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REVIEW PAPER

Medicinal plants as a hopeful therapeutic approach against COVID-19 infection

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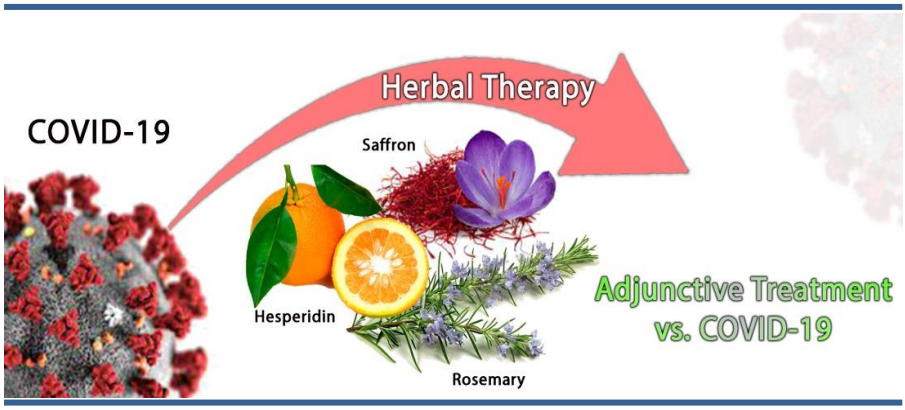
Highlights

- Virus of SARS-COV-2 results in COVID-19 disease and mainly attacks the lung tissue.
- Medicinal plants can control COVID-19 by host cell entry prevention.
- Medicinal plants can control the COVID-19 by interfering with inflammatory reactions.

Graphical Abstract



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Abstract

The disease of COVID-19 is generated by the SARS-COV-2 virus and principally attacks the lung tissue. In addition, other tissues are also attacked by the virus. Reports have shown that the clinical symptoms of this disease vary from no sign to acute respiratory symptoms in the lungs and the occurrence of septic shock with an effect on the immune system in other organs. Although the number of patients is continuously increasing, there is still no approved drug for COVID-19. Currently, the treatment provided to injured people is usually based on symptoms. However, so far, various treatment methods have been proposed and used to solve this problem. One of the most important therapeutic methods for curing this disease is the use of drugs whose action is usually based on the inhibition mechanisms of enzymes of virus including RNA and DNA polymerase, glycosylation of viral protein, assembly of virus, etc., and includes antiviral, antimalarial, anti-inflammatory, anti-HIV, and corticosteroid drugs. Medicinal plants have fewer side effects than chemicals due to their natural origin. Today, medicinal plants are considered a valuable source of natural compounds for use in the production of antimicrobial and antioxidant drugs. Medicinal plants with certain properties, such as fighting the entrance of the coronavirus into the host cell and interfering with inflammatory reactions, can control the pathogenesis of COVID-19. Among these medicinal plants, we can mention hesperidin, saffron, and rosemary. The aim of this study is to introduce some effective medicinal plants in the COVID-19 treatment based on cellular and molecular mechanisms.

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Introduction

In late 2019 and early 2020, many cases of a novel kind of coronavirus were reported in the seafood market in Wuhan, southern China (1). In January 2020, WHO named this new virus novel coronavirus-2019 and a few days later that pandemic stated it as an emergency concern for international public health. In February 2020, WHO named the disorder caused by the new coronavirus 2019 the coronavirus 2019 disease or abbreviated as COVID-19. At the end of February 2020, 77000 patients with COVID-19 were recorded in China. This number of infections is higher than the prevalence of severe acute respiratory syndrome or SARS in 2002 in China (2). SARS-COV-2 are non-segmented positive ssRNA viruses, and enveloped, of animal origin and members of the Coronaviridae family. The genome of this virus consists of about 30 kilobases, which is one of the largest RNA viruses. In terms of genotyping and serology, the family of Coronaviridae is classified into four genera Delta, Gamma, Beta, and Alpha. Human coronaviruses are caused by alpha and beta genera (3). The disease of COVID-19 can appear in a spectrum from asymptomatic or very mild symptoms to very severe disease. It is pointed out that the symptoms are not fixed and at any time the patient may enter the next stages. The time of incubation of the disease is 3 to 14 days and a mean of 5 days. A spectrum of disease from no sign to intense pneumonia or acute respiratory distress syndrome (ARDS) and death may occur. In 80% of asymptomatic cases or mild to moderate symptoms, 15% of severe symptoms require hospitalization, and 5% of very severe symptoms require hospitalization in ICU is required (4).

Prevention is the best way to deal with this disease. Considering the special characteristics of this virus, including non-specific symptoms, the virus transmission in the incubation time, the preference of this virus for mucous membranes, the long duration of this disease, and the possibility of transmission even after recovery, it is very difficult to prevent this virus (5). The treatment against this virus consists of two parts. Supportive treatments include water and electrolyte adjustment, fluid administration, proper oxygenation and respiratory support, antipyretics, and painkillers. Specific treatments include the administration of antiviral drugs (5). Specific treatments for cases hospitalized to the intensive care unit include the simultaneous administration of antiviral drugs and immune system modulators, such as Oseltamivir along with hydroxychloroquine and coltra drug, in addition to these three drugs, ribavirin or even antibiotics can also be used based on the condition of patient. In cases with slight pneumonia, only the administration of Oseltamivir and hydroxychloroquine is indicated (6).

Medicinal plants have fewer side effects than chemicals due to their natural origin. Today, medicinal plants are considered as a valuable source of natural compounds for usage in the production of antimicrobial and antioxidant medications (7). Scientific observations have shown that plants have various properties, including anti-inflammatory, antimicrobial, anticonvulsant, and antipyretic properties, and the presence of compounds such as polyphenolic matters including kaempferol and quercetin have been introduced as effective compounds in the treatment of several disorders (8, 9). Medicinal plants with some properties such as fighting the entrance of the coronavirus into the host cell and interfering with inflammatory reactions can control the pathogenicity of COVID-19. Among these herbs, we can mention hesperidin, saffron, and rosemar. The purpose of this study is to introduce some effective medicinal plants in the COVID-19 treatment by relying on cellular and molecular reactions.

Hesperidin

Hesperidin as a usual flavon glycoside is found in citrus fruits including sweet oranges and lemons. This compound has several medicinal functions including anti-atherogenic, anti-lipid, anti-diabetic, heart protection, anti-inflammatory, and anti-blood pressure properties. The anti-inflammatory function of this compound principally involves the mechanism of antioxidant defense and suppressing the production of pro-inflammatory cytokines (10). Hesperidin significantly decrrases the replication of the influenza virus and therefore has antiviral activity against the influenza virus. When infected cells are treated by hesperidin the autoimmune activity of cell increases through activation and increased expression of JNK and p38, which are

nessecary for cell protection mechanisms vs. the virus of influenza (11). For a long time the hesperidin was considered an herbal medicine. At the request of the FDA, the hesperidin safety has been approved by the Federation of American Societies for Experimental Biology (FASEB). High safety of this compound after oral administration was established by toxicity examinations (12). There is a mixture of hesperidin and Diosmin in tablets called Daflon 500 and it is applied as a vasoconstrictor (13). The mentioned mixture is known for its great safety features. Continuous hesperidin administration in oral way for rats for 13 and 26 weeks did not show significant toxic effects. Clinical trials using treatement of more than 2850 cases with hesperidin for six weeks to one year showed normal blood parameters and liver and kidney function without any toxicity (12, 14).

The hesperidin role in the prevention and treatment of COVID-19

The cell receptor of SARS-COV-2 causes the virus entrance to the host cell. The virus entrance into the cell depends on two consecutive steps: 1- spike virus attachment to the host cell receptor and 2- spike virus priming by cellular proteases. Recently, researchers proved that the spike virus (protein S) attaches to the ACE-2 receptor located on cell membrane, and via this, the virus enters the cell (15). Also, COVID-19 uses cellular TMPRSS2 serine protease for priming its spike. Camostat mesylate is an inhibitor of serine protease that prevents the SARS-COV-2 from entering the cell and was used in Japan to treat COVID-19. This virus attaches to the ACE-2 on the host cell through the spike receptor binding domain (RBD) and forms the complex of SARS-COV-2-RBD-ACE2 (16).

Using computational methods, the antiviral drug against the ACE2 receptor was studied and according to this research, hesperidin is the only matter which disrupts the binding of ACE2 receptor with SARS-COV-2-Spike. As a result, it prevents the enterance of virus to the lung cells (17). Therefore, the application of hesperidin can inhibit COVID-19 infections (Figure 1). The immune system activation and the defense mechanisms of the host cell causes an antiviral response. Hence, immunity plays a major role when dealing with viral infections (18). Hesperidin exerts antiviral function vs. the virus of influenza by activating the pathway of mitogen-activated protein kinase (MAPK). The pathway of interferon-MAPK has a main role in immunity against SARS-COV-2infection (12, 19). Patients affected by SARS-COV-2 experience a cytokine storm. The available evidence shows that the cytokine storm includes the generation and secretion of active molecules in immune system including tumor necrosis factor-alpha (TNF-α), chemokines, interleukins, and interferons, and is one of the main reasons of acute respiratory distress syndrome (ARDS) (20). Hesperidin, with high anti-inflammatory function, prevents the release of pro-inflammatory cytokines, and it could be applied as an adjuvant treatment to inhibit the intense inflammatory reaction vs. SARS-COV-2 (Figure 1) (12).

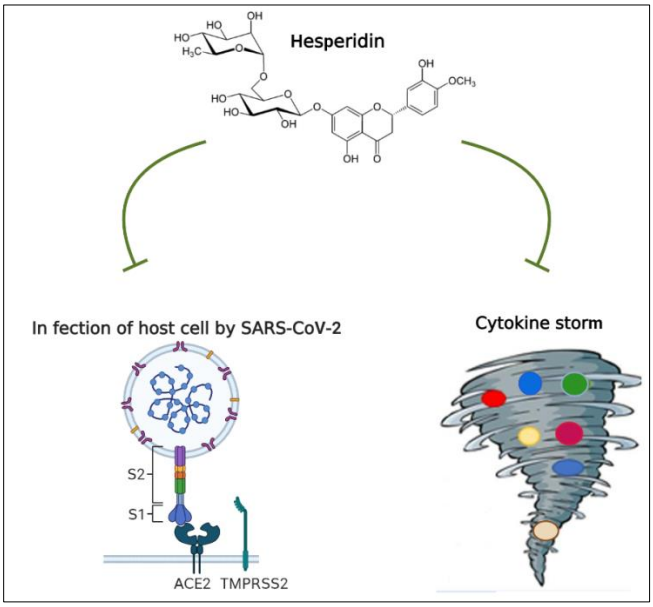

Figure 1. The action of hesperidin against covid-19.

This compound can act against COVID-19 both by disrupting the entrance of the virus into the host cell and by preventing the cytokine storm.

Saffron

Several pharmaceutical features of saffron are of interest to modern medicine. These properties are due to the existence of non-volatile and volatile perfume complexes in saffron. The red stigma of Crocus sativus accumulates various active compositions, among which alpha, and beta carotenes, crocetin, picrocrocin, kaempferol, crocin, and safranal are of great significance. Not all types of saffron can produce these compounds. Picrocrocin and crocetin are present only in saffron species Buddleja and Gardenia. A large number of researches have been done with focus on its antioxidant, anticancer features, calming influence on nerve damage, etc. (21, 22). Saffron and its compounds can be used as an effective treatment for diseases such as coronary arteries, nervous damages, fever, colds, diabetes, asthma, and bronchitis (23). This powerful natural antioxidant is applied in traditional medical approach to treatment of colds, scarlet fever, asthma, and metabolic syndrome (23). According to the studies conducted, aqueous or ethanol extract of saffron, crocetin and safranal play an anti-inflammatory and antioxidant role in the body (24). Also, consumption of crocetin and crocin reduces the level of bilirubin, cholesterol, and triglycerides in the blood (25).

Saffron in the management of COVID-19

Coronavirus acts more strongly on people who have weak immunity. The main path for the destruction of cell in COVID-19 condition is mainly immune-mediated programmed cell death. So, people who have a strong immune system could decrease the viral infection severity. Cellular immunity results in injury via a cytokine storm, at which point suppression of inflammation can be beneficial (26). Immune-enhancing medicinal plants could be helpful in the initial stages of the disease, while plants with anti-thrombotic and anti-inflammatory features have a significant effect in advanced or more severe stages (27). Currently, immunomodulatory drugs targeting interleukins are effective in treating COVID-19 infection in moderate to severe conditions. The bioactive compounds of saffron have a significant influence on the action of the cellular and humoral immune system. Immune modulation by these saffron compounds could be a helpful approach to manage COVID-19. This might directly target the TLRs moleculs attributed to NF-κB, AP-1, and downstream signaling paths (23). A placebo-controlled randomized clinical trial was conducted and it was detected that saffron elevates the concentration of IgG and reduces the concentration of IgM than the placebo. In addition, it elevates the monocytes percentage compared to placebo. Therefore, the regular usage of less than 100 milligram of saffron was proposed as a temporary immunomodulatory activity without any side effects (23). These features can help modulate the immune response in COVID-19 condition.

Rosemary

According to the in vivo researches, rosemary extract could modify the levels of plasma lipid and glucose and reduce weight gain. Rosemary extract and its identified composites, including caffeic acid, carnosol, carnosic acid, rosmarinic acid, and might control adipocyte differentiation and PPAR activity and inhibit pancreatic lipase (28). Furthermore, in vitro studies on HepG2 cell line have shown that the extract of rosemary positively regulates the metabolism of glucose and lipid by activating various paths (29). SIRT1 upregulation could increase sensitivity insulin, consumption of cellular glucose, and oxidation of fatty acid in the liver. Likewise, with the consumption of rosemary, LDLR increases and creates a potential mechanism that can reduce blood cholesterol levels (30). Rosemary is applied to improve the products' taste in various fields. It is used in the Middle East to season meats and in Mexico to prepare tea. In India, rosemary leaves flavor drinks and soups. Rosemary has high amounts of vitamins and minerals as well as many biological functions such as antifungal, antibacterial, and antioxidant, functions. Also, rosemary extract could inhibit microbial contamination and oxidation and is applied as a food preservative. Therefore, it is very useful in the food packaging industry (30).

Rosemary, SARS-COV-2, and the renin-angiotensin system

The renin-angiotensin system (RAS) is typically regarded as a regulator of cell migration and proliferation, inflammatory disorders, and cellular synthesis of cytokines, chemokines, and immune transcription factors (31). Angiotensin-converting enzyme (ACE) is a metallopeptidase and the key enzyme in the RAS, which is present on the surface of the membrane. ACE results in convertion of angiotensin I (Ang I) to angiotensin II (Ang II) (32). Angiotensin II increases blood pressure and oxidative stress and could elevate the levels of reactive oxygen species (ROS). Rosmarinic acid, a natural compound from plants belonging to the family of Lamiaceae, including rosemary and Salvia officinalis, plays substantial antioxidant, anti-inflammatory, and anti-apoptotic properties (Figure 2) (33). Rosmarinic acid consumption can reduce ACE expression and induce ACE2 expression, disrupt the cascade of RAS through degradion of AngII, and downregulate angiotensin receptor type 1 (Figure 2) (30, 34). Overexpression of ACE2 enables virus entrance and replication in host cells. In addition, the virus downregulates the expression of ACE2 and disrupts the balance of AngII-Angl in favor of Ang II more than other infections of respiratory system. In addition, the amount of AngII is higher in more severe viral infections, so the inhibition of ACE could improve the disorder condition. Inhibitors of RAS are extensively imployed for treatment purposes, which can exert their effects via an inhibitory influence on the production of AngII. Based on the molecular evidence, the application of ACEI/ARB for the treatment of SARS-COV-2 has become controversial.

Also, RAS prevents acute lung injury by reducing Ang II production and reduces mortality in SARS-COV-2 infection. Moreover, RAS blocks the risk of infection by the virus by increasing the expression of ACE2. Though, there is no evidence to support that ACEIs/ARBs could improve COVID-19 entrance by increasing expression of ACE2. Therefore, more studies are needed in this field (35, 36). As mentioned, during a SARS-COV-2 infection, the immune system plays a key function in protection and clear of pathogens. Rosemary is a chief plants that was investigated due to its anti-inflammatory effect. The impact of extract of rosemary on MDD was studied in rats under chronic restraint stress (CRS). According to research, the microbiome and its metabolites have an effect on several autoimmune and inflammatory disorders and function of brain, and carnosic acid decreases the concentration of TNFa-mediated cytokines in a concentration-dependent manner. The administration of rosmarinic acid also reduces the generation of pro-inflammatory cytokines in various inflammatory problems (30, 37). Rosemary essential oil has been shown to affect the migration and reduction of leukocytes in the inflamed area by improving levels of CRP, TNF, and MDA (38).

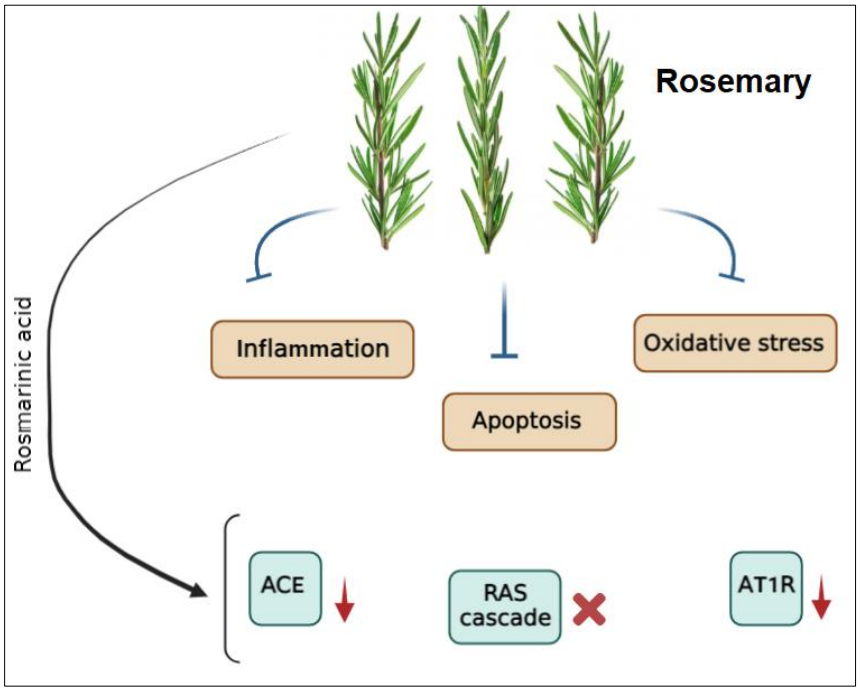

Figure 2. Molecular functions of Rosemary against COVID-9.

Rosemary has anti-apoptotic, anti-inflammatory, and antioxidant properties. The treatment with RA could reduce the expression of ACE, disturbs the cascade of RAS, and results in the down-regulation of angiotensin type 1 receptor (AT1R).

Catechins; General medicinal properties

Catechins are natural compounds with polyphenolic features a member of the of flavonoids group, which are existed in a widespread range of vegetables, fruits, and plant-based foods and beverages, including leaves of fresh tea, red grapes, cocoa beans, black grapes, apricots, etc. (39). Extract of green tea is a well-known catechin-rich food source that contains significant amounts of catechins, epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC). EGCG is the most plentiful and active polyphenol compound in green tea, constitutes about fifty percent of polyphenols in green tea (40, 41). Researches have demonstrated that oral consumption of catechins results in absorbion of them and and also their metabolites through th gastrointestinal tract and in humans might undergo three kinds of transformation: sulfation, glucuronidation, and methylation in the intestinal tissues and liver (42). Recently investigations have shown a wide variety of medicinal functions of catechins, such as neuroprotection, anticancer, anti-inflammatory, antiviral, antibacterial, and antihypertensive properties (43, 44).

Catechins have direct antioxidant properties, by inhibiting chelating metal ions and free radicals, and aslo indirect antioxidant impacts, by inhibiting pro-oxidant enzymes, inducing antioxidant enzymes, and producing detoxifying enzymes. Remarkably, researches have demonstrated that catechins might exert a pro-oxidant influence in a dose-dependent manner leading to ROS production (45). Plants containing high levels of catechins or pure catechins have anti-inflammatory impacts in inflammatory disorders (46, 47). Also, catechins decrease the generation of pro-inflammatory cytokines. Catechins reduce the generation of pro-inflammatory cytokines including INF-γ, IL-6, IL-1β, and TNF-α, decrease the adhesion molecules expression, prevent the proliferation and penetration of immune cells and reduce their function (48).

The anti-SARS-CoV-2 activity of catechins

Due to the crucial need to progress efficient treatment vs. COVID-19, several studies examined numerous candidate drugs, such as herbal composites, for activity against this virus. Polyphenol compounds including catechins are recognized for their antiviral function vs. numerous RNA viruses such as coronaviruses (49, 50). Epigallocatechin-3-gallate (EGCG) prevents the Mpro main protease of COVID-19 (51). The studies found that the Mpro-catechins complexes were highly stable, indicating that they could be further established into potent inhibitors of Mpro and COVID-19 antivirals. In an in vitro study, the high affinity of EGCG and ECG to Mpro was confirmed (50). Mmolecular binding study on plant compounds showed that EGCG binds with high affinity to some viral proteins of the virus, including Mpro, protein S, 2S subunit of protein S, 2RBD-ACE complex, and endoribonuclease 15NSP (52). EGCG's ability to target the S protein and its potential to disrupt and bind to the receptor of ACE2 suggest that it can be further established as a SARS-CoV-2 entry inhibitor. The catechins function shows that it could be imployed not only to prevent virus replication but also to reduce the symptoms of cytokine storm caused by COVID-19 and enhance immunity vs. COVID-19 (53).

Conclusion

Medicinal plants have fewer side effects than chemicals due to their natural origin. Today, medicinal plants are considered a valuable source of natural compounds for use in the production of antimicrobial and antioxidant drugs. Medicinal plants with certain properties, such as fighting the entry of the coronavirus into the host cell and interfering with inflammatory reactions, can control the pathogenesis of COVID-19. Among these medicinal plants, we can mention hesperidin, saffron, and rosemary. With its high anti-inflammatory function, hesperidin prevents the release of pro-inflammatory cytokines and could be employed as an adjunctive treatment to prevent the intense inflammatory reaction vs. COVID-19. Immune modulation by some

saffron compounds can help as a management strategy against SARS-CoV-2. Rosemary essential oil has been shown to affect the migration and reduction of leukocytes in inflamed areas by improving TNF, CRP, and MDA levels. The catechins function shows that it could be employed not only to prevent virus replication but also to reduce the symptoms of cytokine storm caused by COVID-19 and enhance immunity against COVID-19. Finally, herbal therapy against the disease of COVID-19 could be considered a promising approach in the treatment of this disease.

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