Aspects of Molecular Medicine 3 (2024) 100032

Contents lists available at ScienceDirect

Aspects of Molecular Medicine

journal homepage: www.journals.elsevier.com/aspects-of-molecular-medicine

In silico study of the flavonoid compound of *Sauropus androgynus* leaves ON *RNA-Dependent RNA polymerase* (RdRp) SARS-CoV-2

Aghnia Nabila Ananda [a], Triawanti Triawanti [b], Bambang Setiawan [b,*], Annisa Camellia Makati [a], Jasmine Aisyah Putri [a], Sentot Joko Raharjo [c]

[a] *Faculty of Medicine and Health Sciences, Universitas Lambung Mangkurat, Banjarmasin, South Kalimantan, Indonesia*
[b] *Department of Biochemistry and Molecular Biology, Faculty of Medicine and Health Sciences, Universitas Lambung Mangkurat, Banjarmasin, South Kalimantan, Indonesia*
[c] *Diploma of Food and Pharmacy Analyst, Polytechnic of Health of Putra Indonesia Malang, Malang, East Java, Indonesia*

ARTICLE INFO

Handling Editor: Prof A Angelo Azzi

Keywords:
SARS-CoV-2
RdRp
Flavonoid
Binding affinity
In silico

ABSTRACT

Objective: RNA-dependent RNA polymerase (RdRp) is a protein that is essential in the replication and transcription processes of SARS-CoV-2. RdRp inhibitors must be sought, particularly in the identification of active substances in herbal or human dietary sources. The purpose of this study was to investigate the molecular docking of phytochemistry from the leaves of *Sauropus androgynus* against the RdRp protein.
Methods: This in silico study was performed using AutoDock Tools 1.5.7, AutoDock Vina v1.2.3 software, and BIOVIA Discovery Studio Visualizer 4.1.
Results: Afzelin, kaempferol, and trifolin were found as phytochemistry in Sauropus androgynus leaves. Among the three flavonoid molecules, afzelin has the lowest negative binding affinity (−7.677 kcal/mol), followed by trifolin (−6.906 kcal/mol) and kaempferol (−6.65 kcal/mol). All three flavonoid compounds have a binding affinity that is more negative than the three conventional drugs (favipiravir, remdesivir, ribavirin).
Conclusions: Flavonoid from the leaves of *Sauropus androgynus* leaves can be utilized as candidate for herbal or complementary medicine as an inhbitor of RdRp for COVID-19 treatment.

1. Introduction

The Coronaviridae genus has given rise to various diseases in the world, namely Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is the cause of COVID-19 (Adzdzakiy et al., 2023). In March 2020, Indonesia declared COVID-19 a national disaster (Arifin, 2020). Indonesia recorded 6.2 million cases in July 2022, triggering 157 thousand deaths. Even though mass vaccination has been carried out since April 2021 in Indonesia, the number of active cases remains (Task Force COVID-19, 2021). One of the causes of active cases is the high level of virus mutations and furthermore, mutations underlie the reduction in vaccine efficacy (Funk et al., 2020; Moore and Offit, 2021; Lubis et al., 2022). On the other hand, both globally and nationally indicate that the management of the COVID-19 disaster is not significant (Putera et al., 2022). The interesting thing is that the increase in COVID-19 outbreaks is associated with an increase in deaths at referral hospitals in Jakarta (Habib et al., 2023).

The two main factors for viral genome replication to occur include the host and the virus. When the virus approaches the host cell, the process of replication and translation of viral proteins begins. The completeness of this process takes place in the cytoplasm through the activation of RNA-dependent RNA polymerase (RdRp). RdRp is a multivalent enzyme that acts as a nucleotdyl transferase (EC 2.7.7.48). The RdRp product is an RNA strand through the addition of ribonucleotides to the 3′-hydroxyl end, resulting in synthesis of the RNA molecule in the 5′-3′ direction. The factors required for RdRp activity are an RNA template, two magnesium ions in the active site which are required for the formation of phosphodiester bonds, ribonucleoside 5′-triphosphate (ATP, CTP, UTP, and GTP) as a constituent of nascent RNA. The RdRp structure has two channels, each of which leads to the active site. The primary channel goes to the RNA template position and the secondary

* Corresponding author. Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Lambung Mangkurat, Jalan Veteran, Sungai Bilu No.128 Melayu, Kecamatan, Banjarmasin, Tengah Banjarmasin, South Kalimantan, 70122, Indonesia.
E-mail addresses: aghnianabila08@gmail.com (A.N. Ananda), triawanti@ulm.ac.id (T. Triawanti), ganesh79setiawan@gmail.com (B. Setiawan), annisacmedu@gmail.com (A.C. Makati), jasmineasyh18@gmail.com (J.A. Putri), sentotjoko@yahoo.co.id (S.J. Raharjo).

https://doi.org/10.1016/j.amolm.2023.100032
Received 18 March 2023; Received in revised form 22 October 2023; Accepted 25 November 2023
Available online 7 December 2023

Table 1
Binding affinity Interaction of flavonoid compounds with RdRp SARS-CoV-2.

Flavonoid Compounds	Binding affinity (kcal/mol)
Afzelin	−7.677*
Kaempferol	−6.65
Trifolin	−6.906

Note: *the most negative interaction energy compared to other compounds.

Table 2
Types of bonds and amino acid residues from the interaction of afzelin and RdRp SARS-CoV-2.

Compound	Type of Bonds	Amino Acid Residues
Afzelin	Conventional hydrogen bond	Glu811
	Carbon-hidrogen bond	Asp 761
	Pi-anion	Asp760
	Pi-alkyl	Cys 622, Cys813
	van der Waals	Phe812, Trp800, Asp618, Lys798, Trp617, Asp623, Gln815
	Unfavorable Donor-Donor	Tyr619, Ser814

channel goes to the input nucleoside triphosphate (NTP) position (Hashemian et al., 2022; Gao et al., 2020). RdRp has a catalytic core, namely nsp12 and cofactors nsp7 and nsp8. Drugs targeting nsp12 may become a focus for antiviral development (Gao et al., 2020; Kirchdoerfer and Ward, 2019; Wu et al., 2022; Yi et al., 2023). There are three nsp12 domains, namely NiRAN (residues 1–250), interface (residues 251–397), and conserved polymerase (residues 398–932) (Itoh et al., 2021).

Sauropus androgynus (traditionally known as Katuk in South Kalimantan) is a plant species native to Southeast Asia and South Asia that thrives in hot and humid environments (Zhang et al., 2020). This leaves are abundantly grown and used in the community as a meal, antipyretic, to increase milk production, and to relieve hoarseness (Andarwulan et al., 2010). The natives of South Kalimantan have used this leaf to make a unique delicacy known as green sticky rice. Several previous studies discovered high quantities of phytochemicals such as flavonoids, terpenoids, steroids, tannins, phenols, alkaloids, fatty acids, and essential oils (Bose et al., 2018). The leaves of this plant are widely employed in Chinese herbal medicine to treat antipyretic, slimming agents, cough, hepatitis, constipation, and enteritis (Li et al., 2008; Bunawan et al., 2015). Flavonoids, active compounds found in *Sauropus androgynus* leaves, have little systemic toxicity and can operate in tandem with conventional treatments. Furthermore, flavonoids are pleiotropic, which means that their functional groups can interact with various cellular targets and block multiple metabolic processes (Russo et al.,

Table 3
Types of bonds and amino acid residues from the interaction of kaempferol and RdRp SARS-CoV-2.

Compound	Type of Bonds	Amino Acid Residues
Kaempferol	Conventional hydrogen bond	Lys545, Arg624, Thr556
	Pi-cation	Arg553, Arg555
	Pi-anion	Asp623
	Pi-alkyl	Arg624
	van der Waals	Asp542, Tyr455, Cys622, Lys621

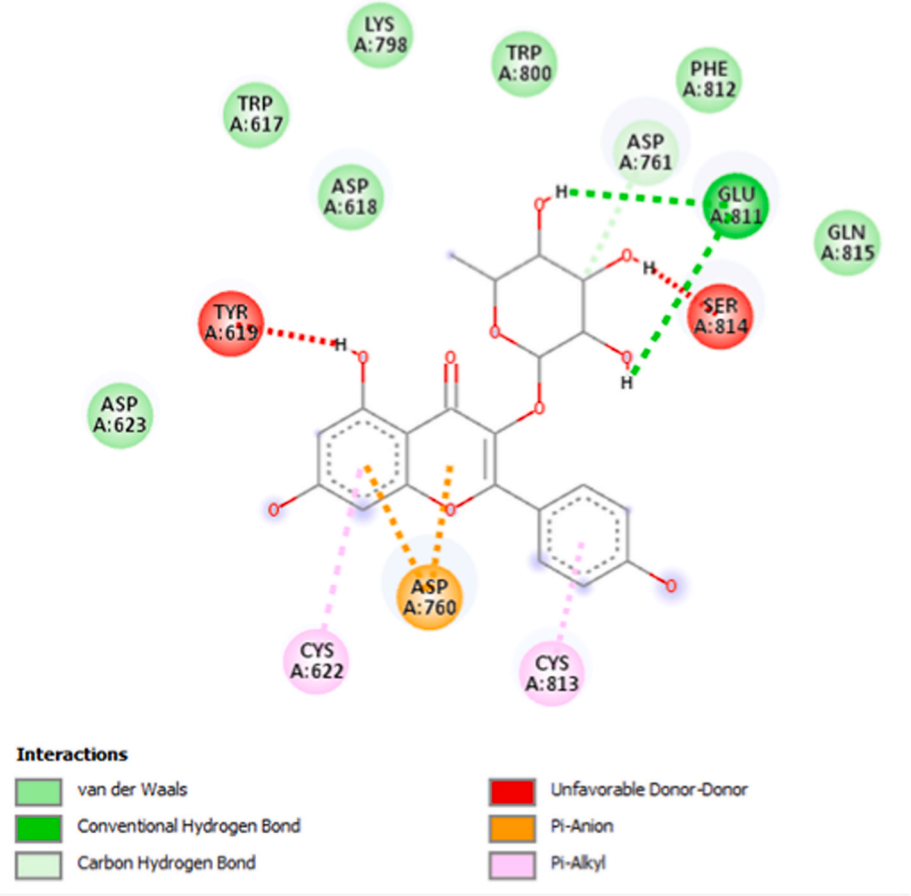

Fig. 1. Two dimensional visualization between azelin interaction with RdRp SARS-CoV-2.

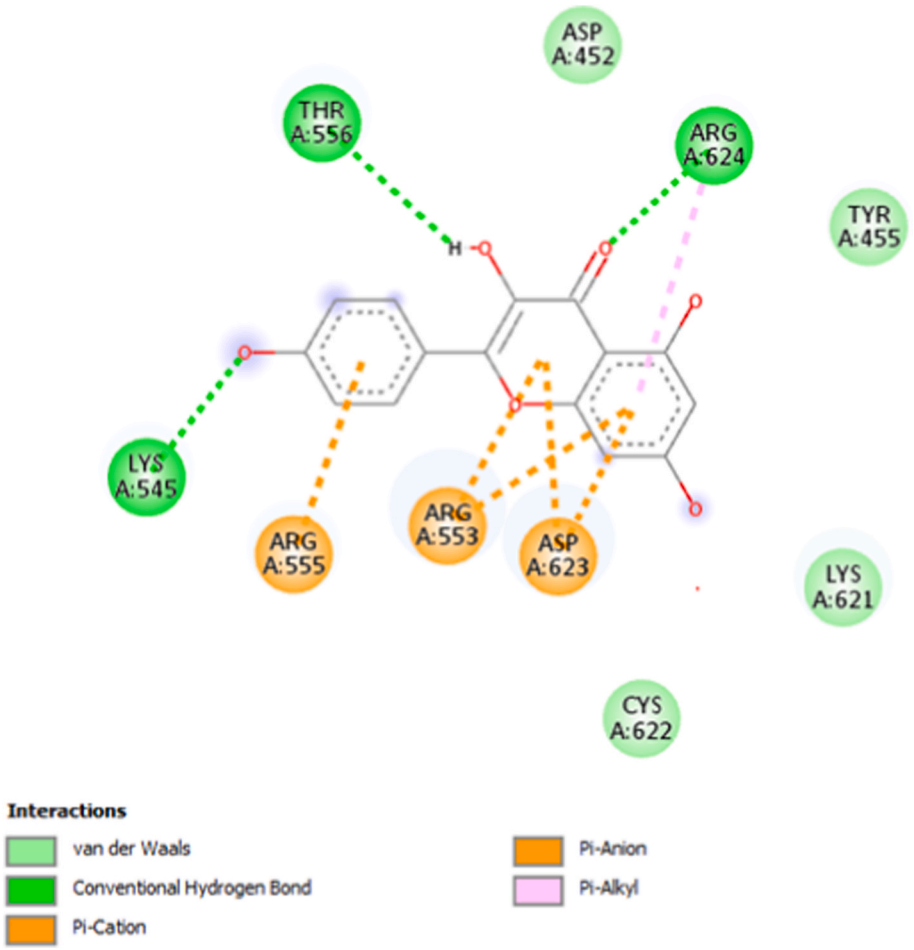

Fig. 2. Two dimensional visualization between kaempferol Interaction with RdRp SARS-CoV-2.

Table 4
Types of bonds and amino acid residues from the interaction of trifolin and RdRp SARS-CoV-2.

Compound	Type of Bonds	Amino Acid Residues
Trifolin	Conventional hydrogen bond	Arg553, Thr680, Ser759, Thr556, Asp760
	Pi-cation	Arg553, Asp623
	Pi-alkyl	Lys621
	van der Waals	Val557, Lys545, Arg555, Asn691, Thr687, Ser681, Ser682, Cys622, Tyr619

2020).

Virtual screening methods based on molecular docking have significant advantages over traditional approaches in the hunt for therapeutic compounds for pharmaceuticals. In severe scenarios, such as a pandemic, this method can provide a quick, dependable, and cost-effective method of selecting medicinal medications. Repurposing of phytochemical-based pharmaceuticals has recently demonstrated significant potential due to fewer side effects, equivalent therapeutic efficacy, and cost-effectiveness (Parihar et al., 2022). Therefore, this study aimed to investigate the potency of flavonoid derived from *Sauropus androgynus* leaves as an alternative antiviral for COVID-19 via inhibition of RdRp, which is involved in the persistence of SARS-CoV-2 replication in the host body.

2. Material and methods

2.1. Design

This in silico method used a molecular docking analysis method between the active flavonoid compounds found in katuk leaves (*Sauropus androgynus*) against the RdRp SARS-CoV-2. In addition, a molecular docking comparison was also carried out between the active compounds of flavonoids and conventional drugs, namely favipiravir, remdesvir and ribavirin.

2.2. Searching for amino acid sequence

Amino acid sequences that make up RdRp SARS-CoV-2 were obtained from The Research Collaboratory for Structural Bioinformatics Protein Data Bank database (https://www.rcsb.org). The three dimension structure of protein was downloaded in *.pdb file format

2.3. Searching for the structure of active compound

The three-dimensional structure of the flavonoid compounds of katuk leaf (*Sauropus androgynus*) was obtained from the PubChem Open Chemistry Database. The three-structure of various compounds in the *.sdf file format was then converted into *.pdb files using Avodgadro software ver 1.2.0.

2.4. Protein preparation

The three-dimensional structure of RdRp SARS-CoV-2 (PDB ID:

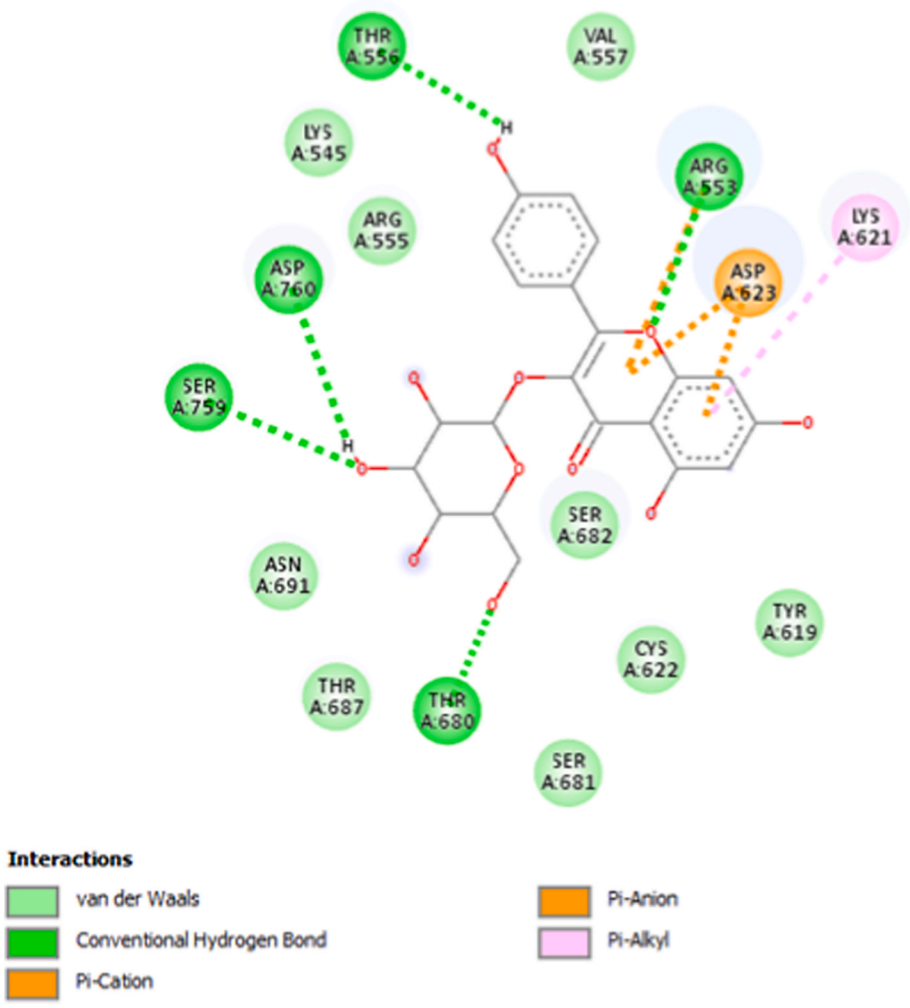

Fig. 3. Two dimensional visualization between trifolin interaction with RdRp SARS-CoV-2.

Table 5
Binding affinity (kcal/mol) interaction of flavonoid compounds and conventional drugs against RdRp SARS-CoV-2.

Flavonoid compounds and conventional drugs	Binding affinity (kcal/mol)
Flavonoid compounds:	
Afzelin	−7.677*
Kaempferol	−6.65
Trifolin	−6.906
Conventional drugs:	
Favipiravir	−5.203
Remdesivir	−6.518
Ribavirin	−6.295

Note: *the most negative interaction energy compared to other compounds.

Table 6
Types of bonds and amino acid residues from the interaction of favipiravir and RdRp SARS-CoV-2.

Drug	Type of Bonds	Amino Acid Residues
Favipiravir	Conventional hydrogen bond	Arg553, Thr556, Asp623
	Halogen	Arg624
	Pi-cation	Arg553
	Pi-anion	Asp623
	Pi-alkyl	Arg624
	van der Waals	Arg555, Asp452, Ala554, Tyr455

6M71, chain A) was prepared separately by removing water molecules, ions and cofactors present in the protein. Furthermore, the protein is edited by adding hydrogen atoms and given a charge by computing the Gasteiger. The grid box is set by focusing on the active site residues of the protein with dimensions (30 × 30 x 30) centered on (114.52, 114.11, 122.91) (Ahmad et al., 2020). Protein preparation was carried out using AutoDock Tools 1.5.7 software. Next, the file is saved in *pdbqt format for use in molecular docking

2.5. Ligand preparation

Preparation of the active compounds of katuk leaf flavonoids was carried out using the AutoDock Tools 1.5.7 software. Ligand files are saved in *pdbqt format for use in molecular docking

2.6. Molecular docking using AutoDock Vina

Docking simulations between the active compounds of katuk leaf flavonoids and target proteins were carried out using AutoDock Vina v1.2.3 software. After receptor and ligand preparation, the docking process was started using the command prompt. Docking results were then visualized with the Discovery Studio 4.1 software.

2.7. Analysis of the binding interaction between protein and ligand

The results of the docking analysis were will then be visualized using

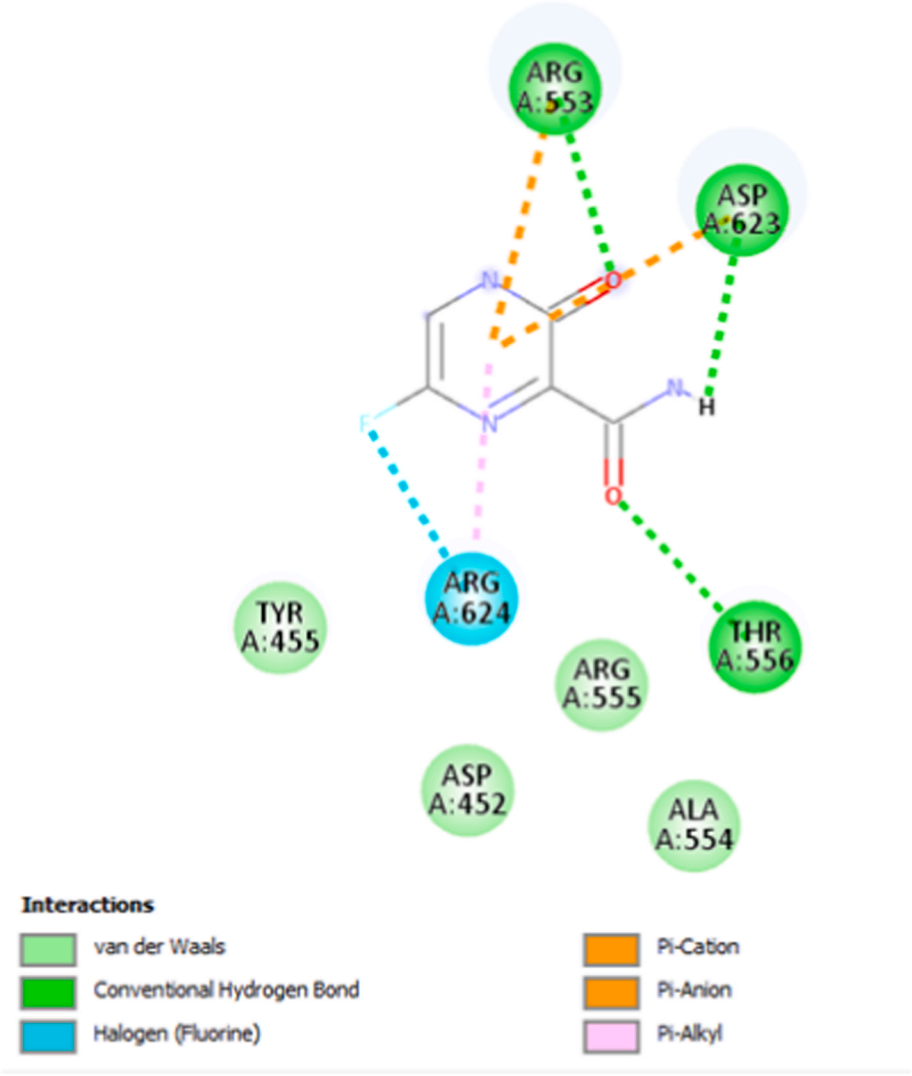

Fig. 4. Two dimensional visualization between favipiravir interaction with RdRp SARS-CoV-2.

Table 7
Types of bonds and amino acid residues from the interaction of remdesivir and RdRp SARS-CoV-2.

Drug	Type of Bonds	Amino Acid Residues
Remdesivir	Conventional hydrogen bond	Cys813, Ser814, Asp760, Trp617, Asp761
	Carbon hidrogen bond	Lys798, Glu811
	Pi-anion	Asp761
	Attractive charge	Asp618
	van der Waals	Trp800, Tyr619, Lys621, Pro620, Cys622, Ala762, Phe812, Lys551

the Discovery Studio 4.1 software. The interaction between proteins and ligands was studied to analyze the number and types of bonds, such as hydrogen, hydrophobic, and van der Waals bonds.

3. Results

3.1. Docking molecular of three flavaonoid

The binding affinity for the interaction of flavonoid compounds with the RdRp of SARS-CoV-2 was obtained from molecular docking which was carried out using AutoDock Vina v1.2.3 in command prompt. The binding affinity value taken is the one with the most negative value. The results showed that the afzelin had the most negative binding affinity among other flavonoid compounds (Table 1).

The interactions that occur between protein and ligand can be visualized in two dimensions and three dimensions using Discovery Studio 4.1 software. Two-dimensional visualization show the number of bonds, types of bonds and amino acid residues from protein and ligand interactions. The interaction that occurs between afzelin and RdRp SARS-CoV-2 has a total of 16 bonds consisting of 6 types of bonds, namely conventional hydrogen bonds, carbon-hydrogen bonds, electrostatic bonds (pi-anions), hydrophobic bonds (pi-alkyl), van de Waals and unfavorable donors. Each of the bond types has different amino acid residues as shown in Table 2. The bond types and amino acid residues in two dimensions are visualized as in Fig. 1.

The interaction that occurs between kaempferol and RdRp SARS-CoV-2 has a total of 13 bonds consisting of 5 types of bonds, namely conventional hydrogen bonds, electrostatic bonds (pi-cation and pi-anion), hydrophobic bonds (pi-alkyl), and hydrophobic bonds. van der Waals. Each of the bonds has a different amino acid residue as shown in Table 3. The types of bonds and amino acid residues in two dimensions are visualized as shown in Fig. 2.

The interaction between trifolin and RdRp SARS-CoV-2 has a total of 18 bonds consisting of 4 types of bonds, namely conventional hydrogen bonds, electrostatic bonds (pi-cation), hydrophobic bonds (pi-alkyl),

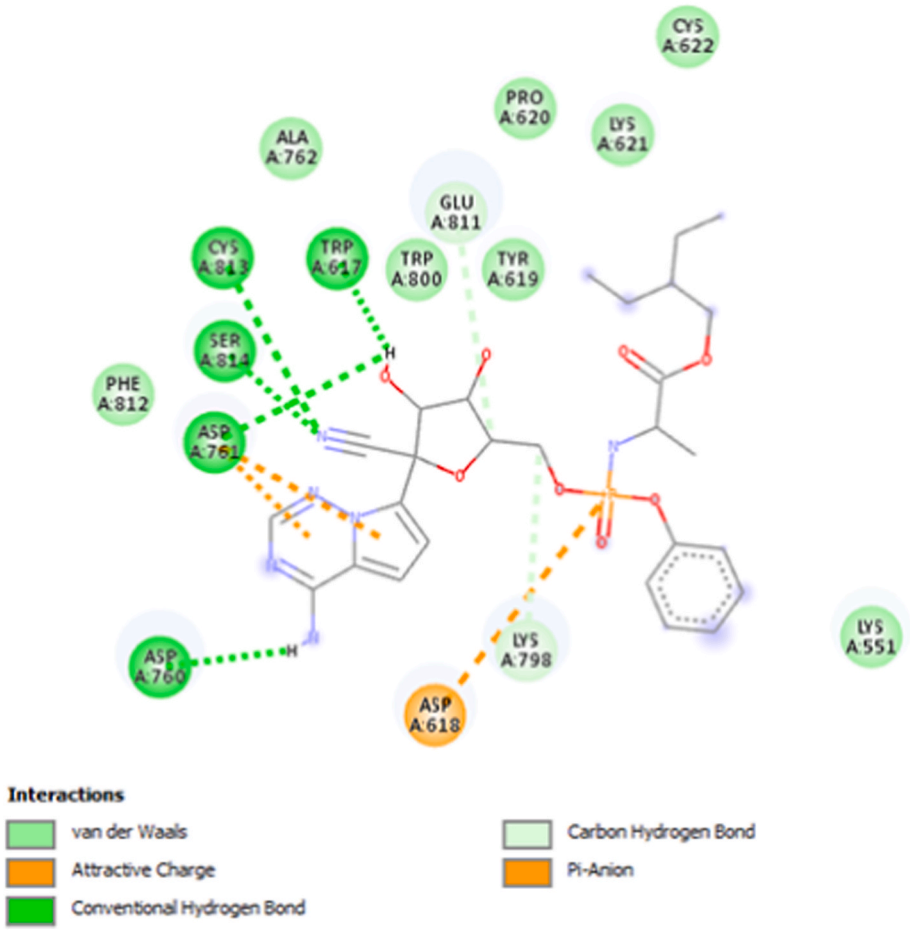

Fig. 5. Two dimensional visualization between remdesivir interaction with RdRp SARS-CoV-2.

Table 8
Types of bonds and amino acid residues from the interaction of ribavirin and RdRp SARS-CoV-2.

Drug	Type of Bonds	Amino Acid Residues
Ribavirin	Conventional hydrogen bond	Trp617, Tyr619, Asp760, Glu811
	Carbon hydrogen bond	Glu811, Asp761
	Van der Waals	Asp618, Ala762, Gly616, Lys798
	Unfavorable donor-donor	Trp800

and van der Waals forces. Each of the bonds has a different amino acid residue as shown in Table 4. The types of bonds and amino acid residues in two dimension are visualized as shown in Fig. 3.

3.2. Docking molecular flavonoid and standard drug

The ability of the flavonoid compounds in katuk leaves to inhibit the RdRp of SARS-CoV-2 can be seen from the binding affinity comparison. To find out how optimal the inhibitory activity of flavonoid compounds is, molecular docking was carried out on conventional drugs (favipiravir, remdesivir, ribavirin) with RdRp SARS-CoV-2. The results show that the three flavonoid compounds (afzelin, kaempferol, trifolin) have a more negative binding affinity than the three conventional drugs (favipiravir, remdesivir, ribavirin) as shown in Table 5.

The interaction between Favipiravir and RdRp SARS-CoV-2 has a total of 11 bonds consisting of 6 types of bonds, namely conventional hydrogen bonds, electrostatic bonds (pi-cation and pi-anion), hydrophobic bonds (pi-alkyl) and van forces. der Waals. Each of the bonds has a different amino acid residue as shown in Table 6. The types of bonds and amino acid residues in two dimensions are visualized as shown in Fig. 4.

The interaction between remdesivir and RdRp SARS-CoV-2 has a total of 21 bonds consisting of 18 types of bonds, namely conventional hydrogen bonds, carbon hydrogen bonds, electrostatic bonds (attractive-charge and pi-anions), hydrophobic bonds (pi-sigma), and van der Waals force. Each of the bonds has a different amino acid residue as shown in Table 7. The types of bonds and amino acid residues in two dimensions are visualized as shown in Fig. 5.

The interaction between ribavirin and RdRp SARS-CoV-2 has a total of 13 bonds consisting of 4 types of bonds, namely conventional hydrogen bonds, carbon hydrogen bonds, van der Waals forces and unfavorable donors. Each of the bonds has a different amino acid residue as shown in Table 8. Types of bonds and amino acid residues in two dimensions as shown in Fig. 6.

4. Discussion

According to our prior study, three flavonoid chemicals found by LC-HRMS in *Sauropus androgynus* leaves include afzelin, kaempferol, and trifolin (Makati et al., 2022). The binding affinity is one of the crucial criteria that can be seen in Table 2 to determine the stability of the connection between the ligand and the protein. According to the findings of this study, afzelin had the highest negative binding affinity (−7.677 kcal/mol) of the three flavonoid compounds studied, followed by trifolin (−6.906 kcal/mol) and kaempferol (−6.65 kcal/mol). The greater the negative value of the binding affinity, the greater the level of stability between the ligand and the receptor, resulting in a stronger relationship (Xue et al., 2022). Our findings confirmed prior study

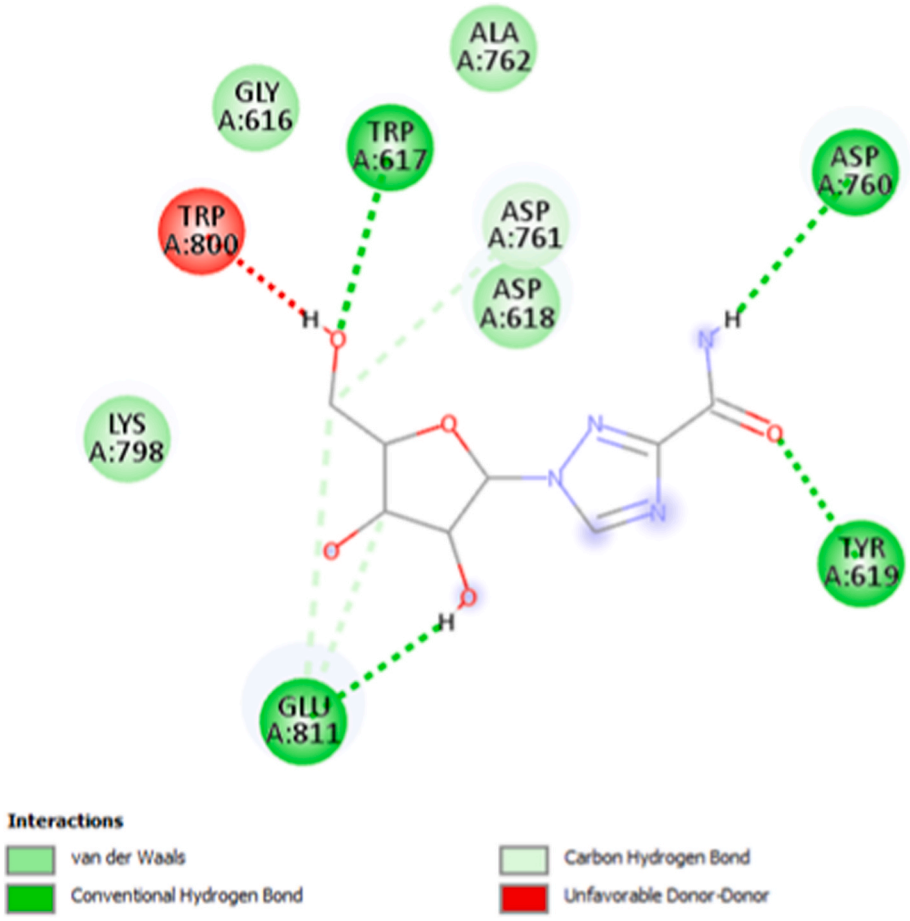

Fig. 6. Two dimensional visualization between ribavirin interaction with RdRp SARS-CoV-2.

indicating the interaction of kaempferol with RdRp SARS-CoV-2 was −6.7 kcal/mol (Singh et al., 2021).

The results of this study also show that the afzelin compound in *Sauropus androgynus* leaves consists of 6 types of bonds. Conventional hydrogen bonds on residue Glu811, carbon-hydrogen bonds on residue Asp761, pi-anion bonds on residue Asp760, pi-alkyl bonds on residues Cys622 and Cys813, van der Waals forces on residues Phe812, Trp800, Asp618, Lys798, Trp617, Asp623, Gln815 and unfavorable donors at Tyr619 and Ser814 residues (Table 3). Afzelin binds to the amino acids aspartate, namely Asp761 and Asp760 where Asp761 is a key residue on the active site of RdRp SARS-CoV-2. Previous study stated that the key residues of the active site are the adjacent amino acids aspartate, namely Asp761 and Asp762, which are involved in the actual reaction of the RdRp. Other major residues involved in the interaction include; Tyr618, Cys622, Asn691, Asn695, Met755, Ile756, Leu757, Leu758, Ser759, Asp760, Asp761, Ala762, Val763, Glu811, Phe812, Cys813 and Ser814 (Ahmad et al., 2020). The binding of the active site on the Asp761 residue indicates that afzelin has high affinity for the active site of the protein. The type of bond formed on the Asp761 residue is a carbon-hydrogen bond. The carbon-hydrogen bond is a type of hydrogen bond which is an important type of bond that makes the formation of protein-ligand complexes stronger. While the type of bond formed on the Asp760 residue is a pi-anion bond. The pi-anion bond is a relatively weak type of non-covalent bond when compared to hydrogen bonds and pi-cation (Balamurugan and Pisabarro, 2021). In addition, afzelin also binds to the amino acid Glu811, which is one of the amino acid residues in the palm domain involved in RdRp polymerase activity (Faisal et al., 2022). The type of bond formed in the Glu811 residue is a conventional hydrogen bond. In addition, RdRp polymerase domain of SARS-CoV-2 consists of three subdomains. Subdomain fingers with a range of amino acid residues L366-A581 and K621-G679. Palm subdomain with amino acid residue ranges from T582-P620 and &680-Q815. The thumb subdomain with amino acid residue ranges from H816–Y920 (Gao et al., 2020).

The interaction that forms between the kaempferol compound in katuk leaves and RdRp SARS-CoV-2 consists of 5 types of bonds. Conventional hydrogen bonds on residues Lys545, Arg624 and Thr556, pi-cation bonds on residues Arg553 and Arg555, pi-anion bonds on residues Asp623, pi-alkyl bonds on residues Arg624 and van der Waals forces on residues Asp542, Tyr455, Cys622, Lys621 (Table 4). All of these amino acid residues are domain finger residues. The domain fingers are domains for the attachment of extra Nsp8 subunits that play a critical role in RdRp activity (Kirchdoerfer and Ward, 2019). Cooperative motion of the NiRAN domain with the core (fingers) domain of RdRp may increase the RdRp activity (Itoh et al., 2021).

There are four sorts of linkages that occur between the trifolin component in *Sauropus androgynus* leaves and the RdRp of SARS-CoV-2. Conventional hydrogen bonding on Arg553, Thr680, Ser759, Thr556, Asp760 residues (Table 5). The Asp760 residue is a critical residue in the palm domain that is crucial in RdRp polymerase activity (Ahmad et al., 2020). The palm domain has Thr680 and Ser759 residues, while the fingers domain contains Arg553 and Thr556 residues. Furthermore, pi-cation bonds are formed between residues Arg553 and Asp623 in the fingers domain, pi-alkyl bonds are formed between residues Lys621 in the fingers domain, and van der Waals forces are formed between residues Val557, Lys545, Arg555, Asn691, Thr687, Ser681, Ser682, Cys622, Tyr619.

The binding affinity value indicates the capacity of *Sauropus androgynus* flavonoid compounds to inhibit RdRp SARS-CoV-2. To determine how effective flavonoid compounds are in inhibiting SARS-CoV-2,

molecular docking was performed on conventional medications (favipiravir, remdesivir, ribavirin) with the RdRp target protein of SARS-CoV-2. Remdesivir is a nucleoside analogue that inhibits RdRp and has broad-spectrum antiviral activity (Zhang and Tang, 2021; Jeans et al., 2020; Dong et al., 2020). Ribavirin is a guanosine analogue antiviral medication that has been used to treat a variety of viral infections (Zhang and Tang, 2021). In cells, favipiravir is phosphoribosylated to its active form, favipiravir-RTP, which is recognized by RdRp as a purine nucleotide and inhibits RdRp enzyme activity (Dong et al., 2020; Furuta et al., 2017). The interaction between remdesivir and fafipiravir is through the "bucket brigade" at lysine residues (Tanimoto et al., 2021).

According to the binding affinity comparison data, the three conventional medications had lower negative binding affinities than the three *Sauropus androgynus* leaf flavonoid compounds (Table 6). The more the negative the binding affinity value, the greater the amount of stability between the ligand and the receptor, resulting in a stronger relationship (Makati et al., 2022). Among the six flavonoid molecules, afzelin had the most negative binding affinity (−7.677 kcal/mol). When compared to the standard medications favipiravir and ribavirin, remdesivir has the lowest binding affinity (−6518 cal/mol). This demonstrates that flavonoid compounds found in *Sauropus androgynus* have a high affinity for the active site of RdRp SARS-CoV-2 when compared to routinely used medicines (remdesivir, ribavirin, favipiravir).

5. Conclusions

The flavonoid chemicals contained in katuk leaves (afzelin, kaempferol, and trifolin) were discovered to have a high affinity for the SARS-CoV-2 RdRp when compared to the standard medicines favipiravir, remdesivir, and ribavirin. This study can serve as a foundation for future research on katuk leaves, which can be used as herbal medication or supplemental medicine to treat COVID-19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Adzdzakiy, M.A., Sutarno, S., Asyifa, I.Z., Sativa, A.R., Fiqri, A.R.A., Fibriani, A., et al., 2023. SARS-CoV-2 genetic variation and bacterial communities of nasoropharyngeal samples in middle-aged and elderly COVID-19 patients in West Java, Indonesia. J. Taibah Univ. Med. Sci. 19 (1), 70–81.

Ahmad, J., Ikram, S., Ahmad, F., Rehman, L.U., Mushtaq, M., 2020. SARS-CoV-2 RNA Dependent RNA polymerase (RdRp) – a drug repurposing study. Heliyon 6 (7).

Andarwulan, N., Batari, R., Sandrasari, D.A., Volling, B., Wijaya, H., 2010. Flavonoid content and antioxidant activity of vegetables from Indonesia. Food Chem. 121 (4), 1231–1235.

Arifin, D., 2020. Presiden Tetapkan Covid-19 Sebagai Bencana Nasional. Badan Nasional Penanggulangan Bencana (BNPB) [cited 2020 May, 25]; Available from URL. https://bnpb.go.id/berita.

Balamurugan, K., Pisabarro, M.T., 2021. Stabilizing role of water solvation on anion-π interactions in proteins. ACS Omega 6 (39), 25350–25360.

Bose, R., Kumar, M.S., Manivel, A., Mohan, S.C., 2018. Chemical constituents of sauropus androgynus and evaluation of its antioxidant activity. Res. J. Phytochem. 12 (1), 7–13.

Bunawan, H., Bunawan, S.N., Baharum, S.N., et al., 2015. Sauropus androgynus (L.) Merr. induced bronchiolitis obliterans: from botanical studies to toxicology. Evid. Based Complement. Alternat. Med. 2015, 714158.

Dong, Hu, s, Gao, J., 2020. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov. Ther. 14 (1), 58–60.

Faisal, S., Lal Badshah, S., Kubra, B., et al., 2022. Computational study of sars-cov-2 rna dependent rna polymerase allosteric site inhibition. Molecules 27 (1).

Funk, C.D., Laferriere, C., Ardakani, A., 2020. A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. Front. Pharmacol. 11, 937. https://doi.org/10.3389/fphar.2020.00937.

Furuta, Y., Komeno, T., NakamuRA, T., 2017. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 93 (7), 449–463.

Gao, Y., Yan, L., Huang, Y., Liu, F., Zhao, Z., Cao, L., et al., 2020. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science 368 (6492), 779–782.

Habib, H., Prabowo, Y., Sulistio, S., Mulyana, R.M., Albar, I.A., 2023. The association of the COVID-19 outbreak with in-hospital mortality: a single-centre study from Indonesia. Clin. Epidemiol. Global Health 20, 101219.

Hashemian, S.M.R., Pourhanifeh, M.H., Hamblin, M.R., Shahrzad, M.K., Mirzaei, H., 2022. RdRp inhibitors and COVID-19: is molnupiravir a good option? Biomed. Pharmacother. 146, 112517.

Itoh, S.G., Tanimoto, S., Okumura, H., 2021. Dynamic properties of SARS-CoV and SARS-CoV-2 RNA-dependent RNA polymerases studied by molecular dynamics simulations. Chem. Phys. Lett. 778, 138819.

Jeans, S.S., Lee, P.I., Hsueh, P.R., 2020. Treatment options for COVID-19: the reality and challenges. J. Microbiol. Immunol. Infect. 53 (3), 436–443.

Kirchdoerfer, R.N., Ward, A.B., 2019. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. Nat. Commun. 10, 2342.

Li, P.T., Chiu, H., MA, et al., 2008. Euphorbiaceae. In: Wu, Z.Y., Rave, P.H., Hong, D.Y. (Eds.), Flora of China, vol. 11. Missouri Botanical Garden Press, Beijing, China, pp. 163–314. St. Louis: Mosby, USA: Science Press.

Lubis, R., Satria, F.B., Zaki, R.A., Nurjazuli, N., Hendrat, L.Y., 2022. Factors influencing the COVID-19 pandemic situation in Indonesia, Malaysia and Taiwan in 2021. Publ. Health Practice 4, 100311.

Makati, A.C., Ananda, A.A., Putri, J.A., Amellia, S.F., Setiawan, B., 2022. Molecular docking of ethanol extracts of katuk leaf (*Sauropus androgynus*) on functional proteins of severe acute respiratory syndrome coronavirus 2. South Afr. J. Bot. 149, 1–5.

Moore, J.P., Offit, P.A., 2021. SARS-CoV-2 vaccines and the growing threat of viral variants. JAMA 325 (9), 821–822.

Parihar, A., Sonia, Z.F., Akter, F., Ali, A., Hakim, F.T., Hossain, S., 2022. Phytochemicals-based targeting RdRp and main protease of SARS-CoV-2 using docking and steered molecular dynamic simulation: a promising therapeutic approach for Tackling COVID-19. Comput. Biol. Med. 145, 105468.

Putera, P.B., Widianingsih, I., Ningrum, S., Suryanto, S., Rianto, Y., 2022. Overcoming the COVID-19 pandemic in Indonesia: a Science, technology, and innovation (STI) policy perspective. Health Pol. Technol. 11, 100650.

Russo, M., Moccia, S., Spagnuolo, C., Tedesco, I., Russo, G.L., 2020. Roles of flavonoids against coronavirus infection. Chem. Biol. Interact. 328, 109211 https://doi.org/10.1016/j.cbi.2020.109211.

Singh, S., Sk, M.F., Sonawane, A., Kar, P., Sadhukan, S., 2021. Plant-derived natural polyphenols as potential antiviral drugs against SARS-CoV-2 via RNA-dependent RNA polymerase (RdRp) inhibition: an in-silico analysis. J. Biomol. Struct. Dyn. 39 (16), 6249–6264.

Tanimoto, S., Itoh, S.G., Okumua, H., 2021. 'Bucket brigade'' using lysine residues in RNAdependent RNA polymerase of SARS-CoV-2. Biophys. J. 120, 3615–3627.

Wu, C.R., Yin, W.C., Jiang, Y., Xu, H.E., 2022. Structure genomics of SARS-CoV-2 and its Omicron variant: drug design templates for COVID-19. Acta Pharm. Sin. 43, 3021–3033.

Xue, Q., Liu, X., Russell, P., Li, J., Pan, W., Fu, J., Zhang, A., 2022. Evaluation of the binding performance of flavonoids to estrogen receptor alpha by Autodock, Autodock Vina and Surflex-Dock. Ecotoxicol. Environ. Saf. 233.

Yi, S., Guk, G., Kim, H., Lee, K.S., Lim, E.K., Kang, T., 2023. RdRp activity test using CRISPR/Cas13a enzyme (RACE) for screening of SARS-CoV-2 inhibitors. Sensor. Actuator. B Chem. 399, 134748.

Zhang, B.D., Cheng, J.X., Zhang, C.F., Bai, Y.D., et al., 2020. *Sauropus androgynus* L. Merr.-A phytochemical, pharmacological and toxicological review. J. Ethnopharmacol. 257, 112778 https://doi.org/10.1016/j.jep.2020.112778.

Zhang, Y., Tang, L.V., 2021. Overview of targets and potential drugs of SARS-CoV-2 according to the viral replication. J. Proteome Res. 20 (1), 49–59.

Task Force COVID-19, 2021. Perkembangan Kasus Per-Hari (Grafik Gabungan) [Internet]. Peta Sebaran [cited 2021 Aug 8]. Available from: https://COVID19.go.id/peta-sebaran.