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In silico Evaluation of the Active Compounds of *Hibiscus sabdariffa* Linn as IL-11 Inhibitor

Yeniar Fitrianingrum[1*], Nurhadi Ibrahim[2], Trinovita Andraini[2], Linda Erlina[3,4]

[1]*Master's Programme in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia*
[2]*Department of Medical Physiology and Biophysics, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia*
[3]*Department of Medical Chemistry, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia*
[4]*Bioinformatics Core Facilities, Indonesian Medical Education and Research Institute (IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia*

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ABSTRACT

Interleukin (IL) 11 is a pro-inflammatory and pro-fibrotic cytokine. Recently, it has been known that IL-11 inhibition can increase health and lifespan. There are still limited compounds that become IL-11 inhibitors. *Hibiscus sabdariffa* Linn. (HSL) is a common herbal drink in Asia with good antioxidant and anti-inflammatory properties. This *in silico* study aims to determine the candidate bioactive compounds in HSL that can act as IL-11 inhibitors. The Protein Data Bank (PDB) database with code 6O4O provided the IL-11 protein, while the PubChem database provided the active compound of HSL. The molecular docking results were displayed using PyMol version 1.3. The best candidates were assessed based on affinity prediction, ADMET profiles, and Lipinski's rules of five criteria. Quercetin 3-7-diglucuronide, delphinidin 3-*O*-beta-D-sambubioside, and quercetin 3-rutinoside have shown strong interactions with the targeted protein IL-11 with the least docking score (-7.4~-7.0 kcal/mol). All those phytochemicals interacted with several active sites of IL-11. Quercetin 3-7-diglucuronide interacts with the amino acids Arg33, Arg40, Gly47, Asp48, His49, His161, Trp166, and Arg169. Delphinidin 3-*O*-beta-D-sambubioside interacts with the amino acids Arg40, Asp48, Gly158, His161, and Arg169. Quercetin 3-rutinoside interacts with the amino acids Arg40, His49, His154, His161, Asp165, and Arg169. Although drug-likeness only met one of five of Lipinski's rules, ADMET profiles are promising and can be further investigated as possible IL-11 inhibitors within *in vitro* and *in vivo* studies to prolong the health and lifespan of mammals.

Keywords: Molecular docking, interleukin 11 inhibitors, *Hibiscus sabdariffa* Linn., Anti-aging, *in silico*

Introduction

Life expectancy has increased significantly as a result of medical improvements. By 2050, two billion individuals will be over the age of sixty.[1] Every five years, a twofold increase in age-related diseases like Alzheimer's, cancer, and heart disease will coincide.[2] This presents issues, with an increasing number of degenerative diseases straining the healthcare system, both socially and economically. As a result, attempts must be made to intervene in the aging process and promote healthy aging for the elderly population to remain productive. Several hypotheses attempt to explain the mechanism of aging. Cellular senescence, telomere shortening, chronic inflammation, increased oxidative stress, stem cell depletion, diminished function, and mortality are all consequences of the aging process.[3] Senescence-associated secretory phenotypes (SASPs) release inflammatory factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a crucial transcription factor, Tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).[4] These can cause chronic inflammation and a reduction in immunological function, leaving the body unable to manage inflammatory factors as it ages. Chronic inflammation related to cell aging occurs systemically.[5]

*Corresponding author. Email: yeniar.fitrianingrum@ui.ac.id
Tel: +62 898 657 3262

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Interleukin (IL) 11 is a pro-inflammatory and profibrotic cytokine. IL-11 upregulation has been implicated in several diseases, such as cancer and fibrosis, by activating multiple intracellular signaling pathways by forming complexes with their cell surface receptors, α-receptors (IL-11Rα), and β-receptors (gp130).[6] IL-11 through major signaling mechanisms, can activate the Extracellular signal-Regulated Kinase-Mammalian target of rapamycin complex (ERK-mTORC) and/or Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT3) pathways and activate aging features, including mitochondrial dysfunction, inflammation, and cell senescence, so that they can affect lifespan.[7] In older organisms, the AMP-activated protein kinase-Mammalian target of rapamycin complex 1 (AMPK–mTORC1) pathway is essential for metabolic health, and its inhibition may extend lifespan in mice. JAK-STAT3 and NF-κB, two pro-inflammatory signaling factors, are particularly implicated in aging, and JAK inhibitors may mitigate age-related dysfunction.[5] Recent research suggests that IL-11/ IL-11Rα deletion in mice may prevent metabolic decline and morbidity in old age. The use of anti-IL-11 can also improve metabolism, muscle function, and aging biomarkers.[7] So, inhibition of IL-11 can be upstream to prevent activation of these pathways and prolong the life span.

Researchers are developing monoclonal antibodies, omega-3s, and plant-derived active substances to inhibit the IL-11 activation pathway.[7,8] One of the plants currently the focus of research is *Hibiscus sabdariffa* Linn. (HSL) which has anti-inflammatory effects.[9] Research supports the anti-inflammatory effects of HSL extract, i.e. maintaining the IL-1β/IL-1ra ratio in the plasma and hippocampus of overtrained Wistar rats. [10] HSL extract also suppresses MCP-1, TNF-α, IL-1β, and IL-6 levels, decreasing overall inflammatory/immune response.[11]

Administration of HSL at a dose of 300-500 mg/kg body weight in inflammation-induced mice significantly reduced the inflammatory markers examined.[11] Based on several anti-inflammatory effects studies, HSL is also expected to inhibit IL-11. Moreover, the process of developing new medications through high-throughput screening is both lengthy and costly. An alternative method for creating new drugs is virtual screening (*in silico*), which is characterized by a shorter timeline and reduced costs. A biocomputational analysis utilizing molecular docking is commonly employed to efficiently predict how ligands and macromolecules will preferentially interact.[12] Therefore, considering the established anti-inflammatory properties of HSL and the absence of current *in vivo* research investigating its potential as an IL-11 inhibitor, this *in silico* study serves as a crucial initial step to explore HSL's active compounds as candidates for anti-aging strategies targeting IL-11 inhibition, offering a cost-effective and time-efficient foundation for future *in vivo* investigations.

Materials and Methods

Preparation of phytochemicals and target protein

Phytochemicals were used as HSL ligands based on the study by Herranz-López *et al.*[13] Three-dimensional ligand structures in.sdf format were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). IL-11, the target protein, was obtained using the PDB code 6O4O from the Protein Data Bank (PDB; www.rscb.org).[6] Using AutoDock Tools 1.5.6, 2022 (https://ccsb.scripps.edu/mgltools/downloads/), the IL-11 protein was altered to improve its polarity in the binding pockets by adding hydrogen atoms and removing water molecules.[14] Grid box size and grid center coordinate surrounded the active site of IL-11 (Arg33, Met59, Ala61, Gly62, Asp165, Trp166, Arg169, Leu172, Leu173),[6] with x=-4.744, y=21.264, and z=5.142. This structure was then converted to pdbqt format.

Molecular docking of interleukin-11 and phytochemicals

The mean docking scores of all phytochemicals were compared after they were molecularly docked with IL-11 twice using Autodock Vina on PyRx software 0.9, 2021 (https://pyrx.sourceforge.io/downloads).[15] Docking score data were displayed as the average of the first and second docking scores. Interaction between selected phytochemicals and IL-11 was then visualized using Pymol 2.6, 2025 (https://pymol.org/2/) to obtain molecular conformation, binding sites, and bond types.[16]

Phytochemicals selection, characterization of drug-likeness and ADMET

The top phytochemicals were selected based on the docking score (kcal/mol). The Lipinski's rule of five was determined by using SCFBio (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp).
Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties were analyzed from pkCSM-Pharmacokinetics (https://biosig.lab.uq.edu.au/pkcsm/) and Protox-3.0 (https://tox.charite.de/protox3/).

Results and Discussion

Interleukin-11 inhibitor from the active compound of Hibiscus sabdariffa Linn.

All ligands of the active HSL compound obtained from the literature were molecular docked on the active side of the IL-11 protein,[13] and the results were obtained in Table 1. Based on computational analysis of the docking score of those, 5 compounds with the potential to be inhibitors of IL-11 were obtained. Quercetin-3-7-diglucuronide, delphinidin 3-*O*-beta-D-sambubioside, prodelphinidin B3, quercetin 3-rutinoside, and kaempferol 3-*O*-rutinoside showed strong interactions with the targeted IL-11 protein, with the least docking score (-7.4 ~ -7.0 kcal/mol). The docking score or binding energy (ΔG) indicates the strength and affinity of the interaction between a ligand and a receptor. A higher value signifies a weaker interaction; conversely, a low (negative) binding energy results in a more stable interaction between the receptor and the ligand due to the small free energy of the complex.[17] Three of the five compounds with the lowest docking score have hydrogen bonds with the amino acids of the IL-11 protein, i.e., quercetin 3-7-diglucuronide, delphinidin 3-*O*-beta-D-sambubioside, and quercetin-3-rutinoside. Quercetin 3-7-diglucuronide has interactions with the amino acids Arg33, Arg40, Gly47, Asp48, His49, His161, Trp166, and Arg169 with an average docking score of -7.4 kcal/mol. Delphinidin 3-*O*-beta-D-sambubioside interacts with the amino acids Arg40, Asp48, Gly158, His161, and Arg169 with an average bond energy of -7.05 kcal/mol. Meanwhile, quercetin-3-rutinoside interacts with the amino acids Arg40, His49, His154, His161, Asp165, and Arg169 with an average docking score of -7 kcal/mol (Figure 1). Prodelphinidin B3 and kaempferol 3-*O*-rutinoside have no hydrogen binding to the active site protein IL-11. Hydrogen bonding occurs when hydrogen atoms bound to electronegative atoms (such as oxygen, nitrogen, or fluorine) interact with free electron pairs on other electronegative atoms. Hydrogen bonds are relatively strong compared to van der Waals forces, but they are weaker than covalent bonds.[18] Quercetin 3-7-diglucuronide has the most bonds with the active site of IL-11 and has the lowest docking score, making it the best candidate as an IL-11 inhibitor. However, it remains to be seen the pharmacological properties of the compound.

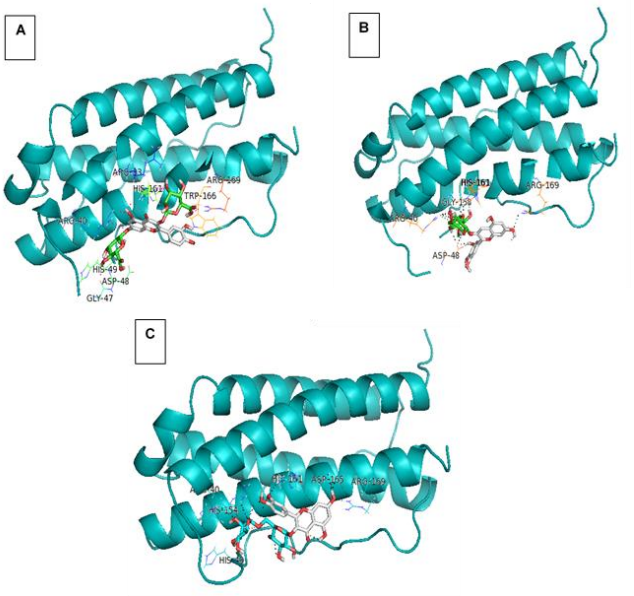

Figure 1: A. Quercetin 3-7- diglucuronide, B. Delphinidin 3-*O*-beta-D- sambubioside, C. Quercetin 3- rutinoside interacted with IL11**.** Quercetin 3-7-diglucuronide has interactions with the amino acids **Arg33**, Arg40, Gly47, Asp48, His49, His161, **Trp166**, and **Arg169**. Delphinidin 3-*O*-beta-D-sambubioside has interactions with the amino acids Arg40, Asp48, Gly158, His161, and **Arg169**. Quercetin-3-rutinoside has interactions with the amino acids Arg40, His49, His154, His161, **Asp165**, and **Arg169**. (Amino acids in bold were the active site of IL-11)

Properties of the best candidate Interleukin-11 inhibitor

Three phytochemicals of HSL that interacted with IL-11 with the lowest docking score and interacted with several amino acids on the active site of IL-11 have been analyzed the Lipinski's rules of five. Quercetin-3-7-diglucuronide, delphinidin 3-*O*-beta-D-sambubioside, and quercetin 3-rutinoside only meet one of Lipinski's rules of five (table 2). However, the drug similarity and ADMET profile are promising and can be further tested to be potential IL-11 inhibitor candidates for lifespan. After determining the docking score of the three compounds to IL11 and determining their interactions, we also analyzed the compounds based on ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) to become drug candidates (table 3). The three compounds cannot penetrate the blood-brain barrier, so special technology is needed to deliver these compounds to the brain if they become the target of therapy.[19] Quercetin 3-rutinoside has the best absorption in the

intestines. However, it is difficult to predict the uptake of a compound mathematically; Therefore, the website provides a probable result. Absorption results should be carefully considered before making decisions about drug candidates.[20] Solubility in water is one of the main properties that affect it, therefore, it also needs to be considered in manufacturing oral drug candidates.[20] All drug candidates have good solubility in water. Although Lipinski's rules of five only meet one point, namely the P<5 log, other conditions in determining drug candidates can be considered for choosing them. All drug candidates had no toxicity parameters, both hepatotoxicity, acute toxicity, carcinogenicity, and mutagenicity (AMES). Quercetin 3-7-diglucuronide and quercetin 3-rutinoside are quercetin derived flavonoid compounds.[21] For centuries, humans have included quercetin, which is present in a wide variety of fruits and vegetables, in their diet. Numerous studies have been conducted on its many properties, which include antibacterial, antiviral, anti-inflammatory, antioxidant, and anticancer.[21] Quercetin as an anti-inflammatory, suppresses the production of inflammatory cytokines such as IL-1β, TNF-α, and IL-6 through increased regulation of TLR4. Furthermore, the suppressed signal results in the decay of inhibitor of kappa B alpha (IκBα) phosphorylation and Mitogen-Activated Protein Kinase (MAPK) expression and thus inhibits the transcription factor NF-κB.[22]

Delphinidin 3-*O*-beta-D-sambubioside is an anthocyanin that is included in flavonoids.[23] In an experimental model using lipopolysaccharide-induced (LPS) cells, delphinidin-3-*O*-beta-D-sambubioside was found to lower the inflammatory mediators iNOS, NO, IL-6, MCP-1, and TNF-α.[24] The NF-kB pathway and MEK1/2 - ERK1/2 signaling are both degraded by delphinidin-3-*O*-beta-D-sambubioside, according to cellular signaling analysis. In mice given lipopolysaccharide (LPS), delphinidin-3-*O*-beta-D-sambubioside lowered the levels of IL-6, MCP-1, and TNF-α.[24]

Table 1: Docking score active compound of HSL with IL-11 protein.

Pubchem ID	Active Compound	Docking score 1 (kcal/mol)	Docking score 2 (kcal/mol)	Average Docking Score (kcal/mol)
44259246	Quercetin 3-7-diglucuronide	-7.3	-7.5	-7.4
10196837	Delphinidin 3-*O*-beta-D-sambubioside	-7.3	-7.3	-7.3
13831068	Prodelphinidin B3	-7.2	-7.3	-7.25
5280805	Quercetin 3-rutinoside	-7	-7	-7
5318767	Kaempferol 3-*O*-rutinoside	-7	-7	-7
5281762	5-*O*- Caffeoylshikimic acid	-6.9	-6.8	-6.85
5280537	N-feruloyltyramine	-6.7	-6.9	-6.8
5281672	Myricetin	-6.8	-6.8	-6.8
5280343	Quercetin	-6.7	-6.7	-6.7
22846027	Kaempferol 3-glucuronid	-6.8	-6.5	-6.65
1794427	Chlorogenic acid	-6.4	-6.9	-6.65
11326520	Ethyl chlorogenate	-6.1	-7.1	-6.6
44258801	Kaempferol 3-sambubioside	-6.6	-6.6	-6.6
44259426	Myricetin 3-glucoside	-6.4	-6.7	-6.55
5274585	Quercetin 3-*O*-glucuronide	-6.4	-6.7	-6.55
24797519	2-*O*- caffeoylhydroxycitric acid	-6.6	-6.5	-6.55
6441280	Coumaroylquinic acid	-6.5	-6.6	-6.55
73759913	Chlorogenoquinone	-6.5	-6.6	-6.55
10196837	Delphinidin 3-*O*-beta-D-sambubioside	-6.3	-6.8	-6.55
9798666	Cryptochlorogenic acid	-6.2	-6.8	-6.5
5280633	Neochlorogenic acid	-6.5	-6.4	-6.45
5281654	3-methylquercetin	-6.5	-6.4	-6.45
44566720	Leucoside	-6.4	-6.5	-6.45
5487635	Quercetin 3-sambubioside	-6.4	-6.5	-6.45
176920	Methyl epigallocatechin	-6.8	-6.1	-6.45
5280863	Kaempferol	-6.4	-6.4	-6.4
5280804	Quercetin 3-glucoside	-6.3	-6.4	-6.35
10155076	1-*O*-caffeoylquinic acid	-6.3	-6.3	-6.3
457801	Gamma-sitosterol	-6.1	-6.5	-6.3
131752859	2-*O*-Feruloylhydroxycitric acid	-6.3	-6.3	-6.3
10155076	1-*O*-caffeoylquinic acid	-6.1	-6.3	-6.2

129629071	Caffeoylglucose	-5.6	-6.2	-5.9
319935	2,5-dioxo-2,5-dihydropyrrol-1-yl) acetic acid	-6.5	-4.6	-5.55
9856782	Hibiscus acid	-5.5	-5.5	-5.5
123908	Hydroxycitric acid	-5.3	-5.3	-5.3
28114	2 -amino-3-hydroxypyridine	-5.2	-5.3	-5.25
532095	2-Butenamide, N-(4-bromophenyl)-3-methyl-	-4.7	-5.3	-5
5370422	N, carboxymethyl maleamic acid dimethyl ester	-4.6	-4.5	-4.55
5282457	Linoelaidic acid	-4.2	-4.6	-4.4
8181	Hexadecanoic acid, methyl ester	-4.4	-4.3	-4.35
11748436	Methyl 9-cis-11-trans-*O*ctadecadienoate	-4	-4.5	-4.25
5284421	9,12 octadecadienoic acid (z,z)-methyl ester	-4.3	-4	-4.15
985	N-Hexadecanoic acid	-3.6	-4.2	-3.9

Table 2: Lipinski's rules of five of quercetin 3-7-diglucuronide, delphinidin 3-*O*-beta-D-sambubioside, and quercetin 3-rutinoside.

Properties	Quercetin 3-7-diglucuronide	Delphinidin 3-*O*-beta-D-sambubioside	Quercetin 3-rutinoside
Molecular weight (<500Da)	654	597	610
H Donor (<5)	11	11	10
H acceptor (<10)	19	16	16
Log P (<5)	-3.0729010	-1.63911	-1.8788
Molar Refractivity (40-130)	140.104279	134.74176	137.495483

Table 3: Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties of quercetin 3-7-diglucuronide, delphinidin 3-*O*-beta-D-sambubioside, and quercetin 3-rutinoside.

Properties	Quercetin 3-7-diglucuronide	Delphinidin 3-*O*-beta-D-sambubioside	Quercetin 3-rutinoside
Blood-brain barrier	-	-	-
Human intestinal absorption (%)	0	1.59	23.446
Aqueous Solubility (log mol/L)	-2.883	-2.892	-2.892
AMES Toxicity	No	No	No
Hepatotoxicity	No	No	No
Carcinogenicity	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive
Inhibitor CYP	No	No	No.
Total clearence (log ml/min/kg)	-0.563	-0.379	-369

Conclusion

Quercetin 3-7-diglucuronide is a better IL-11 inhibitor than delphinidin 3-*O*-beta-D-sambubioside and quercetin 3-rutinoside, based on a lower docking score, and has several interactions in the active site of IL-11. However, the drug similarity and ADMET profile are promising and can be further tested to be a potential IL-11 inhibitor to extend the health and lifespan of mammals with *in vitro* and *in vivo* studies.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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