REVIEW

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Potential of Natural Therapeutics Against SARS-CoV-2: Phenolic Compounds and Terpenes

SARS-CoV-2'ye Karşı Doğal Terapötiklerin Potansiyeli: Fenolik Bileşikler ve Terpenler

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ABSTRACT

Coronavirus disease-2019 caused by severe-coronavirus acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) which emerged in China in late 2019 has created an unprecedented global health crisis affecting every sector of human life and causing great damage to the world economy. SARS-CoV-2 is a viral respiratory tract virus that not only causes upper respiratory tract infection but also causes pneumonia and therefore mortality in some patients. There is currently no proven drug for the treatment of SARS-CoV-2. Many chemical and natural active compounds have been testing by the researchers for the treatment. These herbal-based antivirals have been the subject of many studies as they are less toxic and less likely to develop resistance by infectious microorganisms. It has been reported in many studies that natural therapeutics inhibit viral replication. In this review, phenolic compounds and terpenes, which are natural therapeutics known to have antiviral activity, have been evaluated for their potential in the treatment of SARS-CoV-2.

Keywords: Phenolic, terpene, secondary metabolite, SARS-CoV-2

ÖZ

2019 yılının sonlarında Çin'de ortaya çıkan şiddetli, koronavirüs akut solunum yolu sendromu-koronavirüs-2'nin (SARS-CoV-2) neden olduğu koronavirüs hastalığı-2019, insan yaşamının hemen hemen her sektörünü etkileyen ve dünya ekonomisine büyük zarar veren benzeri görülmemiş bir küresel sağlık krizi meydana getirmiştir. SARS-CoV-2, yalnızca üst solunum yolu enfeksiyonuna neden olmakla kalmayıp aynı zamanda alt solunum yolu mukozası tutulumu da yapabilen ve bu sebeple pnömoniye neden olarak bazı hastalarda ölüme yol açan viral bir solunum yolu virüsüdür. Şu anda SARS-CoV-2 tedavisi için kanıtlanmış bir ilaç olmaması ile birlikte, tedavi için birçok kimyasal ve doğal aktif bileşik araştırmacılar tarafından test edilmiştir. Bu bitkisel bazlı antiviraller, daha az toksik oldukları ve enfeksiyöz mikroorganizmalar tarafından direnç geliştirilmesi daha düşük olasılıklı olduğu için birçok araştırmanın konusu olmuştur. Doğal terapötiklerin viral replikasyonu engellediği de birçok çalışmada bildirilmiştir. Bu derlemede, antiviral aktiviteye sahip olduğu bilinen doğal terapötikler olan fenolik bileşikler ve terpenler, SARS-CoV-2 tedavisinde kullanım potansiyelleri açısından ele alınmıştır.

Anahtar Kelimeler: Fenolik, terpen, ikincil metabolit, SARS-CoV-2

INTRODUCTION

Coronaviruses (CoV) are the family of viruses that caused severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and Middle East respiratory syndrome (MERS-CoV) outbreaks in recent years and came up with a new species of SARS-CoV-2, which was first detected in Wuhan, China at the end of 2019. CoV is an enveloped group of viruses that carry single-stranded ribonucleic acid (RNA) as genetic material in groups of viruses, capable of infecting humans and a wide variety of animal species. Viruses are simple organisms and consist of genetic material and a protein coat called capsid. Some virus species have an envelope consisting of phospholipids and glycoproteins outside the capsid. Viruses cannot reproduce or spread without

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invading a host cell. When the virus encounters host cells, typically epithelial cells in the nose, throat and lungs, it enters the cell by binding to receptors on the membrane of these cells. After it enters the cell, it opens its coating and begins to reproduce using the cell's mechanisms. The spike (S) protein of SARS-CoV-2 is viral attachment to host angiotensin-converting enzyme 2 (ACE2) which is a receptor to get into the host cells. Transmembrane protease serine 2 (TMPRSS2) receptor is also crucial viral gateways in oral, lung, and intestinal epithelial cells of SARS-CoV-2 invasion[1]. 3-chymotrypsin- like protease ($3CL^{pro}$), papain like protease (PL^{pro}), RNA-dependent RNA polymerase, and S proteins must be major target of SARS-CoV-2 drugs[2]. SARS-CoV-2 has similar genomic sequence with SARS-CoV[3]. However, the rate of transmission and spread of SARS-CoV-2 infection is quite fast compared to other viral infections encountered so far[4]. SARS-CoV-2 binds to ACE2 receptor with a higher affinity in comparison to SARS-CoV[5]. Some vaccines are developed for SARS-CoV-2. The most prominent vaccine developers are Pfizer and BioNTech, Tüseb-Tübitak, Sanofi-GSK, SinoVac, AstraZeneca and the University of Oxford, Johnson & Johnson and Moderna. They use different strategies for vaccine development and delivery. The used types of vaccines are inactivated pathogen vaccines, subunit vaccines, deoxyribonucleic acid vaccines and mRNA (messenger RNA) vaccines and virus-like particle vaccines[6]. The Pfizer-BioNTech and Moderna vaccines consist of synthetically produced messenger RNAs (mRNAs) that encode a stabilized form of the S protein formulated in a lipid nanoparticle. In an interim analysis of the 2-dose regimen of the Pfizer-BioNTech coronavirus disease-2019 (COVID-19) vaccine, it was observed to provide 95% protection against symptomatic disease[7]. The studies also showed that Pfizer/BioNTech mRNA vaccine (BNT162b2) was effective in different types of variants[8].

Symptoms of COVID-19 infection can be asymptomatic depending on the immune response of the host and comorbid diseases, as well as mild, moderate, severe or critical. In mild patients, there are no symptoms of pneumonia on imaging, and radiological findings of pneumonia, fever and respiratory symptoms are observed in moderate cases. In critical cases, respiratory failure (severe respiratory tract infection, acute respiratory distress syndrome), septic shock and/or multi-organ dysfunction/failure, myocarditis, arrhythmias, cardiogenic shock, metabolic acidosis, coagulation problems, endocrinopathies, acute kidney injury and hepatic dysfunction etc. are observed[9,10]. Reports also show that 30-60% of patients with COVID-19 suffer from neurological complications[11]. COVID-19 caused high anxiety level in people working different sectors[12]. In clinical practice, approximately 20% of COVID-19 patients have abnormal coagulation function and coagulation disorders occur in almost all critically ill patients[13]. Respiratory failure seen in the severe disease picture in COVID-19 is often in the form of hypoxemic respiratory failure. Advanced age, presence of comorbid diseases (cardiovascular disease, diabetes mellitus, chronic respiratory disease, hypertension, cancer), and male gender are risk factors for the development of severe disease[14]. The symptoms may differ depending on the immune responses of patients. It is extremely important to activate the immune response and combat viral infection by increasing the body's combat mechanism, thereby controlling CoV infections[15]. If the virus infects the body, our strong immune system is one of the most effective methods of avoiding the effects of the infected virus. The immune system fulfills the function of defending the human body against disease-causing microorganisms. The best step you can take to keep your immune system strong and healthy naturally is choosing a healthy lifestyle. The immune system against diseases should be strengthened with food and other natural product supplements[16,17].

Plants have been used in the treatment of various diseases since ancient times. According to World Health Organization, about 80% of the world's population use medicinal herbs to meet their health needs[18]. Plants are able to synthesize diverse classes of chemical compounds, named secondary metabolites. The concept of secondary metabolites was first defined in 1891 by biochemist Albrecht Kossel, the Nobel Prize winner in physiology or medicine[19]. The chemical composition of the herbs provides a better understanding of the herb's medicinal value. Secondary metabolites help plants adapt to environmental conditions, defend, protect, survive and regulate their relationships with the ecosystem. They protect the plant against herbivore; bacterial and fungal pathogen attacks and increases their competitiveness with other plants in the same environment. They also protect the plant against abiotic stress factors such as temperature changes, water, light, ultraviolet and mineral substances[20]. Though the functions of secondary products in the plant differ, those with cytotoxic effects against microbial pathogens are used as "antimicrobial agents" in medicine. It is neurotoxic on the central nervous system against herbivores and they are used as anti-depressants, sedatives, muscle relaxants or anesthetic drugs[21]. Some secondary plant metabolites have shown strong antiviral activity against various viral strains such as CoV, human immunodeficiency virus (HIV), influenza virus, SARS[22-25]. When discovering new drugs from both synthetic and natural sources, *in silico* virtual screening studies should be the first step then *in vitro, in vivo* and clinical studies should be carried out. It has been shown that plant secondary metabolites are probably one of the most significant drugs against SARS-CoV-2 by silico analysis[26-30]. The search for natural agents that inhibit different viruses is important to develop a plant-based drug for SARS-CoV-2. The aim of this study is to report previously researched secondary metabolites (phenolics, and terpenes/terpenoids of

plants with antiviral properties that could potentially be used in SARS-CoV-2) and to contribute to the public health by antiviral natural therapeutics (Figure 1).

PHENOLICS

Phenolic compounds are secondary metabolites abundant in plants. There are various phenolic compounds in different qualities and amounts in all vegetables and fruits[31]. Plant phenolics are thought to play a key role as defense compounds in situations where environmental stresses may cause enhanced production of free radicals and other oxidative species in plants[32]. These compounds also play an important role in the human diet. They are important in terms of their antimicrobial and antioxidative effects and causing enzyme inhibition. Polyphenols comprise a wide range of polyhydroxylated compounds (phenolic acids, cinnamic acids, lignans, coumarins, flavonoids, tannins, among others) and for this reason is divided into classes and subclasses. Flavonoids are low molecular weight secondary metabolites in plants that have positive effects on human health. They are the most prevalent phenolic compounds in the human diet. Flavonoids fall into various classes and in general, six basic classes of flavonoids are reported. These are flavones, flavonones, flavonols, isoflavonoids, anthocyanins and proanthocyanidin. Flavonoids are in aglycon or glycoside structures. The predominant form of flavonoids in foods is the form of glycoside. Absorption of this form from the intestines is more difficult than the lean form. Flavonoid glycosides are separated from the sugar part before entering the intestine, and aglycones can pass freely through cell membranes[33,34]. Phenolic therapeutics are used for the treatment of various disease types[35,36].

EFFECTS ON IMMUNE SYSTEM

The interaction of phenols with the immune system has complex effects on the prevention of the disease, the treatment of the disease and the immune system. When free radicals are more than the antioxidant capacity of our body, oxidative damage occurs in our cells. Phenols reduce oxidative stress by scavenging free radicals and inflammatory prooxidants such as hydrogen peroxide[37]. There is a close relationship between inflammation and oxidative stress. Especially high free radical production by macrophages at the infection site causes oxidative stress. SARS-CoV or SARS-CoV-2-related complications are mostly caused by severe inflammation caused by viral replication. Patients in critical care units with severe COVID-19 had elevated plasma levels of various cytokines, including granulocyte-colony stimulating factor, interferon (IFN) gamma-induced protein 10, and macrophage inflammatory proteins[38]. Polyphenols support immunity against foreign pathogens in a variety of ways. Polyphenol receptors identify and facilitate cellular uptake of polyphenols, which subsequently activate signaling pathways to generate immunological responses in different immune cells. Polyphenols interact with the intestinal immune system, leading to both protective and deleterious reactions in the host. For example, resveratrol has the ability to improve human immunity and antioxidative systems. Resveratrol has been displayed to directly target central cell parts of adaptive immunity, like macrophages, large lymphocytes, and dendritic cells. In animal experiments, resveratrol showed an immunomodulatory effect by diminishing the expression of

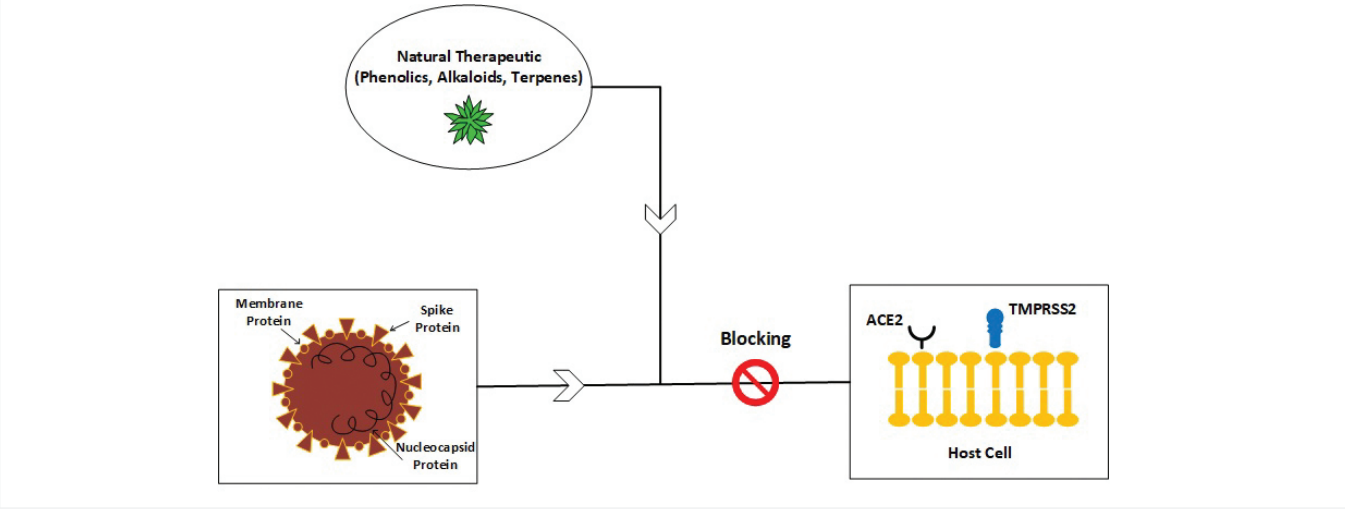

Figure 1. Schematic illustration of SARS-CoV-2 that can bind to a cellular receptor (ACE2) of a host cell with its spike proteins and application of natural therapeutics as anti-COVID-19

COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, ACE2: Angiotensin-converting enzyme 2, TMPRSS2: Transmembrane protease serine 2

activating CD28 and CD80 receptors on immune cells and enhancing the production of the immunosuppressive cytokine IL-10[39].

ANTIVIRAL EFFECTS

There are also many studies in the literature that show antiviral potential of phenolics. Natural polyphenol compounds such as quercetin[40], myricetin[41], apigenin[42] and resveratrol[43] have shown antiviral effect against CoVs. Theaflavin, a polyphenolic compound in black tea, have exhibited broad-spectrum antiviral activity against different viruses such as influenza A and B viruses and hepatitis C virus (HCV)[44,45]. Theaflavin has also been shown to have potential inhibitory effect against SARS-CoV-2 that targets RNA-dependent RNA polymerase (RdRp) which is a significant enzyme that catalyzes the replication of RNA from RNA templates[46]. Stilbenes have antiviral activity against HIV and HCV[47,48]. Flavonoids interfere for NLRP3 inflammasome-associated disorders[49]. SARS CoVs activate the NLRP3 inflammasome in lipopolysaccharide-primed macrophages and cause NLRP3 inflammasome activation[50]. Some flavonoids, such as luteolin[51], myricetin[50], apigenin[52], quercetin[53], kaempferol[54], baicalin[55] and wogonoside[56] , inhibit NLRP3 inflammasome activation. Myricetin has been shown to act as a SARS-CoV inhibitor[41]. Isorhamnetin, apigenin, kaempferol, formononetin and penduletin show antiviral protective efficacy against enterovirus 71 (EV71) infection[57]. Apigenin has also been shown to be active against herpes simplex virus-1 (HSV-1), poliovirus type 2 and HCV[58,59] Apigenin is also anti-adenoviruses and hepatitis B virus (HBV)[60]. Emodin was found to block the interaction of SARS CoV S protein and ACE2. Therefore, it may have therapeutic potential in the treatment of SARS CoVs[61]. Resveratrol has been shown to significantly prevent MERS-CoV infection[62]. Kaempferol, a flavonol, exhibits inhibitory effect against Murine Norovirus and Feline Calicivirus[63]. Kaempferol 3-O-α-L-rhamnopyranoside, extracted from *Zanthoxylum piperitum,* has been shown to have antiviral activity against Influenza A virus[64]. Studies have revealed that quercetin, a natural flavonoid, also display strong antiviral activity against a range of infections caused by HSV, Influenza, HBV, Murine Coronavirus and Dengue viruse in cell culture and mouse models[65-67]. In addition, quercetin was found to inhibit H1N1 and H7N9 viruses *in silico* analysis[68,69]. Quercetin, rosmarinic acid, and hesperitin have also shown good binding affinity with SARS-CoV-2 viral protein targets *in silico* virtual screening[70]. Due to caffeic acid, p-coumaric acid, kaempferol and mainly quercetin, which are the phenolic compounds detected with ethanol of *Origanum vulgar*e, the plant shows an inhibitory effect against Alphaarterivirus equid which causes the equine viral arteritis (EVA) diseases[71]. A study has shown that baicalein, a flavonoid extracted from the roots of *S. baicalensis,* inhibits the activity of SARS-CoV-2 $3CL^{pro}$ *in vitro*. Baicalein has been shown to have anti-SARS-CoV-2 activity by molecular docking analysis[72]. Papyriflavonol A, a flavonol isolated from *Broussonetia papyrifera,* has potent SARS-CoV PL^{pro} inhibitory activity[73]. Antiviral activity of the myricetin derivatives and methoxyflavones obtained from *Marcetia taxifolia* have been evaluated against HBV, HSV and Poliovirus. The methoxyflavones have shown antiviral effect against all the evaluated viruses without cytotoxic effects[74]. Phenolic acids have been reported to show antiviral activity against HSV-1 in a study[75]. Rutin is a very impressive therapeutic as anti-inflammatory and antiviral. Rutin has shown the highest activity as SARS-CoV-2 protease inhibitory in the molecular docking simulation study. Therefore, *in vivo* and docking studies of rutin can be hopeful for SARS-CoV-2 potential[76,77]. Luteolin has been found to have inhibitory activity against EV71, coxsackievirus A1 and SARS CoV[78]. The studies show that flavonoids and polyphenols have antiviral effects against many diseases and can be potentially used against SARS-CoV-2 (Table 1, Figure 2).

TERPENES

Terpenes are a group of compounds commonly found in the plants and are the largest group of secondary metabolites composed of five carbon isoprene subunits. Terpenes are simple hydrocarbons while terpenoids are modified category of terpenes[82]. Terpenes are the major components of essential oils in most herbs and flowers. Terpenoids are a class of modified terpenes with different functional groups. Terpenoids are classified into monoterpenes, diterpenes, sesterpenes, triterpenes and sesquiterpenos according to the units of isoprene. Terpenoids are used in the treatment of many diseases due to their biological activity[83].

EFFECTS ON IMMUNE SYSTEM

Terpenes have strong effects on the immune system. The effects of naturally occurring triterpenoid compounds such as glycyrrhizic acid, ursolic acid, oleanolic acid and nomilin were studied on the immune system using Balb/c mice[84]. It has been observed that intraperitoneal treatments with five doses of terpenoid compounds increase the total white blood cell count. The results demonstrated the immunomodulatory activity of the naturally occurring triterpenoids used in the study. Terpenes also show anti-inflammatory activities. In a study, rats were treated for 11 days with the standard drug sulfasalazine (500 mg/kg po), geraniol (250 mg/kg po), or a combination of the standard drug and geraniol[85]. It was observed that it significantly reduced the total antioxidant capacity and reduced high nitric oxide (NO) and lipid peroxide levels. In a study, D-limonene was orally administered to rats at a dose of 10 mg/kg[86]. According to the results of the study, D-limonene showed important anti-inflammatory effects *in vivo* and *in vitro*, and its effects included protection at

Table 1. Antiviral phenolic compounds, target pathogens and mechanism of action

Compound (References)	Class	Target virus	Mechanism of action
Emodin[61]	Anthraquinone	SARS CoV	Interferes with S protein-ACE2 interaction
Theaflavin[44-46]	Biflavonoid	Influenza A and B viruses, HCV SARS-CoV-2	Binding to RNA-dependent RNA polymerase
Formononetin[57]	Isoflavone	EV 71	-
Apigenin[57-60,79]	Flavone	EV71, HSV-1, poliovirus, HCV ADV and HBV7 SARS-CoV	Inhibits SARS-CoV^{pro} activity
Luteolin[78]	Flavone	EV71, Coxsackievirus A1 SARS-CoV	Binds with S2 subunit and preventing entry
Isorhamnetin[57]	Flavanol	EV 71	Reduces viral genomic RNA replication
Penduletin[57]	Flavonol	EV 71	Reduces viral genomic RNA replication
Myricetin[41,74]	Flavonol	SARS-CoV, HBV, HSV and poliovirus	Inhibits nsP13 by affecting the ATPase activity
Kaempferol[63]	Flavonol	Murine Norovirus and Feline Calicivirus SARS-CoV	Inhibits 3a ion channel of CoVs
Quercetin[40,65-69]	Flavonol	HSV, influenza, HBV, Murine coronavirus, Dengue viruses, H1N1, H7N9	-
Quercetin[80]	Flavonol	SARS-CoV-2	Inhibits of ACE2
Papyriflavonol A[73]	Flavonol	SARS-CoV	Inhibits SARS-3CL^{pro} activity
Rutin[76]	Flavonol	SARS-CoV-2	Binds to the active site of the SARS-CoV-2 3CL^{pro}
Resveratrol[62,81]	Stilbene	MERS-CoV SARS-CoV-2	Expression of nucleocapsid protein regulates ACE2 expression

ADV: Adenoviruses, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HSV: Herpes simplex virus, MERS: Middle East respiratory syndrome, ACE2: Angiotensin-converting enzyme 2, S: Spike

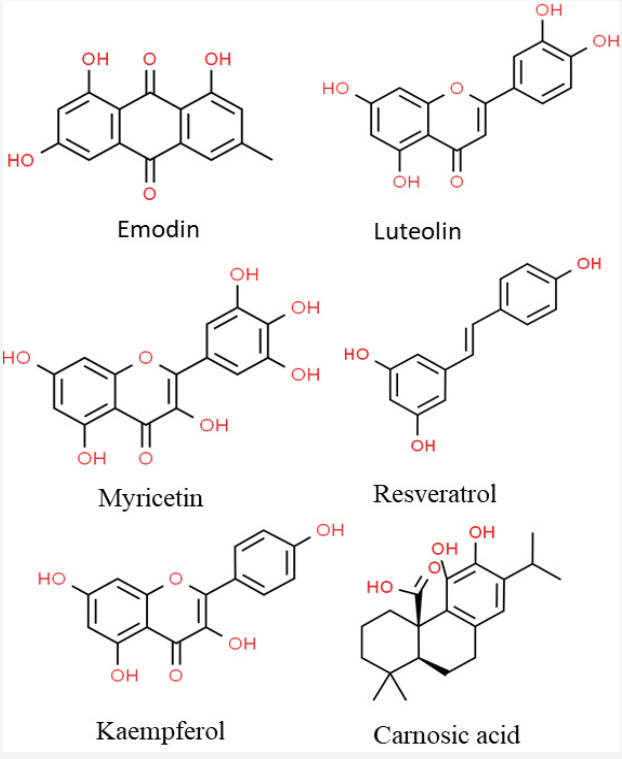

Figure 2. Structures of some phenolic compounds

the epithelial barrier and reduction of cytokines. Nuclear transcription factor-kappa B plays an important role in the regulation of immune and inflammatory responses. Labdane diterpenoids show anti-inflammatory effect by inhibiting NF-κB[87]. Tanshinones, a class of abietane diterpene, can reduce inflammation and increase immune responses[88]. Experimental studies have shown that terpenes are able to decrease pro-inflammatory cytokines [tumor necrosis factor (TNF)-α and β, IL-1, IL-1β, IL-6, IL-17, IFN-γ] and enhance anti-inflammatory cytokines (IL-4, IL-10, TGF-β1)[89]. Emodinol, a triterpene, decreases the levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in the serum of monosodium urate crystal-treated mice and provides a reduction in anti-gouty arthritis activity by improving inflammatory response[90]. In another study, glycyrrhizin (a kind of triterpenoid) was found to provide SARS-CoV-2 inhibition by down-regulating proinflammatory cytokines and preventing the formation of intracellular reactive oxygen species[91].

ANTIVIRAL EFFECTS

There are many studies showing the antiviral properties of terpenes. Glycyrrhizin has shown antiviral effect against SARS, HBV and HIV[92-94]. It also has potential to inhibit SARS CoV-2. Glycyrrhizin has been shown to bind S-RBD and SARS-CoV-2 S-protein attachment with H-ACE2 receptor[95].

1,8-Cineole, a terpene oxide, has been shown to interfere with the binding between RNA and infectious bronchitis virus (IBV) N-protein. So, it exhibits that 1,8-Cineole has anti-IBV properties[96]. (-)-α-pinene and (-)-β-pinene, which are the kinds of terpenoid, have also been shown to possess anti-IBV properties[97]. Triterpenoid saponins are active components isolated from *Bupleurum falcatum*, including saikosaponin A, B, C, and D. Saikosaponin B2 has been found to effectively inhibit HCV by neutralizing virus particles and preventing viral binding[98]. Saikosaponin B2 also has exhibited significant inhibition effect against human coronavirus 229E infection and it has been found that it has potent anticoronaviral activity[99]. Saikosaponin D has been found to have the ability to strongly inhibit EV-71[100]. Terpenoids may interfere with essential amino acid in the enzymatic cavity for inhibiting viral protease enzyme. Some terponoids, including thymoquinone, salvinorin A, bilobalide, citral, menthol, ginkgolide A, noscapine, forscolin, and beta selinene, have been shown to have inhibitory effect against COVID-19 protease molecular insertion by molecular docking method[101]. Isoborneol, an oxygenated monoterpene, has been shown to have a potent antiviral effect against HSV-1 and exactly inhibited glycosylation of viral proteins[102]. A study has shown that limonene, a cyclic monoterpene, is effective in reducing the epithelial expression of ACE2. It has also potential to reduce the mRNA levels of TMPRSS2[103]. Terpenes from *Marrubium vulgare* have been found to interfere with the replication of the HSV-1 and show antiviral effect against HSV-1[104]. Putranjivain A, a diterpen obtained from *Euphorbia jolkini*, has been shown to have an antiviral effect against HSV-2[105]. Moronic acid, extracted from the *Rhus javanica,* has potential to inhibit HSV-1[106]. Andrographolide, a diterpenoid lactone, has been shown to inhibit the replication process of the CKV[107]. Betulinic acid and platanic acid, which are the pentacyclic triterpenoid compounds isolated from *Syzigium claviforum*, have been found to inhibit HIV[108]. Oleanolic acid, a pentacyclic triterpenoid, have also shown anti-HIV activity (Table 2, Figure 3)[109].

CLINICAL TRIALS

There are only a few clinical trials regarding the application of phenolic compounds and terpenes in SARS-CoV-2. A clinical trial covers the administration of zinc and resveratrol (a stilbene, a type of natural phenol) or double placebo for a period of 5 days in 60 ambulatory SARS-CoV-2 positive volunteers (range of 18-75 age) and monitoring for a 14-day period[117]. The aim of this study is to minimize viral load and severity of resulting COVID-19 disease. Combination therapy contains 50 mg of zinc picolinate for five days and 2 mg of Resveratrol for five days. The stage of this study is still phase 2. Another clinical trial has been conducted with the use of Epigallocatechin-3-gallate, a phenol found in green and black tea plants, in 524 volunteer healthcare worker participants[118].

Table 2. Antiviral terpene compounds, target pathogens and mechanism of action

Compound (References)	Class	Target virus	Mechanism of action
Putranjivain A[105]	Diterpene	HSV-2	Inhibits of viral attachment and cell penetration
Tanshinones[110]	Diterpene	SARS-CoV-2	Inhibits SARS-CoV $3CL^{pro}$ and PL^{pro}
Andrographolide[107]	Diterpenoid	CHIKV	Inhibits viral genome replication
Sugiol[111]	Diterpenoid	SARS-CoV-2	Inhibits M^{pro}
Ginkgolide A[101]	Diterpenoid	SARS-CoV-2	Binds to $3CL^{pro}$
Isoborneol[102]	Monoterpene	HSV-1	Inhibits glycosylation of viral polypeptides
Limonene[103]	Monoterpene	SARS-CoV-2	Downregulates ACE2 expression
1,8-Cineole[96]	Monoterpene	IBV	Binds between RNA and IBV N-protein
(-)-α-pinene and (-)-β-pinene[97]	Monoterpene	IBV	Inhibit of viral replication
Geraniol[112]	Monoterpene	SARS-CoV-2	Inhibits of ACE2, spike glycoprotein
α-Cadinol[111]	Sesquiterpenoid	SARS-CoV-2	Inhibits M^{pro}
Saikosaponin B2[98,99]	Terpenoid	HCV, HCoV-229E	Neutralizate of virus particles and inhibits viral entry/fusion
Saikosaponin C[113]	Terpenoid	HBV	Inhibits DNA expression
Glycyrrhizin[92-94]	Triterpenoid	HBV and HIV SARS	Inhibits replication of the SARS-associated virus
Moronic acid[106]	Triterpenoid	HSV-1	-
Betulinic acid[108,114]	Triterpenoid	HIV, HBV	Inhibits of HIV and HBV replication
Oleanolic acid[109]	Triterpenoid	HIV	-
Platanic acid[108]	Triterpenoid	HIV	Inhibits of HIV replication
Celastrol[115,116]	Triterpenoid	SARS-CoV Hepatitis C virus	Inhibits $3CL^{pro}$ inhibits HCV RNA and protein synthesis

COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

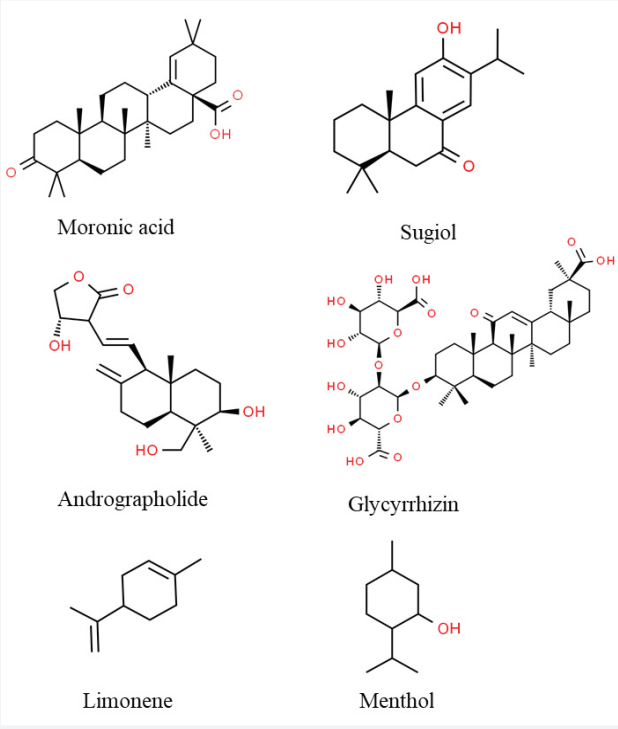

Figure 3. Structures of some terpene compounds

The total dose of EGCG per patient was 750 mg per day, 3 capsules per day for 40 days. Participants also took the same dose of starch as a placebo. The purpose of this clinical trial was to determine the efficacy of Previfenon® (EGCG) in preventing COVID-19, enhancing systemic immunity, and reducing the frequency and intensity of selected symptoms when used as pre-exposure chemoprophylaxis to SARS-CoV-2. The stage of this study is still phase 2. Combination of curcumin (a terpene), quercetin (a flavonoid) and vitamin D is used in an ongoing clinical trial in phase 2 to investigate for early COVID-19 symptoms improvement and viral clearance in outpatients[119]. There are 100 participants who are 18 years old and older, tested positive for SARS-CoV-2 by RT-PCR and exhibit typical symptoms of COVID-19 disease. Soft capsule of the investigational treatment contains 42 mg curcumin, 65 mg quercetin and 90 units Vitamin D. Four capsules per day for 14 days are taken. Quercetin (flavonoid) is administrated on 80 participants in a clinical trial to investigate the effectiveness of phytotherapy in the treatment of SARS-CoV-2[120]. Participants will receive one tablet times three per day from quercetix and placebo groups. This study is still phase 1. Combination therapy of quercetin, bromelain, zinc and vitamin C on the clinical outcomes of patients infected with COVID-19 was studied on 60 participants[121]. A daily dose of drugs included quercetin (500 mg), bromelain (500 mg), zinc (50 mg), vitamin C (1000 mg) by proven COVID-19 cases intervention. The stage of this clinic trial is phase 4.

The biggest problem with the use of natural products in the treatment of diseases is their low solubility and bioavailability, which causes problems in clinical studies. Bioavailability issues can be evaluated before starting high-budget clinical trials. The ways to improve drug delivery, bio distribution, biodegradability and bioavailability of plant-based secondary metabolites such as phenolic compounds and terpenes should be sought. Nano carrier systems can be useful as a solution for these problems. Natural therapeutics administered regularly in low doses can reduce the entry of the virus into cells and thus stop the progression of the infection.

CONCLUSION

The whole world faced a major health crisis with the SARS-CoV-2 pandemic, which caused many human deaths and adversely affected many industries. The fact that it is so widespread and fatal raises the need for improvement of treatment as soon as possible. However, the reliable and certified drug has not yet been developed for the SARS-CoV-2. The use of natural therapeutics has begun with the history of humanity and a significant number of effective plants derived drugs have been developed. They are effective in enhancing the immune response of the host against viral pathogens; therefore, it is considered as a protective and complementary treatment opportunity. Secondary metabolites of plants such as phenolic compounds and terpenes could be highly promising complementary therapeutic agents for the disease. The studies show that secondary metabolites exhibit antiviral activity against different viruses so they can be highly promising therapeutics for the SARS-CoV-2. Natural therapeutics must be subjected to *in vitro* and experimental trials to determine safe and therapeutic levels before conducting clinical trials in humans. This study reveals the antiviral properties of some natural therapeutics for new drug development to overcome these and future pandemic situations. It is thought that the information provided in this study will be useful in the process of developing safe, effective anti-CoV therapeutic agents from compounds derived from natural products.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: D.Y.A., S.G.

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