An Overview on Flavonoids as Potential Antiviral Strategies against Coronavirus Infections

Koronavirüs Enfeksiyonlarına Karşı Potansiyel Antiviral Bileşikler Olarak Flavonoitlere Genel Bakış

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ABSTRACT

Coronaviruses are zoonotic viruses and can infect people, often causing respiratory and gastrointestinal complaints. Three coronavirus types namely, severe acute respiratory syndrome coronavirus (SARS-CoV), middle-east respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 (COVID-19) cause pneumonia in human resulting in severe acute respiratory syndrome (SARS). SARS-CoV-2, first appeared in Wuhan, China, in 2019, has rapidly spread to the whole world in a short time due to the speed of transmission rate. Since there is no specific drug for disease prevention and treatment, drug and vaccine development studies are proceeding rapidly. In drug development studies, natural resources draw attention due to their antiviral activity and fewer side effects. Flavonoids, a secondary metabolite group found in higher plants, have a variety of pharmacological activities, including antiviral activity. In this review, flavonoid-type compounds and plant extracts containing these constituents were summarized in terms of their antiviral activity potential against coronavirus-induced infections. Herein, we can suggest that flavonoids shown to possess antiviral effect against SARS and MERS may be used as potential test materials for the studies of novel drug search for ongoing COVID-19 pandemic.

Key Words: Antiviral, coronavirus, COVID-19, flavonoids, medicinal plants, respiratory infection

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ÖZET

Koronavirüsler zoonotik virüsler olup insanları enfekte ederek çoğu zaman solunum ve mide-bağırsak şikayetlerine neden olabilir. Şiddetli akut solunum yetmezliği sendromu koronavirüsü (SARS-CoV), ortadoğu solunum yetmezliği sendromu koronavirüsü (MERS-CoV) ve SARS-CoV-2 (COVID-19) olmak üzere üç koronavirüs türü, insanlarda şiddetli akut solunum yetmezliği sendromuna (SARS) neden olur. İlk olarak 2019 yılında Çin'in Wuhan kentinde ortaya çıkan SARS-CoV-2, yüksek bulaşma hızı nedeniyle kısa sürede tüm dünyaya yayıldı. Hastalığın önlenmesi ve tedavisine yönelik spesifik bir ilaç olmadığından ilaç ve aşı geliştirme çalışmaları hızla devam etmektedir. İlaç geliştirme çalışmalarında doğal kaynaklar, antiviral aktiviteleri ve daha az yan etki potansiyelleri ile dikkat çekmektedir. Yüksek bitkilerde bulunan sekonder metabolit grubu olan flavonoitler, antiviral aktivite dahil olmak üzere çeşitli farmakolojik aktivitelere sahiptir. Bu derlemede, flavonoit tipi bileşikler ve bu bileşenleri içeren bitki ekstreleri, koronavirüs kaynaklı enfeksiyonlara karşı antiviral aktivite potansiyelleri açısından özetlenmiştir. SARS ve MERS'e karşı antiviral etkiye sahip olduğu gösterilen flavonoitlerin, devam eden COVID-19 pandemisi için yeni ilaç geliştirme çalışmalarında potansiyel deney materyalleri olarak kullanılabileceğini önerebiliriz.

Anahtar Sözcükler: Antiviral, koronavirüs, COVID-19, flavonoit, tıbbi bitki, solunum yolu enfeksiyonu

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INTRODUCTION

Recently, in December 2019, a new coronavirus disease, namely severe acute respiratory syndrome coronavirus (SARS-CoV)-2, caused an international outbreak of acute respiratory disorder named COVID-19. Although the disease appears in China for the first time, owing to its rapid spread, WHO made the assessment that COVID-19 can be characterized as a pandemic in March 2020 (1). This caused a great panic among people worldwide that countries have enhanced their efforts to manage this viral infection. However, it spreads very quickly and easily through droplets of saliva or discharge of the nose. The disease can be fatal in older people and especially ones with chronic medical conditions such as diabetes and heart disease. Unfortunately, no specific therapeutic agent exists currently. Therefore, as an unavoidable pandemic, the researchers are trying to provide the best protection approach for the public before a vaccine is developed. This situation also explains the importance of all these scientific studies in several laboratories worldwide.

Medicinal plants, their extracts, fractions, and secondary metabolites as well as their derivatives have been known to possess an essential role in controlling infections. Thanks to scientific research based on traditional medicine, medicinal plants have been shown to be effective against various diseases and potential sources of effective drug raw materials for the discovery and development of bioactive agents. For the treatment and prevention of epidemic diseases, natural products could be good options evident with previously conducted preclinical and clinical studies. Indeed, a plant-derived compound, hydroxychloroquine, previously used against malaria, is currently being promoted for the treatment of COVID-19. On the other hand, herbal medicines not only decrease the rate of viral infections but also improve the SARS-CoV symptoms when combined with conventional medicine (2,3).

Flavonoids, a secondary metabolite group with benzo-γ-pyron skeleton, are among the several plant-based antiviral constituents especially found in higher plats. In this review, we aimed to summarize the potential antiviral effects of flavonoids in the prevention and treatment of coronavirus infections. In this regard, electronic databases including PubMed, Science Direct, and Scopus were searched using the keywords "flavonoid" and “coronavirus” and several related studies were obtained. Inspired by the previous experience, flavonoids can be considered as one of the important approaches towards COVID-19 treatment. However, detailed mechanistic investigations on each compound should be carried out to clarify this claim.

Understanding the Coronaviruses

Coronaviruses (CoVs), are enveloped, single-chain, positive polarity, and zoonotic RNA viruses belong to the subfamily *Orthocoronavirinae* in the family of *Coronaviridae.* This family includes α-, β- γ-, and δ-coronaviruses, where α- and β-coronaviruses cause infection in humans (4). There are 4 main proteins in the structure of coronaviruses: the spike protein (S), the nucleocapsid (N) protein, the membrane (M) protein, and the envelope (E) protein. The S protein mediates binding to the host receptor and fusion of the virus and cell membrane (5). Because CoVs have positive polarity, they do not contain RNA-dependent RNA polymerase enzyme, but in their genome, they encode this enzyme. Envelope surfaces have stick-like extensions made of glycoprotein. Due to the crown-like appearance of these surface protrusions, these viruses are named Coronaviruses based on the meaning of ‘corona’ which is ‘crown’ in Latin (6).

CoVs are of zoonotic origin and can cause serious respiratory diseases, besides gastrointestinal, cardiovascular, and neurological disorders in a variety of animal species such as rats, mice, chickens, turkeys, various other bird species, cattle, several wild ruminants, white whales, dogs, cats, rabbits, and swine (7). In humans, they can often cause respiratory diseases and gastrointestinal complaints. From simple colds, they can lead to serious symptoms such as bronchitis, pneumonia, coagulopathy, multiple organ failure, and death. The first studies on the human coronavirus were carried out in the mid-1960s in human embryonic tracheal organ cultures. Until 2003, only HCoV-229E and HCoV-OC43 were known. Today, 7 different CoV strains are known to infect humans. HCoV2-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63 are the common coronaviruses among humans and generally cause self-resolving infection (8). The other 3 coronaviruses that infect humans are severe acute respiratory syndrome coronavirus (SARS-CoV) and middle-east respiratory syndrome coronavirus (MERS-CoV) and newly identified SARS-CoV-2, which cause fatal respiratory infections.

Types of Coronaviruses

a. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1)

Severe acute respiratory syndrome coronavirus (SARS-CoV-1) outbreak started in November 2002 in China. With the beginning of the outbreak, it was observed that new coronaviruses can be transmitted from animals to humans. Studies have shown that SARS-CoV-1 has originated in bats, the transmission may have occurred to people from palm civets and raccoon dogs provided intermediate host (9). SARS-CoV-1 is a β-coronavirus and the angiotensin-converting enzyme 2 (ACE2) is an accepted receptor for SARS coronaviruses. It has been suggested that suppression of ACE2 expression in patients with SARS-CoV-1 infections, plays a role in pathological changes in the lung, and contributes to relieving severe pneumonia (10).

The incubation period of SARS-CoV-1 is 2 to 11 days after exposure and transmission occurs following close contact from person-to-person through respiratory droplets. Though symptoms initially mild flu-like symptoms such as cough and sore throat, in later stages acute respiratory distress syndrome was observed in about 25% of the affected patients which required mechanical ventilation. SARS outbreak was taken under control in 2003. 8096 people from 29 countries were infected and around 10% of infected people died. After the SARS-CoV-1, studies were increased on the human coronavirus and new RNA detection methods were developed (11).

b. Middle-East Respiratory Syndrome Coronavirus (MERS-CoV)

Middle-east respiratory syndrome coronavirus (MERS-CoV) was detected in June, 2012 by evaluating a sample from the sputum of a patient with severe pneumonia and kidney failure in Saudi Arabia (12). Contagion to humans was caused by close contact with infected dromedary camels. MERS-CoV was transmitted through exposure to dromedary camel's nasal secretions and other secretions and consumption of raw camel milk. In fact, the virus is thought to originate in bats and passed from bats to dromedary camels. MERS-CoV is from the β-CoVs group and the receptor used to enter the host cell is a serine peptidase, dipeptidyl peptidase 4 (10). The incubation period of the disease is 2 to 14 days, while transmission occurs as a result of close contact with the infected person’s respiratory secretions (13). In addition to respiratory disease, MERS-CoV also causes renal damage due to the high level of dipeptidyl peptidase 4 expression in the kidney. At the end of January 2020, 866 deaths associated with MERS-CoV infections were reported globally (case-mortality rate: 34.3%), and most of the deaths were in Saudi Arabia (14).

c. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

On December 31st, 2019, several local health facilities reported cases of pneumonia of unknown etiology but considered to be linked to the live-animal market in Wuhan, Hubei Province, China. The cause of the viral pneumonia outbreak was a new type of coronavirus, initially called 2019-nCoV, and this viral pneumonia disease was named COVID-19 and its causative factor was called SARS-CoV-2 (15). SARS-CoV-2 belongs to the subgenus Sarbecovirus of the genus β-coronavirus and was isolated from bronchoalveolar lavage samples of patients with unidentified pneumonia for the first time. The virus genome structure is similar to other β-coronaviruses. SARS-CoV-2 is an RNA virus with a linear, single strand, positive polarity containing genome weighing approximately 30 kilobases. SARS-CoV-2 virion contains 4 main structural proteins: nucleocapsid (N) protein, transmembrane (M) protein, envelope (E) protein, and spike (S) protein. Two different features stand out in the genome sequence. First, the receptor-binding domain (RBD) in the spike protein shows a high affinity for human angiotensin-converting enzyme-2 (ACE2) receptors. The second is a polybasic cleavage at the junction of sub-units S1 and S2 of the spike (16). SARS-CoV-2 shows 96.2% structural similarity with a bat coronavirus (CoV RaTG13) and 79.5% similarity with SARS-CoV. However, it is observed that the S protein of SARS-CoV-2 has 10-20 times more affinity for human ACE2 receptors compared with S protein of SARS-CoV. This unfortunately increases the probability of transmission from human to human (17).

ACE2 is a type I transmembrane protein and functions as a carboxypeptidase. It can be found on the surface of many cell types. Mainly in vascular endothelial cells, renal tubular epithelium, and testicles are expressed (18). ACE2 hydrolyzes angiotensin II, a powerful vasoconstrictor, to angiotensin (1-7). It has been reported to be associated with hypertension, cardiac function, heart function, and diabetes (19).

ACE2 serves also as a receptor specific to SARS-CoV. It regulates the entry of the virus into the cell by binding to S protein. In a study, it was reported that COVID-19 uses only ACE2 as a receptor for cell entry, and not other coronavirus receptors, aminopeptidase N, and dipeptidyl peptidase (20).

Studies show that SARS CoV-2 has a structural similarity with bat coronaviruses. This supports the theory that SARS-CoV-2 is derived from bats. Whatever its origin, statistics reveal that the disease spreads more rapidly from person to person (17). It is considered an important way of transmission of the disease is transmission *via* respiratory droplets. The virus can also be transmitted through tears and bodily fluids that come into contact with the eyes, mouth, or nasal mucosa. Viral RNA is also detected in the stool; accordingly, the possibility of an oro-fecal infection path is taken into account. According to studies, 44% of transmission can happen before symptoms begin (21). Information about SARS-CoV-2 and pregnancy process is not sufficient, yet. Since all infected mothers gave birth by cesarean section, there is no information about the transplacental transition. However, SARS-CoV-2 was not detected in cord blood and it is assumed that there is no transition from mother. The incubation period of COVID-19 is 5.2 days on average, ranges from 1 to 14 days. Though a bit of male predominance has been observed, it is seen that women and men are affected equally by the disease. The first symptoms of the disease are dry cough, fever, and shortness of breath. Abdominal pain, diarrhea, headache, muscle pain, malaise, and vomiting are also among the observed complaints. Hypoxemia can occur in the conditions of pulmonary inflammation, this may cause cardiac arrest. People with underlying diseases such as chronic obstructive pulmonary disease, cardiovascular disease, hypertension, and the elderly are more likely to develop acute respiratory distress syndrome (17). The case death rate is %2-3 generally, however in the elderly, it can be up to 8-15% (22).

Importance of medicinal plants and their secondary metabolites against virus infections

Viral infections have an important place in acute infectious diseases. New types of viruses often appear with high incidence and mortality rates as viruses are generally mutated. Antiviral drugs used in the treatment of viral diseases such as nucleosides, biological agents, and enzyme preparations inhibit the development of viruses, shorten the period of the infection, and help to prevent complications, however they do not eliminate their target. The high potential of side effects of existing antiviral agents used in the clinic and the development of drug resistance negatively affect the treatment procedure. Although some viral diseases such as smallpox, polio, encephalitis B, measles, and rabies have been brought under control with clinical use of vaccines, effective, and specific measures are still not sufficient for many common virus infections. Therefore, studies have been carried out on numerous agents including medicinal plants.

The history of medicinal plants dates back to the existence of human civilization in the world. Approximately 70-80% of people worldwide rely on medicinal plants to treat various human diseases, including viral infections (23). Medicinal plants are considered as an important source of various chemical compounds that form the basis for the development of new chemotherapeutic agents. The long traditional use of medicinal plants and their wide therapeutic window with fewer side effects compared to synthetic drugs have led to an increase in the number of drug discovery studies based on herbal formulation.

Higher plants may be potential effective sources in the development of new antiviral agents. Since many plant extracts belonging to different families are effective against various virus types according to the literature. Indeed, there are several important examples of currently used herbal medicines that contain standardized plant extracts as an active ingredient. For instance, *Pelargonium sidoides* DC. (Geraniaceae), a member of the genus *Pelargonium*, is widely used in South African traditional medicine. *P. sidoides* roots are known to be widely used in the treatment of respiratory complaints. The aqueous-ethanolic formulation of *P. sidoides* extracts (EPs® 7630) has been shown to be effective for respiratory disorders by clinical studies. It is known that respiratory infections are frequently caused by viruses (more than 90% of cases). Much research has been done on EPs® 7630 and found to have potent antiviral effects. *P. sidoides* aqueous extract is effective against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus, parainfluenza virus, and Coxsackie virus (24).

Another example is *Cistus* species (Cistaceacea). *Cistus* sp. grows wild in Europe, western Africa, and Asia and are a source of bioactive compounds, *e.g.* mainly flavonoids and polyphenols. The compounds are found to have many medicinal properties, especially antiviral activity. *Cistus incanus* L. extracts have antiviral activity without negative side effects against the influenza virus. It was determined that *C. incanus* is also effective against HIV-1 virus and flaviviruses (25). Furthermore, *Echinacea* (Asteraceae) species are very popular. They are perennial herbaceous plants, and natural endemic plants of Northeast America. Their preparations such as tinctures, sprays, tablets, teas, etc. are popularly used for the treatment of upper respiratory symptoms. It was reported that the standardized ethanol extracts of *Echinacea purpurea* (L.) Moench preparation (Echinaforce®) is a very active virucidal agent. *Echinacea* species are effective against various viruses including influenza viruses A&B (FluV A/B), respiratory syncytial virus (RSV), coronaviruses (HcoV, SARS CoV), rhinoviruses, coxsackieviruses, and herpes viruses (HSV 1/2) (26).

More to the point, natural products of mostly plant origin were shown to have promising activities that can help in the prevention and recovery of viral diseases. For instance, glycyrrhizin, the main active compound of *Glycyrrhiza glabra* L. (Fabaceae) is a triterpene glycoside and consists of glycyrrhetinic acid and glucuronic acid. Studies have shown that glycyrrhizin has a strong antiviral activity against many virus types including hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV), human immunodeficiency virus (HIV), influenza virus, flaviviruses, respiratory syncytial virus (RSV) and SARS-related coronavirus (27). Chloroquine and hydroxychloroquine belong to the group of antimalarial agents, they are the synthetic forms of quinine, an alkaloid. As a drug, quinine was traditionally used by Inca Indians in Peru, isolated from the bark of the *Cinchona* species from the Rubiaceae family. With studies done over time, it has been understood that these drugs can be used in various diseases, including the treatment of viral diseases. The effectiveness of hydroxychloroquine on SARS-CoV has been proven by *in vitro* studies, and currently both *in vitro* and *in vivo* studies have been performed on the SARS-CoV-2 (28). Not only medicinal plants but also other natural compounds play a key role in the development of new and effective antiviral agents. For example, among the antiviral drugs used in the treatment of herpes infections, acyclovir, vidarabine, and cytarabine are the synthetic derivatives of arabinosyl nucleosides from a marine organism *Tethya cripta* (29). Other examples of different secondary metabolite groups are terpenoids, flavonoids, and coumarins effective against HIV infections. Of these, agastanol, agastaquinone, uvaol, ursolic acid, betulinic acid have terpene structure, whereas calanolide A has coumarin structure. Additionally, polyphenols, indole alkaloids, and lignans (rhinacanthin E, F) have been found to be effective against influenza virus infections (30).

a.Flavonoids and their antiviral potential

Flavonoids are polyphenolic secondary metabolites with benzo-γ-pyron skeleton, synthesized in the plant by phenylpropanoid pathway. They can be divided into classes including flavones (apigenin, luteolin), flavonols (quercetin, kaempferol, myricetin), flavanones (hesperetin, naringenin), isoflavones (genistein, daidzein), and flavan-3-ols (catechin, epicatechin). Flavonoids are known to be responsible for a variety of pharmacological activities such as antioxidant, hepatoprotective, antibacterial, anti-inflammatory, anticancer, and antiviral (31). Many studies have been reported on the antiviral activity of flavonoids against various virus types including respiratory syncytial virus (RSV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), human parainfluenza virus (HPIVs), Auzesky's disease virus (ADV), hepatitis B virus (HBV), hepatitis C virus (HCV), dengue virus (DENV), poliovirus, rabies virus, mengo virus, and coronaviruses (CoVs) (32).

b. Flavonoid-type compounds and flavonoid containing plant extracts against coronaviruses

Previously several studies were conducted to find out novel drug molecules against coronaviruses. However, it is no doubt that antiviral drug discovery is of great importance particularly nowadays due to the current pandemic of the new coronavirus (SARS-CoV-2). In this section, flavonoid containing plant extracts and isolated flavonoids that were shown to possess potential inhibitor action against coronaviruses are summarized. The flavonoid-type components and their anti-coronavirus effect were presented in Table 1.

Table 1. Flavonoid-type compounds against coronaviruses

Flavonoid	Coronavirus type	Target	IC_{50}/EC_{50} values	Ref. No
Amentoflavone	SARS-CoV	$3CL^{pro}$	IC_{50} = 8.3 µM	44
Ampelopsin	SARS-CoV	$3CL^{pro}$	IC_{50} = 364 ± 8.7	45
Apigenin	SARS-CoV	$3CL^{pro}$	IC_{50} = 280.8 µM	44
Baicalin	SARS-CoV	Neutralisation test	EC_{50} = 11 µg/mL	35
Bavachinin	SARS-CoV	PL^{pro}	EC_{50}=38.4 ± 2.4 µM	41
Broussuchalcone B	MERS-CoV	$3CL^{pro}$	IC_{50} = 27.9 ± 1.2 µM	46
	MERS-CoV	PL^{pro}	IC_{50} = 112.9 ± 10.1 µM	46
	SARS-CoV	$3CL^{pro}$	IC_{50} = 57.8 ± 0.5 µM	46
	SARS-CoV	PL^{pro}	IC_{50} = 11.6 ± 0.7 µM	46
Corylifol A	SARS-CoV	PL^{pro}	EC_{50}=32.3 ± 3.2 µM	41
Daidzein	SARS-CoV	$3CL^{pro}$	IC_{50} = 351 ± 2.9	45
Diplacone	SARS-CoV	PL^{pro}	IC_{50} =10.4 ± 0.16 µM	42
Epigallocatechin gallate	SARS-CoV	$3CL^{pro}$	IC_{50} = 73 ± 2 µM	45
Gallocatechin gallate	SARS-CoV	$3CL^{pro}$	IC_{50} = 47 ± 0.9 µM	45
Helichrysetin	MERS-CoV	$3CL^{pro}$	IC_{50} = 67.04	48
Herbacetin	MERS-CoV	$3CL^{pro}$	IC_{50} = 40.59	48
	SARS-CoV	$3CL^{pro}$	IC_{50} = 33.17 µM	47
Hesperetin	SARS-CoV	$3CL^{pro}$	IC_{50} = 8.3 µM	43
Isobavachalcone	MERS-CoV	$3CL^{pro}$	IC_{50} = 35.85 µM	48
	SARS-CoV	PL^{pro}	EC_{50} =7.3 ± 0.8 µM	41
Isoliquiritigenin	MERS-CoV	$3CL^{pro}$	IC_{50} = 33.9 ± 7.7 µM	46
	MERS-CoV	PL^{pro}	IC_{50} = 82.2 ± 7.7 µM	46
	SARS-CoV	$3CL^{pro}$	IC_{50} = 61.9 ± 11.0 µM	46
	SARS-CoV	PL^{pro}	IC_{50} = 24.6 ± 1.0 µM	46
Juglanin	SARS-CoV	Inhibition of ion channel	IC_{50} = 2.3 µM	40
Kazinol F	MERS-CoV	$3CL^{pro}$	IC_{50} = 135.0 ± 5.1 µM	46
	MERS-CoV	PL^{pro}	IC_{50} = 39.5 ± 5.1 µM	46
	SARS-CoV	$3CL^{pro}$	IC_{50} = 43.3 ± 10.4 µM	46
	SARS-CoV	PL^{pro}	IC_{50} = 27.8 ± 2.5 µM	46
Luteolin	SARS-CoV	Spike(S) protein	EC_{50}=10.6 µM	39
	SARS-CoV	$3CL^{pro}$	IC_{50} = 20.2 µM	44
Mimulone	SARS-CoV	PL^{pro}	IC50 =14.4 ± 0.27 µM	42
Myricetin	SARS-CoV	Helicase-ns P13	IC_{50} =2.71 µM	38
Eobavaisoflavone	SARS-CoV	PL^{pro}	EC_{50}=18.3 ± 1.1 µM	41
Papyriflavonol A	MERS-CoV	$3CL^{pro}$	IC_{50} = 64.5 ± 4.9 µM	46
	MERS-CoV	PL^{pro}	IC_{50} = 112.5 ± 7.3 µM	46
	SARS-CoV	$3CL^{pro}$	IC_{50} = 103.6 ± 17.4 µM	46
	SARS-CoV	PL^{pro}	IC_{50} = 3.7 ± 1.6 µM	46
Pectolinarin	SARS-CoV	$3CL^{pro}$	IC_{50} = 37.78 µM	47
Psoralidin	SARS-CoV	PL^{pro}	EC_{50} =4.2 ± 1.0 µM	41
Puerarin	SARS-CoV	$3CL^{pro}$	IC_{50} = 381 ± 12.5	45
Quercetin	MERS-CoV	$3CL^{pro}$	IC_{50} = 34.8 ± 1.2 µM	46
	MERS-CoV	PL^{pro}	-	46
	Murine coronavirus	Neutralisation test	IC_{50} =125 µg/mL	36
	SARS-CoV	$3CL^{pro}$	IC_{50} = 73 ± 4 µM	45
	SARS-CoV	$3CL^{pro}$	IC_{50} = 34.8 ± 1.2 µM	46
	SARS-CoV	$3CL^{pro}$	IC_{50} = 23.8 µM	44
	SARS-CoV	PL^{pro}	IC_{50} = 8.6 ± 3.2 µM	46
Quercetin 3-β-D-glucoside	MERS-CoV	$3CL^{pro}$	IC_{50} = 37.03 µM	48
Rhoifolin	SARS-CoV	$3CL^{pro}$	IC_{50} = 27.45 µM	47
Scutellarein	SARS-CoV	Helicase-nsP13	IC_{50} =0.86 µM	38
Tomentin A	SARS-CoV	PL^{pro}	IC_{50} =6.2 ± 0.04 µM	42
Tomentin B	SARS-CoV	PL^{pro}	IC_{50} =6.1 ± 0.02 µM	42
Tomentin C	SARS-CoV	PL^{pro}	IC_{50} =11.6 ± 0.13 µM	42
Tomentin D	SARS-CoV	PL^{pro}	IC_{50} =12.5 ± 0.22 µM	42
Tomentin E	SARS-CoV	PL^{pro}	IC_{50} =5.0 ± 0.06 µM	42
3´-*O*-methyldiplacol	SARS-CoV	PL^{pro}	IC_{50} = 9.5 ± 0.1 µM	42
3´-*O*-methyldiplacone	SARS-CoV	PL^{pro}	IC_{50} = 13.2 ± 0.14 µM	42
4´-*O*-methylbavachalcone	SARS-CoV	PL^{pro}	EC_{50}=10.1 ± 1.2 µM	41
4´-*O*-methyldiplacol	SARS-CoV	PL^{pro}	IC_{50} = 9.2 ± 0.13 µM	42
4´-*O*-methyldiplacone	SARS-CoV	PL^{pro}	IC_{50} = 12.7 ± 0.19 µM	42
6-Geranyl-4´,5,7-trihydroxy-3´,5´-dimethoxyflavanone	SARS-CoV	PL^{pro}	IC_{50} =13.9 ± 0.18 µM	42
7-*O*-arylmethylquercetin with 3''-Cl	SARS-CoV	NTPase/helicase	IC_{50} =5.2 µM	37
7-*O*-arylmethylquercetin with 3''-CN	SARS-CoV	NTPase/helicase	IC_{50} =2.7 µM	37
7-*O*-arylmethylquercetin with 4''-Cl	SARS-CoV	NTPase/helicase	IC_{50} =4.1 µM	37

Opuntia dillenii (Ker Gawl.) Haw. (Cactaceae) is a succulent shrub, used in traditional Chinese medicine, growing in semi-desert in the tropics and subtropics regions. *O. dillenii* contains flavonoids including quercetin, kaempferol, 3-*O*-methylquercetin, isorhamnetin, isoquercitrin, and kaempferide. In a study on the methanol extract of *O. dillenii* flowers, antiviral activity was investigated against various viruses including feline coronavirus (FCoV) belonging to the α-coronavirus family. As a result of the study, the moderate antiviral effect of *O. dillenii* methanol extract against FCoV was observed with an EC_{50} value of 100 µg/mL (33).

Sesbania grandiflora (L.) Pers. (Fabaceae) is a small, cultivated tree and contains several flavonoids such as isovestitol, medicarpin, sativan, quercetin, myricetin, and kaempferol. Antiviral and cytotoxic activities of the methanol extract of *S. grandiflora* flowers were investigated against 12 different viruses. The methanol extract displayed moderate activity on feline coronavirus (FCoV) and the EC_{50} value was calculated as 100 µg/mL (34).

In a study of *in vitro* antiviral susceptibility of the SARS coronavirus, baicalin, a flavonoid-type compound isolated from *Scutellaria baicalensis* Georgi (Lamiaceae) was investigated against 10 clinical isolates of SARS-CoV by neutralisation tests. In the mentioned study, it was reported that baicalin had antiviral activity. The results were confirmed by plaque reduction assay and the EC_{50} value of baicalin was determined to be 11 µg/mL (35).

The murine coronavirus, mouse hepatitis virus is classified under the genus β-coronavirus and causes an epidemic murine illness. In a study, *in vitro* antiviral activity of the ethyl acetate fraction of *Houttuynia cordata* Thunb. (Saururaceae) and its flavonoid-type compounds, namely, quercetin, quercitrin, and rutin were investigated against murine coronavirus. At the end of the study, the IC_{50} value of the ethyl acetate fraction of *H. cordata* was determined to be 0.98 mg/mL. The isolated flavonoids exhibited comparatively weaker antiviral activity, only quercetin inhibited the mouse hepatitis virus with an IC_{50} value of 125 µg/mL (36).

Antiviral activity of 7-*O*-arylmethylquercetins, derivatives of quercetin, which is a popular and common flavonol type compound with numerous biological effects, were evaluated against SARS-CoV. As a result of the study, it was reported that three derivatives with 3''-Cl, 3''-CN, and 4''-Cl aromatic substituents exerted selective inhibitory activity against SARS-CoV NTPase/helicase. (IC_{50} = 5.2 µM, 2.7 µM, 4.1 µM, respectively) (37).

A study by Keum and Jeong (2012) investigated 64 natural compounds to find out a promising target for the suppression of SARS-CoV helicase-nsP13. As a result of the study, only 2 compounds strongly inhibited the ATPase activity of nsP13 and these compounds were flavonoids namely, myricetin, and scutellarein. IC_{50} values of myricetin and scutellarein were designated to be 2.71 µM and 0.86 µM (38).

In a study by Yi et al. (2004), new small molecules of Chinese herbal medicine that bind avidly with the surface Spike (S) protein of SARS-CoV were screened. Due to the binding with S protein, the entry of the virus to its host cells was interfered. A two-step screening method was developed which combines frontal affinity chromatography-mass spectrometry (FAC/MS). Pseudotyped virus infection was assayed to find out the potential drugs that can interfere with the entry of SARS-CoV into host cells. Among 130 small molecules, two were found to possess potent antiviral activity against the wild-type SARS-CoV infection. One of these two molecules was luteolin which has a flavonoid structure with an EC_{50} value of 10.6 µM (39).

The genome of the SARS coronavirus contains open reading frames encoding new proteins. The protein encoded by the open-reading-frame 3a of SARS-CoV demonstrates to form a cation-selective channel which may become expressed in the infected cell. The channel's activity involves the virus release mechanism. Drugs that inhibit the ion channel could be new therapeutic antiviral agents. In a study, the flavonols, *e.g.* kaempferol, kaempferol glycosides, and acylated kaempferol glucoside derivatives were tested according to their potency to inhibit channel 3a. According to the results, the glycoside juglanin that carried an arabinose residue was found to be the most active molecule with an IC_{50} value of 2.3 µM. Kaempferol derivatives with rhamnose residue were also seen to be quite potent (40).

Seeds of *Psoralea corylifolia* L. (Fabaceae) are used as a food additive in many countries, especially in South Korea, and the plant contains flavonoids and chalcones as the main bioactive compounds.

A study on the antiviral activity of the ethanol extract of *P. corylifolia* seeds demonstrated that the extract exerts a strong inhibitory activity against SARS-CoV papain-like protease (PL^{pro}) enzyme, with an IC_{50} of value of 15 µg/mL. SARS-CoV PL^{pro} plays an important role in SARS-CoV replication. Since the ethanol extract of *P. corylifolia* seeds exhibited a significant activity against the SARS-CoV PL^{pro}, bioactivity-guided fractionation was applied to the ethanol extract. Six aromatic compounds were isolated, namely, bavachinin, neobavaisoflavone, isobavachalcone, 4´-*O*-methylbavachalcone, psoralidin, and corylifol A. All isolated flavonoids inhibited PL^{pro} in a dose-dependent manner with EC_{50} values of 38.4 ± 2.4 µM, 18.3 ± 1.1 µM, 7.3 ± 0.8 µM, 10.1 ± 1.2 µM, 4.2 ± 1.0 µM, and 32.3 ± 3.2 µM, respectively. Thus, this study indicates that the plant may be a rich source of potent PL^{pro} inhibitors and can be used as an option in the treatment of SARS (41).

In another study, the SARS-CoV PL^{pro} inhibitory activity of the methanol extracts of *Paulownia tomentosa* (Thunb) Steud. (Paulowniaceae) fruit was assessed by using a fluorogenic assay. A total of twelve PL^{pro} inhibitory flavonoids, five of which were with new structures, were isolated from the extract. New flavonoids contained a rare 3,4-dihydro-2*H*-pyran moiety, namely, tomentin A, tomentin B, tomentin C, tomentin D, and tomentin E. The results have indicated that new compounds were the most effective with the IC_{50} values of 6.2 ± 0.04 µM, 6.1 ± 0.02 µM, 11.6 ± 0.13 µM, 12.5 ± 0.22 µM, 5.0 ± 0.06 µM, respectively. The other tested flavonoids were also able to inhibit the enzyme in a dose-dependent manner. The mentioned flavonoid compounds were 3´-*O*-methyldiplacol (IC_{50} =9.5 ± 0.1 µM), 4´-*O*-methyldiplacol (IC_{50} = 9.2 ± 0.13 µM), 3´-*O*-methyldiplacone (IC_{50}: 13.2 ± 0.14 µM), 4´-*O*-methyldiplacone (IC_{50} =12.7 ± 0.19 µM), mimulone (IC_{50} =14.4 ± 0.27 µM), diplacone (IC_{50} =10.4 ± 0.16 µM), and 6-geranyl-4´,5,7-trihydroxy-3´,5´-dimethoxyflavanone (IC_{50} =13.9 ± 0.18 µM) (42).

The 3C-like protease ($3CL^{pro}$) of SARS-CoV is vital for the viral life cycle and promising target for the development of antiviral drugs against CoV infections. *Isatis indigotica* Fort. (Brassicaceae) is a plant grown in China and its roots have an antiviral effect. In a study, the water extract of *I. indigotica* roots and compounds from the root extracts [indigo, indirubin, indican (indoxyl-β-D-glucoside), β-sitosterol, γ-sitosterol, and sinigrin] was investigated against SARS-CoV $3CL^{pro}$. It was determined that the root extract inhibited $3CL^{pro}$ with an IC_{50} value of 191.6 ± 8.2 µg/mL in cell-based assay. Aloe-emodin, hesperetin, quercetin, naringenin, daidzein, emodin, and chrysophanol were also analyzed in the same study. Results showed that hesperetin, a flavanone type compound, was the most potent compound with an IC_{50} value of 60.3 µM and 8.3 µM in cell-free and cell-based assays (43).

In a study by Ryu et al. (2010) the leaf extract of *Torreya nucifera* (L.) Siebold et Zucc. (Taxaceae) growing in Korea and its active flavonoids were investigated against SARS-CoV $3CL^{pro}$. The leaf extract displayed a good level of SARS-CoV $3CL^{pro}$ inhibitory activity (62% at 100 µg/mL). Through activity-guided isolation studies, amentoflavone, luteolin, quercetin, and apigenin were identified and the IC_{50} values of the mentioned compounds were determined as 8.3 µM, 20.2 µM, 23.8 µM, and 280.8 µM, respectively (44).

Seven flavonoid derivatives were evaluated for their inhibitory activity against $3CL^{pro}$ expressed and purified from a methylotrophic yeast *Pichia pastoris.* Flavonoid compounds as the test substances in the study were quercetin, daidzein, puerarin, epigallocatechin, epigallocatechin gallate gallocatechin gallate, and ampelopsin. Quercetin, epigallocatechin gallate, and gallocatechin gallate showed a good inhibition against $3CL^{pro}$ with IC_{50} values of 73, 73 and 47 µM, respectively. The relationship between structure inhibition activity in flavonoid compounds was also investigated. As a result, it was reported that gallocatechin gallate is the best inhibitor and shows numerous hydrophobic and H-bonds interactions with amino acid residues in the $3CL^{pro}$ active site pocket (45).

In another study, a series of flavonoid compounds isolated from the root extract of *Broussonetia papyrifera* (L.) Vent. (Moraceae) were tested against both SARS-CoV and MERS-CoV $3CL^{pro}$ and PL^{pro}. As a result of against MERS-CoV; it was reported that broussuchalcone B inhibited $3CL^{pro}$ with an IC_{50} value of 27.9 ± 1.2 µM, and PL^{pro} with 112.9 ± 10.1 µM, papyriflavonol A inhibited $3CL^{pro}$ with an IC_{50} value of 64.5 ± 4.9, and PL^{pro} with 112.5 ± 7.3 µM, kazinol F inhibited $3CL^{pro}$ with an IC_{50} value of 135.0 ± 5.1 µM and PL^{pro} with 39.5 ± 5.1 µM, isoliquiritigenin inhibited $3CL^{pro}$ with an IC_{50} value of 33.9 ± 7.7 µM and PL^{pro} with 82.2 ± 7.7 µM, kaempferol inhibited $3CL^{pro}$ with an IC_{50} value of 35.3 ± 5.3 µM, PL^{pro} with 206.6 ± 1.7 µM, quercetin inhibited $3CL^{pro}$ with an IC_{50} value of 34.8 ± 1.2 µM but was not able to show inhibition against PL^{pro}.

Against SARS-CoV; it was reported that broussuchalcone B inhibited $3CL^{pro}$ with an IC_{50} value of 57.8 ± 0.5 μM, and PL^{pro} with 11.6 ± 0.7 μM, papyriflavonol A inhibited $3CL^{pro}$ with an IC_{50} value of 103.6 ± 17.4 μM, and PL^{pro} with 3.7 ± 1.6 μM, kazinol F inhibited $3CL^{pro}$ with an IC_{50} value of 43.3 ± 10.4 μM and PL^{pro} with 27.8 ± 2.5 μM, isoliquiritigenin inhibited $3CL^{pro}$ with an IC_{50} value of 61.9 ± 11.0 μM and PL^{pro} with 24.6 ± 1.0 μM, kaempferol inhibited $3CL^{pro}$ with an IC_{50} value of 116.3 ± 7.1 μM, PL^{pro} with 16.3 ± 2.1 μM, quercetin inhibited $3CL^{pro}$ with an IC_{50} value of 34.8 ± 1.2 μM, PL^{pro} with 8.6 ± 3.2 μM. It was concluded that all compounds were more potent against PL^{pro} than against $3CL^{pro}$ and papyriflavonol A was the most potent inhibitor of PL^{pro} with an IC_{50} value of 3.7 μM (46).

According to abovementioned studies, it is assumed that the antiviral activity of some flavonoids against CoVs is directly related by the inhibition of $3CL^{pro}$. In a study, flavonoid-type compounds were applied to the FRET (Fluorescence resonance energy transfer) method for a systematic investigation of inhibitory compounds against SARS-CoV $3CL^{pro}$. As a result of the evaluation of the potential proteolytic activity of flavonoids and an induced-fit docking experiment, herbacetin, rhoifolin, and pectolinarin were found to possess the best inhibitory effect against SARS-CoV $3CL^{pro}$ with IC_{50} values of 33.17, 27.45 and 37.78 μM, respectively (47).

In a similar study by Jo et al. (2019), a flavonoid library was applied to probe inhibitor compounds against MERS-CoV $3CL^{pro}$. Herbacetin, isobavachalcone, quercetin 3-β-D-glucoside and helichrysetin were found to prevent the enzymatic activity of MERS-CoV $3CL^{pro}$ in a dose-dependent manner with IC_{50} values of 40.59, 35.85, 37.03, and 67.04 μM, respectively. A comparison of the binding affinity of flavonoids provided an understanding of their scaffolds and functional groups that required to bind with MERS-CoV $3CL^{pro}$. It was revealed by an induced-fit docking analysis that S1 and S2 sites play a role in interacting with flavonoids. At the end of the study, it has been observed that flavonol and chalcone were the favorite scaffolds to bind to the catalytic site. It was also concluded that some hydrophobic flavonoid derivatives or carbohydrate attached to the core structures provide a good inhibitory effect (48).

AutoDock Vina was utilized to screen potential drugs by molecular docking with the structural protein and non-structural protein sites of new coronavirus in a study by Ran et al. (2020). It was seen that luteolin, the main flavonoid in honeysuckle, bound with a high affinity to the same sites of the main protease of SARS-CoV-2 (49).

CONCLUSION

CoVs are RNA viruses that can infect various hosts, including avian, swine, and humans. Among them, human coronaviruses represent a major group of CoVs related with the respiratory diseases such as common cold and serious pneumonia. The first confirmed atypical pneumonia was SARS, a recent pandemic was MERS and currently ongoing is SARS-CoV-2. Since there is no protective and therapeutic approach against these viral infections, anti-SARS drugs are of urgent demand for future outbreaks. According to the literature review, several studies have been conducted on the flavonoid-type compunds against coronaviruses. The objective of the present study was to review a number of flavonoids as promising drug targets against SARS-CoV-2. Flavonoids with different structures, namely amentoflavone, baicalin, bavachinin, broussuchalcone B, corylifol A, diplacone, epigallocatechin gallate, gallocatechin gallate, helichrysetin, herbacetin, hesperetin, isobavachalcone, isoliquiritigenin, juglanin, kazinol F, luteolin, mimulone, myricetin, neobavaisoflavone, papyriflavonol A, pectolinarin, psoralidin, quercetin, quercetin 3-β-D-glucoside, rhoifolin, scutellarein, tomentin A-E, 3´-*O*-methyldiplacol, 3´-*O*-methyldiplacone, 4´-*O*-methylbavachalcone, 4´-*O*-methyldiplacol, 4´-*O*-methyldiplacone, 6-geranyl-4´,5,7-trihydroxy-3´,5´-dimethoxyflavanone, 7-*O*-arylmethylquercetin with 3''-Cl, 7-*O*-arylmethylquercetin with 3''-CN, and 7-*O*-arylmethylquercetin with 4''-Cl were shown to possess high antiviral activity against coronoviruses. On the other hand, ampelopsin, apigenin, daidzein, and puerarin were reported to have lower antiviral activity. These flavonoids may act as active compounds for the development of effective drugs against SARS-CoV-2.

Conflict of interest

No conflict of interest was declared by the authors.

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