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Original Article

Pharmacological Potential of Some Indonesian Medicinal Plants as Promising Options for COVID-19 During the Pandemic Era: A Literature Review

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ABSTRACT

The utilization of traditional medicine in Indonesia is highly prevalent and favoured by the Indonesian people for maintaining health and treating ailments, drawing upon the experience, knowledge, and skills of ancestors, family, or parents. Traditional medicine, known for its natural properties and minimal side effects, is extensively employed in local healing practices to address various diseases. This is evident in literary works like *Serat Kawruh* and *Serat Centhini*. In response to the pandemic, approximately 79% of Indonesia's population turned to medicinal plants to bolster their immunity during the COVID-19 outbreak. The Indonesian government also lends support by providing online resources in the form of books that offer recommendations on the usage of several medicinal plants. The literature review followed the PRISMA guidelines. Between April and June 2022, a literature search was conducted in many databases, including Scopus, Pubmed, NCBI, and EBSCO, with an article publication timeframe of 2012-2022. Some Indonesian medicinal plants may prevent and treat COVID-19. 1300 articles on SARS-CoV-2-fighting Indonesian plants were found in various databases. After the screening, 48 qualified scientific articles were found suitable for this review article. The results found that many Indonesian local plants have a potential effect as antivirals to inhibit COVID-19. However, further experimental and animal studies are needed to investigate the antiviral activities of each plant in vitro before proceeding with clinical trials in humans.

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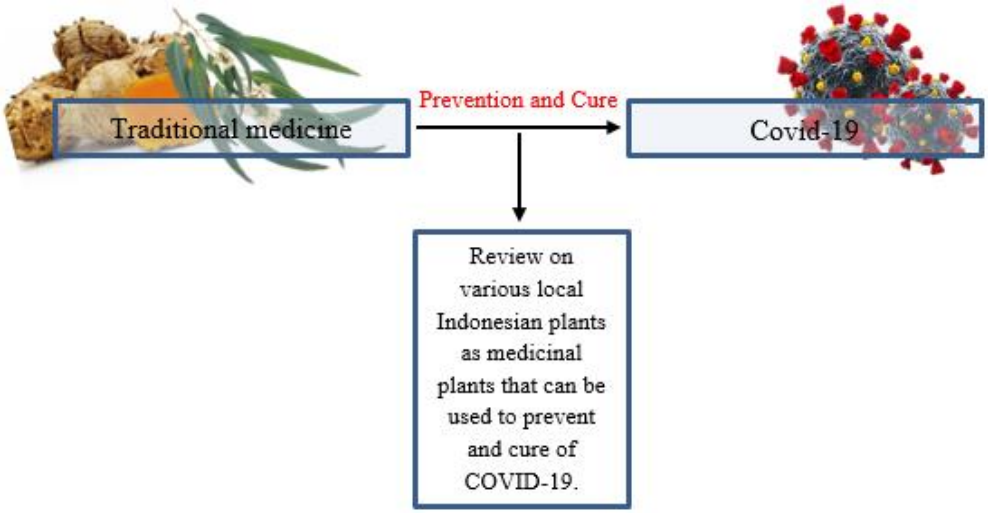
GRAPHICAL ABSTRACT



Introduction

Based on their experience, knowledge, and skills, ancestors, family, or parents have passed down the tradition of using medicinal plants to treat diseases from generation to generation [1]. Indonesia has an abundant wealth of medicinal plants. This plant is a source of traditional medicine that plays an important role in maintaining the health of Indonesians. Since ancient times, this plant has been used in making traditional medicines in various cultures [2].

The use of traditional medicine in Indonesia is very popular and widely used as an effort to maintain health and treat diseases among the Indonesian people [3]. According to the World Health Organization (WHO), traditional medicine is knowledge, skills, and practices based on indigenous beliefs and experiences used in health care as well as in the prevention, diagnosis, improvement, or treatment of physical and mental disorders. The WHO encourages the use and development of traditional medicines as affordable health solutions for the community. Traditional medicine is widely used in the treatment of diseases in local healing practices due to its natural nature and minimal side effects [4]. For example, in literature such as *Serat Kawruh* and *Serat Centhini*, the Javanese have long used boiled javanese turmeric (*Curcuma xanthorrhiza*) as an effort to maintain their health. Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5]. This disease has had catastrophic effects worldwide, with the death toll reaching over 6 million people. After the first case of this disease was reported in Wuhan, Hubei Province, China, at the end of December 2019, the SARS-CoV-2 virus spread quickly to more than 200 countries around the world in a short time [6]. Consequently, on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. During the pandemic, around 79% of Indonesia's population tended to consume medicinal plants in an effort to increase immunity during the COVID-19 outbreak [7].

The Indonesian government also provides support by providing online information sources in the form of books that provide recommendations for the use of several medicinal plants, such as turmeric (*Curcuma longa* L.), javanese turmeric (*Curcuma zanthorrhiza* Roxb.), ginger (*Zingiber officinale* Roscoe), guava (*Psidium guajava* L.), meniran (*Phyllanthus niruri* L.), and sambiloto (*Andrographis paniculata* (Burm.) Nees), which can increase the body's resistance to COVID-19 based on existing scientific evidence and safety [8].

During this pandemic, all types of these plants are difficult to find because of the high demand in the market. Therefore, this review puts more emphasis on various local Indonesian plants as medicinal plants that can be used to prevent the spread of COVID-19. It was reported that these plants have properties as an immune system booster, antioxidant, immunomodulator, antimicrobial, and antiviral, and it will be investigated further on how these properties relate to the viral components of ACE2 or SARS-CoV-2.

Materials and Methods

Based on the Preferred Report Item Guide for Systematic Review and Meta-analysis (PRISMA), this review applies a scoping review methodology (Figure 1). Between April and June 2022, a thorough literature search was conducted in many databases, including PubMed, NCBI, EBSCO, and Scopus, with an article publication timeframe of 2012-2022. The keywords were used in the search strategy: "Pharmacological potentials of some Indonesia medicinal plants: a promising option for COVID-19 prevention and cure" (Table 1 and 2).

Based on the inclusion criteria, the relevant articles were picked. Next, the articles are evaluated based on the abstract and full text, and then explained to find commonalities and discrepancies in each study, and finally, conclusions are drawn (Table 3).

Results and Discussion

1300 articles were retrieved from the search, and 48 qualified scientific articles were found after screening. The articles are as follows in Table 4, this table explains the local names in Indonesia along with the locations where they grow:

Red Ginger (Zingiber officinale)

Ginger is one of the spice plants in Indonesia which is quite popularly used as traditional medicine. Ginger has a distinctively spicy taste. Therefore, it is often used as a drink to warm the body. Nowadays, apart from white ginger, which is generally consumed by the public, it turns out that there is another type of ginger with more properties and a more pungent spicy taste, red ginger (*Zingiber officinale*).

The red ginger rhizome contains bioactive compounds, including diarylterpenoids, phenylbutenoids, flavonoids, diterpenoids, sesquiterpenoids, gingerols, and shagaol. In addition, a red ginger essential oil contains compounds such as zingiberene (β-bisabolene, -sesquiphellandrene), citral, cineol, zingiberol, ar-curcumene, farnesence, and geraniol [9]. The compounds in red ginger are reported to have antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, anticancer, analgesic, and diuretic properties [10, 11].

It was claimed that the components in red ginger could prevent viral infection, particularly that caused by the SARS-CoV-2 virus, based on computational analyses (molecular docking). Ar-curcumene, gingerol, geraniol, shagaol, zingiberene, gingerenone, and zingiberenol are bioactive components in red ginger that can be used as ligands that will intervene between the viral S protein and the ACE2 receptor on human cells [12, 13].

When compared to other compounds in red ginger, the molecular docking studies showed that gingerenone gave the lowest binding energy with S protein and Mpro. Gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone can interact with the main residues responsible for the catalytic domain of MPro. In contrast, geraniol, shogaol, zingiberene, zingiberenol, and zingerone can interfere with the binding between the S protein and ACE2. As a result, red ginger is anticipated to be an effective oral medicinal drink and to be able to block the SARS-CoV-2 virus' ability to infect human host cells [12].

To combat COVID-19, individuals in Sudan have started drinking ginger tea, which is made by combining 12 grammes of red ginger powder with 250 ml of warm water three times each day. If COVID-19 is the targeted condition, this dose is

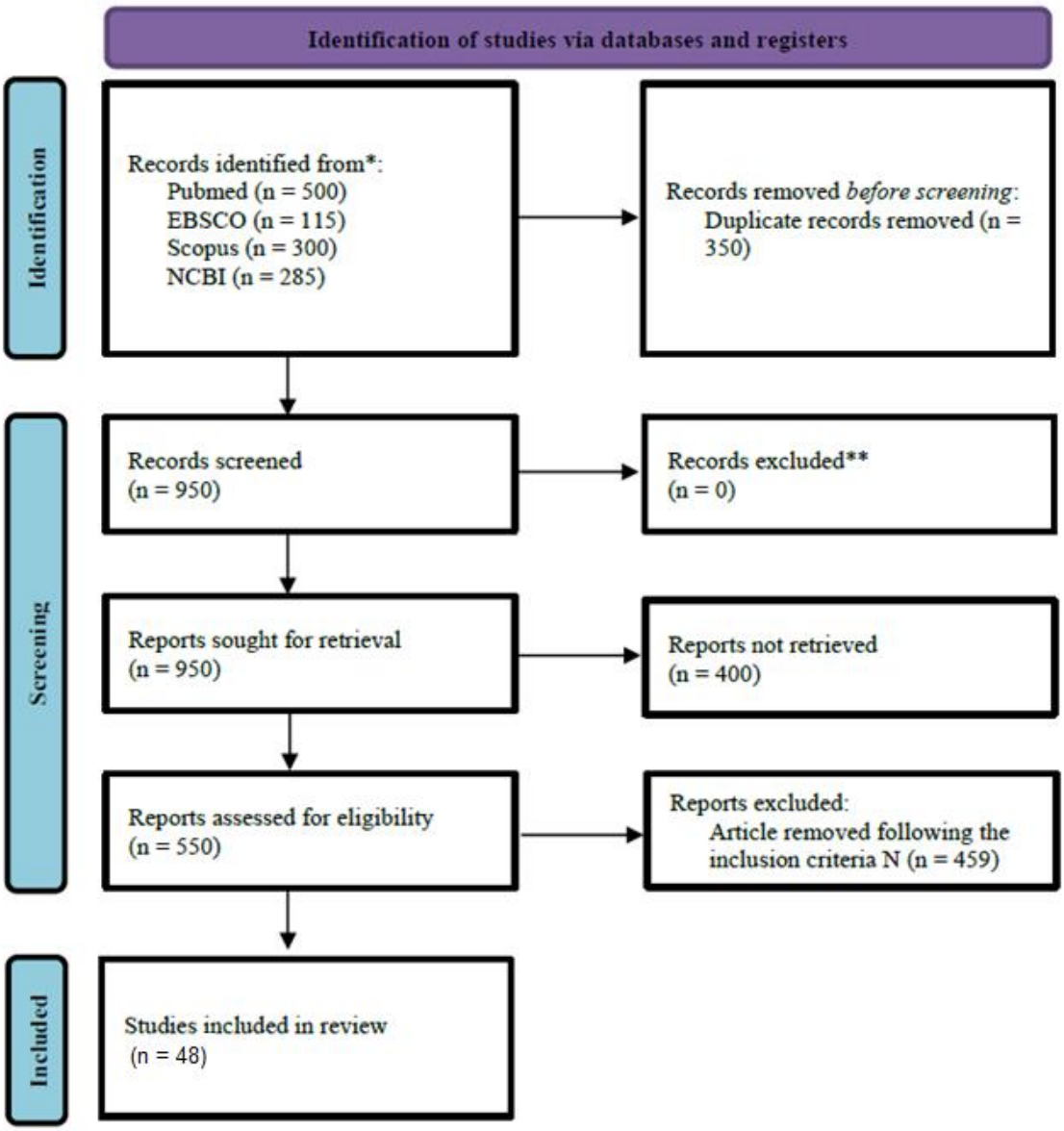


Figure 1: Search results and article selection process using the PRISMA method data extraction and processing

increased by two. Based on Magzoub's observations, Sudanese people who regularly drink red ginger do not get the flu/COVID-19. Furthermore, people who exhibit coronavirus symptoms usually recover rapidly from their symptoms, which are often minor. This is due to evidence that red ginger boosts immunity, raises IgM levels, and inhibits the release of pro-inflammatory cytokines [14].

Turmeric (Curcuma longa L.) and Javanese turmeric (Curcuma xanthorriza Roxb)

Turmeric and Javanese turmeric are spice plants popular in Indonesia as medicinal or herbal ingredients. Turmeric contains compounds that function as antioxidants, anti-inflammatory, anti-tumors, antiviral, and immune system strengthening. The results of a chemical study on turmeric simplicia powder (turmeric) showed that it contained essential oils, fatty oils, and curcuminoid compounds as the main ingredients. The curcuminoid compounds are divided into curcumin, demethoxy curcumin, and bisdemethoxy curcumin [15]. Likewise, javanese turmeric contains essential oils and curcuminoid compounds in its rhizome, which are efficacious as an antibacterial, anticancer, antitumor, and antioxidant [16].

Various viruses, including influenza, hepatitis, herpes, Zika, HIV, chikungunya, and human papillomavirus (HPV) have been reported to be

sensitive to curcumin compounds [13]. It has been proven that curcumin compounds can directly fight infection by H6N1 and H1N1 viruses by interrupting virus attachment and inhibiting hemagglutination without resistance to curcumin. In addition, computational studies have been carried out that prove by molecular simulations that curcumin can bind directly to the S protein of the SARS-CoV-2 virus and the ACE2 receptor, which will inhibit the attachment of the virus to human host cells.

Studies on oral doses of curcumin 150 mg/kg body weight in myocardial fibrosis experimental animals (7500 mg for humans weighing 50 kg) led to increased expression of ACE2. Therefore, it is advised to be careful in consuming curcumin if it is intended to prevent COVID-19 infection from exceeding the dose. Curcumin herbal drink can be prepared using 100 grams of fresh turmeric/ javanese turmeric rhizome, producing 5 grams of dry weight containing 3.60-7.99% curcumin. Thus, there is only 180-400 mg of curcumin in a cup of drink. However, it is recommended that this dose be taken twice daily to improve the immune system so that only 360-800 mg/day is safe. This drink can be prepared by boiling the rhizomes in boiling water to increase solubility due to the lipophilic nature of curcumin and not readily soluble in water [17].

Green Tea (Camellia sinensis)

The leaves of the Indonesian native plant *Camelia sinensis* are used to make tea. Green tea is one variety of tea frequently consumed as a nourishing health beverage. It is a type of tea with pharmacological potential, including as an antioxidant, anticancer, anti-inflammatory immunomodulator, antiviral, and antibacterial. The content of epigallocatechin gallate in green tea can allegedly increase the body's immune system. In addition, green tea contains flavonoid compounds such as flavonols, flavones, flavanols, isoflavones, anthocyanins, and catechins. Furthermore, green tea also contains essential oils, tannins, caffeine, vitamins, and pigments such as chlorophyll and carotenoids [18].

Green tea's catechins are known to have potent antiviral properties. Catechin-7-O-gallate, (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC) are catechins found in green tea. According to the reports, EGCG has antiviral, antitumor, antibacterial, and anticancer properties. When used as an antiviral, EGCG and ECG are more effective than EGC or EC at inhibiting HIV replication. Besides being able to be used as an HIV antiviral, EGCG can also inhibit influenza viruses, and SARS-CoV-2 [19].

According to catechin compound molecular docking experiments, these substances can bind to the Mpro and S protein of SARS-CoV-2. In SARS-CoV-2, catechin-7-O-gallate can act as an inhibitor of S protein and RNA-dependent RNA polymerase (RdRp), interfering with coronavirus infection and replication. The molecular docking results showed that EGCG was able to bind to Mpro (3CLpro inhibitor) from the virus and had the lowest binding energy (-8.3 kcal/mol) to RdRp compared to the other catechin compounds so that it had the best potential as an *in vitro* inhibitor to inhibit the replication of the SARS CoV-2 virus. Compared with curcumin, catechins' binding energy with S protein and ACE2 is lower with greater affinity. Catechins can bind to the S protein around the RBD (Receptor Binding Protein) of the virus which will cause fluctuations in amino acids around the RBD S protein of the virus, so that catechins have the potential to be developed into potential drugs for COVID-19.

Meniran (Phyllanthus niruri L.)

Phyllantus niruri L. has a synonym for the name *Phyllantus urinaria* L. known as meniran by Indonesian people. This plant is a wild plant that grows in forests, fields, bushes, riverbanks, beaches, or along grassy dirt roads, and other places with loose and rocky soil. Meniran contains lignans such as phyllantin, hypophyllanthin, niranthin, nirtetralin phyltetralin, seco-4-hydroxylintetralin, secoisoarisiresmol trimethyl ether, hydroxynirantin, dibenzilbutiro-lactone, nirfilin, and neolignane. The roots and leaves contain flavonoid compounds such as quercetin, quercitrin, isoquercitrin, astraglin, and rutin. In addition, meniran also contains flavonones,

flavonoid glycosides, triterpenes, tannins, alkaloids, saponons, phenolic acids, and vitamin C [20].

Meniran, a medicinal drink, has a diuretic effect, boosts the immune system, reduces fever, ulcer medicine, destroys kidney stones and gallstones, malaria medicine, acne medicine, cough medicine, and healing burns. In addition, Meniran can be used as antioxidants and anti-cancer because it contains flavonoid compounds quercetin phyllantin, hypophyllanthin, flavonoids, and tannins in meniran can act as anti-hepatotoxic and increase the immune system [20]. Furthermore, meniran has been reported to have antiviral activity for HIV, Herpes, and Hepatitis B and C. Thus, it is thought to have the potential to prevent infection with the SARS-CoV-2 virus.

The antiviral activity of meniran comes from compounds such as phyllantin, hypophyllanthin, quercetin, quercetrin, and astraglin. Based on molecular docking results, it is known that the compound quercetin can bind to Mpro from SARS-CoV-2. Therefore, it has the potential to be an inhibitor of Mpro from SARS-CoV-2 (lowest binding energy for quercitrin -10.36 kcal/mol, -8.47 kcal/ mole for quercetin) and can be developed into drugs against coronavirus [21]. The recommended dose for the use of meniran in humans varies depending on what disease to be treated. The general use of meniran dosage for adult humans (18 years old and over) is 26 ml of meniran concentrated extract for a daily dose taken 2-3 times per day, or 1-3 cups if in the form of water-infusion or boiled water of meniran. There is no proven safe reference for the consumption of meniran in children. Meniran has side effects when consumed in excess. It can cause bleeding, impotence, and miscarriage in pregnant women [22].

Indonesia bay leaf (Syzygium polyanthum)

Indonesia bay leaf is one of the most popular plants used by the people of Indonesia. Not only known as a spice plant, but Indonesian people also often use bay leaves as an alternative plant to treat several diseases such as hypertension, diabetes, ulcers, and diarrhea. Based on research conducted by Zarmi *et al.*, the flavonoid content of bay leaves has the potential as antibacterial, antioxidant, anti-inflammatory, and anti-allergic [23]. Furthermore, the saponins in bay leaves have the potential as antidiabetic, while the steroids and triterpenoids in them are thought to have analgesic properties.

Besides being rich in secondary metabolites, bay leaves are also known to contain essential oils that can act as antioxidant and antibacterial. Bay leaves contain an essential oil of 17%, with the main ingredients being eugenol and methyl chavicol [24]. Based on *in vivo* and *in vitro* tests of eugenol compounds that have been carried out, it was reported that eugenol could inhibit the development of the herpes virus [10].

Eugenol molecules can act as Mpro COVID-19 inhibitor, with ACE2 serving as the receptor, according to the *in silico* study's findings. A good affinity of -6.3 kcal/mol for inhibiting the COVID-19 protease has also been observed for eugenol. Eugenol, along with other chemicals curcumin, quercetin, artemisinin, and hispidulin, is one of the best possibilities with the potential to act as an inhibitor for the COVID-19 protease, according to the molecular docking studies [11].

Studies on the oral dose of Indonesia bay leaf to prevent COVID-19 have yet to be carried out. However, most Indonesian people consume boiled water of bay leaves to treat various diseases. This boiling method can be an alternative to using bay leaves to maintain the body's resistance to avoid the COVID-19 dangers.

Guava (Psidium guajava)

Guava is one of the local fruits that the people of Indonesia favour. Guava has been known to have many benefits. Not only is the fruit delicious to eat, but also other parts of the guava have many properties. During this time, guava leaves were also often used as herbal medicine by the people of Indonesia. Guava leaves contain many bioactive compounds such as gallic acid, catechins, epicatechins, rutin, naringenin, and kaemferol [25]. In addition, guava leaves also contain phenolic compounds, isoflavonoids, quercetin, sesquiterpenoids, and quercetin glycosides [25].

Several research results have proven that guava leaves have various pharmacological activities, including analgesic, anti-inflammatory, antimicrobial, hepato-protective, anticancer, anti-hyperglycemic, and antioxidant [25]. A recent study found that guava leaves can inhibit the activity of several viruses such as Infectious Haematopoietic Necrosis Virus (IHNV), Oncorhynchus Masou Virus (OMV), and Yellow-Head Virus (YHV). Another study also proved that guava leaves have the potential antiviral effect against Newcastle Disease Virus (NDV), and H5N1 influenza viruses [26].

The molecular docking showed that kaempferol and quercetin compounds could be candidate compounds as inhibitors of Mpro and glycoprotein spike (protein S). In addition, quercetin and kaempferol compounds can act as non-competitive inhibitors of 3CLPro and PLpro [27]. Based on this study, guava leaf is predicted to be one of the plants that can inhibit COVID-19 infection because it contains both of these compounds. Therefore, people can consume guava leaves by boiling leaves and drinking boiled water from the guava leaves.

Clove (Syzygium aromaticum)

Clove is a plant that is not foreign to Indonesia. This plant is known as a spice plant native to the archipelago with various benefits. Some Indonesian people consume cloves as a plant that can increase the body's immune system. Many researchers have researched cloves. Cloves have been shown to have various pharmacological activities, such as antimicrobial, analgesic, antioxidant, anticancer, anti-inflammatory, anti-depressant, anthelmintic, antitumor, antibiotic, anesthetic, antithrombotic, antifungal, anti-diabetic, and antibacterial [28].

Clove leaves have a very high essential oil content, with the main components consisting of carvacrol, thymol, eugenol, and cinnamaldehyde. In addition, research on the isolation of cloves found that there are various bioactive compounds in it such as eugenol, -karyophyllene, vanillin, maslinic acid, kaemferol, ramnetin eugenitin, gallic acid, biflorin, myrisetin, campesterol, stigmasterol, and oleanolic acid [28].

The essential oil content in cloves is reported to have antiviral activity. A previous study proved that the compound eugenol is effective *in vivo* for herpes simplex virus type 1 (HSV type 1) infection. Furthermore, -caryophyllene compounds have also been shown to be used as therapeutic agents to treat herpes infections. In addition, -caryophyllene compounds have the potential as an antiviral for the dengue virus [29]. The molecular docking results on eugenol and -caryophyllene compounds gave relatively low bond energy with S protein and Mpro. This indicates that these two compounds have the potential to be inhibitors of SARS-CoV-2. Based on the *in silico* study, cloves can also be an alternative plant to prevent COVID-19 and increase body immunity. This is due to the high content of two main components of clove essential oil, namely eugenol and -caryophyllene. Furthermore, like bay leaves, clove consumption can be done orally by drinking boiled water from clove leaves.

Garlic (Allium Sativum)

Garlic is one of the most popular spice plants in Indonesia. Apart from being a spice, garlic is also often used as a traditional medicine by the people of Indonesia. Sulfur compounds are the main components in garlic. Garlic is composed of allicin compounds (diallyl thiosulfate) with a percentage of 70-80%. These compounds affect the pharmacological effects, taste, and smell of garlic. Allicin is an unstable compound that readily breaks down into other sulfur compounds when exposed to oxygen, including ajoene, diallyl sulphide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and hydrogen sulfide [30].

Garlic has several properties for various diseases, such as high blood pressure, high cholesterol, coronary heart disease, heart attacks, and arteries-related diseases. Various studies have reported that garlic has various pharmacological activities such as antibacterial, antifungal, antiprotozoal, anti-parasitic, wound healing, anti-diabetic, antihypertensive, antitumor antioxidant, anticancer, and protective against Alzheimer's

disease. Garlic is also reported to have antiviral activity. Garlic has been shown to act as an antiviral against coxsackievirus, herpes simplex virus (HSV) type 1 and type 2, influenza B, parainfluenza virus 3, vaccinia virus, vesicular stomatitis virus, immunodeficiency virus type 1, and human rhinovirus type 2 [30].

The molecular docking results show that allisin has the potential to be an inhibitor of COVID-19 protease replication and is a candidate to inhibit this coronavirus [13]. The recommended oral dose for garlic is around 4000 mg or about two cloves of garlic daily. In garlic consumption, it is recommended to initially chop it and mix it with honey [30].

Minyak kayu putih (Eucalyptus globulus)

Eucalyptus globulus is included in the Myrtaceae family, consisting of 140 genera and approximately 3800 species spread across tropical and subtropical regions of the world. Eucalyptus is a tree species native to Australia and represents over 90% of its natural forests. This plant is also found in Tasmania (an island in Oceania, southeast of the Australian continent) and in the Indonesian archipelago. The content of eucalyptol (1.8 cineole), the main compound in Eucalyptus essential oil, can be used as a potential inhibitor of COVID-19 infection [31].

Mechanism of action of viral inhibition

There are four subgroups of Betacoronavirus: A, B, C, and D. The Betacoronavirus subgroup B includes both SARS-CoV and SARS-CoV-2. Betacoronavirus belongs to the Coronaviridae family of the order Nidovirales. SARS-CoV-2 is a single-stranded RNA virus with at least four structural proteins: nucleocapsid (N), membrane protein (M), envelope (E), and spike (S). The attachment of SARS-CoV-2 spike protein and its receptor angiotensin-converting enzyme 2 (ACE2) mediates the entry of the virus into the host cells. The virus can then enter the cell cytoplasm by fusing the viral and host cellular membranes, which typically occurs within acidified endosomes after type II transmembrane serine protease cleaves the S protein in an acid-dependent manner. Viral polyproteins are synthesized in the host cell, where they further encode for the replicase-transcriptase complex. Next, the virus produces its RNA using its RNA-dependent RNA polymerase (RdRp). The next step is the synthesis of structural proteins, after which the new viral particles are assembled and finally released [32].

Active compounds with antiviral effects against SARS-CoV and its mechanism of action in vitro

The active compounds of medicinal plants with antiviral effects have various inhibitory mechanisms. The ability to prevent a virus spread in its early stages reduces the chance that it will evolve and develop drug resistance, making viral entry an appealing target for therapy. SARS-CoV adhesion is known to occur due to the bond between the S protein and the ACE2 receptor on the host cell's surface. Small molecules that can bind with high affinity to the S2 protein from SARS-CoV can interfere with the function of S protein, thereby preventing SARS-CoV from entering the host cell. Emodin is a compound obtained from ketepeng medicinal plants (*Cassia alata*), which can inhibit protein S attachment [19]. Luteolin compound can be obtained from celery (*Apium graveolens*) which has disruptive activity against the SARS-CoV S2 protein so that it inhibits the attachment of SARS-CoV to host cells. After the virus enters the host cell, the virus will release its genetic material, followed by the propagation of this genetic material to assemble new virions. Several proteins responsible for this stage can be targeted by antiviral agents, one of which is 3CLpro. 3CLpro plays a role in helping convert polypeptide replicase into functional proteins that play an essential role in viral propagation, thus making this protein one of the antiviral targets.

Black tea extract (*Camellia sinensis*) and its active compound Teaflavin3,3'-digalate (TF3) were reported to have inhibitory activity against SARSCoV's 3CLpro. In addition, curcumin, commonly found in the rhizomes of the Curcuma genus, has also been reported to inhibit the enzymatic activity of SARS-CoV 3CLpro. Apart from 3CLpro, another cysteine protease that can be used as an antiviral target is PLpro. PLpro is

responsible for processing viral polyproteins and is also involved in the immune response to viruses, so it functions as an important virulence factor for viruses. Kaempferol and quercetin compounds that can be found in guava (*Psidium guajava*) and orange peel (*Citrus aurantium*) have PLpro inhibitory activity from SARS-CoV [27]. Another target that could be aimed at inhibiting virus development is RdRp. RdRp in SARS-CoV is the main enzyme synthesising positive and negative RNA strands. RdRp is an essential enzyme in the replication complex, which is expected to contain additional viral and cellular proteins. The extract of the fishy medicinal plant (*Houttuynia cordata*) has RDRp enzyme inhibitor activity. It has been reported to decrease the activity of this enzyme compared to controls. Apart from RdRp, helicase is an enzyme that plays a vital role in viral replication. Mirisetin compounds, which are known to be found in cloves (*Syzygium aromaticum*) and skutelarein, which can be found in sweet broom plants (*Scoparia dulcis*), have been reported to have helicase enzyme inhibitory activity. In addition, an overwhelming inflammatory or inflammatory response has resulted in the death of patients infected with SARS-CoV, MERS-CoV, or SARS-CoV-2. Therefore, anti-inflammatory agents may reduce severity and mortality. 10-gingerol is a compound in the ginger plant (*Zingiber officinalis*) which has been reported to have the ability to inhibit inflammatory trigger agents IL-1β, IL-6, and TNF-α. Furthermore, ginger plant contains compounds that can increase the body's natural immunity (immunostimulators). Oleoresin has immunostimulatory activity by increasing the production of CD4 + helper T cells and CD8 + cytotoxic T cells.

Active compounds with antiviral activity against SARS-CoV-2 and its mechanism of action in silico

Recent molecular docking studies report that several medicinal plant compounds can inhibit some SARS-CoV-2 proteins. A recent study reported that several compounds from plants have anti-SARS-CoV-2 activity. Mangostin compounds in mangosteen (*Garcinia mangostana*) and Piseatanol isolated from grapes (*Vitis vinifera*) can inhibit protein S from SARS-CoV-2. Allyl disulfide and allyl trisulfide from garlic (*Allium cepa*) can bind strongly to the ACE2 receptor and the main protease SARS-CoV-2, thus blocking the attachment of the virus to the host cell.

Table 1: Material search strategy for this research

Keywords	Search Strategy
Pharmacological	"Pharmaceutical", Or "Pharmaceutic", Or "Prophylactic", Or "Therapeutic", Or "medicative"
Medicinal plants	"Medicinal herb", Or "healthy plant", Or "healing herb", Or "healing plant", Or "herbal medicinal products", Or "herbal medicine"
COVID-19	"Pandemic", Or "SARS CoV2", Or "Corona Virus"

Table 2: PCC framework

Population	Medicinal plants
Concept	Pharmacological
Context	Nation
Keywords	Pharmacological, Indonesia medicinal plants, Covid-19

Table 3: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Consisting of articles reporting on "Pharmacological potentials of Indonesia medicinal plants: a promising option for COVID-19 prevention and cure"	Consists of articles that do not report "Pharmacological potentials of some Indonesia medicinal plants: a promising option for COVID-19 prevention and cure"
Full-text articles published from 2012-2022	Unpublished full-text articles between 2012-2022
Studies published in peer-reviewed journals	The source of the article is a book or poster

Table 4: Indonesian local plants (wild type and introduction) used in handling COVID-19 and their distribution in Indonesia

No.	Species	Family	Local Name (English name)	Location	Reference
1	*Zingiber officinale*	Zingiberaceae	Jahe (Red Ginger)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[12]
2	*Curcuma longa*	Zingiberaceae	Kunyit (Turmeric)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[15]
3	*Curcuma xanthorrhiza*	Zingiberaceae	Temulawak (Javanese turmeric)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[33]
4	*Camellia sinensis*	Theaceae	Teh hijau (Green tea)	Sumatra, Java	[12]
5	*Syzygium polyanthum*	Myrtaceae	Salam (Bay)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, and Maluku	[24]
6	*Psidium guajava*	Myrtaceae	Jambu biji (Guava)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[26]
7	*Syzygium aromaticum*	Myrtaceae	Cengkeh (Clove)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[28]
8	*Allium sativum*	Amaryllidaceae	Bawang putih (Garlic)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[30]
9	*Andrographis paniculata*	Acanthaceae	Sambiloto (Creat)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, and Papua	[34]
10	*Blumea balsamifera*	Asteraceae	Sembung (Sambong)	Sumatra, Java, North Sulawesi, and Bali	[35]
11	*Cinnamomum verum*	Lauraceae	Kayu manis (Ceylon cinnamon tree)	West Sumatra, Jambi, Java, South Kalimantan, North Sulawesi, and	[36]

				North Maluku	
12	*Citrus sinensis*	Rutaceae	Jeruk manis (Sweet oranges)	Maluku, East Java, and North Sumatra	[37]
13	*Cordyceps militaris*	Cordycipitaceae	Jamur cordyceps (Cordyceps fungi)	Jakarta, Java (Introduction from Himalayas and Tibet)	[38]
14	*Cymbopogon citratus*	Poaceae	Sereh; Serai (Lemon grass)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[39]
15	*Kaempferia galanga*	Zingiberaceae	Kencur (Aromatic ginger)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[40]
16	*Moringa oleifera*	Moringaceae	Kelor (Drumstick tree)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, and Maluku	[41]
17	*Nigella sativa*	Ranunculaceae	Jintan hitam (Black cumin)	North Sumatra, Java, and South Sulawesi	[42]
18	*Phyllantus niruri*	Phyllanthaceae	Meniran hijau (Stonebreaker)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[22]
19	*Phyllanthus urinaria*	Phyllanthaceae	Meniran merah (Shaterstone)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[20]
20	*Curcuma amada*	Zingiberaceae	Temu manga (Mango ginger)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[43]
21	*Alpinia galanga*	Zingiberaceae	Lengkuas (Blue ginger)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[44]
22	*Capsicum annuum L*	Solanaceae	Cabe merah (Chili)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[19]
23	*Centella Asiatica*	Apiaceae	Pegagan (Asiatic pennywort)	Sumatra, Java, Kalimantan, Sulawesi, Nusa	[45]

				Tenggara, Bali, Maluku, and Papua	
24	*Morinda citrifolia*	Rubiaceae	Mengkudu (Noni)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[46]
25	*Cocos nucifera*	Arecaceae	Kelapa (Coconut)	Sumatra, Java, Kalimantan, Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[47]
26	*Eucalyptus sp*	Myrtaceae	Minyak kayu putih (Blue gum)	Sulawesi, Nusa Tenggara, Bali, Maluku, and Papua	[48]

Andrographic and Andrograpanin compounds in the sambiloto plant (*Andrographis paniculata*) and the Biorobin from the banyan plant (*Ficus benjamina*) have inhibitory activity against 3CLpro. Neohesperidin from oranges and (-) - Epigalocatekin error from tea can inhibit PLpro. In addition, the 14-Hydroxyciperotundone and Sugetriol-3,9-diacetate compounds found in nut grass (*Cyperus rotundus*) and Teaflavin 3,3'-di-O-galat from tea plants can inhibit the viral RdRp enzyme. The SARS-CoV-2 helicase enzyme activity can be inhibited by Filaemblisin B and Filaemblinol compounds isolated from the fruit plant malacca (*Phyllanthus emblica*).

Conclusion

From the conducted research, 1300 articles were obtained, and 48 qualified scientific articles were obtained after screening. Therefore, many local Indonesian plants have the potential as antivirals inhibiting SARS-CoV-2 and reducing the impact of COVID-19. However, further studies are needed to test each plant with antiviral potential as in various experimental animals and clinical trials in humans.

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