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Original Article

Bioactive Compounds from Purslane (*Portulaca oleracea* L.) and Star Anise (*Illicium verum* Hook) as SARS-CoV-2 Antiviral Agent via Dual Inhibitor Mechanism: *In Silico* Approach

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the COVID-19 pandemic that infects humans and attacks the body's immune system. The purpose of the study was to identify the potential of bioactive compounds in purslane (*Portulaca oleracea* L.) and star anise (*Illicium verum* Hook) via a dual inhibitor mechanism against SARS-CoV-2 proteases with an *in silico* approach. The samples were obtained from PubChem and RSCB PDB. Antivirus probability prediction was performed on PASS Online. Virtual screening was performed with PyRx via molecular docking. Visualization was used by PyMol and Discovery Studio. Compounds with the best antiviral potential are indicated by the low binding affinity value to the target proteins, namely SARS-CoV-2 TMPRSS2 and PLpro. The results showed that purslane luteolin has the best antiviral potential. However, further studies are required to validate this computational prediction.

Key words: SARS-CoV-2, *Portulaca oleracea* L., *Illicium verum* Hook, *In silico*, Antiviral agent.

INTRODUCTION

Coronavirus disease 2019 or the COVID-19 pandemic caused by severe acute respiratory syndrome (SARS-CoV-2) causes numerous economic and health losses.[1,2] According to the most recent data, over 530 million cases have been reported worldwide. Furthermore, there are 6 million cases of infection and over 150 thousand deaths in Indonesia.[3] So far, three coronavirus outbreaks have been reported in the 21st century, namely SARS-CoV (2002-2003), MERS-CoV (2012), and SARS-CoV-2 (2020-present).[4] Humans can be infected by four other coronaviruses including HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43 which cause mild respiratory illnesses such as common fever.[5,6] SARS-CoV-2 shares 80% genomic similarity with the SARS-CoV virus.[7,8]

SARS-CoV-2 has a genome length of 29.903 bp and ssRNA as genetic material.[9] This virus has 4 structural proteins: envelope protein (E), membrane glycoprotein (M), nucleocapsid phosphoprotein (N), and spike glycoprotein (S).[10] In addition, there are two proteases that play an important role in this viral infection such as transmembrane protease serine 2 (TMPRSS2) and papain-like protease (PLpro).[11,12] TMPRSS2 plays a role in viral entry along with furin in the activation of angiotensin converting enzyme 2 (ACE2).[13,14] Meanwhile, PLpro aids in viral protein maturation and folding as well as the suppression of immune response in host cells.[15]

Indonesia is a megabiodiversity country with 7500 medicinal plant species either native or introduced, wild or cultivated.[16] Some such plants are used as folk remedies for a long time such as purslane (*Portulaca oleracea* L.) and star anise (*Illicium verum* Hook). Purslane is a weed member of the Portulacaceae.[17] The plant is distributed in tropical and subtropical regions around the world and native to South America and Africa.[18] Meanwhile, star anise is a member of the Magnoliaceae which is found in the tropics and subtropics. The plant is native to China and Vietnam.[19]

Several studies have shown the potential of purslane as an antiviral for influenza A (IAV) and herpes simplex type 2 (HSV-2).[20,21] Meanwhile, star anise has antiviral potential against influenza A and B as well as herpes simplex type 1 and 2.[22-24] However, the anti-SARS-CoV-2 potential of purslane and star anise bioactive compounds is unknown. Therefore, this study aims to identify the potential of purslane and star anise bioactive compounds using *in silico* approach *via* the mechanism of two inhibitors against SARS-CoV-2 proteases.

MATERIALS AND METHODS

Sample preparation

The bioactive components found in purslane are apigenin, isorhamnetin, and luteolin. Meanwhile, star anise has shikimic acid, illicinole, and illicinone A. Data were provided by PubChem. Furthermore, non-structural target protein databases TMPRSS2 and PLpro were obtained from RSCB PDB.

Antiviral probability prediction

Prediction of the probability of bioactive compounds is carried out with the PASS Online web server.

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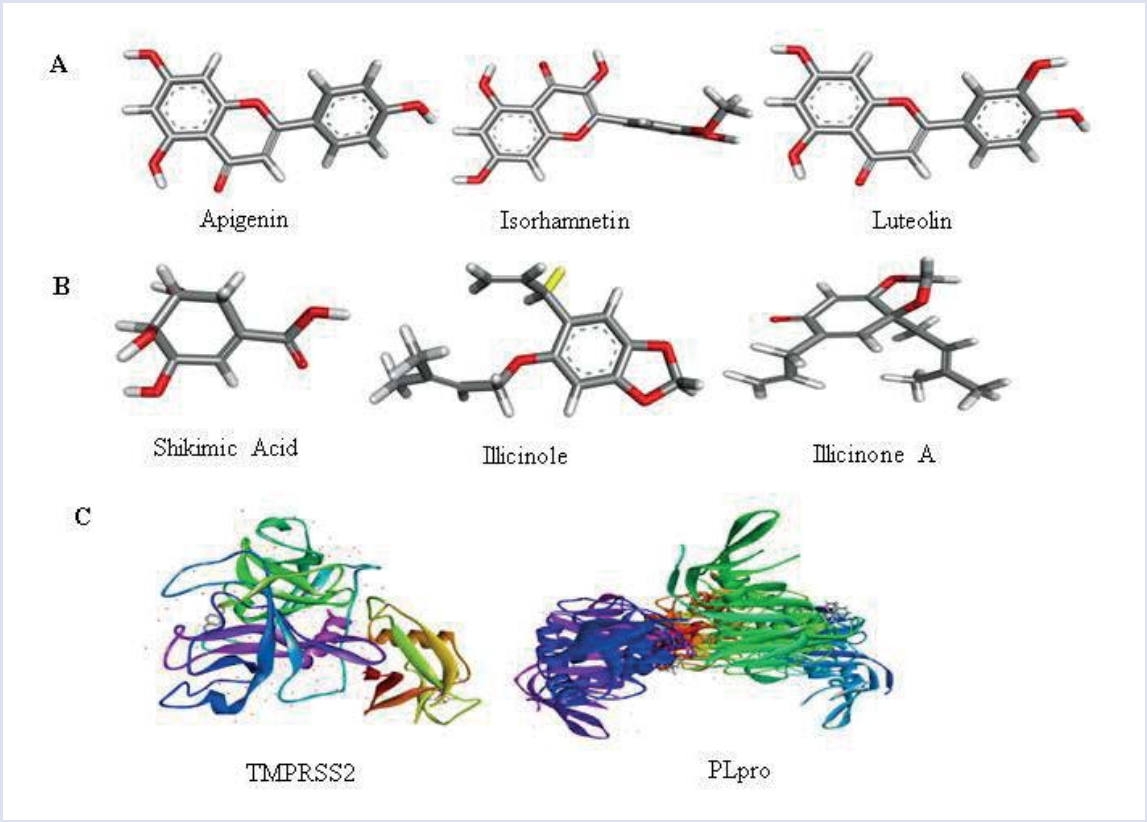

Figure 1: Visualization of ligand and targeted protein. Bioactive compounds from: A) purslane, B) star anise, and C) targeted proteins on the SARS-CoV-2.

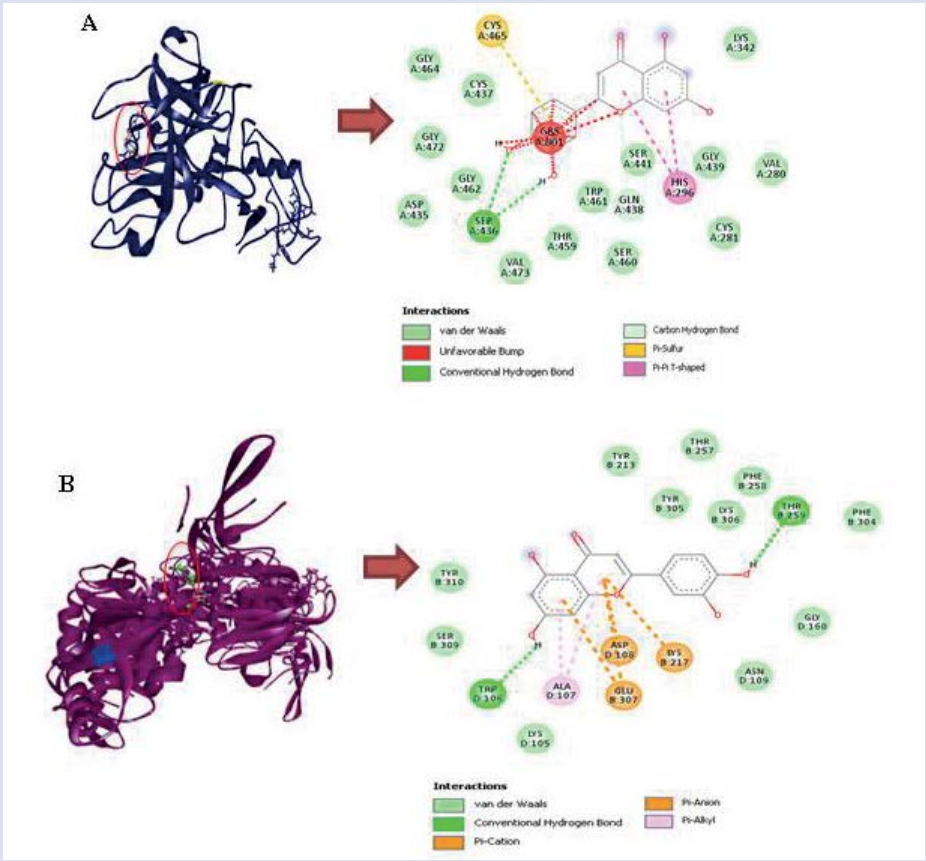

Figure 2: The binding visualization of luteolin on the targeted proteins: A) TMPRSS2 and B) PLpo.

Predictions are expressed as potential antivirals if the activity probability value (Pa) is greater than 0.3.[12]

Virtual screening

Virtual screening was performed by molecular docking between the selected bioactive compounds and the targeted proteins TMPRSS2 and PLpro. Molecular docking was performed using PyRx software.[25] The molecule that has the most negative results is the molecule that has the most potential as an antiviral in both target proteins. The bond between the ligand and the target protein is expressed in the bond affinity value (kcal/mol).[26]

Interaction and visualization

Compounds with the highest negative binding affinity values were then analyzed to determine the position and interaction of their chemical bonds using PyMol and Biovia Discovery Studio.[27]

RESULT AND DISCUSSION

Online PASS results revealed that drug candidate compounds performed well and were computationally proven if the Pa score was higher than the Pi score as well as the Pa score >0.3. However, *in vivo* and *in vitro* analysis are required to confirm the antiviral potential of bioactive compounds.[12] However, four compounds have a Pa value of <0.3 and the other two do not (Table 1).

The results of molecular docking are expressed in binding affinity indicating the energy of the stabilized bond formed between the ligand-receptor complexes. The degree of binding affinity influences biological activity when binding to proteins.[28] In this study, biological activity was demonstrated by inhibiting SARS-CoV-2 and body cells through interaction of bioactive compounds and target proteins.[29] The bond affinity value that used in this study is the smallest because it indicates the presence of additional stability and higher inhibition activity performed by the ligand towards the protein target.[30,31] The presence of bond types, amino acids on the active side, and amino acid residues on the ligands affects the affinity of the bond between the ligands and receptors.[12] The more hydrogen bonds, the more stable the ligand-protein interaction.[32] According to molecular docking simulations, luteolin has the compound with the most negative energy of two target proteins and has the potential to be a potential antiviral two inhibitors (Table 2).

Table 1: Antiviral probability of selected compounds from purslane and star anise.

Plant	Compound	Antiviral Probability	
		Pa	Pi
Purslane (*P. oleracea* L.)	Apigenin	0.209	0.089
	Isorhamnetin	0.204	0.092
	Luteolin	0.220	0.080
	Shikimic acid	0.217	0.082
Star anise (*Illicium verum* Hook)	Illicinole	-	-
	Illicinone A	-	-

Table 2: Binding affinity (kcal/mol) of ligand protein complexes.

Plant	Compound	Binding Affinity (kcal/mol)	
		TMPRSS2	PLpro
-	Nirmatrelvir	-6.4	-7
Purslane (*P. oleracea* L.)	Apigenin	-7	-8
	Isorhamnetin	-7.1	-8.5
	Luteolin	-7.3	-8.5
	Shikimic acid	-5.6	-5.2
Star anise (*Illicium verum* Hook)	Illicinole	-5.9	-6.2
	Illicinone A	-5.6	-7

TMPRSS2 has a catalytic region composed of triads of amino acid residues His296, Asp345, and Ser461.[33] This position is targeted by drug candidate bioactive compounds to inhibit SARS-CoV-2 entries through human cell membranes. Luteolin may interact with Ser436 through hydrogen bonds and with His296 through Pi-Pi T shaped bonds. The negative binding energy generated by hydrogen bonds aids stabilizes the binding between luteolin and TMPRSS2.[30] Pi-pi T shaped interaction is the interaction of electron pi clouds between two aromatic groups in the form of T.[34] The presence of pi-pi T shaped interaction affects the protein stability and flexibility and is important in drug intercalation and supramolecular chemistry.[35,36]

PLpro has catalytic triads and important catalytic residues. The catalytic triad consists of Sys111Ser, His272, and Asp286. Catalytic residues in these non-structural proteins include Trp93, Trp106, Asp108, and Asn109.[37] During the molecular docking process, luteolin interacts with Trp106 and Thr259 residues through hydrogen bonds; Ala107 *via* Pi-alkyl; and Asp108, Lys217; and Glu307 *via* Pi-anion. The presence of hydrogen bonds aids stabilization of bonds during screening *via* molecular docking.[26] Furthermore, the Pi-alkyl interaction is an interaction of the aromatic group electron cloud with other alkyl group electron clouds. While the Pi-anion interaction is a contact between the aromatic system of the electron (pi-acid) and an anion.[38] Some amino acid residues have van der Waals bonds to ligands shown in light green color. This weak bond affects the binding affinity between the ligand and protein complex affecting the inhibition of viral entries, maturation, and protein folding.[39,40] The existence of such non-covalent interactions is preferred in molecular docking because it plays a role in catalytic processes and stabilization.[36,41]

Research on massive SARS-CoV-2 has been conducted in recent years. Several medicinal plants were tested for antiviral activity against this virus. TMPRSS2 in human cell membranes and PLpro SARS-CoV-2 are two examples of such studies. *In silico* studies involving herbal plants reported that niazirin, quercetin, and moringyne from moringa (*Moringa oleifera*) and curcumin from several Indonesian herbal products have potential as TMPRSS2 inhibitors.[42,43] Meanwhile, mangostin compound in mangosteen (*Garcinia mangostana*) and quercetin in several dietary plants have the potential to be an *in silico* inhibitor of PLpro.[1,44,45] The entire *in silico* research aims to develop SARS-CoV-2 antiviral candidates. However, further *in vivo* and *in vitro* analyses are required to confirmation of potency.[46-51]

CONCLUSION

The combination of purslane (*Portulaca oleracea* L.) and star anise (*Illicium verum* Hook.) bioactive compounds has the potential to be an antiviral of SARS-CoV-2. Luteolin is a purslane bioactive compound with the lowest binding energy to SARS-CoV-2 TMPRSS2 and PLpro. However, more research is required to support the results of this study.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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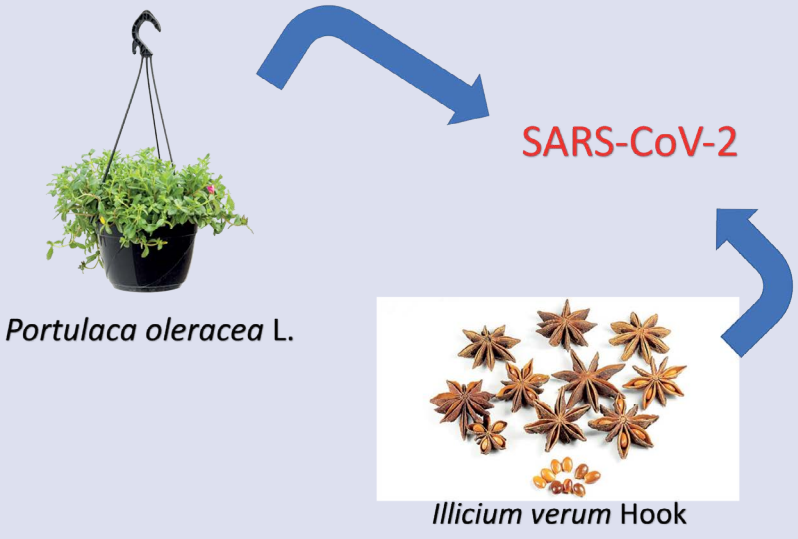
GRAPHICAL ABSTRACT



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