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In Silico Investigation of Phytoconstituents as Inhibitor Candidate from Indonesian Medicinal Plants against Sars-CoV2 3CL^{pro}, PL^{pro}, and RdRp Protein

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Recently the COVID-19 pandemic, which was driven by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented humanity with significant health and financial challenges globally. Because a successful medication for the treatment of COVID-19 has not yet been discovered, the quest for medications to treat the disease has continued up until the present time. In today's world, a growing number of people are turning to the healing properties of medicinal plants rather than turning to man-made pharmaceuticals. These natural remedies have less negative side effects than their synthetic counterparts. Thus, the purpose of the study was to assess the antiviral activity of bioactive compounds derived from diverse medicinal plants against Sars-CoV2 by focusing on multiple critical biomarkers, including as 3CL^{pro}, PL^{pro}, and RdRp. The search for potential drug candidates was conducted through *in silico* approaches. On the basis of Lipinski's rule of five, a drug-likeness screen was conducted on active compounds. Prior to the step of molecular docking, chemicals and protein targets are optimised. Several indicators, including binding affinity score, 3D and 2D visualisation of ligand position, chemical interaction, and amino acid residues, are used to visualise and analyse the results of molecular docking to assess their quality and potential as therapeutic candidates for protein targets. In this study, we demonstrated several bioactive compounds from Indonesian medicinal plants such as common bean (*Phaseolus vulgaris*), black tea (*Camelia sinensis*), clove (*Syzygium aromaticum*), and black pepper (*Piper ningrum*) have great potency as antiviral drug candidate against SARS-CoV2 3CL^{pro}, PL^{pro}, and RdRp protein. Interestingly, we found eight compounds from top ten list that interacts to 3CL^{pro}, PL^{pro}, and RdRp protein at the same time and condition, including theaflavin-3.3′-digallate, ledene, eugeniin, kahweol, β-elemene, γ-elemene, β-selinene, and γ-selinene. Thus, this study provided the preliminary basis for drug devopment for COVID19 treatments.

Keywords: 3CL^{pro}; medicinal plants; PL^{pro}; RdRp; SARS-CoV2

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I. INTRODUCTION

Recently the COVID-19 pandemic, which was driven by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented humanity with significant health and financial challenges globally (Zhou *et al.*, 2020). The clinical signs and severity of SARS-CoV-2 infection greatly depend on many factors. Most of the remaining affected patients only display influenza-like symptoms, such as a fever, cough, sore throat, runny nose, weakness, myalgia, headache, conjunctivitis, hemoptysis, olfactory and taste dysfunction, and diarrhoea (Whitcroft & Hummel, 2020). Several factors, such as the age distribution of a nation and the detection rate, may have played a significant part in defining the current case-fatality rates because it has been demonstrated that age and comorbidities significantly impact mortality risk. Factors such as how cases are recorded, including the healthcare systems and mitigation measures, could influence the current case-fatality rates (Iosa *et al.*, 2020; Boccia *et al.*, 2020; Meyerowitz-Katz & Merone, 2020).

Importantly massive studies revealed that the SARS-CoV-2 genomic had been found in every clinical specimen, including blood, stool, bronchoalveolar lavage fluid, sputum, fibro bronchoscope brush biopsy, nasopharyngeal swabs, and ocular fluid (Wang *et al.*, 2020; Colavita *et al.*, 2020; Backer *et al.*, 2020). However, recent studies have shown that interaction and inhalation droplets are the primary means of spreading the virus from infected persons (Huang *et al.*, 2020; Liu *et al.*, 2020; Chan *et al.*, 2020). Positive-sense single-stranded RNA viruses with an envelope make up the family Coronaviridae. SARS-CoV-2 is a group of highly pathogenic CoVs belonging to the Betacoronavirus genus, group 2 (Gorbalenya, 2020). The SARS-CoV-2 genome sequence is 80% identical to that of SARS-CoV and 50% identical to that of MERS-CoV (Zhou, 2020; Lu, 2020). Its genome contains 14 open reading frames (ORFs), of which 16 nonstructural proteins (nsp 1–16) are encoded by two-thirds (Lu, 2020; Zhang, 2020). Spike (S), envelope (E), membrane (M), and nucleocapsid (N), four structural proteins, and nine auxiliary proteins (ORF) are encoded by the remaining one-third (Perlman & Netland, 2009). Spike mediates SARS-CoV entrance into host cells (Harrison *et al.*, 2020).

Individual nonstructural proteins (nsps) are generated as a result of the proteolytic processing of these two viral polyproteins by two viral cysteine proteases known as the coronavirus main protease ($3CL^{pro}$; nsp5) and the papain-like protease (PL^{pro}; nsp3). These nsps are then utilised to form complexes with host membrane components. As a result of the fact that the catalytic activities of $3CL^{pro}$ and PL^{pro} are necessary for viral replication, inhibition of these enzymes is an appealing technique for treating viral infections (Shen *et al.*, 2022; Thiel *et al.*, 2003). Further, coronavirus replication and transcription are dependent on an enzyme called RNA-dependent RNA polymerase (RdRp), which is found in nsp12. This enzyme is essential to the replication and transcription process. Therefore, the RdRp is a significant target for antiviral medication (Wang *et al.*, 2020).

Current antiviral medications have failed to combat the COVID-19 pandemic effectively, and we are now learning that it is important to proactively develop new antiviral agents to combat future outbreaks of this and other zoonotic viruses (Shen *et al.*, 2022). At this point, researchers are still looking for possible therapies for COVID-19. The desperation that has spread throughout the community, particularly among the middle-income and low-income groups that the economic impact of forced lockdowns has deeply hit, has led to an increased interest in researching alternate possibilities of medicinal plant-based therapies (Lim *et al.*, 2021). In Indonesia, several medicinal plants are widely used not only for the source of foods, but also the plants used for spices, fragrance, and traditional ceremony. Medicinal plants used in this study are the typical plants that widely used as food source or spices which in term the plants ease to find. Due to their therapeutic potency, the medicinal plants contain valuable substances including saponins, alkaloids, and phenolic compounds that exerts the anticancer (Putra *et al.*, 2020; Putra, 2018), antidiabetic (Widiastuti *et al.*, 2023; Sari *et al.*, 2023; Ashar *et al.*, 2023), antiinflamation (Putra *et al.*, 2019), and antiviral potency (Hidayatullah *et al.*, 2021; Hidayatullah *et al.*, 2020). Thus, the aim of study was to evaluate the potential of bioactive compounds from multiple medicinal plants for anti-viral

against Sars-CoV2 by targeting numerous pivotal biomarkers including $3CL^{pro}$, PL^{pro}, and RdRp.

II. MATERIALS AND METHODS

A. Ligand 2D Structure Retrieval

In the study, there were references to around thirty different plant species. The purpose of the study was to investigate the antiviral activity of each bioactive constituent found in these plants. Herbs and spices that are plentiful in the area are typically the kind of plants that are utilised for this purpose. Their common and Latin names are provided for all of the thirty plant species (Figure 1).

Afterwards, the chemical structures of a variety of active chemicals that were derived from the aforementioned thirty plants were collected. Using PubChem (https://pubchem.ncbi.nlm.nih.gov/), we were able to get the chemical structures of the active chemicals. Then after, the chemical structure that was obtained is saved in sdf format, which makes it compatible for molecular docking tools to read (Hidayatullah *et al.*, 2022; Putra *et al.*, 2017).

- ❑ wijen (*Sesamum indicum*)
- ❑ vanili (*Vanilia planifolia*)
- ❑ ubi (*Ipomoea batatas*)
- ❑ teh hitam (*Camelia sinensis*)
- ❑ talas (*Colocasia esculenta*)
- ❑ serai (*Cymbopogon citratus*)
- ❑ saffron (*Crocus sativus*)
- ❑ pala (*Myristica fragrans*)
- ❑ lengkuas (*Alpinia galanga*)
- ❑ lada (*Piper ningrum*)
- ❑ kluwek (*Pangium edule*)
- ❑ ketumbar (*Coriandrum sativum*)
- ❑ kencur (*Kaempferia galanga*)
- ❑ kemukus (*Piper cubeba*)
- ❑ kemiri (*Aleurites moluccanus*)
- ❑ kelor (*Moringa oleifera*)
- ❑ kedelai (*Glycine max*)
- ❑ kayu secang (*Caesalpinia sappan*)
- ❑ kayu manis (*Cinnamomum burmannii*)
- ❑ kapulaga (*Amomum compactum*)
- ❑ kacang hijau (*Phaseolus vulgaris*)
- ❑ jinten (*Plectranthus amboinicus*)
- ❑ jahe (*Zingiber officinale*)
- ❑ daun salam (*Syzygium polyanthum*)
- ❑ cengkeh (*Syzygium aromaticum*)
- ❑ bunga lawang (*Illicium verum*)
- ❑ beras hitam (*Oryza sativa*)
- ❑ asam jawa (*Tamarindus indica*)
- ❑ andaliman (*Zanthoxylum acanthopodium*)
- ❑ adas (*Foeniculum vulgare*)

Figure 1. The various medicinal plants list used in this study.

B. Drug Likeness Screening

Each collected chemical structure is saved as an SDF file and then analysed for its chemical properties and drug-likeness using the web server http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp. Drug likeness screening was carried out by applying the Lipinski rule of five. Each compound that complies with the Lipinski rule's will then be included in the molecular docking stage of the target protein (Hidayatullah *et al.*, 2023).

C. Protein 3D Structure Modelling

Three protein targets were used in this study: $3CL^{pro}$, PL^{pro}, and RdRp protein. The 3D structure of each protein was modeled using the SWISS-MODEL webserver (https://swissmodel.expasy.org/). In detail, the $3CL^{pro}$ protein has a template code of 5b60.1.B with a sequence similarity percentage of 93.99%. Meanwhile, the PL^{pro} protein uses the 7nfv.1.A template with a sequence similarity of up to 100%. Finally, the RdRp protein has a template code of 7aap.1.A and has a sequence similarity of up to 100%.

D. Molecular Docking and Visualisation

Molecular docking was performed just after active compounds and protein targets from each plant have been prepared and optimised. Molecular docking was done using PyRx software (https://pyrx.sourceforge.io/). The docking coordinates used for $3CL^{pro}$ protein were X: -17.864; Y: 0.4026; and Z: -14.3001, while the dimensions (angstroms) used were: X: 49.1904; Y: 73.7093; and Z: 48.0433. The coordinates of the PL^{pro} protein were: X: 37.0321; Y: 9.4947; and Z: 16.1767, while the dimensions (angstrom) were: X: 66.0924; Y: 56.9546; and Z: 68.8459. Finally, the docking coordinates for the RdRp protein were: X: 107.654; Y: 102,968; and Z: 99.2821, and the dimensions (angstroms) used were: X: 95.7011; Y: 81.3354; and Z: 88.3253.

E. Data Visualisation and Data Analysis

Molecular docking results in the form of ligand and protein complexes were then visualised using PyMOL (https://pymol.org/2/) and LigPlot+ software (https://www.ebi.ac.uk/thornton-srv/software/LigPlus/). Furthermore, several data were obtained showing parameters including binding affinity score, 3D and 2D visualisation - ligand position, chemical interaction, and amino acid residues, which determine the quality and prospects for developing drug candidates against protein targets (Heikal *et al.*, 2023; Putra *et al.*, 2023).

III. RESULTS AND DISCUSSION

In this current study, we demonstrated that the top ten binding affinity score from multiple plants bioactive compounds against $3CL^{pro}$ protein included kahweol, theaflavin-3,3′-digallate, eugeniin, tannic acid, ledene, thearubigin, γ-elemene, β-elemene, β-selinene, and γ-selinene (Figure 2). Meanwhile, due to its binding affinity toward target proteins, potential active compounds can be used for the target protein in the form of PL^{pro}. These compounds include cafestol, β-elemene, theaflavin-3,3′-digallate, kahweol, β-selinene, γ-selinene, γ-elemene, ledene, eugeniin, and sesamin (Figure 3).

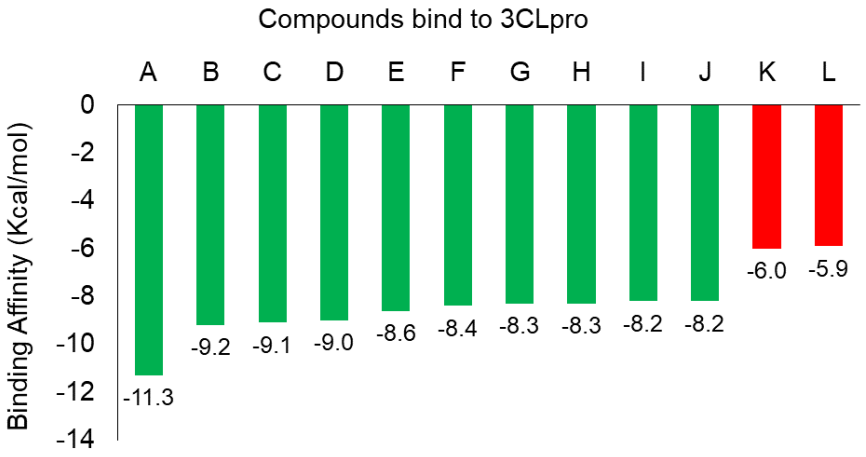

Figure 2. The binding's affinity result of multiple plants bioactive compounds and control drugs toward the $3CL^{pro}$ protein. (A). Kahweol; (B). Theaflavin-3,3′-digallate; (C). Eugeniin; (D). Tannic acid; (E). Ledene; (F). Thearubigin; (G). γ-Elemene; (H). β-elemene; (I). β-selinene; (J). γ-Selinene; (K). Arbidol; and (L). Chloroquine.

In addition, putative active chemicals were derived from the target protein in the form of RdRp. These compounds include cafestol, kahweol, eugeniin, ledene, β-selinene, γ-selinene, γ-elemene, β-elemene, theaflavin-3,3′-digallate, and tannic acid (Figure 4). It is interesting to note that when compared to the two control medications that were employed, namely arbidol and chloroquine, the binding affinity values of the top 10 active compounds displayed a propensity for a higher preference. This indicates a higher likelihood of the active chemical interacting effectively with the target protein's active site.

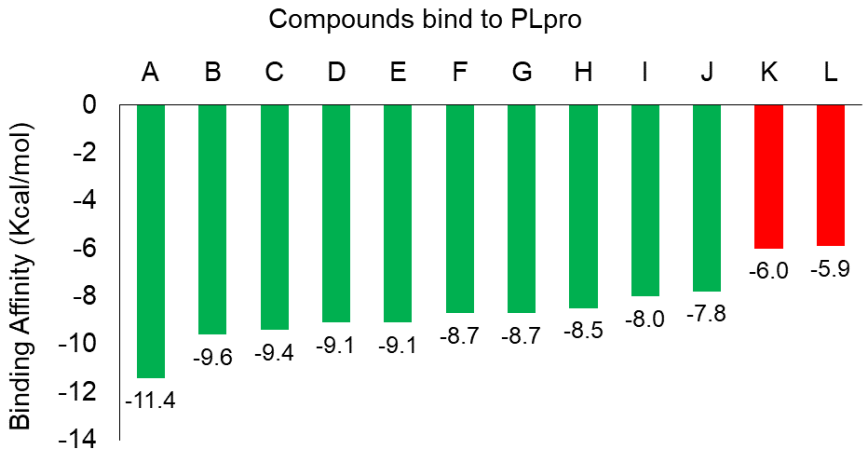

Figure 3. The binding's affinity result of multiple plants bioactive compounds and control drugs toward the PL^{pro} protein. (A). Cafestol; (B). β-elemene; (C). Theaflavin-3,3′-digallate; (D). Kahweol; (E). β-selinene; (F). γ-Selinene; (G). γ-Elemene; (H). Ledene; (I). Eugeniin; (J). Sesamin; (K). Arbidol; and (L). Chloroquine.

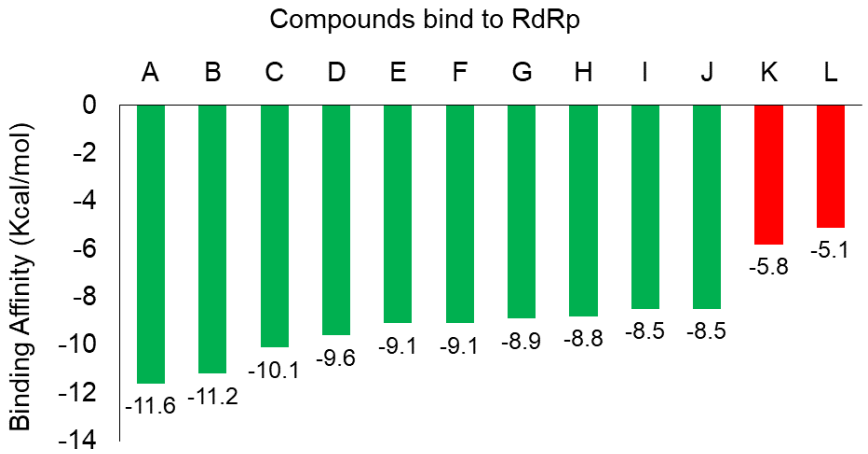

Figure 4. The binding's affinity result of multiple plants bioactive compounds and control drugs toward the RdRp protein. (A). Cafestol; (B). Kahweol; (C). Eugeniin; (D). Ledene; (E). β-selinene; (F). γ-Selinene; (G). γ-Elemene; (H). β-elemene; (I). Theaflavin-3,3′-digallate; (J). Tannic acid; (K). Arbidol; and (L). Chloroquine.

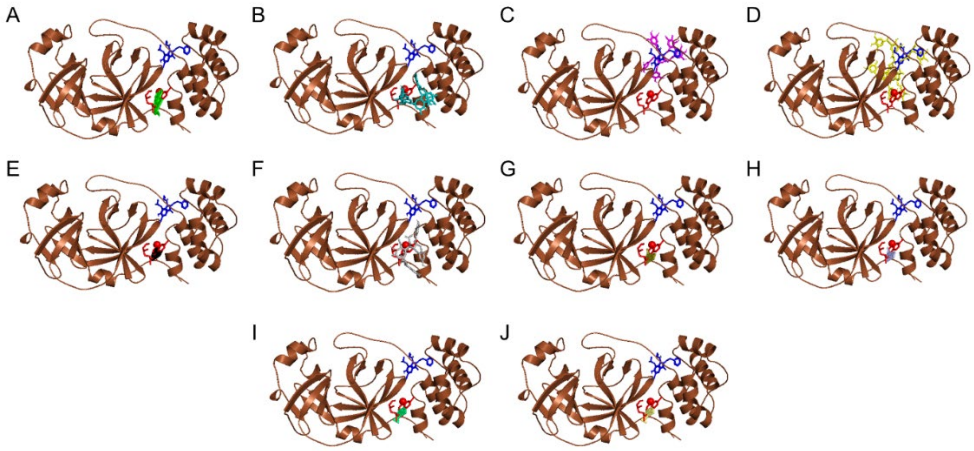

Figure 5. The 3D structure visualisation of multiple plants bioactive compounds and control drugs toward the $3CL^{pro}$ protein. (A). Kahweol and control drugs; (B). Theaflavin-3,3′-digallate and control drugs; (C). Eugeniin and control drugs; (D). Tannic acid and control drugs; (E). Ledene and control drugs; (F). Thearubigin and control drugs; (G). γ-Elemene and control drugs; (H). β-elemene and control drugs; (I). β-selinene and control drugs; and (J). γ-Selinene and control drugs.

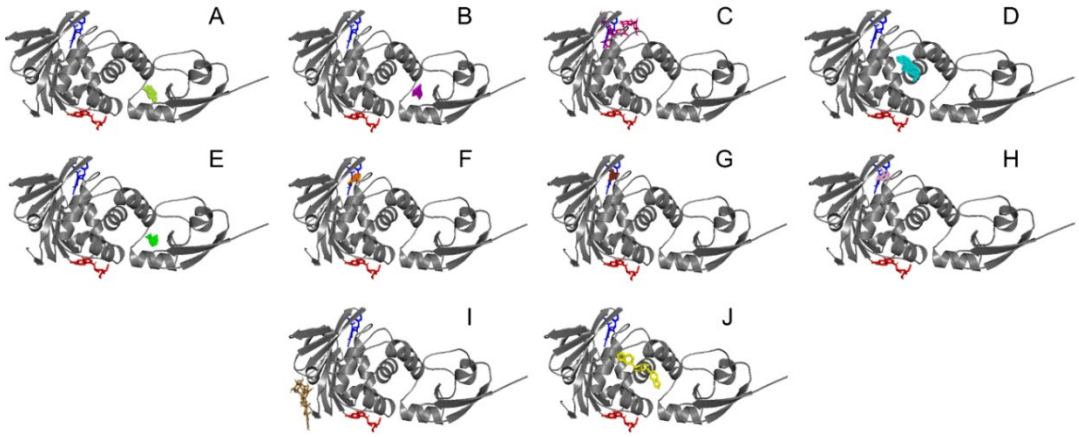

Figure 6. The 3D structure visualisation of multiple plants bioactive compounds and control drugs toward the PLpro protein. (A). Cafestol and control drugs; (B). β-elemene and control drugs; (C). Theaflavin-3,3′-digallate and control drugs; (D). Kahweol and control drugs; (E). β-selinene and control drugs; (F). γ-Selinene and control drugs; (G). γ-Elemene and control drugs; (H). Ledene and control drugs; (I). Eugeniin and control drugs; (J). and Sesamin and control drugs.

Another cause for concern is the proximity of the ligand to the drug control at the binding site of each protein, CL^{pro} (Figure 5), PL^{pro} (Figure 6), and RdRp (Figure 7). These findings suggest that the active molecule shares the same binding locations and interactions as the standard control medication. In addition, the types of chemical interactions and amino acid residues involved in the interaction of the ligand-protein complexes CL^{pro} (Figure 8), PL^{pro} (Figure 9), and RdRp (Figure 10) must be addressed while searching for potential therapeutic candidates.

In general, two different sorts of interactions might occur during the ligand's interaction with the protein complex. These two forms of interaction are known as hydrophobic interaction and hydrogen bonding. In addition, many amino acid residues characterise the bonds between the ligand-protein complexes for each target protein, CL^{pro} (Table 1), PL^{pro} (Table 2), and RdRp (Table 3). The chemical interaction among the proteins and the ligands, for example small compounds or drug, is important for living cell networks or communication (Zhou & Zhong, 2017). The interaction among the ligands and the amino acid residues also can determine the binding affinity of the complex (Hughes *et al.*, 2011). The common bean (*Phaseolus vulgaris*), black tea (*Camellia sinensis*), clove (*Syzygium aromaticum*), and black pepper (*Piper ningrum*) are the sources of three of the most important active chemicals that have the ability to serve as inhibitors of protein targets. In addition, as a result of the findings of this research, eight active compounds were identified as having the potential to act as inhibitor candidates on three different protein targets simultaneously. These eight compounds include theaflavin-3.3′-digallate, ledene, eugeniin, kahweol, β-elemene, γ-elemene, β-selinene, and γ-selinene (Figure 11).

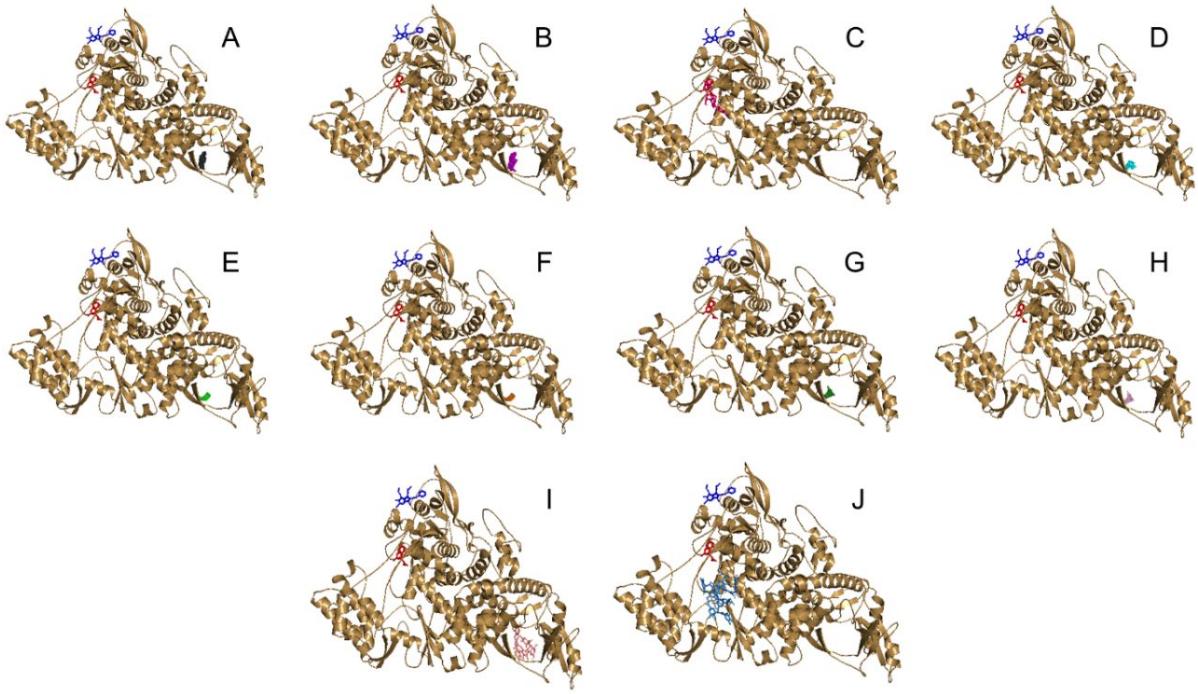

Figure 7. The 3D structure visualisation of multiple plants bioactive compounds and control drugs toward the RdRp protein. (A). Cafestol and control drugs; (B). Kahweol and control drugs; (C). Eugeniin and control drugs; (D). Ledene and control drugs; (E). β-selinene and control drugs; (F). γ-Selinene and control drugs; (G). γ-Elemene and control drugs; (H). β-elemene and control drugs; (I). Theaflavin-3,3′-digallate and control drugs; and (J). Tannic acid and control drugs.

In spite of the fact that intensive research operations are still being carried out, no treatments that are effective against SARS-CoV-2 have yet been reached. This is despite the creation of effective vaccines or medicinal compounds currently being worked on (Salata *et al*., 2019). Interferon therapies, monoclonal antibodies, oligonucleotide-based treatments, peptides, small-molecule drugs, and vaccines are considered key strategies for managing or preventing COVID-19 (Wilder-smith *et al*., 2020; Li & De Clercq, 2020). Existing medications have the potential to be employed as the initial treatment for coronavirus epidemics; nevertheless, this is not the optimal strategy for completely eliminating the disease (Andersen *et al*., 2020). Consequently, substantial effort has been dedicated to researching and developing therapeutic drugs to treat the COVID-19 outbreak. In contrast, testing drug combinations experimentally can be expensive and time-consuming, whereas computational analysis can quickly generate testable hypotheses for systematic drug combinations (Zhou *et al*., 2020; Bhuiyan *et al*., 2020).

Since ancient times, natural products have been used extensively in home treatments, over-the-counter medications, and as raw materials for the production of several medicines, cosmeceuticals, and nutraceuticals (Fathy *et al*., 2016; Ashour *et al*., 2018). They offer a natural treatment that is beneficial and economical for a wide range of conditions, and their efficacy is comparable to manufactured medications. They have a multi-systemic action, but compared to synthetic ones, they have considerably fewer dangerous adverse effects (Janibekov *et al*., 2018; Thabet *et al*., 2018; Aboulwafa *et al*., 2019).

The common bean (*Phaseolus vulgaris* L.) is an annual plant cultivated in temperate and subtropical regions for its edible dry seeds. These beans are known by various names, such as navy beans, kidney beans, red beans, black beans, pinto beans, and cranberry beans. Traditionally, beans have been used in medicine to treat a wide range of conditions, including eczema, diabetes, burns, acne, heart issues, itching bladder problems, digestive disorders, dropsy, dysentery, itching, hiccups, and rheumatism (Ganesan & Xu, 2017). The bean in its dry form has a rich supply of polyphenols. Studies have shown that phenolic chemicals are most commonly found in the seed coat of the bean rather than in the cotyledon and testa (López *et al*., 2013). Flavones, monomers and oligomers of flavanols and flavanones, isoflavonoids, anthocyanins, chalcones, and

dihydrochalcones are the phenolic chemicals that can be found in the seeds (Ganesan & Xu, 2017).

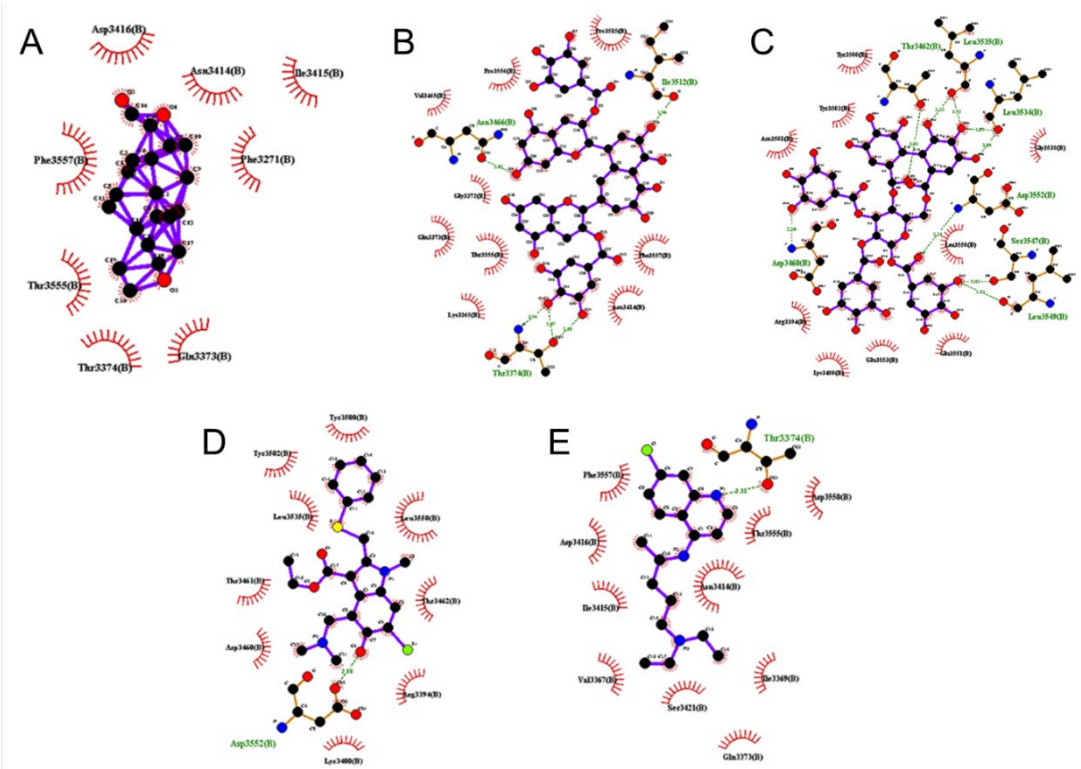

Figure 8. The 2D structure visualisation of ligands (top three) and control drugs against the 3CL^{pro} protein. (A). Kahweol; (B). Theaflavin-3,3′-digallate; (C). Eugeniin; (D). Arbidol; and (E). Chloroquine.

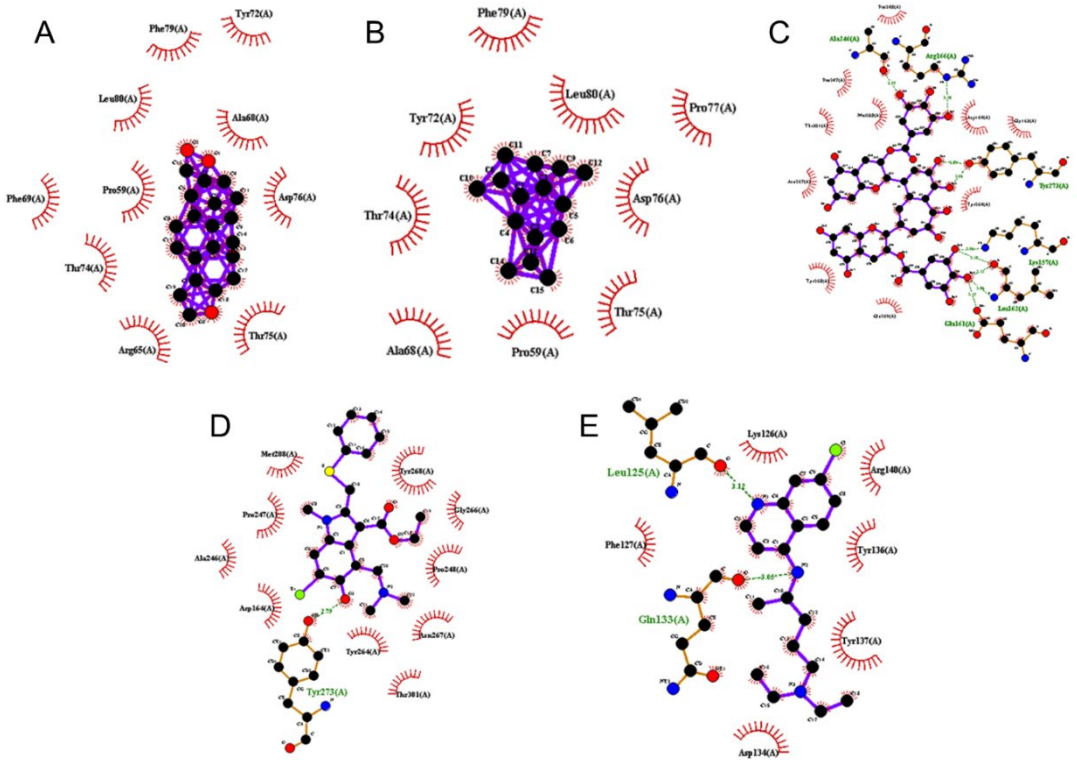

Figure 9. The 2D structure visualisation of ligands (top three) and control drugs against the PLpro protein. (A). Cafestol; (B). β-elemene; (C). Theaflavin-3,3′-digallate; (D). Arbidol; and (E). Chloroquine.

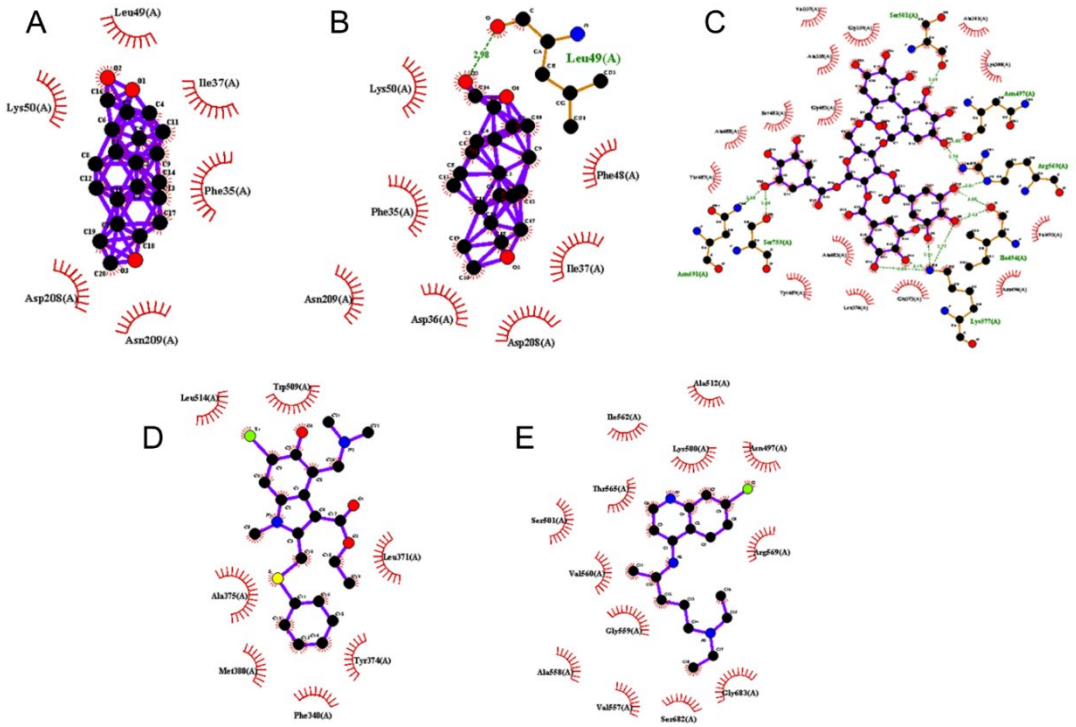

Figure 10. The 2D structure visualisation of ligands (top three) and control drugs against the RdRp protein. (A). Cafestol; (B). Kahweol; (C). Eugeniin; (D). Arbidol; and (E). Chloroquine.

Table 1. A summary of the amino acids residues and chemical interaction of the top three bioactive compounds and the control drug with the $3CL^{pro}$ protein

No.	Compound	Source	Amino Acids Residue	Interaction
1	Kahweol CID. 114778	Common bean (*Phaseolus vulgaris*)	Asp3416(A); Asn3414(B); Ile3415(B); Phe3271(B); Gln3373(B); Thr3374(B); Thr3555(B); Phe3557(B)	Hydrophobic interaction
2	Theaflavin-3,3'-digallate CID. 136277567	Black tea (*Camelia sinensis*)	Asn3466(B); Ile3512(B); Thr3374(B)	Hydrogen bond
			Phe3557(B); Asn3414(B); Lys3365(B); Thr3555(B); Gln3373(B); Gly3372(B); Val3465(B); Pro3556(B); Pro3515(B)	Hydrophobic interaction
3	Eugeniin CID. 442679	Clove (*Syzygium aromaticum*)	Asp3552(B); Ser3547(B); Leu3549(B); Asp3460(B); Thr3462(B); Leu3535(B); Leu3534(B)	Hydrogen bond
			Leu3550(B); Glu3551(B); Glu3553(B); Lys3400(B); Arg3394(B); Asn3501(B); Tyr3502(B); Tyr3500(B); Gly3538(B)	Hydrophobic interaction
4	Arbidol CID. 131411	Antiviral drug (control)	Asp3552(B)	Hydrogen bond
			Thr3462(B); Arg3394(B); Lys3400(B); Asp3460(B); Thr3461(B); Leu3535(B); Tyr3502(B); Tyr3500(B); Leu3550(B)	Hydrophobic interaction
5	Chloroquine CID. 2719	Antiviral drug (control)	Thr3374(B)	Hydrogen bond
			Asp3558(B); Thr3555(B); Asn3414(B); Ile3369(B); Gln3373(B); Ser3421(B); Val3367(B); Ile3415(B); Asp3416(B); Phe3557(B)	Hydrophobic interaction

Theaflavins from black tea have been found to decrease the virulence of *Porphyromonas gingivalis* by preserving the integrity of tight junctions in gingival keratinocytes and demonstrating anti-inflammatory effects. These findings indicate their potential for preventing and managing periodontal inflammatory diseases, possibly through the downregulation of inflammatory cytokines in macrophages stimulated by *P. gingivalis* (Ben Lagha & Grenier, 2017). Additionally, black tea showed protective effects on peripheral immune responses in rats administered colchicine intracerebroventricularly. This was reflected in enhanced phagocytic activity of white blood cells and splenic polymorphonuclear cells, increased cytotoxicity, and a decreased leukocyte adhesion inhibition index in splenic mononuclear cells (Sil *et al*., 2018).

Clove (*Syzygium aromaticum*), a dried flower bud from the Myrtaceae family (Cortés-Rojas *et al*., 2014; Batiha *et al*., 2019) stands out among aromatic herbs like cinnamon, oregano, thyme, and mint, which are known for their antibacterial, antiviral, anticarcinogenic, and antifungal properties. Due to its potent antibacterial and antioxidant activities, clove has gained particular attention as a leading spice in this regard (Shan *et al*., 2005). Its effectiveness in combating various degenerative disorders is largely attributed to its high concentration of antioxidant compounds (Hu *et al*, 2002; Astuti *et al*., 2019).

Cloves have a long history of medicinal use for treating conditions like nausea, vomiting, flatulence, and digestive issues affecting the liver, colon, and stomach. In tropical Asia, cloves have been effective against infections caused by microorganisms such as scabies, cholera, malaria, and tuberculosis. Furthermore, in the United States, cloves have traditionally been used to control foodborne pathogens and manage viruses, worms, candida, and various bacterial and protozoan infections (Bhowmik *et al*., 2012; Batiha *et al*., 2020).

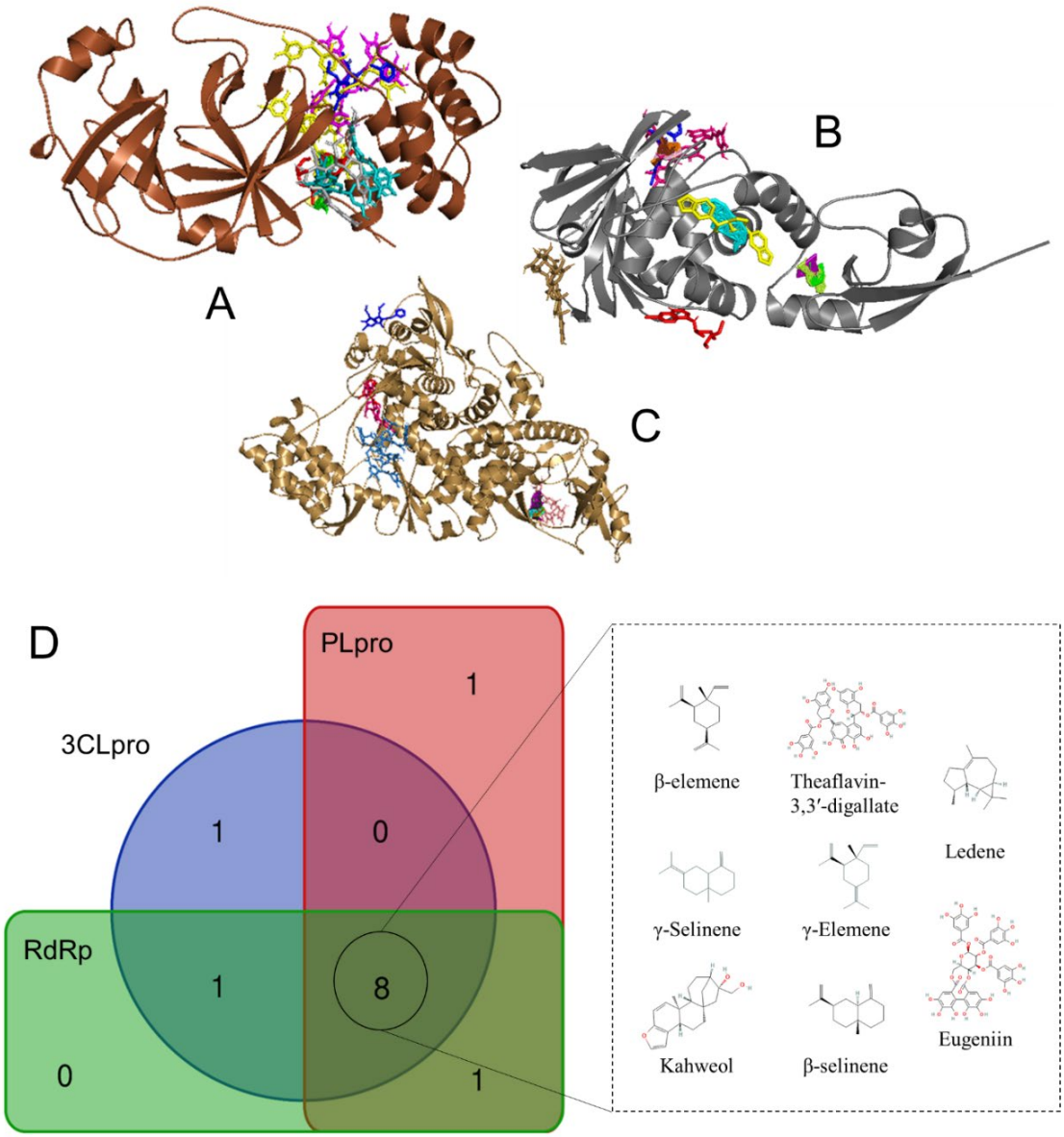

Figure 11. The 3D structure visualisation of multiple plants bioactive compounds (top ten) and control drugs toward the $3CL^{pro}$ protein (A), PLpro protein (B), RdRp protein (C), and the Venn diagram showed theaflavin-3.3′-digallate; ledene; eugeniin; kahweol; β-elemene; γ-elemene; β-selinene; γ-selinene are present in three target proteins (D).

Piper nigrum, a species from the Piperaceae family, is indigenous to India, where it grows naturally. It is well renowned for the medicinal benefits that the plant possesses. Because it is the spice that is used the most, it is also referred to as the king of spices. The active components of *Piper nigrum* are utilised in both, the food and medical industries. It contains the alkaloid piperine, which is recognised for its diverse pharmacological properties, including antioxidant, antihypertensive, antiasthmatic, antitumor, antispasmodic, anti-inflammatory, immunomodulatory, antifungal, antibacterial, and antimutagenic effects (Salehi *et al.*, 2019; Srinivasan, 2009).

Table 2. List of amino acids residue and chemical interaction of top three bioactive compounds and control drug against PLpro protein

No.	Compound	Source	Amino Acids Residue	Interaction
1	Cafestol CID. 108052	Common bean (*Phaseolus vulgaris*)	Ala68(A); Asp76(A); Thr75(A); Arg65(A); Thr74(A); Phe69(A); Pro59(A); Leu80(A); Phe79(A); Tyr72(A)	Hydrophobic interaction
2	B-elemene CID. 6918391	Black pepper (*Piper ningrum*)	Pro77(A); Asp76(A); Thr75(A); Pro59(A); Ala68(A); Thr74(A); Tyr72(A); Phe79(A); Leu80(A)	Hydrophobic interaction
3	Theaflavin-3,3'-digallate CID. 136277567	Black tea (*Camelia sinensis*)	Ala246(A); Arg166(A); Tyr273(A); Lys157(A); Leu162(A); Glu161(A)	Hydrogen bond
			Thr301(A); Ser245(A); Tyr264(A); Asp302(A); Glu167(A); Val165(A); Lys157(A); Asn267(A); Pro247(A)	Hydrophobic interaction
4	Arbidol CID. 131411	Antiviral drug (control)	Tyr273(A)	Hydrogen bond
			Tyr268(A); Gly266(A); Pro248(A); Asn267(A); Thr301(A); Tyr264(A); Asp164(A); Ala246(A); Pro247(A); Met208(A)	Hydrophobic interaction
5	Chloroquine CID. 2719	Antiviral drug (control)	Leu125(A); Gln133(A)	Hydrogen bond
			Arg140(A); Tyr136(A); Tyr137(A); Asp134(A); Phe127(A); Lys126(A)	Hydrophobic interaction

Table 3. List of amino acids residue and chemical interaction of top three bioactive compounds and control drug against RdRp protein.

No.	Compound	Source	Amino Acids Residue	Interaction
1	Cafestol CID. 108052	Common bean (*Phaseolus vulgaris*)	Leu49(A); Ile37(A); Phe35(A); Asn209(A); Asp208(A); Lys50(A); Leu49(A)	Hydrophobic interaction
2	Kahweol CID. 114778	Common bean (*Phaseolus vulgaris*)	Leu49(A)	Hydrogen bond
			Phe48(A); Ile37(A); Asp208(A); Asp36(A); Asn209(A); Phe35(A); Lys50(A)	Hydrophobic interaction
3	Eugeniin CID. 442679	Clove (*Syzygium aromaticum*)	Lys577(A); Arg569(A); Ile494(A); Tyr689(A); Asn496(A); Ser759(A); Ser501(A); Lys500(A)	Hydrogen bond
			Val495(A); Thr687(A); Lys545(A); Ser682(A); Asn691(A); Gly683(A); Gly559(A); Ala502(A); Ala512(A); Thr565(A); Ala558(A); Val557(A); Asn543(A); Asn497(A)	Hydrophobic interaction
4	Arbidol CID. 131411	Antiviral drug (control)	Leu371(A); Tyr374(A); Ala375(A); Met380(A); Leu514(A); Trp509(A)	Hydrophobic interaction
5	Chloroquine CID. 2719	Antiviral drug (control)	Arg569(A); Gly683(A); Ser682(A); Val557(A); Ala558(A); Gly559(A); Val560(A); Ser501(A); Thr565(A); Ile562(A); Ala512(A); Lys500(A); Asn497(A)	Hydrophobic interaction

IV. CONCLUSION

In this study, we demonstrated several bioactive compounds from Indonesian medicinal plants have great potency as antiviral drug candidate against SARS-CoV2 $3CL^{pro}$, PL^{pro}, and RdRp protein. Interestingly, we found eight compounds from top ten list that interacts to $3CL^{pro}$, PL^{pro}, and RdRp protein at the same time and condition, including theaflavin-3.3′-digallate, ledene, eugeniin, kahweol, β-elemene, γ-elemene, β-selinene, and γ-selinene. Interestingly, these compounds similarly have functional group as aromatic compounds. Thus, this study provided the preliminary basis for drug development for COVID-19 treatments.

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