Review Article

Potential Thai Herbal Medicines for COVID-19

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Abstract

SARS-CoV-2 is a cause of COVID-19 a contagious respiratory disease, in which there are many signs and symptoms such as fever, dry cough, shortness of breath, muscle ache, and pneumonia. Meanwhile, antiviral drug mechanisms which are being used to treat SARS-CoV-2 with Western drugs can be divided into three groups as follows: increasing acidic conditions by endosomal formation; viral replication; and affinity interaction with ACE-2 receptor via S-protein. Therefore, hydroxychloroquine/chloroquine, lopinavir, remdesivir, favipiravir, and molnupiravir which have been utilized to treat HIV and influenza via inhibiting viral replication and alkalinization could also modulate COVID-19 symptoms. However, antiviral drugs also have limited use in hospitalized and severe COVID-19 cases. The objective of this review is to provide a comprehensive analysis of Thai Herbal Medicine findings suggesting antiviral property potential that natural compounds derived from Thai plants could be further developed or provide mechanistic understanding of current drug treatment of COVID-19. Cinchona bark constituents create an alkaline environment to reduce viral replication and perfusion in cells. Certain medicinal plants which possess antiviral replication and blockage of the affinity binding between S-protein of SARS-CoV-2 and ACE2 receptor include *Andrographis paniculata, Boesenbergia rotunda, Zingiber officinale, Phyllanthus amarus, Phylanthus emblica, Glycyrrhiza glabra,* and *Citrus medica.* These plants were summarized for their potential in COVID-19 treatment. Integrating Thai Traditional Medicine principles with contemporary COVID-19 treatment mechanisms would certainly have valuable provide more efficient clinical therapy.

Keywords: SARS-CoV-2, COVID-19, Thai herbs, Mechanism of action

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Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a cause of contagious respiratory disease, discovered around December 2019 from afflicted patients at Wuhan, Hubei province, China.[1, 2] The outbreak of coronavirus disease distributed within every province of mainland in China, and there have been more than 70,000 confirmed cases.[3] This pandemic has gone on to affect the global public health system and the global economy. WHO announced that the SARS-CoV-2 pandemic was a heavy contagious infectious disease, which it was a public health emergency of international concern (PHEIC) and officially named it as Coronavirus Disease-2019 (COVID-19).[4] The global epidemiology of confirmed cases of COVID-19 infection has been reported world-wide as greater than 185 million persons and total deaths of more than 4.0 million.[5] At present, the confirmed reports of COVID-19 in Thailand have elevated, with more than 290,000 confirmed cases, death accumulattion are higher than 2,300 cases and new cases are more than 6,000/day and escalating.[6]

This review described the characteristics of SARS-CoV and symptoms, the use or potential use of herbal extracts and their compounds reported in the therapeutic treatments. We also analysed and integrated the Thai Traditional Medicine principle with the results of COVID-19 research reports. Only the Thai herbs which were reported as effective aganist COVID-19 and coronavirus were presented in this review.

Characteristic symptoms, structure and mechanism of COVID-19

The most common distinctive symptoms of COVID-19 are fever, dry cough, and shortness of breath. These are often followed by other symptoms composed of muscle aches, headache, confusion, chest pain, sore throat, rhinorrhea, diarrhea, nausea, and vomiting. Chest x-rays in some patients have manifested unilateral pneumonia, bilateral pneumonia, and multiple mottling and ground-glass opacity after COVID-19 infection.[7, 8] All symptoms can be categorized as follows: asymptomatic (period in 5 days); mild symptom of fever, fatigue and dry cough, ground-glass opacities, and pneumonia; severe symptoms include dyspnea and coexisting illness (developed in 8 days after symptom). A critical period symptom is acute respiratory distress syndrome (ARDS), acute cardiac injury, and multi-organ failure (occurring at 16 days after symptom).[9] Recently, SARS-CoV-2 is associated with the virulence infection symptom likewise it also can be mutated to be several different variants.[10, 11] All variants have locally mutated at amino acids residues on surface/spike glycoprotein (S protein) to contribute against an immune response which affects an increase in virulence factor of symptoms.[12-18]

The characteristic structure of SARS-CoV-2 or Coronaviruses, are a helically symmetrical enveloped virus, with nucleocapsids and polyadenylated single strand of positive-sense-RNA virus, categorized belong to the Coronaviridae family. Moreover, this virus is composed of three groups; an **alpha group** found only on one type called 229E virus; a **beta group** consisting of a human respiratory coronavirus (HCoV) OC43, bovine coronavirus (BCoV), severe acute respiratory syndrome (SARS)-coronavirus, and Middle East Respiratory Syndrome (MERS)-coronavirus; and a **gamma group** which is an avian infectious bronchitis virus.[19-21]

Large polypeptides of Corona virus contain hemagglutinin-esterase protein, large surface glycoprotein (S protein), small envelope protein (E protein), membrane glycoprotein (M protein), and nucleocapsid protein (N protein) as shown in Figure 1A. Hemagglutinin-esterase protein is on the surface of human respiratory coronavirus (HCoV) OC43 which binds to 9-O-acetylated sialic acids of human cells which the protein-interaction activities are stimulated via spike S protein-mediated cell to enhance virus propagation through the mucosa.[20, 22] Large surface glycoprotein (S protein) locates on the surface of virus in the form of spike structure for attachment to the angiotensin-converting enzyme 2 (ACE2) receptor on host cell, viral-mediated cell entry but all spikes also coated with polysaccharide to camouflage from host immune system.[20] Recently, total length of S protein in SAR-CoV-2 was shown to play an important role compared to mutants of various types.[20, 23] The function of S protein can be summarized in that it is able to stimulate neutralizing antibodies (NAbs) and T-cell immune responses.[23, 24] Membrane protein or M protein subunit, is a small protein (~25 - 30 kDa) and contained with long COOH terminus domain inside the virus and a short NH_2-terminal domain outside the virus, mostly

found in structural protein of this virus, expands to the lipid bilayer. It can contribute to the stabilization of N and S protein regions for binding to the membrane of the host cell.[20, 25] The enveloped protein (E protein) region in SAR-CoV-2, is a transmembrane protein that is composed of N-terminal ectodomain (hydrophobic) and C-terminal endodomain (hydrophilic), surrounded with a transmembrane helical hairpin to modify lipid bilayers and forms into ion channel to motivate monovalent cation and monovalent anion that pivotally contributes ion permeability and facilitates to release the virus.[20, 26] Lastly, a nucleocapsid protein (N protein) of SAR-CoV-2 binds to a packing signaling subunit in genomes and restricts and condensates them to package the genome during E, S, and M protein interactions to the membrane. This protein is presented in the nucleocapsid and composed of N-terminal domain (NTD), C-terminal domain (CTD), RNA-binding domain (RBD), predicted disordered central linker (LINK), and dimerization domain. It is surrounded with a transmembrane helical hairpin to modify the lipid bilayer.[27] The mechanism of virus infection is demonstrated in Figure 1B.

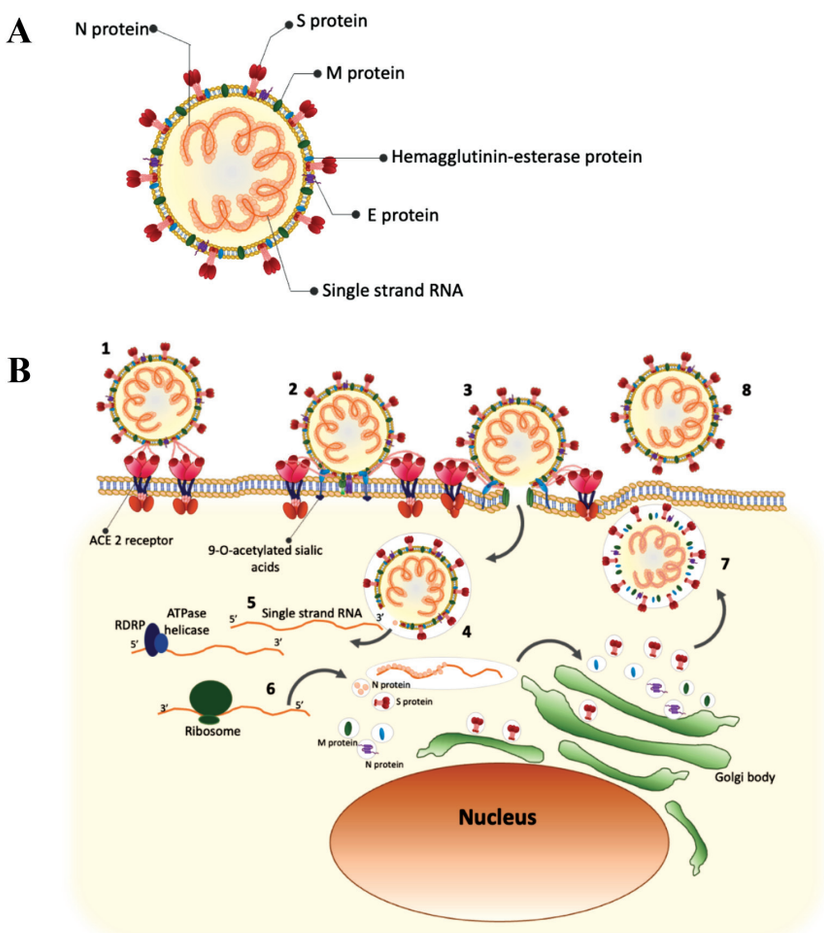

Figure 1 Diagram of SARS-CoV-2 **(A)** S protein, M protein, E protein, and hemagglutinin esterase are proteins mainly located on surface of SARS-CoV-2 and inside of virus consist of N protein binds to single strand RNA. **(B)** Processes of the virus transmission to host cells are as follows: (1) S protein binds to ACE2 receptor on host cell, (2) hemagglutinin-esterase protein attaches to 9-O-acetylated sialic acid receptor, (3) pores on cell surface are formed via M protein and E protein for virus-cell fusion process, (4) virus releases mRNA to cell, (5) mRNA is replicated by RNA-dependent RNA polymerase and ATPase helicase, (6) ribosome translates mRNA into proteins-indicated in each part, (7) protein fragments are transferred from Golgi body, and (8) liberated outside the host cell.

Mechanism of Antiviral Activity and Utilization of Thai Herbs

The development of medication targeting the virus is an inhibitory effect on viral replication which is the best suited effect on viral inhibition in early infection.[28] Recently, several potential theraputic drugs used for COVID-19 infection included hydroxychloroquine, chloroquine, lopinavir, remdesivir, flavipiravir, and molnupiravir.[29-31] Each drug exhibits differential effects through their antiviral mechanism which is described below.

Alkalization of drug to reduce virus

Hydroxychloroquine (HCQ) and chloroquine (CQ) are plant derived alkaloids. HCQ was found in Chincona bark or Quinine and Neem leave called Sa-Dao in Thai.[32, 33] HCQ is commonly used for the prevention or treatment of malaria, autoimmune diseases, rheumatic fever, and virus infection and is sometimes used in co-treatment with CQ. The anti-viral effect of HCQ/CQ are mostly characterized as alkalinity.[34] Alkalization properties of chloroquine can reduce virus perfusion and penetration during infection because many viruses have been regulated to be present in acidic conditions by endosomal formation. From previous studies it was believed that the properties of HCQ/HQ might help to reduce coronavirus infection and replication leading to an effective treatment of SARS-CoV-2. A study of Liu and colleague, proposed that HCQ (50μM) increased the pH of acidic intracellular organelles and triggered a block in the infection of SARS-CoV-2 viruses in Vero E6 cells through changed in the S-protein.[35] The mechanism of action of CQ and HCQ is represented in Figure 2. The potential effect of CQ and HCQ have been proposed anti-SARS-CoV-2 agents *in vitro* such that it has been attractive for treatment or prevention in clinical trials. In a clinical study, Huang et al predicated the efficiency of CQ on 373 SAR-CoV-2 infectious patients to eliminate virus.[36] On the other hand, the observational data usages of CQ/HCQ in hospitalized patients demonstrated that severely illness was evident in CQ/HCQ-treated patients greater than those patients who did not receive CQ/HCQ.[37] However, plants containg alkaloids have been shown to reduce fever in Thai traditional medicine such as *Tinospora crispa* (L.) Hook. f. & Thomson (Borapet), *Tinospora cordifolia* (Willd.) Miers (Chingchachalee), *Tiliacora triandra* (Yanang), and *Azadirecta indica* A. Juss. (Sa Dao).[38] These alternative Thai Herbal alkaloids may be useful for COVID-19 treatment instead of CQ/HCQ. This remains to be tested.

Viral Replication

The mechani sm of antiviral drug for COVID-19 treatment by inhibiting viral replication are based on using the drugs which could inhibit HIV-1 protease and HIV-1 integrase enzymes. Anti-Influenza virus is also used because the drug can inhibit viral replication.

HIV-1 Inhibitor

A fixed dose HIV-1 inhibitor combination was used for treatment of COVID-19 including Lopinavir/ritonavir which inhibit HIV protease. In addition, it also had also been used to effectively treat SARS as well.[39, 40] Moreover, the concentration dependent effect of lopinavir/ritonavir against SARS in an *in vitro* study (4 and 50 μg/mL) has been demonstrated to inhibit viral replication and refusion (as shown in Figure 2).[39] Recently, lopinavir/ritonavir has been applied to study the inhibitory effect on SARS-CoV-2 after inoculation to Vero cells, which found that lopinavir/ritonavir at 7 and 1.75 μg/mL could help to eliminate virus replication, but the efficacy of lopinavir/ritonavir was lower than lopinavir/ritonavir combination with hydroxychloroquine.[41] From a traditional Thai Herbal Medicine perspective there are many Thai plants reported with HIV protease inhibitor activity such as *Boesenbergia rotunda* (L.) Mansf.,[42,43]*Dioscorea membranacea* Pierre ex Prain & Burkill,[44] *Nigella sativa* L.,[45] *Eclipta prostrata* (L.) L.,[46, 47] *Combretum adenogonium* Steud.Ex A.Rich.[48] Thus, they have been used to treat COVID-19.

B. rotunda or Krachai luang in Thai had panduratin A which inhibited HIV-1 protease with an IC_{50} of 18.7 μM.[42] In addition, *B. rotunda* extract was also reported to inhibit SARS-CoV-2.[43] *D. membranacea* or Hua-Khao-Yen Tai is traditional used by Thai folk doctors for HIV treatment, it has been reported to have an inhibitory effect on HIV-1-Protease and HIV-1 Integrase.[44] *N. sativa* (Tien Dam) also exhibited HIV-1 protease and HIV-1 Integrase inhibition.[45] *E. prostrata* is called in Thai as 'Kameng', it is used as an anthelmintic drug. It was also reported to possess anti HIV1 protease and HIV-1 integrase activities.[46, 47] *C. adenogonium*

which was used to treat schistosomiasis in Tanzania also inhibited HIV-1 Protease. The species of *Combretum* spp. in Thailand such as *Combretum quadrangulare* Kurz (Sa-Kae-Na in Thai) has long been used in Thai traditional medicine for taenifuge.[48] Surprisingly in India, ivermectin is used as taenifuge for tapeworm in animals has also been used to treat COVID-19,[49] so it is possible that *E. prostrata* and *C. adenogonium* which are anthelmintic drugs and anti-HIV-1 protease inhibitors could be used to treat COVID19. It is also possible that the five traditional plants above which inhibit HIV1 protease similar to lopinavir/ritonavir may be useful for the treatment of COVID-19.

Effect on Influenza Virus

Favipiravir was used in the treatment of Ebola fever, and it had also normally been applied as a treatment of influenza in Japan. In previous reports, the main function of favipiravir was to effectively disrupt RNA virus and act as an inhibitor of virus replication against influenza virus, Ebola virus, polio virus, and rhinovirus via inhibiting RNA-dependent RNA polymerase as demonstrated in Figure 2.[50-52] Moreover, favipiravir has been evaluated for efficacy against SARS-CoV-2 in Phase 3 clinical trials in (mild and moderate symptomatic patients). Viral shedding and anti-viral loading were achieved in patients who received favipiravir (1,800 mg/day).[30] Accordance with the clinical study of Dabbous and colleague, they demonstrated the efficacy of favipiravir that could reduce the mechanical ventilation requirement and increase oxygen saturation higher than 90%.[53] For Thai plants which were reported on Influenza (H1N1) such as *Andrographis paniculata* (Brum.f.) Nees (Fah-Talai-Jone), *Phyllanthus amarus* Schumach. & Thonn. (Look-Tai-Bai), *Phyllanthus emblica L.* (Makham-Pom), *Curcuma longa* L. (Kamin-Chan), *Zingiber officinale* Roscoe. (Khing), *Illicium verum* Hook. f. (Jan-Pad-Kleeb), *Allium sativum* L. (Garlic or Kra-tium in Thai, *Tiliacora triandra* Diels (Ya-Nang).[54-59] A previous report, used Benchalogawichian as a Thai traditional remedy to reduce fever to treat H1N1 through pretreatment or an inhibitory effect of virus in host cells.[60] Thus, these plants should be used to reduce fever and evaluated scientifically for their potential use to treat COVID-19 patients.

Molnupiravir is a ribonucleoside analog prodrug (β-D-N4-hydroxycytidine) (NHC) antiviral drug. Molnupiravir essentially converts NHC to the active 5'-triphosphate through host kinases. The active 5'-triphosphate acts as a competitive binding agent to RNA-dependent RNA polymerase. Recently, a study found that molnupiravir was able to reduce viral RNA replication and decrease nasopharyngeal SARS-CoV-2 infectious virus in patients who received 800 mg of molnupiravir. In addition, molnupiravir also has a satisfactory safety profile.[31] The mechanism of action of these drugs has been described in Figure 2.

ACE inhibitor

Because of the S-protein on SARS-CoV-2 has high affinities with the ACE2 receptor which is related to hypertension and cardiovascular disease. Captopril and candesartan are commonly used to treat high blood pressure and heart failure acting as ACE inhibitor and angiotensin type-1 receptor blocker, respectively. The effects of captopril and candesartan were estimated against SARS-CoV-2 and it has been reported that these drugs inhibit viral replication via blocking S-protein entry to cells and decrease inflammation.[61] In plant sciences, previous reports also indicate that *Hibiscus sabdariffa* L. extraction could reduce hypertension, via inhibiting ACE and plasma renin activity.[62] These extracts also inhibit proinflammatory mediator release.[63] Thus, these activities of *H. sabdariffa* could be potentially used to alleviate COVID-19 symptoms.

Thai herbs reported for COVID-19 Treatment

Commercially developed Western antivirals mentioned above are often limited to use only in the hospital and with severe cases. Many herbal remedies including Thai Traditional Medicines could be tested, examined and utilized to scientifically further our knowledge. Several herbs have been reported and utilized in the treatment of COVID-19 such as *A. paniculata, B. rotunda, P. amarus, P. emblica* L., *Citrus medica* L., and *Z. officinale* as summarized in Table 1.

Andrographis paniculata leaves were used to reduce fever described in National List of Essential drug in Thailand. It is the first line drug for sore throat. Many reports found that it had antimicrobial activity. Its major component

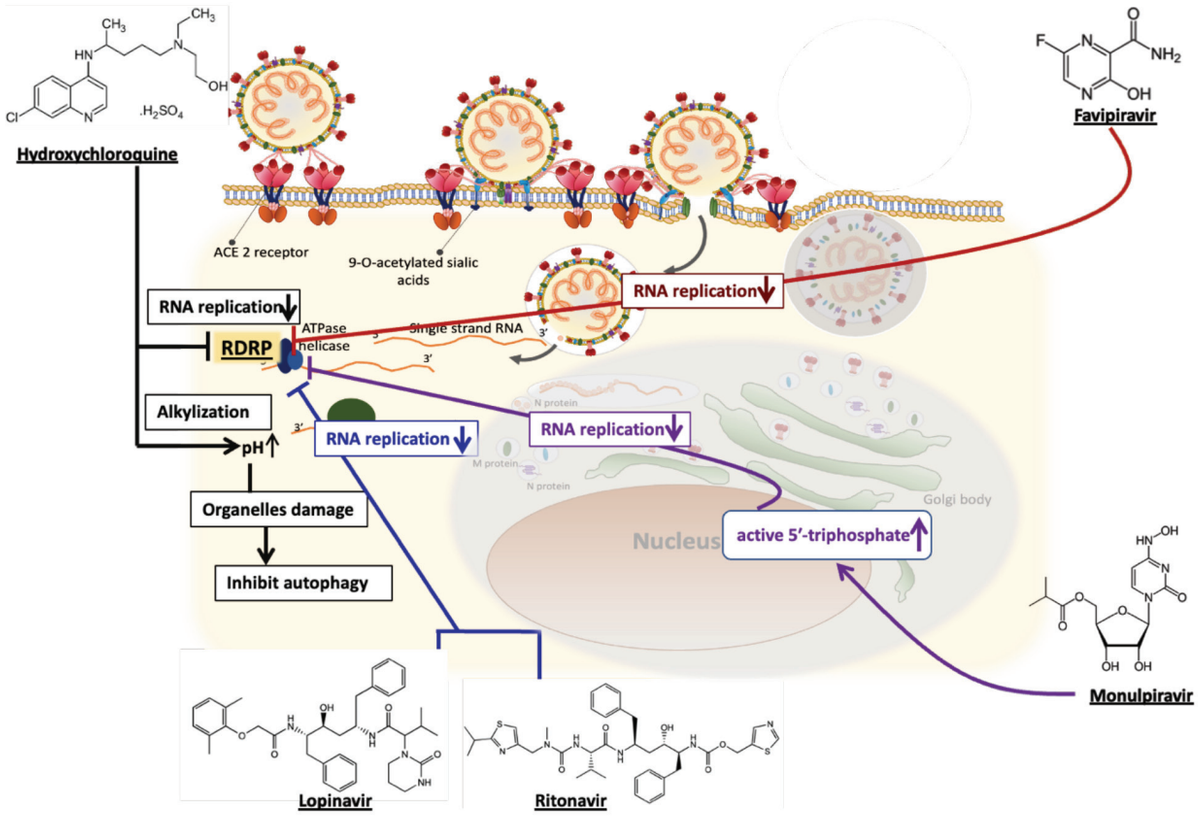

Figure 2 Schematic the mechanism of action of some drugs against SARS-CoV-2. Black line presents the efficacy of hydroxychloroquine against SARS-CoV-2 infection as following: inhibits RNA replication via blocking RDRP activity; increases pH condition in endosome to induce organelles damage and suppresses autophagy. The mechanism of lopinavir/ritonavir against SARS-CoV-2 is the inhibition of RDRP (blue line), which is the same as favipiravir in the red line. Monulpiravir generates active 5'-triphosphate to competitively bind with RDPR and block RDRP activity as demonstrated in the purple line.

is andrographolide. Early studies mentioned that, andrographolide reduced virus propagation and infection in various viruses such as, Chikungunya virus, Influenza virus, HIV, Denge virus, and *Herpes simplex* virus type 1.[64-68] The *in-silico* docking analysis study has also demonstrated that 15 phytochemicals of *A. paniculata* had affinity and interacted with S-protein, and C-terminal cleavage of virus, N-terminal cleavage of viral polyprotein of SARS-CoV-2.[69] *In vitro* study, demonstrated that the *A. paniculata* ethanolic extract and andrographolide as its main compound inhibited viral replication after inoculation with SARS-CoV-2 in Calu-3 cells (IC_{50} = 9.54 µM and 1.68 µM).[70] This study confirms that the efficiency of *A. paniculata* that it could reduce viral replication while the efficacy in a clinical study remains to be determined. One trial has already shown a decrease in pneumonia symptoms of patients who received 94.3% pure *A. paniculata* ethanolic extract with a reduction in the requirement for mechanical ventilation of patients.[71]

Meanwhile, the effectiveness of ***B. rotunda*** on SARS-CoV-2 has been reported that the *B. rotunda* ethanolic extract and panduratin A could potently inhibited viral loading and viral activity after infection in Vero E6 cells with IC_{50}'s of 3.62 µg/mL and 0.81 µM respectively.[43] In addition, this plant and pandulatin A were also reported as HIV1-protease inhibitors and possessed antinociceptive effects in thermal and mechanical pain models.[42, 72] This pharmacodynamic effect also reduce body temperature and nociception caused by viral infection. The ethanolic extract also exhibited antiinflammation, antimicrobial, anti-foot and mouth disease virus, and anti-dengue virus activity. In addition, it also inhibits *Staphylococcus aureus* and *Klebsiella*

pneumonia which are the cause of pneumonia.[73] Thus, the ethanolic extract of this plant could be potentially used to treat COVID-19 because it can eradicate SARS-CoV-2 and it can reduce symptoms of this diseases especially the resultant pneumonia.

Moreover, ***C.medica*** (Manoa-Kwai in Thai), and *Z. officinale* (Ginger, Khing in Thai) have been evaluated for their affinity binding to the spike protein and other proteins on SARS-CoV-2 by *in silico* analysis and these components (Rhoifolin, Naringin, Neohesperidin, Apigenin 6,8-di-C-glucoside, Adenine, Hesperidin, 6-Gingerol Z, and Xanthine) have high affinity binding to S protein and also anti-inflammatory activity and exhibited the antiviral activity on spike protein of SAR-CoV-2 and ACE-2 receptor.[74] However, *C. medica* or other *Citrus* spp. have a high vitamin C content, this can facilitate mucolytic properties and, reduce cough and reduce fever. *Citrus* spp. peel contains coumarin compounds which can help to improve blood circulation and have anticoagulant properties. *Z. officinale* in Thai traditional medicine principle is used to treat air cavity diseases such as allergic rhinitis, nausea, sore throat, lung cancer, and viral infection in the respiratory tract. The research of ginger on antiviral activity against respiratory tract virus demonstrated that hot water with fresh ginger also had anti-viral activity against human respiratory syncytial virus (HRSV) in human respiratory tract cell lines by induced plaque formation of HRSV on airway epithelium and through blocking viral attachment and internalization.[75] This report also found that fresh ginger had better antiviral activity than dried ginger. The extract of ginger also inhibited acute pneumonia caused by *Pseudomonas aeruginosa* which is a symptom of COVID-19.[76] In addition, ginger had also many reports about its anti-inflammatory activity which helps to reduce lung tissue damage. Its principal consistent compounds such as gingerol and shogaol, also showed high acute and chronic anti-inflammatory activity.[77] Thus, ginger and *Citrus* spp. (lime, lemon) should be further evaluated for treatment of the symptoms and antiviral activity against COVID-19.

The whole plant of ***P. amarus*** is used as an antipyretic drug in Thai traditional medicine and it is a widely distributed tropical medicinal plant. It also exhibits a broad spectrum of therapeutic activities included antibacterial, antiviral, antimalarial, anti-inflammatory, anticancer, and anti-oxidant.[78,79] The aforementioned activity of *P. amarus* has been evaluated against SARS-CoV-2 infection. Previous study of the interaction of *P. amarus* in an *in-silico* docking model exhibited that its flavonoid compounds (astragalin, kaempferol, quercetin, quercetin-3-O-glucoside and quercetin) and tannins (corilagin, furosin, and geraniin) have a better affinity binding to RdRp (RNA-dependent RNA polymerase) and papain like protease on SARS-CoV-2 than Remdesivir. It has been suggested that *P. amarus* has 2 anti-replication activity against SARS-CoV- via blocking those proteins (RdRp).[69] Moreover, *P. amarus* was also reported to have antiviral HIV-1 activity[80] as mentioned above.

Meanwhile, (2S)-Eriodictyol 7-O-(6"-O-galloyl)-βD-glucopyranoside (EBDGp) as a compound of ***P. emblica*** (Makham-Pom in Thai) was analyzed by an *in-silico* model that it has high-affinity binding to RdRp (-23.32 kcal/mol) to reduce viral propagation.[81] The mechanism of these components has been described in Figure 3. However, *P. emblica* as a component in Thai traditional remedy called Triphala was reported as an antiviral activity on HIV-1 activity.[82, 83] The known glochicoccinoside D was isolated from its extract, also showed potent activity against influenza A virus strain H3N2 and hand, foot and mouth virus EV71, with IC_{50} values of 4.5 ± 0.6 and 2.6 ± 0.7 μg/ml, respectively.[84] In many previously reported studies, *P. emblica* fruits exhibited the adjuvant properties for COVID-19 treatment such as its immunological, antiallergy, anti-tussive and laxative effects.[83] These activities could relieve such symptoms of patients infected with COVID-19 although further study is required.

Moreover, Emodin as anthraquinone group was isolated from root tubers of ***Rheum officinale* Baill** (Rhubarb or Kod Num Taow in Thai), and it has been reported to block the SARS-CoV spike protein and angiotensin-converting enzyme 2 interaction by inhibitory effect on the infectivity of S protein-pseudotyped retrovirus to Vero E6 cells.[85] A perusal of Thai traditional medicine demonstrated that, emodin has been reported in *Cassia* species such as *Cassia siamea* Lam. (Khe-lhek in Thai), *Cassia alata* (L.) Roxb. (Chum-Hed-Thet in Thai) and *Cassia angustifolia* M. Vahl (Makham-Kak). These plants all demonstrate laxative properties. The laxative property in Thai traditional medicine

principle is used to reduce fever. Thus, *C. siamea* curry as a food for COVID-19 patients may possibly have therapeutic ingredients.

Glycyrhhizin as an active anti-inflammatory of Licorice (***Glycyrrhiza glabra* L.**) has a sweet taste. Glycyrrhizin demonstrated activity against two clinical isolates of coronavirus from patients with SARS admitted to the clinical center of Frankfurt University.[86] It inhibited replication of the SARS-associated virus. Moreover, it also blocked the SARS-CoV-2 replication through inhibiting the main viral protease.[87] This finding has suggested its possible use for the treatment of SARS. Morever, glycyrrhizin as a triterpenoid saponin also has effects on chronic and acute inflammation.[88] Thai traditional medicine principles suggest licorice in herbal remedies can provide relief of cough and reduce inflammation from a sore throat.

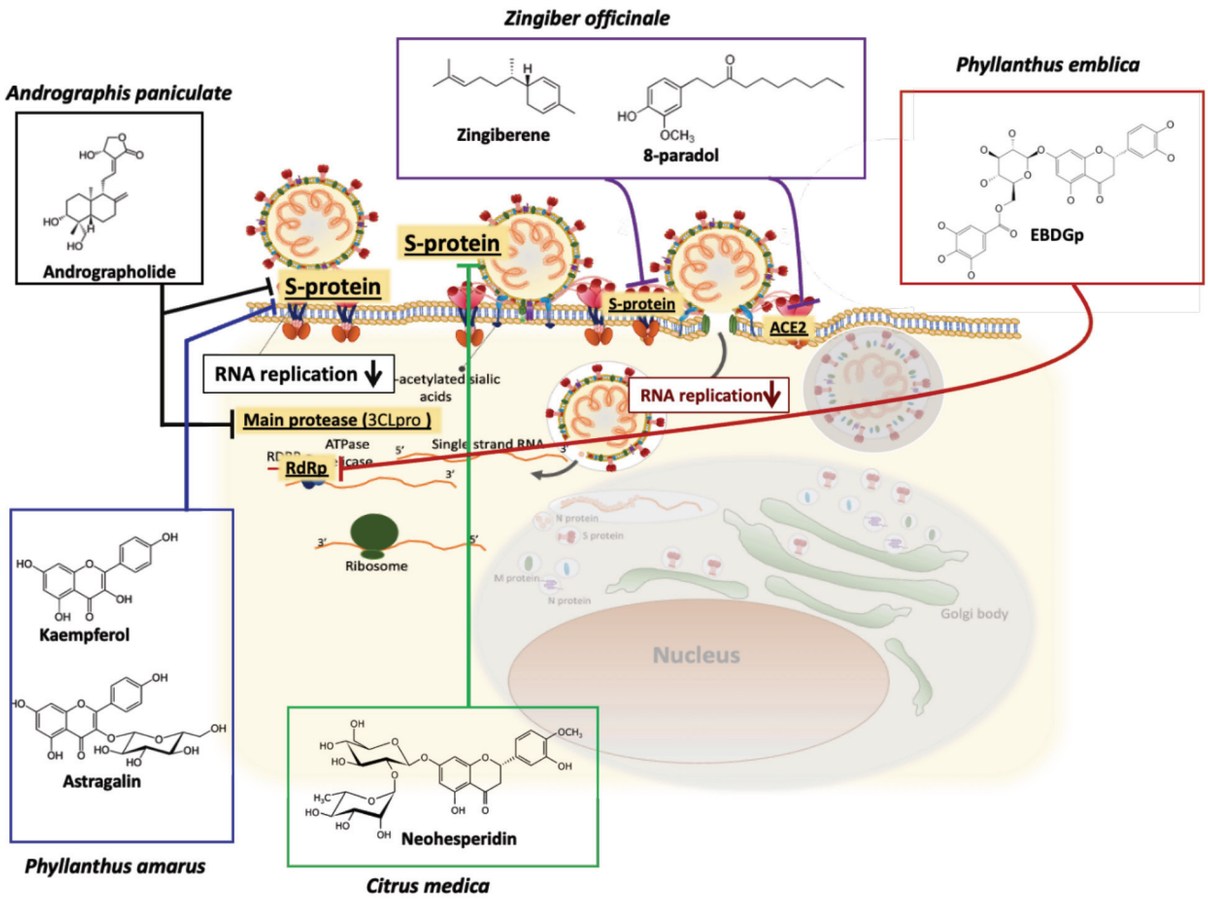

Figure 3 Schematic the mechanisms of action of natural products against SARS-CoV-2 (in silico model). Black line presents the efficacy of Andrographolide against SARS-CoV-2 infection as following: inhibits RNA propagation via blocking S-protein and 3CLpro. The mechanism of Kaempferol, Astragalin, and Neohesperidin from *Phyllanthus amarus* and *Citrus medica* can inhibit the activity of virus through blocking S-protein (blue and green line). Zingiberene and 8-paradol are effective against SARS-CoV-2 via blocking S-protein and ACE2 receptor (purple line). EBDGp inhibits the expression of RDRP (red line), which is equivalent to favipiravir in the red line.

Table 1 The therapeutic efficiency of natural product against SARS-CoV-2

Botanical Names	Thai Names	Active compounds	Mode of Action
Andrographis paniculata (Burm.f.) Wall. Ex Nees. **(Acanthaceae)**	Fah Ta Lai Chone	Andrographolide	***In Vitro*** -Anti-SAR-CoV-2 activity via suppressing virus proliferation.[70] ***In silico:* Docking analysis**[69] -Against SAR CoV-2 virus by affinity binding to S-protein of SAR CoV-2 (-6.00 kcal/mol and -8.4 kcal/mol) -Docked with 3 CLpro (C-terminal cleavage of virus polyprotein) to control viral replication (-6.1 kcal/mol) -Docked with PLpro (N-terminal cleavage of viral polyprotein) to regulate viral replication (-6.8 kcal/mol). **Clinical study** -Alleviated pneumonia symptoms > 94.3%.[71]
Boesenbergia rotunda (L.) Mansf. **(Zingiberaceae)**	Krachai luang	**Extracted with 95% EtOH** 3.62 μg/mL of *B. rotunda* extract, 0.81 μM of panduratin A	***In vitro:* Vero E6 cells** -Reduced viral loading and viral replication[43]
Citrus medica L. **(Rutaceae)**	Manoa-Kway	Rhoifolin Naringin Neohesperidin Hesperidin	***In silico:* Docking analysis**[74] Rhoifolin -58.43 kcal/mol binding affinity to S protein Naringin -44.48 kcal/mol binding affinity to S protein Neohesperidin -60.95 kcal/mol binding affinity to S protein Hesperidin -59.47 kcal/mol binding affinity to S protein
Glycyrrhiza glabra L. **(Fabaceae)**	Cha-em-thet	**Glycyrhhizin**	-Blocked viral replication via viral main protease[87]

Table 1 The therapeutic efficiency of natural product against SARS-CoV-2 (Cont.)

Botanical Names	Thai Names	Active compounds	Mode of Action
Phyllanthus amarus Schumach. Thonn. **(Euphorbiaceae)**	Look Tai Bai	**Flavonoid** - Astragalin - Kaempferol - Quercetin - Quercetin-3-O-gluco-side **Tannins** - Geraniin	***In silico:*** **Docking analysis**[69] -Astragalin -9.8 kcal/mol binding affinity to S protein -Kaempferol -9.6 kcal/mol binding affinity to papain like protease -Quercetin -9.2 kcal/mol binding affinity to S protein -Quercetin-3-O-glucoside -9.8 kcal/mol binding affinity to S protein -Geraniin -10.60 kcal/mol binding affinity to S protein -9.1 kcal/mol binding affinity to RdRp
Phyllanthus emblica L. **(Euphorbiaceae)**	Makham Pom	(2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside (EBDGp)	***In silico:*** **Docking analysis**[81] EBDGp -23.32 kcal/mol binding affinity to RdRp more than Remdisivir -EBDGp has an inhibitory effect in viral replication via blocking RdRp
Zingiber officinale Roscoe. **(Zingiberaceae)**	Ginger, Khing	**Extracted with 95% EtOH** 1.45 µg/mL of *Z. officinale* extract	**In vitro: Vero E6 cells** -Reduced viral loading and viral replication[43]
		− Gingerenone − Shogaol − Zingiberene − 10-Shogaol − 8-Gingerol − 8-Paradol − 6-Gingerol	***In silico:*** **Docking analysis** Gingerenone[89] -5.87 kcal/mol binding affinity to ACE2 protein Zingiberene[89] -5.77 kcal/mol binding affinity to ACE2 protein -6.23 kcal/mol binding affinity to S protein 10-Shogaol[74] -37.87 kcal/mol binding affinity to ACE2 8-Gingerol[74] -46.85 kcal/mol binding affinity to ACE2 8-paradol[74] -51.27 kcal/mol binding affinity to ACE2 6-Gingerol[74] -38.60 kcal/mol binding affinity to S protein

Discussion

According to the Nine Tastes Theory underpinning Thai Traditional Medicine (TTM), the plants with bitter taste are used to reduce fever. The results of a literature review; *Andrographis paniculata, Phillanthus amarus, Tiliacora crispa, Tinospora triandra, Rheum offinale, Cassia siamea* all reduce pyresis, and also have laxative properties. In Thai traditional medicine, laxatives help to reduce fever or reduce heat in the body. Moreover, these plants with bitter taste were also reported and described as antiviral against COVID-19. The spicy taste of TTM theory is used for promoting blood circulation and reducing inflammation. Zingiber plants in TTM theory are used for treatment of organs which have air cavities or hollow such as lung, throat, nose, stomach, bone, and joint. From this review, *Boesenbergia rotunda* (L.) Mansf. and *Zingiber officinale* Roscoe. were reported to have antiviral activity and affected virus replication. Two of these plants had also anti-inflammatory, immunomodulatory, anti-allergy and antimicrobial activities which can reduce the symptomatic effects due to COVID-19 such as sore throats by infection and inflammation from cough, and they may also protect lung tissue damage. The sour taste of plants is used as laxative and for their mucolytic activity. In this review, *Citrus medica* and *Phyllanthus embelica* which possess sour tastes were reported to reduce virus replication of COVID-19. In addition, *Hibiscus sabdariffa* also has a sour taste, it has also been reported to be an ACE inhibitor which can inhibit COVID-19 virus attachment to the ACE-2 receptor. Thus, *Hibiscus sabdariffa* could be used to inhibit the virus, furthermore, its diuretic and laxative properties can reduce fever according to TTM theory. However, TTM theory mostly uses many plants in a herbal remedy as for synergistic effect including to reduce possible toxic or side effect, such that some plants can enhance activity of each other or synergistic effect, some plants are tonic. For example, the previously used ginger and *Citrus medica* for treatment COVID-19.[74] Described by TTM, ginger is spicy in taste which can help relieving inflammation and *Citrus* as sour taste used for mucolytic effect and laxative which can reduce fever. Thus using these two herbs can help in COVID-19 treatment or reduce many symptoms derived from this disease such as fever, cough, inflammation of lung, and sore throat. In addition, ginger and *Citrus* spp. can enhance immunomodulatory activity.

A comprehensive analysis of Thai Herbal Medicine literature coupled with the Western scientific basis and clinical literature analysis suggested the potential of Thai Herbal medicine, specific plant derived extracts and individual natural compounds could be further developed to provide additional mechanistic insight into the treatment of COVID-19. Coronavirus Disease-2019 (COVID-19) has dreadfully resulted in a global pandemic of contagious respiratory disease with significant physiological and pathological sequelae caused now millions death and suffering. Despite significant and welcomed advances in vaccines for prophylaxis against the virus, there are a paucity of clinical treatments for active disease which are still required for afflicted patients. The potential use of Thai Herbal Medicine as well as other traditional derived medicines and development of herbal extracts or isolation and development of plant derived compounds for therapeutic treatments remains a promising approach. The use of Thai Herbal Medicine could most likely be the best solution to fight against the problem arises from the mutation of virus, a problem very difficult to be solved by the use of vaccine. Integrating Thai Traditional Medicine principles with contemporary COVID-19 research may further unlock clinical therapeutic potential and requires urgent research funding and studies.

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Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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