Journal of Applied Pharmaceutical Science Vol. 13(08), pp 101-112, August, 2023
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.133107
ISSN 2231-3354

The *in-silico* potential of *Andrographis paniculata* phytocompounds as antiviral for the treatment of COVID-19: A systematic review

Shafa Shavira[1], Septi Handayani[2], Fatmaria Fatmaria[3*]

[1]Faculty of Medicine, University of Palangka Raya, Palangka Raya, Indonesia.
[2]Department of Biochemistry and Biology Molecular, Faculty of Medicine, University of Palangka Raya, Palangka Raya, Indonesia.
[3]Departement of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Palangka Raya, Palangka Raya, Indonesia.

ARTICLE INFO

Received on: 27/02/2023
Accepted on: 03/05/2023
Available Online: 04/08/2023

Key words:
Andrographis paniculata, *in silico*, antiviral, COVID-19, systematic review.

ABSTRACT

Since the outbreak of coronavirus disease 2019 (COVID-19), many studies have been conducted to develop definitive therapeutic agents for this viral disease. The *in-silico* method has become the best solution for the initial step in discovering potential antiviral compounds. Several phytocompounds from a medicinal plant, *Andrographis paniculata*, were reported to have activity inhibiting SARS-CoV-2 proteins. The present systematic review aims to determine the potency of *A. paniculata* compounds against COVID-19. We undertook a systematic search in two databases, PubMed and Google Scholar, and included original articles that applied *in-silico* methods for phytocompounds of *A. paniculata* in COVID-19. Twenty-nine original articles were included in the systematic review. We report that 50 of the 107 *A. paniculata* phytocompounds (46.73%) were against SARS-CoV-2. We found that five protein targets of SARS-CoV-2 are highly conserved structures mostly used in the articles, which are main protease, papain-like protease, RNA-dependent RNA polymerase, Nsp15, and spike protein. Six *A. paniculata* phytocompounds have an inhibition activity of those five protein targets including andrographolide, neoandrographolide, isoandrographolide, 14-deoxyandrographolide, 14-deoxy-11,12-didehydroandrographolide, and andrographidin C as main diterpenoid compounds. Based on the literature evidence, some of the *A. paniculata* phytocompounds could be potential antiviral agents due to their strong binding affinities and stable conformations toward SARS-CoV-2 proteins.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) refers to a respiratory infection brought on by the SARS-CoV-2 virus and has emerged as a pandemic since 2020. The discovery of effective therapy with accessible raw materials for patients with COVID-19 is a critical attempt that is being intensified. Utilizing molecular databases to investigate different compounds that may have therapeutic effects on the virus is one of the methods explored by researchers to find new medications to combat SARS-CoV-2 (Wu *et al*., 2020).

**Corresponding Author*
Fatmaria Fatmaria, Department of Pharmacotherapy, Faculty of Medicine, University of Palangka Raya, Palangka Raya, Indonesia.
E-mail: rfatma64 @ yahoo.com

Through the latest advances in computational biology and molecular bioinformatics, a number of natural phytocompounds have been published to have antiviral potential against several specific targets of SARS-CoV-2 including angiotensin-converting enzyme-2 (ACE-2) and several viral important proteins, such as spike protein, which contains S1 and S2 domains, 3-chymotrypsin-like protease (3-CLpro), papain-like protease (PLpro), helicases, and RNA-dependent RNA polymerase (RdRp) (Khare *et al*., 2020). The *in-silico* prediction of possible phytochemical compounds on key SARS-CoV-2 proteins has been extensively investigated. *Andrographis paniculata* (Burm. F.) Nees or *Justicia paniculata* Burm. F. is a medicinal plant whose natural compounds have been shown to have potential as SARS-CoV-2 antivirals (Murugan *et al*., 2021; Vijayakumar *et al*., 2022).

The main phytocompounds of *A. paniculata* are diterpene compounds including andrographolide, 14-deoxyandrographolide, 14-deoxy-11,12-didehydroandrographolide, 14-deoxy-11-

oxoandrographolide, neoandrographolide, andrographiside, deoxyandrographoside, andrograpanin, deoxyandrographolide-19-D-glucosi-de, 14-deoxy-12-methoxyandrographolide, and flavonoid compounds (Dwivedi *et al*., 2021). The outcomes of *in-silico* testing on the main compounds of *A. paniculata* have varied according to several researches. These take into account the importance of affinity energy, bond conformation stability, and comparisons to currently available reference medications like remdesivir, lopinavir, and hydroxychloroquine. This systematic review's objective was to determine the phytochemical compounds of *A. paniculata* that may be active against SARS-CoV-2 using an *in-silico* technique as a reference and scientific support for prospective herbal COVID-19 treatment options.

METHODS

This systematic review included data from two databases, PubMed and Google Scholar, covering original English language articles which applied *in-silico* methods for *A. paniculata* phytochemical compounds on SARS-CoV-2 protein. A systematic search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2020 starting from August to September 2022. Keywords for the search included "*Andrographis paniculata,*" "*in silico*," and "COVID-19." The inclusion criteria were applied to a total of 38 scientific articles, and 29 articles were chosen for review. Three authors independently evaluated the quality of each article using Duffy's Research Appraisal Checklist Approach. Nine articles were excluded because the target proteins used in the *in-silico* assays were not derived from proteins in SARS-CoV-2 and the intervention utilized derivatives of *A. paniculata* phytochemical compounds (Fig. 1).

The extracted data were analyzed to determine the *in-silico* method used, the *A. paniculata* compounds tested, the SARS-CoV-2 protein target, and the authors' conclusions (Table 1). The data were synthesized according to the Synthesis Without Meta-analysis guide to determine *A. paniculata* compounds as potential protein inhibitors in SARS-CoV-2. Afterward, the potential antiviral phytochemical compounds of *A. paniculata* are further elaborated according to their protein targets in the form of highly conserved sites from changes in the evolutionary phylogenetic tree, such as 3CLpro (main protease), PLpro, RdRp, and spike proteins.

RESULTS

Literature evidence showed that 107 phytochemical compounds of *A. paniculata* were *in silico* tested on SARS-CoV-2 protein. Fifty of these compounds showed their potential as inhibitors of the SARS-CoV-2 protein target. The main

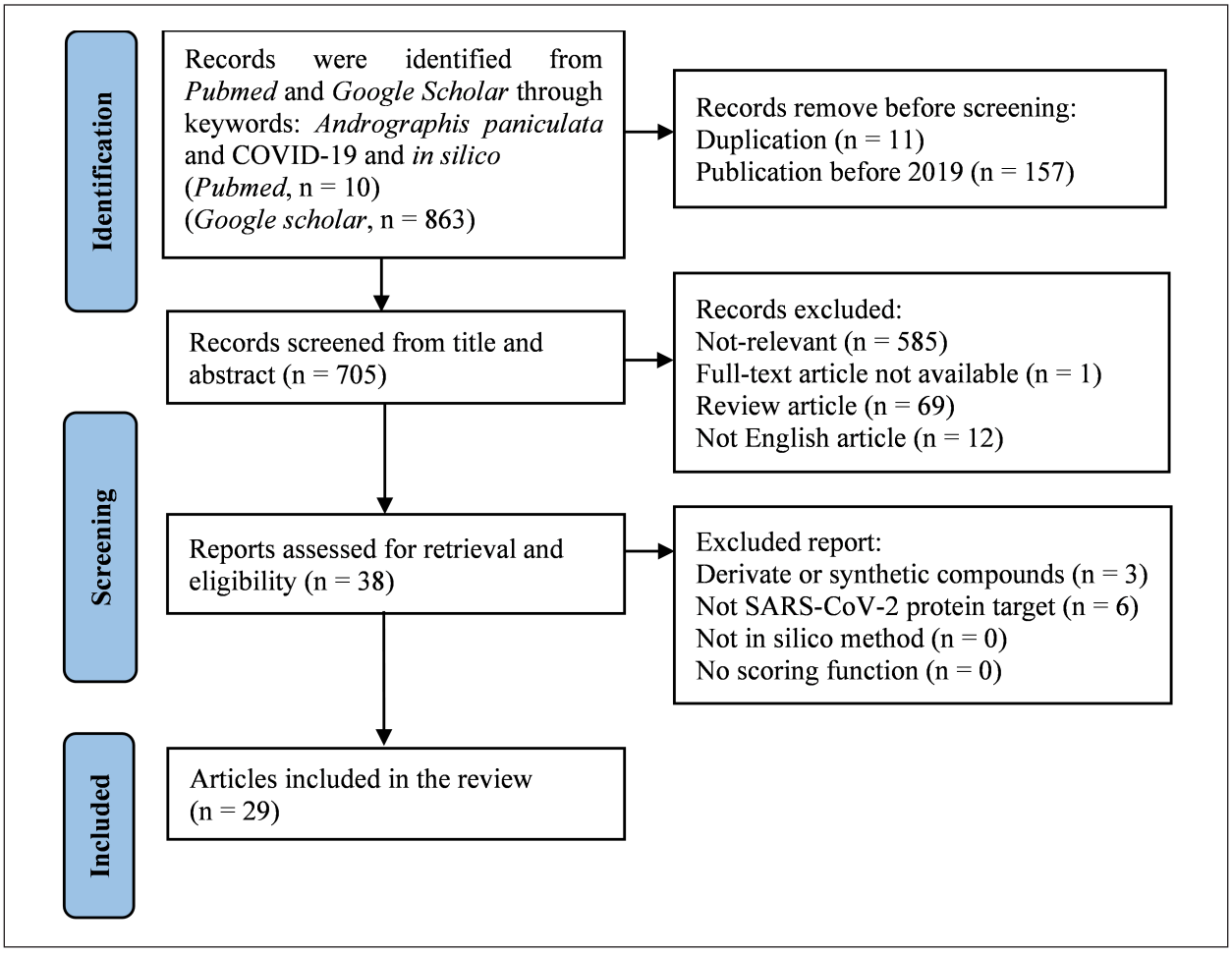

Figure 1. Flowchart on search strategies.

Table 1. Characteristicsics and the main finding of studies included in the systematic review.

First author, publication year	Method and Software	Target	*A. paniculata* compounds	Author's finding
Rajagopal *et al*., 2020	Molecular docking (Glide XP) and MM-GBSA calculation (Schrödinger 2019-4).	Main protease of SARS-CoV-2 (PDB ID: 5R82)	Andrographolide, dihydroxydi methoxyflavon, stigmasterol, 14-deoxyandrographolide, cin-namate esters, β-sitosterol, β-Sitosteryl-fatty acid esters, and 14-deoxy-12-hydroxyandrogra pholide.	Glide score of andrographolide (−6.26 kcal/mol) and dihydroxydimethoxyflavone (−6.23 kcal/mol) that have more significant binding energy with the site of the main protease compare to hydroxychloroquine show good potency as the antiviral agents.
Enmozhi *et al*., 2020	Molecular docking (DOCK6 program and UCSF Chimera), ADME prediction (Swiss AD- ME), and toxicity prediction (pkCSM database).	Main protease of SARS-CoV-2 (PDB ID: 6LU7)	Andrographolide	Andrographolide can bind to the active site of SARS-CoV-2 main protease (−3.094357 kcal/mol) with good affinity. I forms 4 hydrogen bonds with Gly143, Cys145, and Glu-166 residue.
Hiremath *et al*., 2021	Molecular docking (AutoDock -MGL, and PyMOL), ADMET prediction (Swiss ADMET).	Spike protein, 3CL-Pro, PL-pro, and RdRp of SARS-CoV-2 (PDB ID: 6VSB, 6LU7, 4O VZ, 6NUS).	14 phytocompounds of *A. paniculata*	Four phytocompounds show good binding affinity on spike protein and RdRp, namely isoandrographolide, 14-deoxy 14,15 didehy droandrographide, 14-deoxyandrographoli-de, 5-hydroxy-7,8,2',5'-tetramethoxyflavo-ne (<−7.60 kcal/mol).
Majumdar *et al*., 2022	Molecular docking (Autodock *version* 4.2.6 and Glide-v8.3 *Schrodinger*), molecular dyna-mics simulation, MM-GBSA, and ADME/T prediction.	SARS-CoV-2 main protease (PDB ID: 6LU7) and SARS-CoV *main protease* (PDB ID: 2GTB).	14-deoxy-11,12-didehydroan-drographolide, and andrograpanin.	The *in-silico* studies found that androgra-panin can be considered as the potent inhibitor against SARS-CoV-2 main prote-ase due to its strong binding affinities involving identical amino acid residues.
Saliu *et al*., 2021	Molecular docking (AutoDock Vina *Tools* and PyMOL soft-ware) and predicting ADME/T with dmetSAR web.	SARS-CoV-2 methyltransfer-ase (nsp16) (PDB ID: 6YZ1).	Andrographolide and andrograpanin.	Andrographolide could bind the active site of Nsp16 with good potential negative energy (−7.9 kcal/mol). This suggests that andrographolide could serve as therapeutic agent to prevent viral survival and replication in cells.
Latha *et al*., 2022	Molecular docking (Glide v7. 8. Schrodinger 2019–2).	SARS-CoV-2 spike glycopro-tein, RdRp, and main protease	Andrographidin C	Andrographidine C has the strongest bind-ing affinity on the site of RdRp that can be potential as an antiviral agent by inhibiting replication and transcription of SARS-CoV-2.
Sukardiman *et al*., 2020	Molecular docking (AutoDock Vina 1.1.2 and Chimera 1.13. 1).	SARS-CoV-2 main protease or 3-chymotrypsin-like protease (PDB ID: 6LU7)	45 *A. paniculata* phytochemical compounds.	5,4'-dihydroxy-7-O-β-D-pyran-glycuronate butyl ester and andrographolide glycoside 3-O-β-D-glucopyranosyl-andrographolide have lower free binding energy and highest similarity in types of interaction with amino acid residues compared to its co-crystal ligands (6LU7) and Indinavir or Remdesivir
Srikanth and Sarma, 2021	Molecular docking (AutoDock dan MOE *softwares*).	ACE-2 receptor binding doma-in of spike protein (PDB ID: 6L ZG) and Nsp12 (RdRp) SARS-CoV-2 (PDB ID: 6M71)	Andrographolide	Andrographolide has very strong affinity to RBD of spike protein (−10.3460 kcal/mol) and Nsp12 of the SARS-CoV-2 (−10.7313 kcal/mol) indicating andrographolide acts as an inhibitor of spike protein and Nsp12.

Continued

First author, publication year	Method and Software	Target	*A. paniculata* compounds	Author's finding
Swaminathan *et al*., 2021	Molecular docking (AutoDock Vina v1.1.2), toxicity profile and ADME (pk-CSM online tool), MM-GBSA calculation and molecular dynamics simulation (Desmond v3.6).	SARS-CoV-2 proteins: main protease (6LU7), Nsp9 (6WX D), envelope protein (5X29), ORF1a polyprotein (2G9T), receptor binding domain (6M 0J), ORF3a (6XDC), Nsp3 (6V XS), membrane protein (3I6 G), Nsp15 (6VWW) and spike protein (6CRV).	38 phytocompounds of *A. paniculata* were tested in docking molecular	There are 25 phytocompounds of *Androgra phis paniculata* (65.78%) that can be druggable agents against SARS-CoV-2. The two phytosterols, stigmasterol and stigmasta-5,22-dien-3-ol act as potential lead molecules against multiple target proteins of SARS–CoV-2.
Murugan *et al*., 2021	Molecular docking (AutoDock Vina) and molecular dynamics simulation (Amber16 *softwa-re)*.	SARS-CoV-2 proteins: 3-CL pro (PDB ID: 6LU7), PL-pro (PDB ID: 5Y3E), RdRp (PDB ID: 6NUR), *Spike*-ACE-2.	Andrographolide, neoandro-grapholide 14-deoxy 11,12-di dehydroandrographolide, and 14-deoxy andrographolide.	Neoandrographolide could be used as a cost-effective drug analog for treating COVID-19 due to its binding free energy toward all four targets.
Rathinavel, 2020	Molecular docking (AutoDock and Autogrid) and *Drug Like-liness* and ADME prediction (Swiss ADME online server).	Receptor binding domain ACE-2 of spike protein, main protease, nucleocapsid protein N-terminal RNA binding dom-ain of SARS-CoV-2 (PDB ID: 6LZG, 7BUY dan 6M3M)	21 phytocompounds of *A. paniculata*.	Bisandrographolide A is one of the best ligands from *A. paniculata* that was considered as best drug candidate for SARS-CoV-2. It showed strong binding affinity and possesses good drug likeliness, pharmacokinetic, and electrostatic profile.
Sahithya *et al*., 2021	Molecular docking (Molegro Virtual Docker) and Drug Like -liness and ADME calculation (ALOGPS 2.1 web server).	SARS-CoV-2 protein: SG-pro (PDB ID: 6VSB), Npro (6YI 3), 3CLpro (6LU7), PLpro (6 W9C), RdRp (6M71) Nsp9 (6 W4B), and Nsp15 (6VWW).	17 phytocompounds of *A. paniculata*	Nine phytocompounds of *A. paniculata* have shown higher inhibition at multiple targets of SARS-CoV-2 potential proteins that could be developed as traditional thera-peutic formulation to fight against COVID-19 with few side effects.
Kongsune *et al*., 2022	Molecular docking (AutoDock 4.2).	SARS-CoV-2 main protease, protein spike and Nsp15 (PDB ID: 6XBG, 7BZ5, and 6WXC)	24 phytocompounds *A. paniculata*	The calculation result revealed that mostly bioactive compounds from *A. paniculata* are a good binding affinity with the main protease than that of Nsp15 and spike protein. 7,8-dimethoxy flavone-5-β-D-glucopyranosyloxyflavone (−11.65 kcal /mol and stigmasterol (−11.33 kcal/mol) had a superior binding affinity toward the main protease.
Rizqillah *et al*., 2021	Molecular docking (Ligand Docking *tool*), molecular dyna mics simulation, and MM-GBSA (Prime MM-GBSA)	SARS-CoV-2 main protease (PDB ID: 7AOL)	Andrographolide, neoandrographolide, and 5-hydroxy-7,8,2',3'-tetra-methoxyflavone.	Andrographolide, neoandrographolide, and 5-hydroxy-7,8,2',3'-tetramethoxyflavone have comparable inhibition activity to SARS CoV-2 main protease in comparison to Remdesivir. The flavonoid compound has the lowest docking score, which was further validated by protein-ligand contact fraction examination, although MMGBSA score is lowest for Remdesivir.
Shi *et al*., 2020	Molecular docking (Argus lab 4.0.1).	Main protease of 2019-nCoV (PDB ID: 6LU7) and main protease SARS-CoV (PDB ID: 1UK4)	Andrographolide	Molecular modeling analysis and docking results showed andrographolide bonds in the catalytic pockets of both main proteases so that they could potentially be inhibitory agents on the target proteins.

Continued

First author, publication year	Method and Software	Target	*A. paniculata* compounds	Author's finding
Prabha *et al*., 2021	Molecular docking (Lond-on dG *scores*).	SARS-CoV-2 main protease (PDB ID: 6LU7)	Andrographolide	Although the docking score was below remdesivir, andrographolide (−13.01 kcal/mol) was identified as having a promising binding affinity with Mpro receptors because it belongs to a binding energy with a narrow range.
Verma *et al*., 2021	Molecular docking (AutoDock Vina), ADME (SwissADME), molecular dynamics simulat-ion (GROMACS 5.12 MD and GROMOS96 43a1), and MM-PBSA (GROMACS v.2018.1).	SARS-CoV-2 proteins: papain-like protease (PLpro) and 3-chy motrypsin-like protease (3CLpro/ Mpro) with PDB ID: 6W9C and 6M2N.	15 phytocompounds of *A. paniculata*	Almost all A. paniculata compounds have a bond affinity of less than −7 kcal/mol in PLpro which shows strong potential as an inhibitor, except paniculide C. While in the main protease target, potential compounds based on parameters are neoandrographo-lide, 14-deoxy-11,12 didehydroandrogra-pholide, 14-deoxy-11-oxoandrographolide.
Laksmiani *et al*., 2020	Molecular docking (AutoDock Tools 1.5.6 and Chimera 1.11. 1).	SARS-CoV-2 proteins: RdRp, 3CLpro and PLpro (PDB ID: 6N UR, 2GTB, 4O W0).	Andrographolide	The result of docking andrographolide on almost all SARS-CoV-2 protein targets of <−7 kcal/mol, except for RdRp (−3.18 kcal/ mol) so that it binds well to be able to be-come inhibitor agents on Mpro and PLpro.
Dound *et al*., 2020	Molecular docking (AutoDock 4.2).	SARS-CoV-2 main protease and SARS coronavirus main peptid-ase (PDB ID: 6LU7 dan 2GTB)	Andrographolide and andrograpanin	Andrographolide and andrograpanin bind to main protease of SARS-CoV-2 with strong binding affinities (less than −7 kcal/mol) so can be potential inhibitor of this target.
Kiran *et al*., 2022	Molecular docking (Cresset Flare software).	Spike protein of SARS-CoV-2 (PDB ID: 6VSB)	Andrographolide, androgra-panin, and 5-hydroxy-7,8-dimethoxyflavanone.	5-hydroxy-7,8-dimethoxyflavanone (−9.03 kcal/mol) on the target spike protein SARS-CoV-2 can be the best drug candidate with good synthetic accessibility
Kumar *et al*., 2020	Molecular docking (iGEMDOCK)	Spike glycoprotein of corona virus (PDB ID: 3JCL	Andrographolide	The docking results show that the andrographolide compound (−89.34 kcal/mol) has inhibitory activity on the SARS-CoV-2 spike glycoprotein but not one of the five compounds with the most potential in this study.
Alagu Lakshmi *et al*., 2020	Molecular docking (Autodock v.4.2 and Biovia Discovery Studio 4.5), molecular dyna-mics simulation (Gromacs 5.1. 4), and MM-PBSA (*software* Gromacs).	Main protease (PDB ID: 5R82) and spike of SARS-CoV -2 (PDB ID: 6VYB).	Andrographolide, bisandro-grapholide A, caffeic acid.	Bisandrographolide A has a strong bond affinity with the main protease and andro-grapholide on spike protein of SARS-CoV-2 so can become a potential inhibitor agent.
Dey *et al*., 2020	Molecular docking (AutoDock v.4.0), Drug-likeness ADMET (MolSoft and ADMET SAR 2.0).	SARS-CoV-2 proteins: main pro-tease/ 3CLpro (PDB ID: 6LU7), papain like protease (PDB ID: 4M0W) and spike protein (PDB ID: 6V SB	Andrographolide, and 14-de oxy-11,12-didehydroandro-grapholide	Andrographolide and 14-deoxy-11,12-dide hydroandrographolide are predicted to have good binding affinities with PLpro and interact with equally large bond energy on 3-CLpro and spike protein of SARS-CoV-2
Adejoro *et al*., 2020	Molecular docking (AutoDock v.4.2.6, Pymol and Discovery Studio) and molecular dyna-mics simulation (AMBER 14).	SARS-CoV-2 proteins: 3Cl-pro and two spike proteins (PDB ID: 6LU7, 6VXX, and 6LZG).	5-hydroxy-7,8,2-trimethoxy flavone, neoandrographolide dan andrographolide.	Neoandrographolide (−8.7 kcal/mol) and 5-hydroxy-7,8,2-trimethoxyflavone (−8.4 kcal /mol) have strong interactions with spike glycoprotein (6LZG) so it has the potential to be an inhibitor agent on the protein target.

Continued

First author, publication year	Method and Software	Target	*A. paniculata* compounds	Author's finding
Rizma *et al*., 2021	Molecular docking (*software* PLANTS).	SARS-CoV-2 PLpro and 3-CL pro (PDB ID: 3E9S and 5R7Y)	Andrographolide and neoandrographolide	The interaction between neoandrographo-lide and 3-CLpro showed a docking more negative than remdesivir trifosfat and could act as the most potent 3CLpro inhibitor.
Pitakbut, 2020	Molecular docking (AutoDock Vina v.1.1.2 and USFC Chi-mera versi 1.11.2).	SARS-CoV-2 *main protease* and RdRp (PDB ID: 6LU7 and 6NU R).	Andrographolide	The results indicate that andrographolide can only inhibit 3-CLpro or the main protease of SARS-CoV-2 more strongly than lopinavir.
Vincent *et al*., 2020	Molecular docking (GEM DOCK v2.0).	SARS-CoV-2 main protease (PD B ID: 6LU7)	Andrographidine C	Andrographidine C is a compound of *A. paniculata* that has the best binding energy at the active site of SARS-CoV-2 main protease.
Sharma *et al*., 2022	Molecular docking (AutoDock Vina Wizard from PyRx soft-ware), ADME (Swiss ADME), molecular dynamics simulat-ion (GRO-MACS veri 2016.4), dan MM/PBSA.	SARS-CoV-2: RNA-dependent RNA polymerase (RdRp) and main protease (PDB ID: 6M71 and 6LU7)	Andrographolide, hydroand-rographolide, isoandrograph-olide, neoandrographolide, oxoandrographolide.	Andrographolide showed a stronger bind-ing affinity at the main protease site than the reference drug that was a positive control, so it is quite potential as a drug candidate with a target inhibitor in Mpro.
Vijayakumar *et al*., 2022	Molecular docking (AutoDock versi 4.2), ADME (Swiss AD ME), and molecular dynamics simulation (GROMACS v.20 20.1).	SARS-CoV-2 main protease (PD B ID: 6LU7)	Andrographolide, androgra-panin, neoandrographolide, 14-deoxyandrographolide and 14-deoxy, 11,12-didehy droandrographolide.	All diterpenoid compounds tested, in particular andrographolide can effectively inhibit the interaction between main protease of SARS-CoV-2 and its receptors.

parameter used to assess the docking results is the affinity binding energy, which in some studies is amplified by the results of molecular dynamic simulations and Molecular Mechanics Poisson-Boltzmann Surface Area. Additionally, many *in-silico* studies also assessed the Absorption, Distribution, Metabolism, and Excretion (ADME) and toxicity predictions of *A. paniculata* compounds. Overall, the determination of a compound's potential as a SARS-CoV-2 inhibitor was carried out in three ways, including the determination of binding affinity energy value parameters, comparison with reference drugs, and consideration of bond conformations at protein amino acid residues. The articles reviewed showed several variations of *in-silico* tests, particularly molecular docking in terms of methods, software, targets, and ligand modeling. The two most popular docking programs were AutoDock (37.93%) and AutoDock Vina (24.14%). *In-silico* experiments on a number of SARS-CoV-2 protein targets were carried out in most of the study (58.62%). The majority of these protein targets were found in the NCBI GenBank and RCSB Protein Bank Database.

The reviewed *in-silico* studies of *A. paniculata* phytochemical compounds used a total of 15 SARS-CoV-2 proteins as targets, namely, 3-CLpro (Mpro), PLpro (Nsp3), RdRp (Nsp12), spike protein, non-structural protein 15 (Nsp15), Nsp9, Nsp16, envelope protein, ORF1a, ORF3a, membrane protein, nucleocapsid N-terminal RNA-binding domain, SGpro, Npro, and main peptidase. Main protease (Mpro) was the most widely used target protein, with 25 articles. Spike protein (11 articles), RdRp (8 articles), PLpro (7 articles), Nsp15 (3 articles), and Nsp9 (2 articles) followed sequentially. Only one article of the remaining nine SARS-CoV-2 proteins was focused on. The five most used SARS-CoV-2 proteins were conserved structures from phylogenetic changes and therefore were highly potential antiviral drug targets, namely, Mpro, PLpro, RdRp, nsp15, and spike protein. Furthermore, the potential of compounds will be reviewed based on these five potential targets.

There are 22 diterpenoid compounds, 18 flavonoids, four phytosterols, three sesquiterpene compounds, and one compound each from the triterpene and phenylpropanoid classes among the 50 *A. paniculata* compounds reported as potential inhibitors of various potential protein targets of SARS-CoV-2. Interestingly, several studies involving many *A. paniculata* compounds as populations for molecular docking tests showed that andrographolide, recognized as the main herbal compound, performed lower in binding affinity energy, indicating that other compounds from this plant also have better potential as antivirals on several SARS-CoV-2 protein targets. These compounds include neoandrographolide, andrographidin C, or stigmasterol and stigmasta-5,22-dien-3-ol from the phytosterol class which are considered to be multi-target antiviral drug agents (Swaminathan *et al*., 2021) (Table 2).

Based on the protein target, the majority of *A. paniculata* phytochemical compounds were found as inhibitors of spike

Table 2. Literature evidence of multi-target *A. paniculata* phytocompounds for COVID-19.

No	Senyawa Berpotensi	Target protein SARS-CoV-2				
		Mpro	PLpro	RdRp	Nsp15	Spike
	Diterpenoid					
1	Andrographolide	13[6,7,10,22,23,27,28,29,32,34,38,44,45*]	2[6,22*]	1[40*]	2[34,42*]	5[4,6,34,40,42*]
2	Andrograpanin	3[7,23,42*]	1[43*]	-	1[42*]	1[42*]
3	Andrographic acid	-	1[34*]	1[34*]	-	-
4	Andropanoside	1[42*]	1[42*]	-	1[42*]	1[42*]
5	Neoandrographolide	7[11,25,31,32,34,42,44*]	3[25,34,43*]	3[11,25,34*]	1[34*]	3[1,11,25*]
6	Isoandrographolide	1[34*]	2[34,42*]	3[2,11,42*]	1[34*]	2[11,25*]
7	Bisandrographolide A	2[3,29*]	-	-	-	1[29*]
8	Deoxyandrographolide	-	1[43*]	-	1[42*]	1[42*]
9	Deoxyandrographolide-19β-d-glucoside	-	1[43*]	-	-	-
10	14-deoxyandrographoside	1[42*]	1[42*]	-	1[42*]	1[42*]
11	14-deoxyandrographolide	2[34,44*]	2[34,42*]	2[11,34*]	2[34,42*]	2[11,42*]
12	14-deoxy-11,12-didehydroandrographolide	5[6,25,34,43,44*]	3[6,34,43*]	1[34*]	1[34*]	16[*]
13	14-deoxy 14,15-didehydroandrographide	-	1[34*]	2[11,34*]	-	1[11*]
14	14-Deoxy-11-oxoandrographolide	1[43*]	1[43*]	-	-	-
15	14-Deoxy-12-methoxyandrographolide	-	1[42*]	-	1[42*]	1[42*]
16	3,19-isopropylidene andrographolide	1[19*]	-	-	1[19*]	1[19*]
17	14-acetyl-3,19-isopropylidene andrographolide	1[19*]	-	-	1[19*]	1[19*]
18	19-O-acetyl-14-deoxy-11,12 didehydro andrographolide	-	-	-	-	1[11*]
19	3-O-β-D-glucopyranosyl androgapholide	1[41*]	-	-	-	-
20	3-O-beta-D-glucopyranosyl 14,19-dideoxy andrographolide	1[30*]	-	-	-	1[30*]
21	Dehydroandrographoline	-	-	-	1[42*]	1[42*]
22	Diterpene II (Lactone)	1[42*]	1[42*]	-	1[42*]	1[42*]
	Flavanoid					
23	Andrographin	-	1[42*]	-	1[42*]	1[42*]
24	Andrographidine A	1[42*]	1[42*]	-	1[42*]	1[42*]
25	Andrographidine C	2[42,45*]	1[42*]	1[21*]	1[42*]	1[42*]
26	Andrographidine E	1[42*]	1[42*]	-	1[42*]	1[42*]
27	Dihydroxydimethoxyflavone	1[29*]	-	-	-	-
28	5-Hydroxy-7,8-dimethoxyflavanone	-	-	-	-	1[18*]
29	5-Hydroxy-7,2',3'-trimethoxyflavone	-	1[43*]	-	-	-
30	5-Hydroxy-7,8,2'-trimethoxyflavone	-	-	1[42*]	1[42*]	2[1,42*]
31	5-Hydroxy-7,8,2'-trimethoxyflavone 5-glucoside	1[42*]	2[43*]	-	1[42*]	1[42*]
32	5-Hydroxy-7,8,2',3'-tetramethoxyflavone	1[32*]	-	-	1[42*]	1[42*]
33	5-Hydroxy-3,7,8-trimethoxy-2-(2-methoxy phenyl)-4h-chromen-4-one	-	-	-	-	1[42*]
34	5-Hydroxy-7,8,2',5'-tetramethoxyflavone	-	-	1[11*]	-	1[11*]
35	5,7,2',3'-tetramethoxyflavanone	-	1[43*]	-	-	-
36	5,4'-dihydroxy-7-O-β-D-pyran-glycuronate butyl ester	1[41*]	-	-	-	-
37	7,8-dimethoxyflavone-5-ß-D-glucopyran osyloxyflavone	1[19*]	-	-	1[19*]	1[19*]
38	Onysilin	1[34*]	-	-	-	-
39	Apigenin	-	1[42*]	-	1[42*]	1[42*]
40	Apigenin 7,4'-Dimethyl Esther	-	1[42*]	-	1[42*]	1[42*]
41	Wogonin	-	1[42*]	-	1[42*]	1[42*]

Continued

No	Senyawa Berpotensi	Target protein SARS-CoV-2				
		Mpro	PLpro	RdRp	Nsp15	Spike
	Diterpenoid					
	Fitosterol					
42	Citrostadienol	1[42*]	1[42*]	-	1[42*]	1[42*]
43	Stigmasta-5,22-Dien-3-Ol	1[42*]	1[42*]	-	1[42*]	1[42*]
44	Stigmasterol	2[19,42*]	1[42*]	-	1[19*]	2[19,42*]
45	Indosterol	1[19*]	-	-	1[19*]	1[19*]
	Sesquiterpene					
46	Paniculine	-	1[43*]	-	-	-
47	Paniculide-A	-	1[43*]	-	-	-
48	Paniculide-B	-	1[43*]	-	-	-
	Triterpene					
49	Oleanolic acid	1[19*]	-	-	1[19*]	1[19*]
	Fenilpropanoid					
50	3,4-dicaffeoylquinic acid	1[34*]	1[34*]	1[34*]	-	-

* The source of the article is based on a number in this literature review bibliography.

proteins, namely, 37 compounds, followed by PLpro with 32 compounds, Mpro (main protease) with 30 compounds, Nsp15 with 30 compounds, and RdRp with 11 compounds (Fig. 2). This finding is in line with the results of Kongsune *et al*. (2022), which showed that most of the *A. paniculata* compounds have greater binding energy values to the main protease, followed by spike protein and Nsp15. However, more hydrogen bonds were found at the active site of Nsp15, then spike protein and Mpro sequentially. This is due to the docking results that also consider other interactions, such as Van der Waals and electrostatic bonds (Kongsune *et al*., 2022).

Scientific evidence from *in-silico* studies shows the potential of several *A. paniculata* compounds being multi-target inhibitors of SARS-CoV-2 (Fig. 3). Andrographolide, neoandrographolide, isoandrographolide, 14-deoxyandrographolide, 14-deoxy-11,12 didehydroandrographolide, and andrographidine C are the six compounds that have inhibitory activity on all five protein targets. A total of 10 compounds interact with four protein targets, 15 compounds interact with three protein targets, 6 compounds interact with two protein targets, and 13 other phytochemical compounds interact only with one potential protein of SARS-CoV-2.

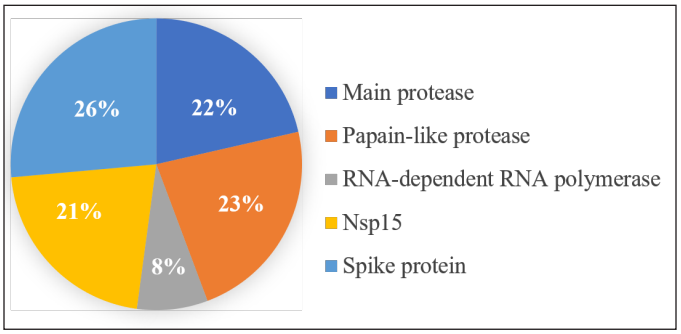

Figure 2. Percentage of target-based *A. paniculata* compounds.

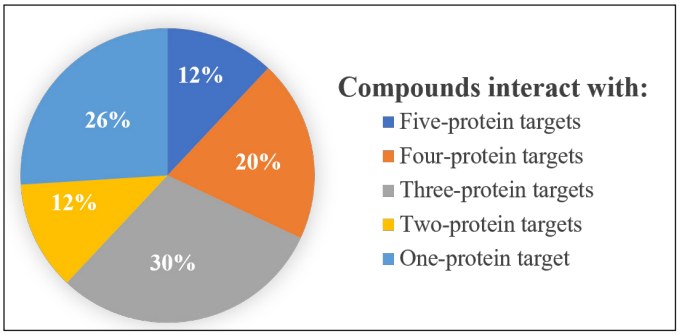

Figure 3. Percentage of multi-target *A. paniculata* compounds.

DISCUSSION

An *in-vivo* study revealed that 14-deoxy-11,12-didehydroandrographolide, the primary diterpenoid compound of *A. paniculata*, significantly reduced lung titers in infected mice when administered at non-toxic concentrations of 1,000 or 500 mg/kg/day 4 or 48 hours prior to H5N1 influenza A virus infection (Cai *et al*., 2016). Several *in-vitro* studies also showed the potency of *A. paniculata* phytocompounds as an antiviral. In Calu-3 cells infected with SARS-CoV-2, post-infection therapy with *A. paniculata* extract and andrographolide dramatically decreased virion generation with an IC50 of 0.036 µg/ml and 0.034 µm, respectively, limiting the transmission of COVID-19 (Sa-Ngiamsuntorn *et al*., 2021). Andrographolide also suppressed the main protease activity of SARS-CoV-2 in the cleavage assay by producing an IC50 value of 15.05 ± 1.58 M (Shi *et al*., 2020). Furthermore, exploration of potential phytochemical compounds in essential proteins of SARS-CoV-2 with *in-silico* predictions has been carried out. Based on existing literature evidence, *A. paniculata* phytochemical compounds are capable of inhibiting the activity of several potential protein targets in SARS-CoV-2. In addition, below is a more detailed discussion of the mechanism of inhibition based on the protein targets from existing *in-silico* studies.

Main protease

The main protease is a highly conserved cysteine hydrolase class protein in β-coronavirus (Hu *et al*., 2022). This enzyme mediates the cleavage of 11 non-structural proteins that are necessary for viral replication and transcription. Inhibition of viral proteases will reduce the formation of mature functional proteins (Mengist *et al*., 2021). According to research, the most alluring residue for SARS-CoV-2 Mpro to make hydrogen bonds with diverse ligands is Gly143, followed by Glu166, Cys145, and His163 (Nguyen *et al*., 2020). Some of the amino acid residues with crucial roles in the main protease are targeted by *A. paniculata* phytochemical compounds through hydrogen bonding. Andrographolide forms four hydrogen bonds to the main protease through residues Gly143, Cys145, and Glu166 (Enmozhi *et al*., 2020). This electrophilic compound inhibits the main protease activity of SARS-CoV-2 by entering the catalytic site through hydrogen bonds on amino acid residues and several water molecules (Rajagopal *et al*., 2020; Shi *et al*., 2020). The following list of molecular mechanisms that andrographolide possesses as antiviral characteristics was shown by *in-silico* investigations to be possible inhibitors of the SARS-CoV-2 main protease: 1) improved H1N1 virus-I which caused cell death by blocking virally induced activation of the retinoic acid-inducible gene-I- like receptors signaling pathway and reduced lung virus titer through its immune modulatory action, 2) modification of the virus replication route caused by Endoplasmic Reticulum stress-mediated Unfolded Protein Response, 3) induction of heme oxygenase-1 expression, 4) involvement of multiple pathways including Nuclear Factor kappa B and Janus kinase/signal transducers and activators of transcription, 5) inhibition of protease activity, 6) limiting of antigen expression, 7) inhibition of glycoprotein expression, and 8) suppression of lytic protein expression (Banerjee *et al*., 2020).

The non-covalent bond interactions of the four diterpenoid compounds studied by Majumdar *et al*. (2022) on amino acids of main protease proteins are hydrogen, pi-alkyl, alkyl, carbon-hydrogen, hydrophobic, and polar bonds. The *in-silico* study carried out by Sukardiman *et al*. (2020) presented another finding stating that the glycoside form of andrographolide, 3-O-β-D-glucopyranosyl andrographolide, produces more negative binding energy than its aglycone form. The physicochemical properties of the glycoside affect the solubility and polarity of the compound thus inducing the receptor site of main protease (Sukardiman *et al*., 2020). The study conducted by Rajagopal *et al*. (2020) demonstrated that dihydroxy dimethoxy flavone compounds have the same excellent affinity as andrographolide on the SARS-CoV-2 main protease receptor due to lipophilic properties and hydrogen bond formation. Stigmasterol from the phytosterol class of *A. paniculata* forms hydrogen bonds, ionic interactions, and strong hydrophobicity on various amino acid residues of the main protease and exerts a stable configuration on the spike and Mpro protein targets (Swaminathan *et al*., 2021).

However, different results were also reported for some major diterpene compounds such as andrographolide, andrograpanin, 14-deoxyandrographolide, and 14-deoxy-11,12-didehydroandrographolide where these compounds were reported to have no stable binding to the main protease target. Research by Sukardiman *et al*. (2020) assessed the potential of compounds with standard reference ligand bond affinity values, where the main diterpene compound is found to have a weaker binding affinity. This was also confirmed by the results of Swaminathan *et al*. (2021) concerning the lack of potential of several main diterpene compounds as main protease inhibitors with an affinity energy assessment greater than −7 kcal/mol.

Papain-like protease

PLpro is a crucial coronavirus enzyme necessary to process viral polyproteins to activate the replication complex and facilitate virus spread. This protein in SARS-CoV-2 shares 83% sequence identity making it highly conserved (Shin *et al*., 2020). The antiviral interferon pathway can be maintained with the help of PLpro inhibition, which can also lessen viral replication in infected cells and interfere with virus-induced cytopathogenic effects. The reduction in the replication of the active virus (subgenomic RNA4-encoding E gene in SARS-CoV-2), as determined by genetic surveillance of intracellular viral RNA synthesis, is the outcome of the suppression of PLpro. As a result, the released virus particles from the infected cell are reduced (Shin *et al*., 2020). In order to reduce SARS-CoV-2 infection and improve antiviral immunity, PLpro should be targeted. Flexible binding sites at residues Tyr269 and Gln270 for small molecules present in SARS-CoV PLpro are also found in SARS-CoV-2 PLpro. Research by Ibrahim *et al*. (2020) showed that the key residues that appear on SARS-CoV-2 PLpro are Tyr268 and Gln 269.

The compound reported to bind most extensively to Plpro is 14-deoxy-11,12-didehydroandrographolide with stable binding to the active site of this protein through hydrogen (Gln269), carbon-hydrogen (Gly160), and Van der Waals bonds on other residues (Verma *et al*., 2021). Meanwhile, neoandrographolide binds to the active site through hydrogen bonds (Asn109, Gln269, and Va159) and carbon-hydrogen bonds (Gly160 and Thr158). This is in line with the results by Sahithya *et al*. (2021), which showed that *A. paniculata* compounds interact with the main amino acid residue of SARS-CoV-2 PLpro, namely, Tyr268 and several other residues. Andrographolide, as the main compound, was found to bind toward the active site of PLpro through hydrogen bonds at the Tyr274 residue (Dey *et al*., 2020). Van der Waals interactions and hydrogen bonds are the main factors in the inhibitory bonding process of flavonoid phytochemical compounds from *A. paniculata* on the target protein PLpr (Rajagopal *et al*., 2020). The two main compounds of the phytosterol class, stigmasterol and stigmasta-5,22-dien-ol, display hydrophobic interactions at Arg131, Thr199, Tyr239, and Leu286 residues with high affinity, making them potential inhibitors of the SARS-CoV-2 PLpro protein (Swaminathan *et al*., 2021).

However, *in-silico* research conducted by Rizma *et al*. (2021) suggested that the two main diterpenoid compounds of *A. paniculata*, andrographolide and neoandrographolide, have no potential as PLpro inhibitors. The study assessed the potential of the compound based on the comparison of the estimated affinity energy of the docking results with the natural ligand PLpro and the reference drug remdesivir (Rizma *et al*., 2021). The study by Dey *et al*. (2020) also found that the compound 14-deoxy-11,12-didehydroandrographolide lacked a hydrogen bond to the amino residue PLpro despite having a fairly high-affinity value.

RNA-dependent RNA polymerase

RdRp is a highly conserved protein in three coronaviruses, namely, SARS-CoV, SARS-CoV-2, and MERS-CoV. This protein is suggested to be a broad-spectrum antiviral

target in coronaviruses. RdRp is predicted to be the pivotal enzyme responsible for viral replication and transcription complexes (Jiang *et al*., 2021). Aside from that, these proteins also play a role in aiding viral escape from host defense mechanisms which has important implications during viral evolution. Potential treatment strategies to prevent viral replication include antiviral medications that specifically target the active sites of RdRp, Asp760, and Asp761 (Aftab *et al*., 2020). The FDA has approved the anti-RdRp medications, remdesivir and ribavirin.

The major diterpenoid compound of *A. paniculata*, andrographolide, inhibits RdRp activity by binding to residue Thr556 through the formation of four hydrogen bonds (Srikanth and Sarma, 2021). Neoandrographolide and isoandrographolide are the two compounds reported to mostly interact with RdRp. A study by Hiremath *et al*. (2021) reported that neoandrographolide interacts with the active site of this protein through hydrogen bonds at four residues, namely, Ala125, Asp126, Arg132, and His133. This finding is supported by the results from Murugan *et al.*'s (2021) study, which suggested that neondrographolide is a compound with the potential as an inhibitor of RdRp even though its binding affinity value is greater than that of remdesivir drugs, which is due to the stability of its binding to the Asp336, Thr440, and Asp507 residues of the target protein. The study by Latha *et al*. (2022) showed that andrographidin C, being one of the major diterpenoid compounds of *A. paniculata*, interacts with RdRp similarly to nucleotide analog drugs, that is, through non-obligate RNA chain breaks. Such interaction is stable due to the presence of pi-pi bonds from uracil bases and the affinity is also strengthened by hydrogen bonds at amino residues Glu811 and Lys551 (Dey *et al*., 2020). The phytochemical compound was also discovered to interact with the major site of RdRp, Asp761, making it a potential inhibitor of this protein (Sahithya *et al*., 2021).

However, *in-silico* research conducted by Laksmiani *et al*. (2020) concluded that andrographolide has less potential as an RdRp inhibitor by having a more positive affinity value than remdesivir drugs. This is supported by the results of Sharma *et al*. (2022) which showed that some of the main diterpenoid compounds of *A. paniculata*, including andrographolide and neoandrographolide, have no interaction with amino acid residues of the RdRp target protein. Although reported as having good binding affinity, isoandrographolide does not have hydrogen bonding with the amino residue RdRp (Hiremath *et al*., 2021).

Non-structural protein 15

Coronaviruses use the uridine-specific endoribonuclease known as Nsp15 to break viral RNA and circumvent the host immune system (Saramago *et al*., 2022). This protein features a conserved active site across Coronaviridae. Nsp15 is crucial for the pathogenesis of coronaviruses. According to research, this RNase is in charge of destroying viral dsRNA intermediates that would otherwise hinder host cells from recognizing them. Additionally, this protein dramatically slows down the type I interferon response (Saramago *et al*., 2022). As a result, developing antiviral drug candidates that target these proteins in particular could be a possible treatment for COVID-19.

The active site of Nsp15 shares six essential residues that are conserved among SARS-CoV-2, SARS-CoV, and MERS-CoV proteins, namely, His235, His250, Lys290, Thr341, Tyr343, and Ser294 (Kim *et al*., 2020). Based on the results by Sahithya *et al*. (2021), *A. paniculata* phytochemical compounds bind to the Nsp15 active site more efficiently than hydroxychloroquine at the amino acid residues Thr (167), Lys (71, 90), Glu (203), Asn (200), Arg (199), Thr (196, 275), Lys (277), Val (295), Tyr (89, 279), Ser (198, 274), Glu (69), Asp (268, 273, 297), Gly (165), and Met (272). Although it does not bind to the key residue of Nsp15, the compound has a stronger affinity than the antiviral drugs nelvinafir and hydroxychloroquine to many other residues (Sahithya *et al*., 2021). Andrographidin C is reported to have high binding affinity energy and interacts with amino residues Asn29, Asn30, and Pro51 (Swaminathan *et al*., 2021). However, some of the main compounds of *A. paniculata* have also been reported to have less potential due to having a more positive binding affinity energy than existing reference drugs (Kongsune *et al*., 2022).

Spike protein

Spike glycoproteins have an essential role in the attachment, fusion, and entrance of the virus into the host cell (Duan *et al*., 2019). A spike protein that binds to the ACE-2 receptor enables SARS-CoV-2 to enter human cells and cause infection (Banerjee *et al*., 2022). The spike protein, which is involved in the process of membrane fusion and receptor recognition, is made up of the S1 and S2 subunits. The coronavirus must bind to the specific receptor ACE-2 in order to enter the target cell. This is accomplished by the S1 subunit of the spike protein, while the S2 subunit facilitates the fusing of viral membrane cells by establishing a six-helix bond via a two-heptad repetitive domain (Huang *et al*., 2020). Located on the surface of the virus, the spike glycoprotein is targeted by the host immune response as the main target by neutralizing antibodies. Therefore, targeting this protein as an ativirus drug target may reduce the potential for SARS-CoV-2 infection in humans.

Results by Srikanth and Sarma (2021) indicated that the main compound of the diterpenoid group, andrographolide, binds to the spike glycoprotein at the tyrosine kinase phosphorylation site suggesting inactivation of the target protein. Andrographolide creates a hydrogen bond interaction with the amino residue Lys807 on the spike protein. The diterpene lactone compound from *A. paniculata* binds to the core site located under the surface area of the spike protein complex and ACE-2 thereby indirectly modulating the interaction between the two proteins (Murugan *et al*., 2021). Research by Kiran *et al*. (2022) stated that the compound 5-hydroxy-7,8-dimethoxyflanone, one of the main flavonoid compounds of *A. paniculata*, has moderate affinity energy on spike protein targets through hydrogen bonding interactions with amino residues Asp 364 and Gly339.

CONCLUSION

The potential proteins of the SARS-CoV-2 have been discovered to be inhibited by a number of phytocompounds from the plant *A. paniculata* using *in-silico* tests. The most studied and highly conserved SARS-CoV-2 potential proteins from phylogenetic changes for inhibitory targets of phytochemical compounds of *A. paniculata* are the main protease, PLpr, RdRp, Nsp15, and spike protein. A number of six phytochemical compounds of *A. paniculata* showed inhibitory activity on the five SARS-CoV-2 target proteins including andrographolide, neoandrographolide,

isoandrographolide, 14-deoxyandrographolide, 14-deoxy 11,12-didehydroandrographolide, and andrographidine C which are the main diterpenoid compounds of *A. paniculata*.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES

Adejoro IA, Babatunde DD, Tolufashe GF. Molecular docking and dynamic simulations of some medicinal plants compounds against SARS-CoV-2: an *in silico* study. J Taibah Univ Sci, 2020; 14(1):1563–70.

Aftab SO, Ghouri MZ, Masood MU, Haider Z, Khan Z, Ahmad A, Munawar N. Analysis of SARS-CoV-2 RNA-dependent RNA polymerase as a potential therapeutic drug target using a computational approach. J Transl Med, 2020; 18(1):1–15.

Alagu Lakshmi S, Shafreen RMB, Priya A, Shunmugiah KP. Ethnomedicines of Indian origin for combating COVID-19 infection by hampering the viral replication: using structure-based drug discovery approach. J Biomol Struct Dyn, 2021; 39(13):4594–609.

Banerjee A, Czinn SJ, Reiter RJ, Blanchard TG. Crosstalk between endoplasmic reticulum stress and anti-viral activities: a novel therapeutic target for COVID-19. Life Sci, 2020; 255:117842; doi:10.1016/j.lfs.2020.117842.

Banerjee S, Wang X, Du S, Zhu C, Jia Y, Wang Y, Cai Q. Comprehensive role of SARS-CoV-2 spike glycoprotein in regulating host signaling pathway. J Med Virol, 2022; 94:4071–87.

Cai W, Chen S, Li Y, Zhang A, Zhou H, Chen H, Jin M. 14-Deoxy-11,12-didehydroandrographolide attenuates excessive inflammatory responses and protects mice lethally challenged with highly pathogenic A(H5N1) influenza viruses. Antiviral Res, 2016; 133:95–105.

Dey YN, Khanal P, Patil BM, Wanjari MM, Srivastava B, Gurav SS. The role of andrographolide and its derivative in COVID-19 associated proteins and immune system 2020. Available via https://doi.org/10.21203/rs.3.rs-35800/v1

Dound YA, Chaudhary S, Sehgal R, Chaudhary SS, Dound BA. Plant based molecules for the management of Covid-19 2020. Available via https://pubchem.ncbi.nlm.nih.gov/

Duan L, Zheng Q, Zhang H, Niu Y, Lou Y, Wang H. The SARS-CoV-2 spike glycoprotein biosynthesis, structure, function, and antigenicity: implications for the design of spike-based vaccine immunogens. Front Immunol, 2019; (11):576622.

Dwivedi MK, Sonter S, Mishra S, Singh P, Singh PK. Secondary metabolite profiling and characterization of diterpenes and flavones from the methanolic extract of *Andrographis paniculata* using HPLC-LC-MS/MS. Futur J Pharm Sci, 2021; (1):1–28..

Enmozhi SK, Raja K, Sebastine I, Joseph J. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an *in silico* approach. J Biomol Struct Dyn, 2020; 39:1–7.

Hiremath S, Kumar HDV, Nandan M, Mantesh M, Shankarappa KS, Venkataravanappa V, Basha CRJ, Reddy CNL. *In silico* docking analysis revealed the potential of phytochemicals present in *Phyllanthus amarus* and *Andrographis paniculata*, used in ayurveda medicine in inhibiting SARS-CoV-2. 3 Biotech, 2021; 11(2):44.

Hu Q, Xiong Y, Zhu GH, Zhang YN, Zhang YW, Huang P, Ge GB. The SARS-CoV-2 main protease (Mpro): structure, function, and emerging therapies for COVID-19. MedComm (Beijing), 2022; 3(3):e151.

Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin, 2020; 41:1141–9.

Ibrahim TM, Ismail MI, Bauer MR, Bekhit AA, Boeckler FM. Supporting SARS-CoV-2 papain-like protease drug discovery: *in silico* methods and benchmarking. Front Chem, 2020; 8:996.

Jiang Y, Yin W, Xu HE. RNA-dependent RNA polymerase: structure, mechanism, and drug discovery for COVID-19. Biochem Biophys Res Commun, 2021; 538:47.

Khare P, Sahu U, Pandey SC, Samant M. Current approaches for target-specific drug discovery using natural compounds against SARS-CoV-2 infection. Virus Res, 2020; 290:98169.

Kim Y, Jedrzejczak R, Maltseva NI, Wilamowski M, Endres M, Godzik A, Michalska K, Joachimiak A. Struktur kristal Nsp15 endoribonuklease NendoU dari SARS-CoV-2. Protein Sci, 2020; 29(7):1596–605.

Kiran G, Karthik L, Shree Devi MS, Sathiyarajeswaran P, Kanakavalli K, Kumar KM. In silico computational screening of kabasura kudineer - official siddha formulation and JACOM against SARS-CoV-2 spike protein. J Ayurveda Integr Med, 2022; 13(1): 100324.

Kongsune P, Innok W, Rungrotmongkol T. *In silico* screening of potential inhibitor from *Andrographis paniculata* constituents against three targets of SARS-CoV-2: main protease, spike protein, and Nsp15. ASEAN J Sci Technol Rep, 2022; 25(1):69–76.

Kumar MP, Sundaram KM, Ramasamy MS. Coronavirus spike (S) glycoprotein (2019-Ncov) targeted siddha medicines kabasura kudineer and thonthasura kudineer in silico evidence for corona viral drug. Asian J Pharm Res Health Care, 2020; 12(1):20–7.

Latha D, Hrishikesh D, Shiban G, Chandrashekar C, Bharath BR. *In silico*, *in vitro* screening of plant extracts for anti-SARS-CoV-2 activity and evaluation of their acute and sub-acute toxicity. Phytomedicine Plus, 2022; 2(2):100233.

Laksmiani NP, Larasanty LP, Santika AA, Prayoga PA, Dewi AA, Dewi NP. Active compounds activity from the medicinal plants against SARS-CoV-2 using *in silico* assay. Biomed Pharmacol J, 2020; 13(2):873–81.

Majumdar M, Singh V, Misra TK, Roy DN. *In silico* studies on structural inhibition of SARS-CoV-2 main protease Mpro by major secondary metabolites of *Andrographis paniculata* and *Cinchona officinalis*. Biologia (Bratisl), 2022; 77(5):1373–89.

Mengist HM, Dilnessa T, Jin T. Structural Basis of Potential Inhibitors Targeting SARS-CoV-2 Main Protease. Front Chem, 2021; 9:7.

Murugan NA, Pandian CJ, Jeyakanthan J. Computational investigation on *Andrographis paniculata* phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds in drug trials. J Biomol Struct Dyn, 2021; 39(12):4415–26.

Nguyen DD, Gao K, Chen J, Wang R, Wei GW. Unveiling the molecular mechanism of SARS-CoV-2 main protease inhibition from 137 crystal structures using algebraic topology and deep learning. Chem Sci, 2020; 11(44):12036–46.

Pitakbut T. The Antiviral activity of andrographolide, the active metabolite from *Andrographis paniculata* (Burm. f.) Wall. ex Nees. against SARS-CoV-2 by using bio-and chemoinformatic tools. Walailak J Sci Technol, 2020; 17(8):851–66.

Prabha T, Kapoor VK, Selvamani P, Latha S, Sivakumar T, Jubie S. Dual modulators of selected plant secondary metabolites targeting COVID-19 main protease and interleukin-2: an *in-silico* approach based novel hypothesis. Coronaviruses, 2020; 2(2):223–34.

Rajagopal K, Varakumar P, Baliwada A, Byran G. Activity of phytochemical constituents of curcuma longa (turmeric) and *Andrographis paniculata* against coronavirus (COVID-19): an *in silico* approach. Futur J Pharm Sci, 2020; 6(1):104.

Rathinavel T. Virtual screening of COVID-19 drug from three Indian traditional medicinal plants through *in silico* approach antioxidant assay of phytoconstituents from *Eclipta alba* view project hyaluronic acid-drug conjugation technology view project [Internet]. Article Res J Biotechnol, 2020. Available via www.rcsb.org

Rizma BRP, Ananto AD, Sunarwidhi AL. The study of potential antiviral compounds from Indonesian medicinal plants as anti-COVID-19 with molecular docking approach. J Mol Docking, 2021; 1(1):32–9.

Rizqillah RK, Fatriansyah JF, Fadilah F, Sulhadi S, Wahyuni S, Sudirman MA, Nafisah HC, Lestari SD. *In silico* molecular docking and molecular dynamics examination of *Andrographis paniculata* compounds of Andrographolide, Neoandrogra-pholide, and 5-hydroxy-7,8,2',3'-tetramethoxyflavone inhibition activity to SARS-CoV-2 main protease. BIO Web Conf, 2021; 41:07002.

Sa-Ngiamsuntorn K, Suksatu A, Pewkliang Y, Thongsri P, Kanjanasirirat P, Manopwisedjaroen S, Charoensutthivarakul S, Wongtrakoongate P, Pitiporn S, Chaopreecha J, Kongsomros S, Jearawuttanakul K, Wannalo W, Khemawoot P, Chutipongtanate S, Borwornpinyo S, Thitithanyanont A, Hongeng S. Anti-SARS-CoV-2 activity of *Andrographis paniculata* extract and its major component andrographolide in human lung epithelial cells and cytotoxicity evaluation in major organ cell representatives. J Nat Prod, 2021; 84(4):1261–70.

Sahithya MD, Srinath M, Kumar BC, Giri CC. Molecular *in silico* docking interventions in various SARS-CoV-2 receptor targets involving bioactive herbal compounds of *Andrographis paniculata* (Burm. f.) Nees against COVID-19. Ann Phytomed Int J, 2021; 10(1) (COVID-19):S4–12.

Saliu TP, Umar HI, Ogunsile OJ, Okpara MO, Yanaka N, Elekofehinti OO. Molecular docking and pharmacokinetic studies of phytocompounds from Nigerian medicinal plants as promising inhibitory agents against SARS-CoV-2 methyltransferase (nsp16). J Genet Eng Biotechnol, 2021; 19(1):172.

Saramago M, Costa VG, Souza CS, Bárria C, Domingues S, Viegas SC, Lousa D, Soares CM, Arraiano CM, Matos RG. The nsp15 nuclease as a good target to combat SARS-CoV-2: mechanism of action and its inactivation with FDA-approved drugs. Microorganisms, 2022; 10(2):342.

Sharma A, Vora J, Patel D, Sinha S, Jha PC, Shrivastava N. Identification of natural inhibitors against prime targets of SARS-CoV-2 using molecular docking, molecular dynamics simulation and MM-PBSA approaches. J Biomol Struct Dyn, 2022; 40(7):3296–11.

Shi TH, Huang YL, Chen CC, Pi WC, Hsu YL, Lo LC, Chen WY, Fu SL, Lin CH. Andrographolide and its fluorescent derivative inhibit the main proteases of 2019-nCoV and SARS-CoV through covalent linkage. Biochem Biophys Res Commun, 2020; 533(3):467–73.

Shin D, Mukherjee R, Grewe D, Bojkova D, Baek K, Bhattacharya A, Schulz L, Widera M, Mehdipour AR, Tascher G, Geurink PP, Wilhelm A, van der Heden van Noort GJ, Ovaa H, Müller S, Knobeloch KP, Rajalingam K, Schulman BA, Cinatl J, Hummer G, Ciesek S, Dikic I. Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. Nature, 2020; 587(7835):657–2.

Srikanth L, Sarma PVGK. Andrographolide binds to spike glycoprotein and RNA-dependent RNA polymerase (NSP12) of SARS-CoV-2 by *in silico* approach: a probable molecule in the development of anti-coronaviral drug. J Genet Eng Biotechnol, 2021; 19(1).

Sukardiman, Ervina M, Fadhil Pratama MR, Poerwono H, Siswodihardjo S. The coronavirus disease 2019 main protease inhibitor from *Andrographis paniculata* (Burm. f) Ness. J Adv Pharm Technol Res. 2020; 11(4):157–62.

Swaminathan K, Karunakaran KN, Vidyalakshmi S. SARS-CoV2 multiple target inhibitors from *Andrographis paniculata*: an *in-silico* report. Eur J Mol Clin Med, 2021; 08(03):1653–85.

Verma D, Mitra D, Paul M, Chaudhary P, Kamboj A, Thatoi H, Janmeda P, Jain D, Panneerselvam P, Shrivastav R, Pant K, Das Mohapatra PK. Potential inhibitors of SARS-CoV-2 (COVID 19) proteases PLpro and Mpro/ 3CLpro: molecular docking and simulation studies of three pertinent medicinal plant natural components. Curr Res Pharmacol Drug Discov, 2021; 2:100038.

Vijayakumar M, Janani B, Kannappan P, Renganathan S, Al-Ghamdi S, Alsaidan M, Abdelaziz MA, Peer Mohideen A, Shahid M, Ramesh T. *In silico* identification of potential inhibitors against main protease of SARS-CoV-2 6LU7 from *Andrographis panniculata* via molecular docking, binding energy calculations and molecular dynamics simulation studies. Saudi J Biol Sci, 2022; 29(1):18–29.

Vincent S, Arokiyaraj S, Saravanan M, Dhanraj M. Molecular docking studies on the anti-viral effects of compounds from Kabasura Kudineer on SARS-CoV-2 3CLpro. Front Mol Biosci, 2020; 7:613401.

Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, Zheng M, Chen L, Li H. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B, 2020; 10(5):766–88.

How to cite this article:
Shavira S, Handayani S, Fatmaria F. The *in-silico* potential of *Andrographis paniculata* phytocompounds as antiviral for the treatment of COVID-19: A systematic review. J Appl Pharm Sci, 2023; 13(08):101–112.