviral potential is also unknown. Chemical compounds of *Sambucus nigra* L. consisting of Cyanidin-3-sambubioside, Cyanidin-3,5-diglucoside, Catechin,

Epicatechin, Naringenin, and Quercetin were obtained from PubChem with information consisting of CID, molecular weight (g/mol), formula, and SMILE Canonical (Table 1).

Table 1. Chemical compounds of *Sambucus nigra* L. from PubChem

Compound	CID	Molecular Weight (g/mol)	Formula	SMILE Canonical
Cyanidin-3-sambubioside	3084569	616.9	$C_{26}H_{29}C_lO_{15}$	C1C(C(C(C(O1)OC2C(C(C(OC2OC3=CC4=C(C=C(C=C4[O+]=C3C5=CC(=C(C=C5)O)O)O)O)CO)O)O)O)O)O.[Cl-]
Cyanidin-3,5-diglucoside	44256718	611.5	$C_{27}H_{31}O_{16}^+$	C1=CC(=C(C=C1C2=C(C=C3C(=CC(=CC3=[O+]2)O)OC4C(C(C(C(O4)CO)O)O)O)OC5C(C(C(C(O5)CO)O)O)O)O)O
Catechin	9064	290.27	$C_{15}H_{14}O_6$	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
Epicatechin	72276	290.27	$C_{15}H_{14}O_6$	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
Naringenin	439246	272.25	$C_{15}H_{12}O_5$	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
Quercetin	280343	302.23	$C_{15}H_{10}O_7$	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O

Ro5 is used to identify drug-like molecule characteristics in a query compound by referring to parameters consisting of molecular mass, high lipophilicity, hydrogen bond donors, hydrogen bond accpetors, and molar refractivity [27,28]. The query compound must meet at least two rules from Ro5 to be categorized as a drug-like molecule. The results showed that the compounds from Sambucus nigra L. that act as drug-like molecule are catechin, epicatechin, naringenin, and quercetin. The four compounds are predicted to circulate in the body and interact with the target then produce therapeutic effects such as antiviral activity. The compounds Cyanidin-3-sambubioside and Cyanidin-3,5-diglucoside are non drug-like molecules and were not used for further analysis because they had negative predictions (Table).

Table 2. Druglikeness prediction by Ro5

Compound	MM (<500 D)	LogP (<5)	HBD (<5)	HBA (<10)	MR (40-130)	Probable
Cyanidin-3-sambubioside	581.000	-1.344	10	15	133.076	Non drug-like molecule
Cyanidin-3,5-diglucoside	611.000	-2.334	11	16	139.180	Non drug-like molecule
Catechin	290.000	1.546	5	6	72.622	Drug-like molecule
Epicatechin	290.000	1.546	5	6	72.623	Drug-like molecule
Naringenin	272.000	2.509	3	5	70.194	Drug-like molecule
Quercetin	302.000	2.010	5	7	74.050	Drug-like molecule

MM: Molecular Mass; LogP: High Lipophilicity; HBD: Hydrogen Bond Donor; HBA: Hydrogen Bond Acceptor; MR: Molar Refractivity

Toxicity prediction through an in silico approach plays a role in reducing the use of experimental animals, cutting time and costs because it is faster or highly selective, and obtaining information about the mechanism of toxicity. Toxicity prediction on chemical compounds from *Sambucus nigra* L. with characteristics as a drug-like molecule was carried out by referring to three parameters consisting of hepatotoxicity, carcinogenicity, and mutagenicity. The results of toxicity prediction showed that catechin, epicatechin, naringenin, and quercetin compounds were not toxic based on three parameters, namely hepatotoxicity,

carcinogenicity, and mutagenicity (Table 3). These compounds can be used in further in silico research such as molecular docking to identify the molecular mechanism of compounds from *Sambucus nigra* L. that can act as antivirals. The three-dimensional structures of the four compounds are shown on sticks (Figure 1).

Table 3. Toxicity prediction of *Sambucus nigra* compound

Compound	Hepatotoxicity	Carcinogenicity	Mutagenicity	Prediction
Catechin	0.72	0.51	0.55	Inactive
Epicatechin	0.72	0.51	0.55	Inactive
Naringenin	0.67	0.62	0.83	Inactive
Quercetin	0.69	0.68	0.51	Inactive

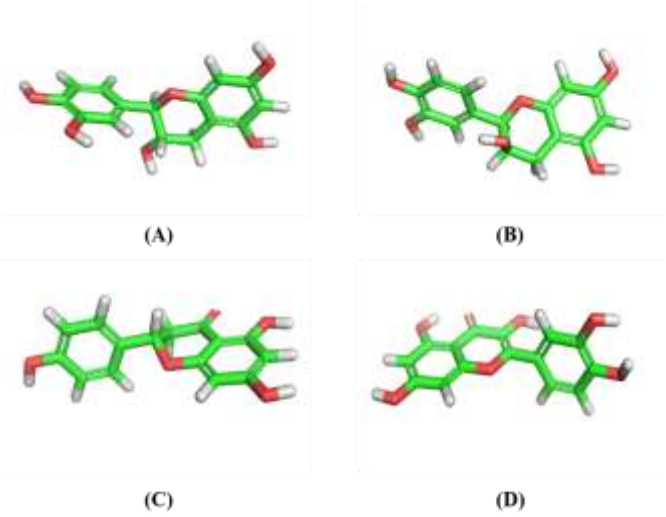

Figure 1. Chemical compounds from *Sambucus nigra* L. that act as drug-like molecules and non-toxins. (A) Catechin, (B) Epicatechin, (C) Naringenin, (D) Quercetin.

CONCLUSION

Compounds from *Sambucus nigra* L. that can be used as antiviral drug candidates consist of catechin, epicatechin, narigenin, and quercetin. The four compounds act as drug-like molecule and have low toxicity. This can be recommended for further tests in identifying molecular mechanisms as antivirals through an *in silico* and *in vitro* approach.

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