Potential compounds from several Indonesian plants to prevent SARS-CoV-2 infection: A mini-review of SARS-CoV-2 therapeutic targets

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ABSTRACT

The outbreak of coronaviruses (CoVs) presents an enormous threat to humans. To date, no new therapeutic drugs or vaccines licensed to treat human coronaviruses remain undiscovered. This mini-review briefly reports the number of potential plants widely distributed in Indonesia for further research and development as anti-SARS-CoV-2 agents and the critical targets for SARS-CoV-2 therapy, such as angiotensin-converting enzyme 2 (ACE-2) receptor, spike protein, 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp), helicase, and serine protease. Indonesia is rich in medicinal plants (herbal); it also has a long history of using plants to treat various hereditary diseases. However, since SARS-CoV-2 is a new disease, it has no history of plant-based treatment anywhere in the world. This mini-review describes natural products from several Indonesian plants that contain compounds that could potentially prevent or reduce SARS-CoV-2 infection, act as potential targeted therapy, and provide new therapeutic strategies to develop SARS-CoV-2 countermeasures.

1. Introduction

CoVs are a family of positive-stranded RNA viruses that cause life-threatening breathing infections and severe pneumonia in humans (which resulted in a significant epidemic only two decades ago). Currently, three single-stranded RNA (ssRNA) beta-coronaviruses, including SARS (severe acute respiratory syndrome) virus, MERS (Middle East respiratory syndrome) virus, and SARS-CoV-2, have been detected (Masters, 2006; Gorbalenya et al., 2020; Huang et al., 2020).

The World Health Organization (WHO) designated the coronavirus discovered in 2019 as 2019-nCoV or SARS-CoV-2. It has been reported that SARS-CoV-2 is exceptionally homologous to SARS-CoV. Therefore, SARS-CoV-2 is believed to be a close relative of SARS-CoV. Accordingly, the International Virus Classification Commission (ICTV) identified SARS-CoV-2 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and concurrently, the WHO recognized the disease generated by 2019-nCoV as COVID-19 (Zhu et al., 2020; Chen et al., 2020a, b). At the time this mini-review was written, the number of confirmed cases was 5,488,825, with a mortality rate of 349,095 people in 217 countries or territories (WHO, 2020).

The Department of Clinical Microbiology, Faculty of Medicine, Universitas Indonesia, conducted a preliminary analysis on COVID-19 cases in Indonesia. The Laboratory of Clinical Microbiology (one of the reference laboratories for COVID-19 specimens) received 4167 specimens from March to April 2020, with 582 specimens showing positive results, indicating that the positivity rate was 12.6%. Demographic data revealed that the average age of COVID-19-positive patients was 44.5 years, with an age range of 2–85 years, and 59% were male. Approximately 17% of patients had comorbidities, predominantly cardiovascular disease (58%) and diabetes (37%). The average age of the COVID-19-positive patients reported in that work was similar to that reported in the Singapore case data (42.5 years) but younger than that reported in Wuhan (55.5 years).

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However, the findings that male sex and cardiovascular disease are COVID-19 comorbidities are concordant with previous studies from other countries (Ibrahim et al., 2020).

Moreover, 8% of the positive patients with COVID-19 were health workers. Another surprising finding was that approximately 22% of COVID-19 patients were asymptomatic, and 34% had mild symptoms, with the remaining 44% exhibiting moderate to serious signs. Although respiratory symptoms are common in patients with COVID-19 (found in 73% of cases), it has been shown that nonspecific symptoms of COVID-19, such as gastrointestinal complaints, lethargy and headaches, cannot be excluded. This fact should definitely be considered due to the transmission risk (Ibrahim et al., 2020).

SARS-CoV-2 interacts with cell surface receptors named angiotensin converting enzyme 2 (ACE-2) once it enters the cells of humans (Li et al., 2003; Han et al., 2006; Ge et al., 2013). The penetration of the virus into the human body triggers an immune system reaction with the aim of eliminating the virus. The working immune system consists of various cells, including macrophage cells, neutrophil cells, lymphocytes, dendrite cells, etc., which produce cytokines. These cytokines activate cells and trigger further mechanisms that elicit symptoms of the disease. Example mechanisms in the lungs (Figure 1): S-ACE2 protein binding leads to viral entry – triggers the immune system: (1) Endothelial cell damage occurs, and fluid from the blood vessels enters the alveoli of the lungs, causing symptoms. (2) The damaged endothelium triggers the coagulation system (blood clotting), and a blood clot can form, which is carried through the bloodstream and causes blockage of the blood vessels. (3) An inflammatory reaction (inflammation) occurs, which induces the production of cytokines and leads to a cytokine storm (Teuwen et al., 2020).

Example mechanisms in the heart (Figure 2): S-ACE2 protein binding leads to viral entry – triggers the immune system: Cytokines are released by macrophages, causing damage to endothelial cells and pericytes, as well as myocyte damage. The resulting damage can lead to myocarditis, acute coronary syndrome, arrhythmia, and heart failure. The symptoms are the same as those of a heart attack (Guzik et al., 2020) and can be mild, moderate, or severe, depending on the amount of cytokines formed. The more cytokines that are formed, the more severe the symptoms will be (illustration in Figure 3) (Zhou et al., 2020a, b).

There are two therapeutic possibilities for anti-coronavirus therapy (depending on the target): enhancing the human immune system (human cells) and attacking the coronavirus itself. The innate immune response is associated with the human immune system and helps to control the infection by preventing coronavirus replication (Omrani et al., 2014). If the human cell signaling pathways required for virus replication can be blocked, a certain antiviral effect could be achieved.

Coronavirus therapies include preventing viral RNA synthesis through the use of genetic virus material to prevent replication by acting on critical virus enzymes and preventing the binding of virus to human cells (ACE-2 receptor and spike protein) or inhibiting the process of self-assembly of the virus by acting on certain structural proteins, including viral papain-like protease (PLpro), main protease (Mpro/3CLpro, also recognized 3-chymotrypsin-like protease), RNA-dependent RNA polymerase (RdRp), helicase, and serine protease (Yu et al., 2012; Clemente et al., 2019; Wu et al., 2020).

Presently, in silico (computational model) techniques are being used to identify plant compounds that can prevent SARS-CoV-2 infection and replication by predicting their activity against disease targets (Gyebi et al., 2020). For example, methoxyflavonoid compounds such as hesperetin, tangerine, naringenin, and nobiletin have been identified in oranges (Citrus sp.; fruit and skin) (Singh et al., 2020; Utomo et al., 2020), and baikalin, scutellarin, glycyrrhizin, rhoifolin, herbacetin, pectolinarin and galangin compounds have been identified in galangal (Alpinia...
The similarity of the SARS-CoV-2 virus gene sequences with SARS-CoV reaches 79.5%, and the similarity in the manner in which the virus enters humans and passes through the ACE-2 receptor suggests common therapeutic targets (Jia et al., 2005; Zhou et al., 2020a, b). The chemical content (compounds) of some plants has been widely studied, and their activity related to SARS-CoV therapy has been documented, which will speed up evaluations of the activity of these compounds against SARS-CoV-2. Some Indonesian plants contain active compounds that could restrict SARS-CoV-2 infection and replication based on their activity against relevant therapeutic targets. Potentially active compounds have been found in vegetables, crops, and mangroves (Indonesian plants) and show activity (binding) against protein targets such as RBD-S, PD-ACE2, and SARS-CoV-2 protease. These compounds (i.e., hesperidin, flavonoids, curcumin, brazilin, and galangin), show the potential for development as SARS-CoV-2 inhibitors that could be applied in daily life as prophylaxis for COVID-19 (Amin et al., 2019; Azminah et al., 2019; Utomo et al., 2020).

2. Method

Data on COVID-19, herbal medicine and dietary therapy were searched and collected for this miniature review and perspective. We used key search engines, namely, Google Scholar, PubMed, Science Direct and SciFinder. The search keywords used comprised coronavirus; etiology; signs; symptoms; allopathic therapy adjacent to COVID-19; immunomodulatory and anti-influenza herbal activity, SARS-CoV-1, and SARS-CoV-2. The authors appraised, evaluated, and interpreted the selected articles. This perspective reflects the opinion of the authors concerning the use of foods and herbs as preventatives and corresponding therapies against COVID-19.

3. Targets for blocking the viral entry point

3.1. Angiotensin-converting enzyme 2 (ACE-2)

ACE-2 is a receptor that has been confirmed as the entry point for the SARS-CoV-2 virus to infect human cells. Scientists suggest a strong interaction exists between human ACE-2 molecules and SARS-CoV-2 (Xu et al., 2020). ACE-2 receptors are widely present in lung cells (especially lung endothelial cells) and in large numbers in type II alveolar cells in the lungs, epithelial cells in the upper esophagus, enterocytes in the ileum (the last part of the small intestine) and colon (large intestine), epithelial cells in the bile, heart muscle cells, proximal tubules in the kidneys, and urothelial cells in the bladder (Zou et al., 2020), meaning that the SARS-CoV-2 virus can attack any organ that has ACE-2 receptors. Symptoms that arise based on the target organ are as follows: in the lungs, it causes shortness–edema–respiratory failure; in the blood, it causes a reduction in the number of blood cells–coagulopathy; in the kidneys, it causes renal failure; and in the heart, it causes tachycardia–arrhythmia and heart failure (Figure 4) (Zhou et al., 2020a, b). ACE-2 is an integral membrane protein type I with an active site domain uncovered outside the cells and has been described in receptor function studies of SARS-CoV-2 (Kuhn et al., 2018; Haslberger et al., 2020; Utomo et al., 2020).

Figure 2. Pathomechanism of the heart (adapted Guzik et al., 2020 with permission).
et al., 2006). The virus starts the infection by spike protein (S-protein) binding between SARS-CoV-2 and ACE-2 in the host cell (Walls et al., 2020). The interaction of ACE-2 and the viral S-protein enables SARS-CoV-2 to enter the circulation (Belouzard et al., 2009). The SARS-CoV-2 receptor-binding domain (RBD) successfully interacts human ACE2-expressing cells but not with any other receptors, ensuring that in the future, human ACE-2 will be required by the newly evolving SARS-CoV-2 for cell entry (Hoffmann et al., 2020; Letko et al., 2020).

This infection risk can be prevented or reduced with plant compounds that can interfere with these interactions. Molecular docking studies have shown that baicalin might bind strongly to the ACE-2 enzyme with an expected $\Delta G$ (kcal/mol) of $-8.46$ and potential binding sites at ASN-149, ARG-273, and HIS-505. These binding sites are situated in the hydrophobic area of ACE-2. Based on the potential binding to ACE-2, it can be suggested that baicalin is a promising candidate for 2019-nCoV treatment. Furthermore, molecular docking found that scutellarin has the potential to bind to ACE-2 with a projected $\Delta G$ (kcal/mol) of $-14.9$ and binding sites at GLU-495, UNK-957, and ARG-482 (Chen and Du, 2020). The molecular docking studies of hesperidin with the ACE-2 enzyme demonstrated that hesperidin can bind to ACE-2 with a predicted $\Delta G$ (kcal/mol) of $-8.3$ and binding sites at TYR-613, SER-611, ARG-482, and GLU-479 (Chen and Du, 2020). These results suggest that hesperidin may bind to ACE-2 and thus block 2019-nCoV infection.

A previous study (Takahashi et al., 2015) demonstrated that nicotianamine is a powerful inhibitor of ACE-2, with an IC$_{50}$ value of 84 nM. The molecular docking studies of nicotianamine to the ACE-2 enzyme
showed that nicotinamide has a promising binding affinity to ACE-2, with an approximate ΔG (kcal/mol) of −5.1 and binding sites at ARG-518, GLU-406, SER-409, GLN-522, and GLN-442. These results indicate that nicotinamide might block 2019-nCoV infection by inhibiting ACE-2 (Chen and Du, 2020). The molecular docking results also showed that glycyrrhizin could bind to ACE-2 with an estimated ΔG (kcal/mol) of −9 and binding sites at ARG-559, GLN-388, ARG-393, and ASP-30. Based on the hydrophobic nature of the ACE-2 binding site, the prediction of the binding site of glycyrrhizin is near this site. GLN-388 and ARG-393 are close to the zinc metallopeptidase that might regulate the activity of ACE-2 in cells (Chen and Du, 2020). The docking scores of the binding sites between natural compounds and ACE-2 of SARS-CoV-2 are presented in Table 1.

Several edible plants found across Indonesia contain emodin and luteolin compounds, which have the potential to prevent or reduce infection with this virus (Table 2). These compounds are capable of preventing interactions between ACE-2 receptors and the S-protein in infection with this virus (Table 2). These compounds are capable of preventing interactions between ACE-2 receptors and the S-protein in infection with this virus (Table 2). These compounds are capable of preventing interactions between ACE-2 receptors and the S-protein in infection with this virus (Table 2). These compounds are capable of preventing interactions between ACE-2 receptors and the S-protein in infection with this virus (Table 2).

As shown in a previous study of several potentially active compounds, the docking scores of cannabinoids, rhoifolin, peplontinarin, morin, kaempferol, epigallocatechin gallate, herbacetin, and hesperidin against the S-protein were −10.2, −9.5, −8.8, −8.5, −9.8, −8.3, and −10.4, respectively (Tallei et al., 2020). Another investigation showed that hesperidin had a docking score against the S-protein of −9.6 (Utomo et al., 2020). The docking scores of these natural compounds with the binding sites (protein) of the S-protein of SARS-CoV-2 are shown in Table 4.

### 4. Targets for blocking RNA synthesis and viral replication

#### 4.1. 3-chymotrypsin-like cysteine protease (3CL\textsuperscript{pro})

3CL\textsuperscript{pro} is a crucial enzyme for coronavirus replication (Liu and Wang, 2020). 3CL\textsuperscript{pro} mediates Nsp5 (nonstructural protein) maturation directly, which is significant in the virus life cycle. Investigations into the structure and catalytic mechanism of 3CL\textsuperscript{pro} have made it an enticing target for anti-coronavirus drug development. Peptide and small molecular inhibitors primarily contain inhibitors of SARS-CoV-2 3CL\textsuperscript{pro} (Pillaiyar et al., 2016).

As presented in a previous study of several potentially active compounds, the best docking scores of cannabinoids, rhoifolin, peplontinarin, morin, kaempferol, epigallocatechin gallate, herbacetin, and hesperidin against 3CL\textsuperscript{pro} were −8.2, −8.2, −7.8, −7.8, −7.8, −7.2, and −8.3, respectively (Tallei et al., 2020).

Hesperidin was found to dose-dependently inhibit the cleavage activity of the 3-C-like protease (3CL\textsuperscript{pro}) of SARS coronavirus in cell-free and cell-based assays, with an IC\textsubscript{50} of 8.3 μM (Lin et al., 2005). A previous study also showed that the docked hesperidin compound against 3CL\textsuperscript{pro} was −13.5 (Utomo et al., 2020), and according to a previous investigation, the best hesperidin position against SARS-CoV-2 3CL\textsuperscript{pro} had a score of −10.1 (Chen et al., 2020a, b).

Another investigation reported that the rhoifolin binding score for SARS-CoV 3CL\textsuperscript{pro} was −9.565, and the induced-fit docking result of peplontinarin against SARS-CoV 3CL\textsuperscript{pro} was −8.054. Based on a previous description, the best binding positions against SARS-CoV 3CL\textsuperscript{pro} of morin, kaempferol, and herbacetin had scores of −8.930, −8.526, and −9.263, respectively (Jo et al., 2020). Epigallocatechin gallate has also been reported to prevent the proteolytic property of SARS-CoV 3CL\textsuperscript{pro} (Nguyen et al., 2012). The docking scores of the binding sites of natural compounds towards 3CL\textsuperscript{pro} of SARS-CoV-2 are presented in Table 5.

### Table 1. Docking scores of the natural compounds towards the ACE-2 binding sites of SARS-CoV-2.

| Plant name | Family | Plant part used | Compound name | Binding energy | Binding site | Reference |
|------------|--------|-----------------|---------------|----------------|--------------|-----------|
| Scutellaria baicalensis Georgi. | Lamiaceae | – | Baicalin | −8.46 | ASN-149, ARG-273, HIS-505 | Chen and Du (2020) |
| Erigeron brevicaulis (Vant.) Hand Mazz. | Asteraceae | – | Scutellarin | −14.9 | GLU-495, UNK-957, ARG-482 | Chen and Du (2020) |
| Citrus aurantium, Citri reticulatae Pericarpium | Rutaceae | – | Hesperidin | −8.3 | TYR-613, SER-611, ARG-482, GLU-479 | Chen and Du (2020) |
| Glycine max | Leguminosae | – | Nicotianamine | −5.1 | ARG-518, GLU-406, SER-409, GLN-522, GLN-442 | Chen and Du (2020) |
| Licorice root (Glycyrrhiza radix) | Fabaceae | Herb | Glycyrrhizin | −9 | ARG-559, GLN-388, ARG-393, ASP-30 | Chen and Du (2020) |
Table 2. Distribution of edible plants containing emodin or luteolin in Indonesia.

| Species            | Tissue                                      | Compound | Reference                                      |
|--------------------|---------------------------------------------|----------|-----------------------------------------------|
| Aloe vera          | Leaves                                      | Emodin   | (Ahlavat and Khattar, 2011)                   |
| Rheum officinale   | Roots                                       | Emodin   | (Hua and Chung, 2012); (Kuo et al., 2020)    |
| Cassia alata or Senna alata | Leaves, stems, fruits                        | Emodin   | (Hennebelle et al., 2009); (Das et al., 2019) |
|                    | Roots                                       | Emodin   | (Aredoyn et al., 2015)                       |
|                    | Stems                                       | Luteolin | (Hennebelle et al., 2009)                     |
| Cassia obtusifolia or Senna obtusifolia | Seeds                          | Emodin   | (Yang et al., 2003)                         |
| Senna alexandrina  | Pods                                        | Emodin   | (Elkhidir et al., 2012)                      |
| Cassia occidentalis | Roots                                       | Emodin   | (Chukwujeokwu et al., 2006)                  |
| Apium graveolens   | Leaves                                      | Luteolin | (Zhu and Row, 2011); (Shivavari et al., 2013) |
| Elephantopus scaber | The whole plant, aerial part, and roots      | Luteolin | (Zuo et al., 2016); (Chang et al., 2011); (Su et al., 2009) |
| Allium cepa        | Bulbs                                       | Luteolin | (Singh and Goel, 2015)                       |
| Brassica oleracea  | Leaves                                      | Luteolin | (Mian and Mohamed, 2001); (Schmidt et al., 2010); (Mageaey et al., 2017) |
| Capsicum annuum    | Fruits                                      | Luteolin | (Mian and Mohamed, 2001); (Materska et al., 2015) |
| Averrhoa bilimbi   | Fruits and leaves                           | Luteolin | (Mian and Mohamed, 2001); (Ramsay and Mueller-Harvey, 2016) |
| Citrus hystrix     | Fruits                                      | Luteolin | (AhuGari et al., 2017)                       |
| Daucus carota      | Fruits                                      | Luteolin | (Mian and Mohamed, 2001)                     |

4.2. Papain-like protease (PLPro)

The papain-like protease of the coronavirus is expressed after the papain-like protease (PLPro) enzyme plays a critical function in cleaving the polyproteins into fewer products, which are utilized for replicating novel viruses (Wrapp et al., 2020). PLPro controls the cleavage of the N-terminus of the replicase polyprotein to release Nsp1, Nsp2, and Nsp3, which is indispensable for modulating virus replication (Harcourt et al., 2004).

The bioactive compounds from natural sources, including platycodin D, baicalin, sugetriol-3,9-diacetate (from Platycodon grandiflorus, Scutellaria baicalensis, Cyperus rotundus, respectively), phaitanthrin D and 2,2'-di (3-indolyl)-3-indolent from Isatis indigotica, catechin compounds ((e)-epigallocatechin gallate and (e)-epicatechin gallate (from Cassine xylocarpa), Andrographis paniculata, Cyperus rotundus, respectively), exhibited strong binding affinity to PLPro protein, illustrating that these compounds could be used for SARS-CoV-2 therapeutics (Wrapp et al., 2020).

Furthermore, the screening results reported in a previous study revealed that a series of drugs, including antivirals (ribavirin, valganciclovir, and thymidine), antibacterials (chloramphenicol, cefamandole, and ticarcillin), muscle relaxants (chlorphenesin carbamate), and antitussives (levodropropizine), muscle relaxants (chlorphenesin carbamate), and antitussives (levodropropizine), might all have a high binding affinity to PLPro. According to the docking model results, ribavirin attached to the active site of the enzyme and was described as a SARS-PLpro inhibitor (Li et al., 2012).

4.3. RNA-dependent RNA polymerase (RdRp)

Coronavirus expresses RNA-dependent RNA polymerase (RdRp) to generate the daughter RNA genome, which is an essential replication step that catalyzes the synthesis of complementary RNA strands utilizing viral RNA templates (Mullard, 2018). The conserved protein in coronavirus (Nsp12) is an RdRp and the viral enzyme of the coronavirus replication or transcription complex (Subissi et al., 2014). According to a study on SARS-CoV and MERS-CoV inhibitors, Nsp12-RdRp has been shown to be a pivotal drug target. However, the targeted inhibition of Nsp12-RdRp might not induce significant toxicity and adverse impacts on host cells, and no particular inhibitors have been identified so far (Chu et al., 2006).

Some bioactive compounds from natural sources and derivatives with antiviral, anti-inflammatory, and antitumor activities have revealed major binding affinity to RdRp, including betulonal, 2,3-di-O-β-d-galactopyranosyloxy-3,4-seco-friedelan-27-lactone, 14-deoxy-11,12-didehydroandrographolide, 1,7-dihydroxy-3-methoxyxanthone, and theflavin 3,3’-di-O-gallate (from Cassine xylocarpa, Andrographis paniculata, Sertia psuedochinensis, and Camellia sinensis, respectively); gudicin and gudinitrin (from Gnidia latramanta); and andrographolide derivatives (Wu et al., 2020). It has been shown that RNA-dependent RNA polymerase was detected in a mangrove plant, Excoecaria agallocha (Li et al., 2012).

4.4. Helicase

SARS-CoV-2 and other coronaviruses have an RNA helicase enzyme, which is important for viral replication and proliferation. A previous

Table 3. Indonesian mangrove plants containing emodin or luteolin.

| Species            | Tissue         | Compound | Reference                                      |
|--------------------|----------------|----------|-----------------------------------------------|
| Kandelia candel    | Stem barks     | Emodin   | (Liu et al., 2010)                           |
| Lumnitza racemosa  | Stems and leaves| Emodin   | (Wu et al., 2008)                            |
| Avicennia marina   | Leaves         | Luteolin | (Montazni-borjeni et al., 2013)               |
|                    | Aerial roots   | Luteolin | (Sharaf et al., 2000)                        |
| Pongamia pinnata   | Stem           | Luteolin | (Li et al., 2006)                            |
|                    | Leaves         | Luteolin | (Ahmed et al., 2010); (Shamsuddin et al., 2015) |
Table 4. Docking scores of natural compounds towards the S-protein binding site in SARS-CoV-2.

| Plant name                  | Family       | Plant part used | Compound name | Binding energy | Binding site (protein) | Reference |
|-----------------------------|--------------|-----------------|---------------|---------------|------------------------|-----------|
| Marijuana (Cannabis spp.)   | Cannabaceae  | –               | Cannabinoids  | -10.2         | S-protein (6VXX)        | Tallei et al. (2020) |
| Rhus plant (Rhus succedanea), Bitter orange, Grapefruit, Lemon, Lablab beans, Tomato, Cynara scolymus, Bananas, Grape | –            | –               | Rhoifolin      | -9.5           | S-protein (6VXX)        | Tallei et al. (2020) |
| Plume thistles (Cirsium spp.), Yellow toadflax | –            | –               | Pectolinarin   | -9.8           | S protein (6VXX)        | Tallei et al. (2020) |
| Osage orange (Maclura pomifera), Almond, Old fustic, Guava, Psidium guajava | –            | –               | Morin          | -8.8           | S-protein (6VXX)        | Tallei et al. (2020) |
| Kale (Brassica oleracea var. sabellica), Beans, Tea (Camellia sinensis), Spinach, Broccoli, Equisetum arvense, Eupatorium perfoliatum | –            | –               | Kaempferol     | -8.5           | S-protein (6VXX)        | Tallei et al. (2020) |
| Tea (Camellia sinensis) (green tea), skin of Apple, Plum, Onion, Hazelnut, Corylus avellana | –            | –               | Epigallocatechin gallate | -9.8           | S-protein (6VXX)        | Tallei et al. (2020) |
| Golden root (Rhodola spp.), Gossypium hirsutum, Common horsetail, Common boneset, Eupatorium perfolatum | –            | –               | Herbacetin     | -8.3           | S-protein (6VXX)        | Tallei et al. (2020) |
| Citrus fruit (Citrus spp.), Peppermint, Mentha spp., Yellow Toadflax | –            | –               | Hesperidin     | -10.4          | S-protein (6VXX)        | Tallei et al. (2020) |
| Citrus sp.                  | Rutaceae     | –               | –             | -9.6           | Spike glycoprotein-RBD (6LXT) | Utomo et al. (2020) |

Figure 5. Mechanism of SARS CoV-2 entry and replication in target cells (adapted from Risitano et al., 2020 with permission).
study demonstrated that myricetin and scutellarin compounds are capable of inhibiting helicase enzyme activity (Yu et al., 2012). Several Indonesian plants contain myricetin and scutellarin compounds; myricetin was found in clove plants (Syzygium aromaticum; flowers), duvet plants (Syzygium cumini; leaves), Semarang guava (Syzygium samarangense; leaves), and rosella (Hibiscus sabdariffa; flower petals), while scutellarin was found in Jakatua plants (Scoparia dulcis; leaves) and senggugu (Clerodendrum serratum; leaves) (Cai and Wu, 1996; Kuo et al., 2004; Ali et al., 2005; Ayyanar and Subash-Babu, 2012; Wu et al., 2012; Wang et al., 2017).

Some bioactive compounds from natural sources have revealed high binding affinity to helicase, including many flavanoids (a-glucosyl hesperidin, hesperidin, rutin, quercetin-3-O-beta-D-glucopyranoside, and homovanillic), xanthones such as 3,5-dimethoxy-1-(6-O-beta-D-glucopyranosyl-beta-D-glucopyranosyl)oxy-1-H-9H-xanthen-9-ones, koumithic acid H, koumithic acid A, 8,2-dihydroxy-3,4,5-trimethoxy-1-(6-O-beta-D-glucopyranosyl-beta-D-glucopyranosyl)oxy-1-H-9H-xanthen-9-one, koumithic acid D, 1-hydroxy-2,6-dimethoxy-8-(6-O-beta-D-glucopyranosyl-beta-D-glucopyranosyl)oxy-1-H-9H-xanthen-9-one and triptexanthoside D from Swertia genus, phyllaemblin B and phyllaemblinol from Phyllanthus emblica (Wu et al., 2020).

In addition, according to structure-modeling helicase proteins, as described previously, several drugs, including antibacterial (lymecycline, cefsulodine, and rolitetracycline), antifungal (itraconazole), anti-HIV-1 (saquinavir), anticoagulant (dabigatran), and diuretic (canrenoic acid) drugs, have been projected through virtual ligand screening to be helicase inhibitors with high mfscores.

### 4.5. Serine protease

As previously described, SARS-CoV-2 infection in humans not only requires ACE-2 receptors as an entry point but also involves the binding of the S-protein on the surface of the virus to ACE-2 receptors. At a later stage, the activity of the serine protease enzyme required by TMPRSS2 (a transmembrane glycop) allows for fusion and entry of the target cell to begin infection. The inhibition of serine protease activity is a target in the prevention of viral infections. Recently, it has been shown that in addition to inhibiting interactions with ACE-2 receptors, the inhibition of protease enzymes (especially serine proteases) is also an impending target for controlling SARS-CoV-2 infection. Compounds that inhibit proteases in serum residues (serine protease inhibitors, hereafter referred to as SPIs) are thought to be good candidate drugs to stop the viral life cycle. SARS-CoV-2 employs proteases to facilitate the infection of host cells, making proteases a significant therapeutic target, as they are involved in many vital processes in the propagation of coronaviruses (Clemente et al., 2019; Hoffmann et al., 2020).

Table 5. Docking scores of the natural compounds towards the 3CLpro binding site of SARS-CoV-2.

| Plant name                        | Family           | Plant part used | Compound name                  | Binding energy | Binding site | Reference        |
|-----------------------------------|------------------|-----------------|--------------------------------|---------------|-------------|-----------------|
| Marijuana (Cannabis spp.)         | Cannabaceae      |                 | Cannabinoids                   | –8            | –           | Tallei et al. (2020) |
| Rhizus plant (Rhus succedanea)    |                  |                 | –                              | –             | –           | Tallei et al. (2020) |
| Bitter orange (Citrus aurantium)  | Rutaceae         |                  | –                              | –             | –           | Tallei et al. (2020) |
| Bergamot (Citrus bergamia)        |                  |                  | –                              | –             | –           | Tallei et al. (2020) |
| Grapefruit (Citrus paradisi)      |                  |                  | –                              | –             | –           | Tallei et al. (2020) |
| Lemon (Citrus limon)              |                  |                  | –                              | –             | –           | Tallei et al. (2020) |
| Lablab beans (Lablab purpureus)   | Fabaceae         |                  | –                              | –             | –           | Tallei et al. (2020) |
| Tomato (Lycopersicon esculentum)  | Solanaceae       |                  | –                              | –             | –           | Tallei et al. (2020) |
| Artichoke (Cynara scolymus)       | Compositae       |                  | –                              | –             | –           | Tallei et al. (2020) |
| Bananas (Musa spp.)              | Zingiberaceae    |                  | –                              | –             | –           | Tallei et al. (2020) |
| Grape (Vitis vinifera)            | Vitaceae         |                  | –                              | –             | –           | Tallei et al. (2020) |
| Yellow toad flax (Linaria vulgaris)| Scrophulariaceae  |                  | –                              | –             | –           | Tallei et al. (2020) |
| Kale (Brassica oleracea var. sabellica), Beans (Phaseolus vulgaris), Tea (Camellia sinensis), Spinach (Spinacia oleracea), Broccoli (Brassica oleracea var. Italica) | Brassicaceae |                  | –                              | –             | –           | Tallei et al. (2020) |
| Tea (Camellia sinensis) (green tea), skin of Apple (Malus domestica), Plum (Prunus domestica), Onion (Allium cepa), Hazelnut (Corylus avellana) | Rosaceae |                  | –                              | –             | –           | Tallei et al. (2020) |
| Golden root (Rhodolol spp.), Gossypium (Gossypium hirsutum), Common horsetail (Equisetum arvense), Common bonestem (Equisetum perfokidum) | Equisetaceae |                  | –                              | –             | –           | Tallei et al. (2020) |
| Citrus fruit (Citrus spp.), Peppermint (Mentha spp.), Yellow Toadflax (Linaria vulgaris) | Rutaceae |                  | –                              | –             | –           | Tallei et al. (2020) |

Reference

Chen et al., 2020a, b
Utomo et al. (2020)
Jo et al. (2020)
Utomo et al. (2020)
Chen et al., 2020a, b
Plants are an abundant source of SPI and have been widely studied. SPI compounds derived from plants are generally in the form of proteins or molecules containing proteins (large molecules). Leguminous family plants (Fabaceae, Poaceae, and Solanaceae) are the primary sources of SPI-producing plants. The protein fraction derived from legumes is rich in SPI compounds. Examples of leguminous plants whose seeds contain SPI are peanuts (Arachis hypogaea), soybeans (Glycine max), beans (Phaseolus vulgaris), peas (Pisum sativum), and snap (Crotalaria juncea). In addition to legumes, several Indonesian plants contain SPI compounds, including moringa (Moringa oleifera); leaves and seeds, bitter melon (Momordica charantia); seeds, cucumber (Cucumis sativus); fruit, pumpkin (Cucurbita moschata); fruit, pineapple (Ananas comosus); fruit, sweet potato (Ipomoea batatas); tuber, and potato (Solanum tuberosum; tuber) (Bijina et al., 2011; Srikant and Chen, 2016). Furthermore, SPI has been reported in the mangrove plant Excoecaria agallocha (Li et al., 2012) and mangrove-associated Derris trifoliate (Bhattacharyya and Babu, 2009).

The Indonesian government encourages the potential use of domestic resources to deal with COVID-19. The efficacy claims of the products available to combat COVID-19 are more focused on the function of maintaining and increasing the human immune system (Hartanti et al., 2020). At the same time, this is a call for Indonesian plants to contribute to the development of drugs to combat SARS-CoV-2. At the same time, this is a call for Indonesian plant-based products to be developed and utilized to combat COVID-19.

5. Conclusion

In conclusion, all the compounds and plants mentioned in this review have not yet been tested for effectiveness in experimental models relevant to SARS-CoV-2 because this virus was only identified at the beginning of 2020. However, these plants possess the potential to prevent infection or inhibit the replication of SARS-CoV-2 based on the identified therapeutic targets in SARS-CoV-2 and their reaction to SARS-CoV.

The results of the abovementioned computational model (in silico) predictions still need confirmation via laboratory testing and experimentation. Many strategies are being developed by researchers to seek out active antiviral compounds, including those derived from natural plant compounds. The rich biodiversity of Indonesian plants provides a variety of structural compounds from natural materials, providing major capital in the effort to identify suitable drug candidates to combat disease, including SARS-CoV-2. At the same time, this is a call for Indonesian researchers to support drug-independence programs.

Declarations

Author contribution statement

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Data availability statement

Data included in article supplementary material/referenced in article.
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