Pharmacogn J. 2023; 15(1): 228-232
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
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Research Article

Curcumin from *Curcuma longa* L. as Dual Inhibitors Against Indonesian SARS-CoV-2 Isolates: A Molecular Docking Study

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ABSTRACT

COVID-19 has become a global pandemic since 2020. The search for promising drugs based on the abundant herbal ingredients in Indonesia is one of the breakthroughs. Curcumin is a chemical compound with various potentials such as antioxidant, anti-inflammatory and antiviral. We conducted a molecular docking analysis to determine the potential of curcumin against SARS-CoV-2 non-structural and structural proteins, such as the main protease and spike protein. This study used the compound of curcumin (PubChem CID: 969516) from *Curcuma longa* L. or turmeric and two Indonesian SARS-CoV-2 isolates that have been deposited in the GISAID database (hCoV-19/Indonesia/JI-PNF-217315/2021 - EPI_ISL_12777089 or lineage B.1.617.2 and hCoV-19/Indonesia/JI-PNF-211373/2021 - EPI_ISL_6425649 or lineage B.1.470). In addition, we used molnupiravir (PubChem CID: 145996610) as a drug control. We performed molecular docking analysis with PyRx software 0.9.9 (academic license) and visualization of molecular docking results with PyMOL software 2.5.4 (academic license). The results of this study found that curcumin had good potential against main protease and spike protein compared to the drug (control). In summary, we suggested that curcumin is a potential drug candidate against SARS-CoV-2. However, there is a need for future wet laboratory-based pre-clinical research such as *in vitro* and *in vivo*.

Key words: *COVID-19, Curcumin, Indonesia, Molecular docking, SARS-CoV-2*

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History

- Submission Date: 09-01-2023;
- Review completed: 10-02-2023;
- Accepted Date: 15-02-2023.

DOI : 10.5530/pj.2023.15.34

Article Available online

http://www.phcogj.com/v15/i6

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INTRODUCTION

The SARS-CoV-2 is the infectious illness known as coronavirus disease (COVID-19). Most virus-infected people will suffer from a mild to severe respiratory illness. Older people and people with underlying medical conditions, such as cancer, diabetes, cardiovascular disease, or chronic respiratory disorders, are more prone to have severe illness. Anyone can get COVID-19 and become seriously ill or die at any age[1-7].

The SARS-CoV-2 belongs to the large family of viruses known as coronaviruses. These viruses can infect humans and certain animals. SARS-CoV-2 was first discovered to be a human disease in 2019. The virus is thought to spread from person to person by droplets released by an infected individual while coughing, sneezing, or talking. Contacting one's lips, nose, or eyes after touching a surface with the virus on it is a less common way to transmit the disease[8-11].

The use of medical plants, their compounds, and traditional herbal treatments has grown significantly worldwide since the COVID-19 pandemic. The FDA authorized chloroquine sulfate and hydroxychloroquine sulfate as first-line treatments on the basis of early clinical studies. However, antiviral medications including molnupiravir, remdesivir, and kaletra (a combination medicine of lopinavir and ritonavir) have also been proposed to help COVID-19 sufferers feel better[12-14].

Indonesia is a country with high biodiversity of medicinal plants. One of the most widely used medicinal plants by the people of Indonesia is turmeric or *Curcuma longa* L. The turmeric has a phytopolyphenol pigment called curcumin, which has a number of pharmacologic effects. Curcumin has anti-inflammatory actions, reduces inflammation by inhibiting cyclooxygenases (COX) and other inflammatory enzymes, and disrupts cell signaling through a number of routes, including protein kinase C inhibition. In addition, curcumin also reported as potent antibacterial and antiviral activities[15-19]. Therefore, we need to perform an *in silico* research for curcumin against Indonesian SARS-CoV-2 isolates in this study.

MATERIALS AND METHODS

Virus isolates

In this study we used two Indonesian SARS-CoV-2 isolates that have been deposited in the GISAID database (hCoV-19/Indonesia/JI-PNF-217315/2021 - EPI_ISL_12777089 or lineage B.1.617.2 and hCoV-19/Indonesia/JI-PNF-211373/2021 - EPI_ISL_6425649 or lineage B.1.470)[6].

Sample retrival

We used curcumin (PubChem CID: 969516) from *Curcuma longa* L. or turmeric and we used molnupiravir (PubChem CID: 145996610) as a drug control. All of the samples came from the PubChem database, which may be found at pubchem.ncbi.nlm.nih.gov. In addition, the targeted proteins are two structural proteins including main protease (Mpro) and spike protein.

Drug-likeness prediction

Using Lipinski's rule of five on the SCFBIO web server (http://www.scfbio-iitd. res.in/software/drugdesign/lipinski.jsp), curcumin was utilized for further drug-likeness analysis. It was regarded as a successful forecast when two minimal guidelines

Cite this article: Nidom CA, Ansori ANM, Nidom AN, Indrasari S, Nidom RV. Curcumin from *Curcuma longa* L. as Dual Inhibitors Against Indonesian SARS-CoV-2 Isolates: A Molecular Docking Study. Pharmacogn J. 2023;15(1): 228-232.

were adhered to. This investigation sought to ascertain the likelihood that the medicine molecule candidate would pass across the cell membrane if the target were pharmacokinetically situated in the cytoplasm.

Antiviral probability prediction

Using the PASS web server (http://way2drug.com/PassOnline/), probability predictions of the curcumin's biological activity as an antiviral agent were made. The probability activation (Pa) score threshold prediction with >0.3 was regarded as probable antiviral.

Virtual screening and visualization

In this work, molecular docking techniques were used to determine how dual inhibitors of curcumin interact with target proteins (SARS-CoV-2 Mpro and spike protein). Using PyRx 0.9.9 software (Scripps Research, USA) with an academic license, the molecular docking was carried out. The substance thought to be capable of inducing a biologic reaction on the proteins as a dual inhibitor is the one with the highest negative affinity scores on both of the targeted proteins. The binding affinity score (kcal/mol), which is created inside complex protein molecules and ligand, indicates the binding capability in molecular docking. The compound with the highest binding affinity score was targeted for further investigation to determine its location and kind of chemical binding interaction. Using PyMOL software v.2.5.4 (Schrödinger, Inc., USA) with an academic license, the visualization procedure was carried out.

RESULTS AND DISCUSSIONS

In order to identify a medicine compound candidate as a drug-like molecule, Lipinski's rule of five—which includes molecular mass 500 Dalton, LogP 5, hydrogen binding donor 5, hydrogen binding donor 10, and molar refractivity between 40 and 130.25—must be met. The curcumin might all adhere to Lipinski's rule of five, according to the drug-likeness prediction (Table 1). Consequently, it may be regarded as a drug-like molecule.

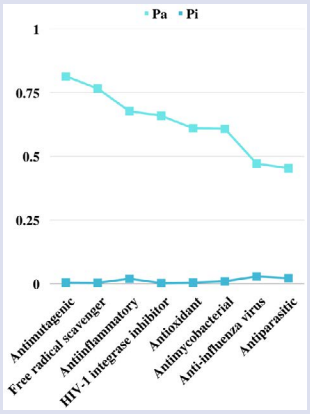

Figure 1: The result of probability predictions of the curcumin's biological activities.

Table 1: Analysis of Lipinski's rule of five.

Compound	MW	HBD	HBA	LogP	MR
Curcumin	368	2	6	3.369898	102.016571

Note: Molecular Weight (MW); Hydrogen Bond Donor (HBD); Hydrogen Bond Acceptor (HBA); High Lipophilicity (Logp); and Molar Refractivity (MR).

Table 2: Binding affinity of complex compounds and protein.

Compounds	Binding Affinity (kcal/mol)			
	Mpro (hCoV-19/Indonesia/JI-PNF-211373/2021)	Spike Protein (hCoV-19/Indonesia/JI-PNF-211373/2021)	Mpro - (hCoV-19/Indonesia/JI-PNF-217315/2021)	Spike Protein - (hCoV-19/Indonesia/JI-PNF-217315/2021)
Curcumin	-7.1	-7.5	-7.5	-7.7
Molnupiravir (drug control)	-6.6	-7.3	-6.6	-7.2

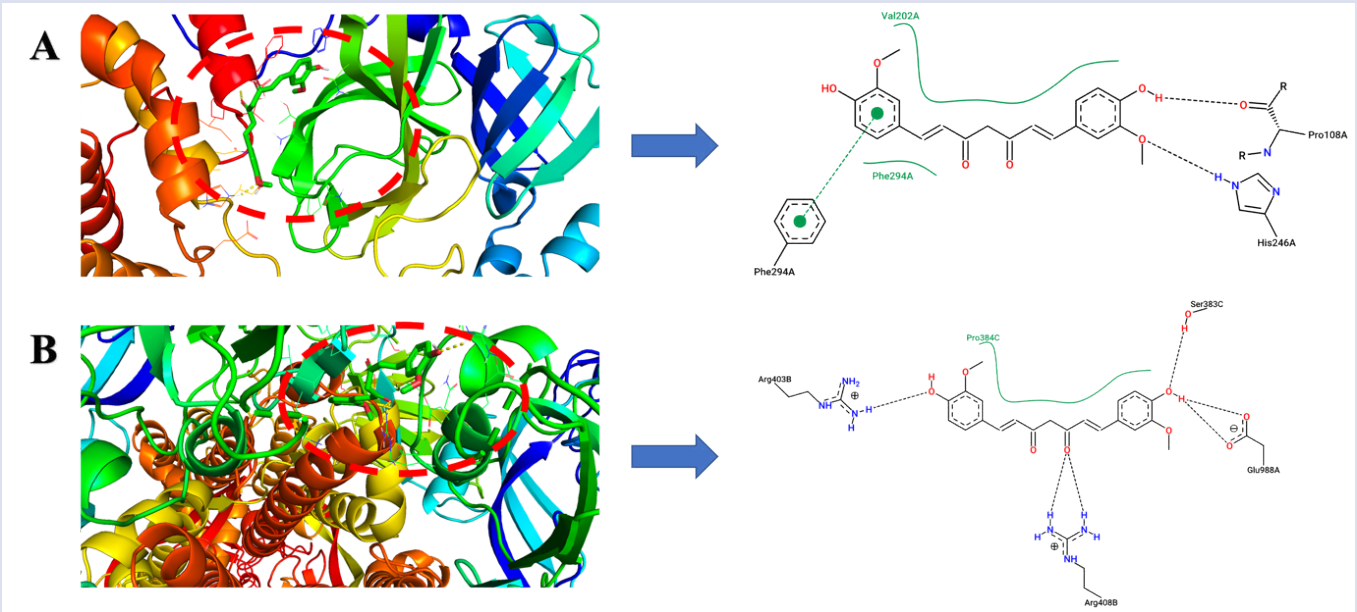

Figure 2. The binding visualization of curcumin on the targeted protein. A: Mpro and B: Spike protein.

According to the PASS online server's analysis results, a chemical with a Pa score higher than a Pi score was expected to have antiviral potential. If the Pa score is more than 0.3, the query compound has been more computationally engaged. This study's antiviral analysis probability used a Pa > 0.3 criterion (Figure 1). Compounds having a Pa score of more than 0.3 are thought to be effective antiviral medicines. Results indicated that every component was regarded as an antiviral agent. However, more testing utilizing in vitro or in vivo methods is still required to assess their potential.

The term "binding affinity" refers to the stable binding energy that a protein-ligand complex form. When a protein attaches to a certain protein domain, the amount of binding affinity score may be affected by biological activity. The inhibitory response to the targeted protein is the biological activity that was estimated. This targeted protein activity suppression may reduce SARS-CoV-2 viral load generation. Curcumin has the greatest negative binding energy on both of the targeted proteins (Mpro and spike protein) according to the molecular docking simulation, and it may be able to act as an antiviral through dual inhibition (Table 2).

Plants that are utilized to treat ailments have value and utility. Regardless of whether their use has been demonstrated clinically, they are designated as possible medicinal plants based on their secondary metabolites chemicals that had health-related impacts. For use as food or cosmetics agents, these plants can be harvested from the wild or produced in a lab. For a very long time, various plant parts, extracts, and sophisticated products had been utilized to treat illness. In summary, more than 50,000 higher plant species are thought to be utilized for therapeutic reasons worldwide[20-24].

The prospect of using several medicinal plants as antivirus to combat SARS-CoV-2 has recently been revealed by numerous studies throughout the world. A number of researchers used in silico to evaluate Chinese herbal medicine against SARS-CoV-2 in Asia. Additionally, an *in silico* investigation of Indian traditional medicine showed that it had high antiviral potential against the SARS-CoV-2. Another study found that herbal remedies from the American continent, particularly those from Brazil, Peru, and Mexico, may be effective against the SARS-CoV-2. Several Indonesian medicinal plants were reported by researchers, which is another viewpoint[25-,29].

CONCLUSION

In summary, we suggested that curcumin is a potential drug candidate against SARS-CoV-2. However, there is a need for future laboratory-based pre-clinical research such as *in vitro* and *in vivo*.

ACKNOWLEDGEMENT

The Professor Nidom Foundation, based in Surabaya, Indonesia, provided funding for this work. We also acknowledge the editing work done by members of Quant Science & Technology, Professor Nidom Foundation (QST-PNF), Indonesia (http://pnfinstitute.org).

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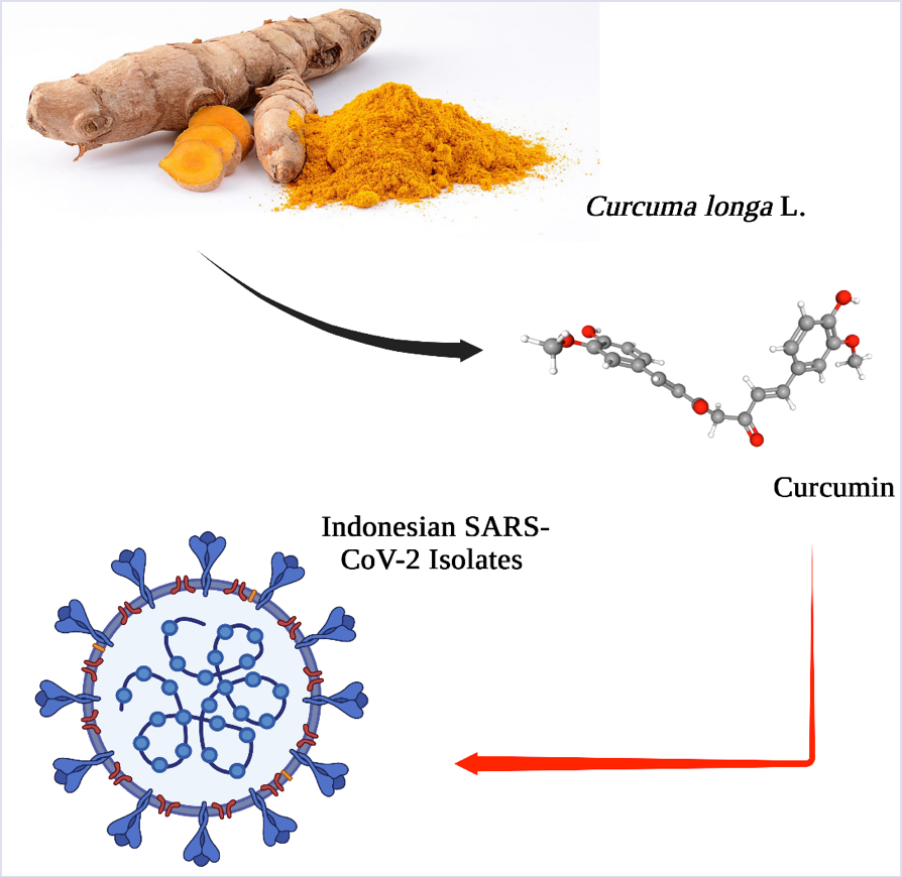
GRAPHICAL ABSTRACT



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Cite this article: Nidom CA, Ansori ANM, Nidom AN, Indrasari S, Nidom RV. Curcumin from *Curcuma longa* L. as Dual Inhibitors Against Indonesian SARS-CoV-2 Isolates: A Molecular Docking Study. Pharmacogn J. 2023;15(1): 228-232.