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Review Article

Medicinal Plants as Recent Complementary and Alternative Therapy for COVID-19: A Review

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ABSTRACT

The World Health Organization stated COVID-19 became a pandemic since March 11, 2020. With the absence of a vaccine and standard treatment for Covid-19 infection, individual protection including maintaining personal hygiene, consumption of food, vegetables and fruit that can increase immunity is the key to preventing COVID-19. The combination of herbs and modern therapy can contribute to lower mortality rates and a faster response in controlling outbreaks. This review is aimed to determine plants that have effect on coronavirus infection, mechanism of action, dosage, toxic effect, thus can be beneficial for strengthening health against covid-19. This research is a literature review that search articles using Google Scholar, ResearchGate, NCBI, PubMed, Web of Science and Semantic Scholar, used a combination keywords related to coronavirus or COVID-19, SARS CoV-2, herb, natural compound, mechanism of action, dosage, toxic effect, meta-analysis, review. *Curcuma longa*, Cinnamon, Glycyrrhizin, *Kaempferia galanga*, Eucalyptus essential oil, black tea, were plants that have pieces of evidence as anti-coronavirus. The molecular mechanism of these plants as anti-virals varies by inhibiting entry, blocking viral receptors, inhibiting enzymes, enhancing immune system, interfering with signal transduction, relief symptoms. Therefore, plant products used in the right dose could be beneficial against coronavirus infection.

Keywords: Anti-viral agents, COVID-19, Medicinal plants, Mechanism of action, Molecular, SARS-CoV.

Introduction

A novel coronavirus was identified as the cause of a respiratory tract infection that started since December 2019 in Wuhan, China.[1] The World Health Organization (WHO) named the virus as 2019 novel coronavirus (2019-nCoV or COVID 19.[2,3] In early March 2020 the viral infection had spread in Indonesia with the discovery of two cases in Jakarta,[4] and has spread in hundreds of countries thus WHO declared COVID-19 a pandemic.[2,3,5]

Among the RNA viruses, the coronavirus has the largest genome of 30 kb. [6] Coronaviruses (CoVs) are an enveloped virus family, zoonotic RNA viruses, with four variances of viruses that generally circulate in humans, namely HCoV2-229E, -HKU1, -NL63 and -OC43.[7]

The genome of SARS-CoV contains one open reading frame (ORF) encodes the polyproteins that has function in viral replication, namely pp1a and pp1ab, and five ORFs that code for structural proteins.[8] The pp1a and pp1ab by 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PL) proteases were cleaved to produce 16 nonstructural proteins.[9,10]

During the viral maturation process, coronaviruses encode papain-like protease (PLP) and 3CLPro proteases.[6, 11] Therefore the 3CLPro protease from SARS-CoV determined as essential target for the discovery of SARS-CoV drugs.[12, 13] Both types of proteases are used as therapeutic targets for SARS-CoV infection drugs because the proteolytic process is the key in the formation of a functional replication complex.[14]

The challenge in the treatment of the coronavirus is the difficulties to find a broadspectrum antiviral that is effective against COVID-19 infection, because COVID-19 virus is a type of RNA virus that mutates easily thus easily becoming resistant to anti-viral that it has been susceptible before. The development of COVID-19 vaccine until it is ready to be marketed requires a long stage and time, likewise some modern synthetic anti-viral drugs used for COVID-19 have major side effects.[15]

Without the existence of vaccines and standard treatment in handling COVID-19 infection, individual protection including maintaining good personal hygiene, properly fitting masks, avoiding crowded places and eating food, vegetables and fruit that can increase endurance is the key to preventing COVID-19. Food, vegetables, fruit consumed daily are categorized as good personal hygiene against COVID-19 because certain active ingredients contained in food would increase the immune system thus making COVID-19 infection preventable.[16]

Medicine from natural resources such as fruit, vegetables are relatively inexpensive, easy to use, relatively less side effects than synthetic drugs, and herbal medicine is trusted to overcome various diseases.[17] Numerous studies had described bioactive natural compounds that have effect as anti-coronavirus or SARS-CoV.[16,17]

This review aimed to determine the effect of various plants that are easily obtained and consumed every day against coronavirus infection,

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their mechanism of action, dosage and toxic effects. Therefore these plants could be used as a complementary therapy for COVID-19.

Materials and Methods

The data used in this study come from various literatures related to the issues discussed. Most of the main types of references used come from scientific journals. All journals that match the keywords: herbal, coronavirus, experimental study, meta-analysis were comprehensively analyzed with the following aims: (1) to determine herbs that have been proven to have an effect on coronavirus infection; (2) the molecular mechanism of these herbs against coronavirus; (3) effective doses, or toxic doses and side effects of herbs that have an effect on the coronavirus. We use search engine PubMed®, Web of Science® and Sci Verse Scopus® using keywords herb, natural plant in COVID-19, controlled trials, docking study, meta-analysis, active compound, mechanism of action, dose, toxic, side effect.
The research method is literature study and the information obtained from various literatures and compiled based on study results and information obtained. This review strives to find related literature, relevant to the topic of discussion, and to minimize the possibility of bias. The data analysis technique is descriptive.

Results and Discussion

We found 8 journals suitable with keywords herbs, coronavirus, experimental study, meta-analysis, and 45 journals with keywords docking study, coronavirus, herbs. Molecular docking (docking study) is a computational method that aims to mimic the interactions of a ligand molecule with the protein it targets.[18] The computational approach to develop drug are increasingly being used in COVID-19 drug development research.[19]
Research with the docking method was carried out to analyze compounds that would interact directly with the 2019-nCoV protein. The most widely used drug discovery approach methods include quantitative structure-activity relationship (QSRA), artificial intelligence, virtual screening, and molecular docking studies.[20]
Docking is part of the science of bioinformatics, which can predict interactions between molecules, such as proteins, enzymes, DNA, carbohydrates, fats and their substrates in order to obtain a stable and spontaneous interaction, characterized by increasingly negative degrees of free energy. With the Docking method, the initial selection stage of many substrates in a wet laboratory is easier because the number of test samples is getting smaller, but the drawback of docking is that there could be a mismatch between the results of bioinformatics or docking with the wet laboratory (false positive or false negative). Two approaches are used in the docking process, namely the technique of matching the substrate with protein as a complement, and calculating the degree of free energy. Each technique has advantages and disadvantages.[18]
The desired protein form is required in the screening process, the protein form is obtained by Crystallographic techniques, NMR spectroscopy, and electron microscopy. Crystallography is the process of obtaining protein crystals and then firing them using X rays on a film, while NMR spectroscopy is the process of seeing the resonance of the magnetic core reacted with the protein. The protein database (RCSB) and its protein substrate are available thus researchers interested in research using docking techniques could use it.[18]

Curcuma longa
Using molecular docking study, it has been concluded that COVID-19 Mpro was inhibited by kaempferol, quercetin, lutheolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate.[21] Curcumin is also used traditionally as anti-anaemic.[22]
Plants containing curcumin such as *Curcuma domestica* and *Curcuma xanthorrhiza* have also been shown to have antioxidant activity.[23]
Various *in vitro* and *in vivo* research indicate that curcumin has anti-diabetic, antioxidant, anti-cancer, and anti-inflammatory activities.[24,25]
It has been reported that Curcumin have beneficial effects on infectious diseases, especially viral infection, treatment of cardiovascular disease, metabolic syndrome, or diabetes.[26]
Curcumin, derived from *Curcuma longa*, overcome *in-vitro* and *in-vivo* infection of influenza A virus that induces pneumonia, decrease inflammatory cytokines and inhibited signaling of NF-kb on macrophage.[27] Other researchers mentioned the molecular mechanism of action of curcumin; it inhibits haemagglutination in influenza virus.[28] The mechanism of curcumin to reduce inflammation in animal models with lethal pneumonia is by immunomodulating pro and anti-inflammatory cytokines, as a scavenger of reactive oxygen species (ROS) and induces apoptosis of PMN cell, thus curcumin has potential effects in the treatment of pneumonia and ALI/ARDS in humans caused by coronavirus infection.[26]
Curcumin has pleotropic ability to modulate a variety of signalling molecules including apoptosis proteins, pro-inflammatory cytokines, NF-κB, phosphorylase kinase, altering growth factor-β. Consuming less than 12 g of curcumin for 3 months is still safe and does not cause toxic effects.[29]
A summary of studies examining medicinal plant that has antiviral effect against coronavirus, their active compound, and mechanism of action, is presented in Table 1.

Citrus
Citrus is the largest source of vitamin C. Vitamins C is also found in red peppers, oranges, strawberries, broccoli, mangoes and lemons.[30]
Previous research by Bucher and White, 2016 shows the relationship between citrus and the immune system in dealing with the common cold.[31]
Lemon is a powerful antioxidant, it contains biologically active compounds such as triterpenoids, coumarins, alkaloids, phytosterols, pectin and polymethoxy flavones.[16] Quercetin, is a potent antioxidant flavonoid derived from the pigment of plant found mostly in cherries, onions, berries, grapes, broccoli, and citrus fruits.[32] The mechanism of action of quercetin and catechin is by inhibiting SARS-CoV proteases (3CLpro and PLpro). Previous research has concluded that quercetin act as an anti-coronavirus by modulating the cellular unfolded protein response (UPR) required by coronavirus to undergo its life cycle during the infection process.[33] Quercetin-3-β-galactoside is a potent inhibitor of SARS-CoV 3CLpro.[27]
Currently, formulas derived from herbal components have been investigated against viral infections. Novirin formula consist of five component; quercetin, green tea, cinnamon, liquorice and selenium. Previous research has shown that novirin is effective against viral infections such as HPV, HSV, EBV and cytomegalovirus by inhibiting viral entry, replication, viral proteases and increasing immunity to viruses, reducing the formation of ROS.[33]
Safety dose for quercetin is 945 mg/m^2. Quercetin causes nausea, increase blood pressure, renal toxicity, and decrease of serum potassium in excessive dose. The distribution half-life of quercetin is 0.7–7.8 min whereas distribution half-life is 86 min. Volume of distribution of Quercetin is 3.7 L/m^2 whereas clearance of quercetin is 0.23–0.84 L/min/m^2. There was a study that had investigated pharmacokinetic of quercetin aglycone orally in healthy volunteers.[32]

Tomato
Solanum lycopersicum or tomato are the major source of lycopene, beta carotene, flavonoids and vitamin C as well as hydroxycinnamic acid derivatives. Since the discovery of lycopene's anti-oxidative, anti-cancer properties, interest in tomatoes has grown rapidly.[34]
Tomatoes are a miracle fruit that is very useful because it contains various compounds including vitamin A, vitamin C, flavonoids, phenols, lycopene, glycoalkaloids or tomatine.[35] Tomatoes also contain lutein. Carotenoids in tomatoes are found in leaves, flowers and fruit.[36] Tomatoes are also useful as antioxidants, anti-inflammatory, anti-cancer, and anti-atherogenic activities.[35] Many studies have proven that vitamin C reduces the risk and shortens the duration of viral infections, prevents and cures acute respiratory infections caused by viruses without significant side effects.[37]
Flavonoids are phenolic compounds that are found in plants and have various biological functions such as antioxidant, anti-inflammatory,

anticancer, antimicrobial and immunomodulatory activities.[38] Rhoifolin, pectolinarin and herbacetin are three kinds of flavonoids that can inhibit 3CL pro of SARS-CoV.[39] Flavonoids is also beneficial in coronary heart disease prevention and some flavonoids exhibit potential antiviral activities.[40]

Many kinds of flavonoids among other polyphenolic group compounds in the human diet are found ubiquitously in plants. Flavonoids are found in many different species of plants and can be subdivided into flavonols, flavones, flavanols, flavanones, anthocyanidins, proanthocyanidins, and isoflavones.[41]

Mechanism of action of flavonoid as antiviral through prophylactic, therapeutic or indirect inhibitors is by interacting with the immune system. The summary of the mechanism of action of flavonoids as antiviral includes: being able to bind to the protein in the capsid or extracellular part of the virus, preventing the attachment or entry of the virus into the host cell, binding to virions and modifying the virus structure thus the virus is unable to uncoat, acting as early-stage replication inhibitors, transcription and translation blockers, inhibit late-stage maturation such as inhibition of assembly/packaging and release and flavonoid can modulate the immune system to reduce viral load.[38]

Daucus carrota

Daucus carrota or carrot contains carotenoids, with beta-carotene being the major form of carotenoid. In one carrot, there are about 16 to 38 mg/100 g carotenoids while vitamin C is found up to 21 mg/kg to 775 mg/kg. Phenol, carotenoids, polyacetylene, and ascorbic acid are four types of phytochemicals found in carrots. Orange carrot contains α and β-carotene, lutein in yellow carrots, lycopene in red carrots, anthocyanins in roots and purple carrot, while black carrots contain phenolic.[30]

The mechanism of vitamin A is to provide protection against acute respiratory infections caused by viruses by being involved in cellular and humoral immunity, metabolism of mucins and keratins, cytokine expression, lymphopoiesis and apoptosis.[37]

Sunflower

Sunflower is a major source of vitamin E. Vitamin E is also found in soybean, walnut, corn, wheat germ, nuts, seeds, spinach, and broccoli.[30] Vitamin E effect is to reduce oxidative stress by binding free radicals.[42]

The factors that determine mild, moderate, severe or fatal COVID-19 are age, sex, metabolic status determined by nutrition, medical conditions, lifestyle, environmental factors. Diet and nutrition affect the immune system, the risk and severity of infection. There has been a proven link between diet, nutrition, infection and immunity. The nutrients that can modulate the immune system can be classified as macronutrients, micronutrients. Many studies mention beta carotene, vitamins C and E, selenium, zinc and polyphenol components that can modulate the immune system.[37]

Olive

Olive oil is a source of various vitamins such as vitamin E, K and A. Olive oil has biological activity as an antioxidant.[43] Olive also contain limonoids and triterpenoids. Other medicinal plants that contain limonoids and triterpenoids are licorice, neem, tulsi and citrus. They have been used as traditional medicine for various purposes.[44]

A study examined the effect of vitamin E in mice infected with Influenza virus showed that pathology of the lung and death was decreased because cytokine response related T helper 1 was enhanced. Vitamin E also can improve synapse of T Cell development and start the activation signal of T cell.[45] Vitamin A influence production of antibody, enhances effector cell of the immune system such as neutrophils, natural killer cells, monocytes, macrophages, T cells, and B cell.[37]

Grain

Grain is an important source of selenium. Alfalfa, cruciferous species such as cabbage, broccoli and cauliflower are sources of selenium. Selenium is not only beneficial for health, but can also cause toxicity, depending on it chemical form. Selenium in the form of redox-active selenite is the only form that can be beneficial for health.[46] Research by Kieliszek and Lipinski, 2020 shows that selenium, in the form of sodium selenite, oxidizes thiol groups in the viral disulfide isomerase protein so that viruses cannot penetrate healthy cell membranes.

Selenium supplementation can induce immune system to viral infections and decrease viral virulence.[33] Selenium provides protective effect against viral infections through redox signaling mechanisms, redox homeostasis as well as anti-oxidants. In conditions of adequate selenium, the immune system will develop towards Th1, while in a state of selenium deficiency the immune system will be polarized towards Th2.[37]

Nuts

Nuts are source of vitamin E and zinc.[30] Zinc also can be found in seed of pumpkin and sesame, beans, lentils.[30] Grapefruit, lemon, orange, kiwi, strawberries, broccoli, cauliflower, pumpkin, spinach, sweet potato, and carrots also are sources of zinc.[47]

Numerous studies have stated that zinc, selenium vitamins A, C, E, B6, B12 can induce acquired immune response through involvement in the process of differentiation, proliferation of T and B cells. The components of these nutrients also influences the production of antibody, contributing to cellular immunity, regulating inflammatory response and having anti-microbial activity.[47]

Non-specific immune system cells require zinc to function properly. Research has proven the protective role of zinc in viral infections such as HIV, hepatitis C, Herpes simplex virus. Zinc increases the immune system, suppresses viral replication in viral infections, thus it can shorten the symptoms and duration of viral infection.[37]

One research concluded that various mechanisms of zinc action, among others, is by affecting non-specific immune system cells, as a component of various transcription factors needed by the virus, affecting T cell function and Th1 cytokine production, affecting macrophage function, including regulation disturbance of cytokine production, phagocytosis and intracellular killing.[37]

Selenium toxicity in humans is found at blood levels of 300 to 7500 µg/L. Median lethal dose for selenium compounds in animal species is 1.5 to 6 mg/kg body weight. The organ most affected by the toxic dose is the central nervous system but it can also affect the liver, heart, lungs. Long-term exposure can cause chronic poisoning, liver cirrhosis in rodents, whereas in domestic animals several changes and deformation were found. Problems of hair and nail were reported as an effect of consuming 1-5 mg selenium per day in humans. Other symptoms in the form of prolonged bleeding time and Garlic breath are found as a result of exhalation of dimethylselenide.[48]

Selenium in a form that is more bioactive and has greater safety is Se-methylselenocysteine (SeMC) which is found to be 3.4 mg/kg BW/day, while the median lethal dose (LD_{50}) is 12.6 in female mice and 9.26 mg/kg BW in male mice.[49]

Kaempferia galangal

Kaempferia galanga is an example of plant containing flavonoid. A study showed that *Kaempferia galangal* had moderate antiviral activity, while lycoris had the strongest anti-viral activity.[27] Consumption of flavonoids 0.2 - 1.2 g/day could prevent upper respiratory tract infections.[41]

There are several flavonoids that can inhibit the 3CLpro. Flavonoid is needed in the replication process of the coronavirus, including COVID-19, SARS and MERS.[37] Herbacetin, isobavaschalcone, quercetin, and helichrysetin are flavonoid that potentially block the enzymatic activity of MERS - CoV 3CL protease.[50]

One study reported LD_{50} of the flavonoid rich fraction was above 5000 mg/kg body weight in mice. Administration of 100 and 200 mg/kg BW after day 14, decreased liver enzyme ALT and AST.[51] Liver failure, skin reaction, hemolytic anemia, and excessive estrogen in male and female had been reported as sign of flavonoid toxicity.[52]

Tea

Many studies have evaluated green tea extract can act as personal hygiene protection that overcome viral infections.[16] Catechin that is found abundant in green tea is Epigallocatechin-3-gallate (EGCG) which has been approved to decrease viral infectivity, also EGCG

and ECG were proven to suppress viral RNA which plays a role in virus propagation. Epigallocatechin-3-gallate (EGCG) has shown antiviral activity against several family of virus.[53]

Green tea has active ingredients, namely catechins, as well as quercetin, both of which are flavonoids that act as anti-oxidant, anti-inflammation, anti-enzymatic.[33] Tannic acid and 3-isotheaflavin-3-gallate based on literature studies are natural polyphenols found in tea which are 3CLpro inhibitor components. Tannic acid is an active compound that inhibits proteases.[54]

The difference between black tea and green tea is that green tea comes from dried tea leaves, low polyphenol oxidation, while black tea is high in fermentation thus the condensation is high, oolong tea composition according to green tea, undergoes partial fermentation. Black tea and puer tea are effective in inhibiting 3CLpro, however, puer tea has a complex structure making it difficult to isolate the active ingredient and identify its structure. Research shows the activity of 3CLpro inhibitors in black tea and puer tea is better than oolong and green tea.[54]

The important content of catechins is oxidized and condensed into theaflavins (TF). There are various TF types, TF2B and TF3 are the most effective 3CL pro inhibitors. TF 1 does not contain gallate components, while TF2B and TF3 contain gallate, thus it is estimated that the gallate component plays a role in the activity of inhibiting 3 CL pro.[54]

Consumption of up to 1.6 g of green tea extract is safe. A dose equivalent to 24 cups of green tea or 9.9 g per day is the maximum tolerated dose in human. Headache, dizziness and nausea have been reported as side effects of high doses of green tea extract, however, the safety and tolerability of long terms use of green tea extracts has not been well defined.[55]

Consumption of black tea up to 2 g/kg orally in Swiss albino mice was still safe without toxicity sign or mortality. There is no evidence of toxicity up to 250 mg/kg/day of black tea in Wistar rats for 90 days.[56] Black tea extract (BTE) caused toxic effect on pregnant rats and offspring.[57]

Glycyrrhizin glabra

Phytoconstituent of licorice root is glycyrrhizin, that is frequently used in Chinese herb, that can inhibit the replication of SARS virus at 4000 mg/L.[50] Glycyrrhizin and components related to reserpine also have anti-SARS-CoV effects.[27]

Glycyrrhizin's mechanism of action against SARS-CoV remains unclear. Glycyrrhizin influence transduction signal pathway through kinase and transcription factors. Glycyrrhizin inhibits replication of viruses through its aglycone metabolite 18 glycyrrhetinic acid that upregulate iNOS expression and NO production.[58] A study has reported that glycyrrhizin has antiviral activity, by blocking the attachment of viral particle to cell membrane binding, or through mechanism of signal transduction.[59] Other studies have reported that anti-SARS effect of glycyrrhizin is by stimulating the proliferation and activation of lymphocytes in humans.[33]

Glycyrrhizin also has been used in the treatment of liver disease, as well as antiviral HIV at a dose of 400-1600 mg/day intravenously. In Vero cell, Glycyrrhizin inhibits the cytopathic effect of SARS-CoV at EC_{50} of 300 mg/mL. Glycyrrhizin inhibits viral replication, adsorption and penetration.[60] Glycyrrhizin have fast metabolism at dose of 200 mg intravenously, it would only be obtained 80 µg/mL while the efficient dose needed for SARS in vitro is 400 µg/mL, thus Glycyrrhizin can be combined with chloroquine and tenofovir to increase the bioavailability of these drugs.[60]

In the life cycle of the SARS CoV virus, lipid raft is indispensable. The virus particles released by infected cells are reduced in the event of depletion of cholesterol with methyl-B cyclodextrin. Statins reduce infection caused by the coronavirus *in vitro* by inhibiting viral adhesion to the cell surface.[60]

Cinnamon

There is a hypothesis that oxidative stress is related to COVID-19, supported by evidence of the occurrence of cytokine storms, coagulopathy, and cell hypoxia in COVID-19 patients, thus it would inspire a new approach to COVID-19 therapy by reducing oxidative stress through antioxidants, iron complexing agents, NF-κB inhibitors and Nrf2 activators.[61]

Cinnamon has long been used in traditional medicine in Indonesia.[62] Cinnamon has various biological activities that are useful for health.[63] Cinnamon has antioxidant, anti-inflammatory, antilipemic, antidiabetic, antimicrobial, and anticancer effect. Oil obtained from the bark of cinnamon contains Cinnamaldehyde, while from the leaves containing eugenol, camphor is found in the roots and stems, while the fruits and flowers contain trans-cinnamyl acetate.[64]

Tenufolin, phytoconstituents acquired from cinnamon inhibited main protease of SARS-CoV2, whereas pavetannin C1 inhibited SARS-CoV2 spike protein by docking study.[63] Cinnamon as an anti-viral, its mechanism by inhibiting the entry of viruses into cells through a blocking mechanism of endocytosis.[33]

Eucalyptus

Medicinal plant that has been investigated for their activity as anti-viral of COVID-19 was *Eucalyptus globulus*, Labill, *Zingiber officinale*, Mentha, *Syzygium aromaticum*, *Cymbopogon citratus*, citrus. Exposure to temperature of 55^{o}C for 10 minutes will denature central protein of SARS CoV.[16]

Eucalyptus leaves are traditionally used to treat asthma.[16] Extraction from herbs and plants using a certain technique produces essential oils (EO) which are aromatic secondary metabolites from a complex natural mixture. Sesquiterpenes, monoterpenes and phenylpropanoids are phytochemical compounds from EO which have antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory activities.[65]

Essential oils (EO) of *Artemisia glabella* has been tested for influenza virus infection, while EO from *Eucalyptus globulus* has been tested for its effect on the HSV1 virus.[65] Research to determine the effect of EO was carried out by calculating the plaque formation in the appropriate host cell tissue culture *in vitro*. Essential oils (EO) has low therapeutic index or the distance between the therapeutic dose and the toxic dose is narrow, thus it is generally used as a disinfectant.[65]

Phytochemical compounds and EO constituents consisting of diterpenoids, sesquiterpenoids, and triterpenoids have been tested *in vitro* on Vero E6 cells showing specific and significant anti-SARS CoV results.[65] Research shows that EO has straight effect on free viral particles compared to intracellular viruses, its mechanism is by blocking the biological membrane of the virus, dislocating the viral envelope. However, *in vivo* and human EO research is still very limited. The anti-viral mechanism of specific EO depends on the plant species and type of EO.[65]

Eucalyptus and *Lonicera japonica* extract showed activities against SARS-CoV at 100 µM.[66] Combination of equal part of eucalyptus, cineol, cinnamomum, *Rosmarinus officinalis*, seed of *Daucus carrota*, *Camelina sativa* oil (seed) decreased viral units of H1N1 and HSV1.[67]

Clinical parameters outcomes of research on herbal ingredients in Covid-19 treatment

The outcomes that can be targeted in research on herbal therapy against COVID-19 infection are the total effective rate, symptom score, and symptom disappearance rate, clinically relevant results, such as blood test results (complete blood count), duration of symptoms, changes in chest CT scans, quality of life (using validated instruments), and side effects, could also be targeted outcomes for this type of study.[68]

Many clinical Parameter of COVID-19 infection can also be targeted for research on herbal therapy against COVID-19 are pulmonary CT, clinical cure rate, duration of hospitalization, clinical symptoms's total score, symptom score of cough, reduction time of fever, fever and fatigue symptom score, reduction cases of cough and fatigue, vanishing time of fatigue, syndrome of traditional chinese medicine (TCM), examination of viral nucleic acid, and biomarkers of inflammation such as C-reactive protein.[69]

There are several studies using the clinical cure rate criteria that consist of 4 criterion of discharge in the guideline of the diagnosis and treatment for COVID-19, namely; heat-free for more than 3 days, respiratory symptoms improvement, lung immunity examination shows inflammation reduction and two consecutive tests found no COVID-19 nucleic acid.[69]

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Table 1: Summary of Antiviral Compounds of Several Medicinal Plants Against Coronavirus and Their Mechanisms of Action

Medicinal plant	Antiviral compound	Virus	Mechanism of action	References	Type of research
Curcuma longa	Curcumin	Coronavirus	Inhibition of COVID-19 Mpro protein by curcumin	15	Review
Cinnamomic cortex	Tannin B1	Wt SARS CoV	Tannin B1 relief symptoms of SARS-CoV	15	Review
Eucalyptus essential oil	Jensenone complexes	Covid-19	Jensenone complexes act as Mpro inhibitor	70	*In vitro* (Docking study)
Essential oil	sesquiterpene hydrocarbon (E)-*β*-farnesene.	SARS CoV	sesquiterpene hydrocarbon (E)-*β*-farnesene. Inhibit M Pro SARS CoV2 by moleculer docing	71	*In vitro* (Docking study)
Tea	Theaflavin-3,3-digallate (TF3) and tannic acid	SARS CoV	Theaflavin-3,3-digallate (TF3) and tannic acid inhibit 3CLPro	54	Review
	Quercetin, betulinic acid, cryptotanshinone, dihydrotanshinone, tanshinone, coumaroyltyramine, feruloyl tyramine, desmethoxyreserpine,dihomo-*Y*-linolenic acid, kaempferol, lignan, moupinamide, sugiol		Inhibit Viral infection, decrease immune inflammation, oxygen consumption (inhibit hypoxia inducible factor-1 signaling pathway	42	
Panax ginseng, *Locinera japonica*	Glycyrrhizin, ginsenosides, flavonoids	SARS-CoV	Inhibit viral replication, act as SARS-CoV enzymes antagonists, for example nsP13 helicase and 3CL protease	65	
			Entry process of the coronavirus is inhibited by induction of lipid rafts which depend on cholesterol	60	
Licorice		coronavirus	Glycyrrhizin block alarmin function of High mobility group box 1 (HMGB1)		
	Glycyrrhizin		Glycyrrhizin influence cellular signalling pathways involved kinase and transcription factors	58,72	
		SARS CoV	induces nitrous oxide synthase inhibits the attachment of virus particles to membrane binding		Review
			through mechanism of signal transduction	58,59	in vitro study
Curcuma, Tea, Kaempferol	kaempferol (Flavonoid) quercetin, curcumin, catechin, epicatechin-gallate	COVID-19	inhibit COVID-19 M^{pro}	21	moleculer docking
	beta –carboline, alkaloid, polyfalvonoids		protease inhibitor SARS-CoV , interact with ligand dyad CYS145 and HIS41	73	ligand based virtual screening (LBVS) and Receptor based virtual screening(RBVS)
Chinese licorice	Glycyrrhizin	SARS-CoV	papain like protease inhibitor	20	LBVS and RBVS
Fruit , vegetable such as tomato, citrus	Flavonoid, anthraquinolone	SARS-CoV	blocking the interaction of SARS-CoV protein and its receptor	19	Moleculer docking study
Fruit , vegetable and such as tomato, citrus	Flavonoids	SARS-CoV	Flavonoids inhibited 3 CL pro of Coronavirus family	39,41	Meta-analysis
Grain, nuts	Selenium		Influencing the stress response and host inflammatory response and maintaining the balance and stability of the interrelated redox	46, 74	Review

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Table 2: Studies describing effective dose, Toxic or side effect of different active compounds of medicinal plants that is effective as anti- coronavirus

Active Compound	Effective Dose	Reference	Toxic/ Side Effect
Curcuma longa	Dosage of 12 g/day over 3 months is safe	75	
Licorice	Dosage of 4000 mg/L blocking viral replication	58	raised blood pressure and hypokalaemia in long term use
Green tea	9.9 grams per day	76	Side effects mild: headache, dizziness, nausea
Black tea	2 g/kg per oral dose	56,57	Pregnant rats and their offspring are toxic to black tea
Quercetin	safety dose is 945 mg/m2		Vomit and nausea, increase blood pressure, toxic to nephron, and lowering potassium of serum
Flavonoid	LD_{50} of the flavonoid rich fraction was found to be above 5 000 mg/kg body weight	51,52	toxic flavonoid-drug interactions, liver failure, skin reaction, hemolytic anemia, problem related to excessive estrogenic in male and female, demotion of liver enzyme
Selenium	1.5 and 6 mg/kg BW. LD_{50} in female mice were 12.6 mg/kg BW while in male mice were 9.26 mg / kg BW.	48, 49	a garlicky breath odor, extended bleeding time

Herb such as *Radix glycyrrhizae*, Scutellaria, Pinellia rhizome, Forsythia fruit, bitter apricot seed in the previous meta-analysis improved several clinical parameters of COVID-19 infection. There has been an improvement in lung CT in thirteen meta-analyses of traditional herbs used in COVID-19, but the difference was not found regarding the effect of herbs on mortality due to COVID-19 infection.[69]

A summary of the studies that examine dosage and side effect of medicinal plant that have anti-viral effect against coronavirus is presented in Table 2.

Safety is a major factor that should be considered in the use of herbal medicine in any treatment and more evidence is needed to support the efficacy of this herbal medicine through controlled clinical trials. To get evidence that a drug or herb component is effective for treating a disease, patience is needed, methodologically it is very difficult and long, it requires a lot of money and time, but safety and efficacy should not be sacrificed.[50]

Traditional medicine experts argue that therapy with herbal medicine cannot be tested because traditional medicine is designed depending on the disease syndrome in each individual. The efficacy of herbal treatment in COVID-19 can be designed by looking at the clinical endpoint, namely death, the number of days needed to recover, and the length of time to stay in the intensive care unit (ICU).[50]

Conclusion

Plant that has anti-corona effect were *Curcuma longa*, Cinnamon, *Glycyrrhizin glabra*, *Kaempferol galanga*, citrus, tomato, *Daucus Carrota*, Eucalyptus essential oil, black tea, grain, nuts, olive and their active compounds; curcumin, tannin B1, Jensenone complexes, sesquiterpene, Theaflavin-3,3-digallate (TF3), flavonoids and Quercetin, vitamin A, C, E, zinc and selenium. The molecular mechanisms of action of these plants varied including inhibition of SARS-CoV enzymes, inhibition of viral entry process, affects cellular signalling pathways and transcription factors, enhance immune system and relief symptoms. Research and clinical trials on the effects of herbal medicine on COVID-19 are still limited, thus, further research is required to develop anti-coronaviruses derived from plants.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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