Functional foods with antiviral activity

Da Hyun Kim[1] · Jae Hwan Kim[1] · Da Hyun Kim[1] · Jay-Young Jo[1] ·
Sanguine Byun[1]

Abstract Viruses are known to cause a variety of diseases, ranging from mild respiratory diseases, such as the common cold, to fatal illnesses. Although the development of vaccines and targeted drugs have significantly improved the mortality rate and disease severity against a number of viral infections, there are still many viruses without proper treatment/prevention options and newly emerging viruses can pose serious health threats. For instance, the coronavirus disease 2019 (COVID-19) pandemic is producing significant healthcare and socio-economic burden worldwide, which may jeopardize the lives and livelihoods for years to come. Studies have identified functional foods with antiviral activity. Certain foods may target the viral life cycle or modulate the host immune system to enhance defense against viral infections. In this review, we will discuss some of the food products reported to display protective effects against viruses including the influenza virus, human immunodeficiency virus, and severe acute respiratory syndrome coronavirus 2.

✉ Sanguine Byun
sanguine@yonsei.ac.kr

Da Hyun Kim
dahyunk@yonsei.ac.kr

Jae Hwan Kim
kjh720@yonsei.ac.kr

Da Hyun Kim
dahyun.kim@yonsei.ac.kr

Jay-Young Jo
jayyjo@yonsei.ac.kr

[1] Department of Biotechnology, Yonsei University, Seoul 03722, Korea

Introduction

Viruses are small infectious agents which can reproduce only in living cells. The virus attaches to the host cell, penetrates into the cytoplasm, and releases its RNA or DNA for viral genome replication/expression. Subsequently, the virion particles are assembled, and new viruses exit the cell, which can go on to infect other cells. Most viruses can infect only certain species and particular types of cells within that host (Ryu, 2017). While respiratory viral infections are the most common, other viruses can target other parts of the body such as the gastrointestinal tract, liver, skin, or the nervous system. Viral infection can lead to various diseases in humans, ranging from the common cold to the acquired immunodeficiency syndrome (AIDS) (Wat, 2004). Based on the report from the world health organization (WHO), seasonal influenza is expected to cause 290,000–650,000 deaths each year due to respiratory diseases. In addition, some viruses such as the human immunodeficiency virus (HIV), hepatitis C virus (HCV), and a number of herpes viruses can cause chronic infections leading to potentially fatal illnesses (Rouse and Sehrawat, 2010). While our body is equipped with immune systems to defend against infections and remove pathogens, there are many cases where the host defense system is insufficient for blocking the spread of viruses.

The development of vaccines, new diagnostic tools, and targeted drugs have significantly improved the mortality rate as well as reduced severe complications against viral infections (Kaufmann et al., 2018). However, many viral

diseases still lack proper vaccines or therapeutic drugs (Mercorelli et al., 2018; Zumla et al., 2016). Moreover, newly emerging viruses such as the Ebola virus, SARS-coronavirus, and Middle East respiratory syndrome (MERS)-coronavirus are posing serious health threats to the public (Chafekar and Fielding, 2018; Jones et al., 2008; Song et al., 2019). For example, since its emergence in late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic has spread rapidly across the world, reaching more than 220 countries. As of March 2022, more than 450 million confirmed cases and over 6,190,000 deaths have been reported (2020). SARS-CoV-2 infections can cause a broad range of symptoms, from mild respiratory problems to severe and fatal complications, including acute respiratory distress syndrome or multi-organ failure (Guzik et al., 2020; Zhou et al., 2020). The coronavirus disease 2019 (COVID-19) pandemic is placing severe pressure on healthcare systems throughout the world and its effects on the global economy are likely to be felt for years to come (Shang et al., 2021). In this regard, additional preventive measures and alternative therapeutic strategies could help fight against viral infections.

Functional foods can provide health-benefits beyond its nutritional value. Functional foods have shown preventive and/or therapeutic effects against a variety of disorders including cancer, diabetes, inflammatory diseases, neurodegenerative diseases, and infectious diseases (Farrand and Byun, 2017; Jang et al., 2019; Shin et al., 2020). And some functional foods have been demonstrated to enhance the host immune system against viral infections as well as directly suppress the activity of viruses. Therefore, consuming these foods may help enhance the antiviral response against invading viruses. In the current review, we will discuss functional foods that have been reported to display antiviral effects via modulating the host immune function or targeting the viral life cycle. We focused on commonly consumed functional food products with reported immune-boosting and antiviral effects, such as red ginseng, probiotics (*L. plantarum*), chlorella, cheonggukjang (*Bacillus subtilis* subsp. *Chungkookjang*), berries, and licorice. In addition, several food-derived compounds with anti-viral effects were selected for review.

Red ginseng

Ginseng (*Panax ginseng* C. A. Meyer) is a perennial root that is widely studied as an herbal remedy for its immunomodulatory effects (Wang et al., 2021; Yun, 2001). Ginseng can be air-dried to produce white ginseng or steamed and heat-processed into red ginseng for longer preservation. Red ginseng is known to exhibit stronger immune-stimulating effects and antiviral effects compared to white ginseng (Wang et al., 2021; Yun, 2001). The ginsenosides and polysaccharides have been reported to be responsible for the antiviral effects observed from red ginseng (Lee et al., 2010; Shibata, 2001).

The antiviral effects of red ginseng were studied on influenza viruses including, influenza virus A/PR8, H1N1 virus, H3N2 virus, and H9N2 virus (Chan et al., 2011; Kim et al., 2016; Kwok et al., 2016; Quan et al., 2007). The effect of red ginseng extracts against H1N1 virus was examined on CD3 + T immune cells and natural killer (NK) cells isolated from human peripheral blood mononuclear cells (PBMCs) (Kim et al., 2016). The treatment of red ginseng extracts significantly increased the surface expression of CD69 and CD25, early and late activation markers on CD3 + T cells and NK cells, respectively. These results suggest that red ginseng may enhance the activation and proliferation of human NK and CD3 + T cells. In the same study, the administration of red ginseng extracts was found to mitigate H1N1 virus-induced lytic gene expression and increase survival rate of the H1N1 virus-infected mice (Kim et al., 2016). The oral administration of red ginseng extracts was also reported to exhibit enhanced cross-protection against antigenically distinct H1N1 and H3N2 influenza viruses (Yoo et al., 2012). In this in vivo study, treatment of red ginseng extracts significantly increased the expression of antiviral cytokine interferon (IFN)-γ, lowered levels of lung viral titers, and moderately improved survival rates of both H1N1 and H3N2 infected mice (Yoo et al., 2012). Red ginseng extract also plays a role as a mucosal adjuvant against influenza virus A/PR8 during viral infection (Quan et al., 2007). The administration of red ginseng extracts to influenza virus A/PR8 virus-infected mice showed significant enhancement of influenza virus-specific IgA antibody expression in lungs. Mice treated with red ginseng extracts also exhibited enhanced production of serum IgA and IgG subtypes and increased secretion of Th1 and Th2-type cytokines in splenocytes upon challenge infection. This adjuvant effect of red ginseng extracts was comparable to that of conventional adjuvants such as aluminum hydroxide and cholera toxin (Quan et al., 2007). Red ginseng extracts were also studied to have antiviral effects against the highly pathogenic H5N1 influenza virus (Park et al., 2014). In vivo mice and ferret models were used to study the effects of red ginseng against H5N1 influenza virus. The oral administration of red ginseng over the duration of 60 days improved survival rates of both mice and ferrets in vivo models infected with the lethal H5N1 virus. Interferon-α and -γ antiviral cytokines were significantly induced in the lungs of mice fed red ginseng, compared to mice fed an unsupplemented diet (Park et al., 2014). This study suggests that immune-enhancing red ginseng may

help to ameliorate the effects of the highly pathogenic H5N1 influenza virus.

Red ginseng has been reported to show inhibitory effects against human immunodeficiency virus (HIV). There are two types of HIV that have been characterized, human immunodeficiency virus type 1 (HIV-1) and human immunodeficiency virus type 2 (HIV-2) (Im et al., 2016). HIV-1 is the more prevalent HIV type virus that produces a persistent and virulent latent infection compared to HIV-2 (Moore and Chaisson, 1999). HIV infection is associated with the progressive depletion of CD4 + T cells from circulation and total body scores (McCune, 2001; Moore and Chaisson, 1999). CD4 + T cells are an essential component of our immune system, it is responsible for orchestrating immune response against viral pathogens by recruiting lymphoid cells and induce the production of cytotoxic and memory CD8 + T cells (Sant and McMichael, 2012). Although there is no cure to HIV infection, there are antiretroviral therapies to slow-down the progression of different stages of infection: acute HIV infection, clinical latency, and acquired immunodeficiency syndrome (AIDS) (Shrivastava et al., 2021). The combination antiretroviral therapy methods comes at a cost of possible treatment failure following drug resistance, poor compliance in 46% of people with HIV and adverse side-effects in 83% of people with HIV (Shrivastava et al., 2021). Red ginseng extracts have been shown to exhibit antiviral effects by maintaining CD4 + T cell counts and delaying the occurrence of resistant mutations in HIV-1 patients (Kim et al., 2015a; Sung et al., 2009, 2005). Red ginseng extract treatment also had anti-HIV effects characterized by delaying disease progression in HIV-1-infected patients (Sung et al., 2005). A clinical study was conducted on sixty-eight HIV-1-positive patients who had not received antiretroviral therapy for more than 5 years prior to the study. These subjects took 4,082 ± 3,928 g of red ginseng extracts over an average duration of two years and found a significant correlation between red ginseng extract intake and reduced serum-soluble CD8 antigen levels (Sung et al., 2005). In addition to this, Sung et al. reported that red ginseng extracts independently and significantly inhibits CD4 + T cell depletion in HIV-patients (Sung et al., 2005). The antiviral effects of red ginseng extracts in combination with highly active antiretroviral therapy was studied on a total of forty-six HIV-patients (Sung et al., 2009). In this clinical study, all patients received antiretroviral therapies and half of the study population additionally received red ginseng capsules for consumption. Subjects taking red ginseng (2.7 g/day for women and 5.4 g/day for men) had significantly increased CD4 + T cell count and reduced resistant-mutations compared to the control group after 3 years of therapy (Sung et al., 2009). The antiviral effects of red ginseng

extracts reported in these studies holds promise that red ginseng may be used as a supplement for aiding the treatment of viral diseases.

Chlorella

Chlorella (*Chlorella*), as a famous unicellular green algae belonging to the division Chlorophyta, has been considered as a functional food material due to their various physiological activities. Some studies have also reported their antiviral effects.

In an in vitro study, *Chlorella sorokiniana* has been proven to have antiviral effects against rotavirus. In rotavirus-infected HT-29 cells, treatment with *C. sorokiniana* at a concentration of 1×10^9 cells/mL reduced focus forming units compared to untreated infected cells. Also, the treatment of *C. sorokiniana* affected viral infectivity against rotavirus in HT-29 cells. When the rotavirus titer of the untreated virus-infected cells was converted to 100%, the *C. sorokiniana*-treated group showed about 4% virus infectivity (Cantu-Bernal et al., 2020). In addition, protective effect of chlorella supplement against chronic hepatitis C virus (HCV) infection has been identified in a clinical trial model (Azocar and Diaz, 2013). This clinical study was conducted in eighteen patients infected with hepatitis C virus, and chlorella supplement was administered for about 12 weeks. After intake of chlorella supplement, alanine aminotransferase (ALT) levels were decreased in the majority of patients (> 85%) compared to before intake of chlorella supplements. In addition, most patients with improved ALT tended to have a decreased HCV viral load. In particular, RNA levels of HCV decreased in about 70% of patients without any adverse side effects. Collectively, chlorella could be a promising functional food material that could help in fighting against virus infections.

Berries

Berries contain various phenolic compounds and have been reported to exert various physiological activities (Szajdek and Borowska, 2008). Among these, some types of berries have also been shown to possess antiviral activities against various strains.

Multiple methanol extracts of berries, including strawberry (*Fragaria vesca L.*), bilberry (*Vaccinium myrtillis L.*), raspberry (*Rubus idaeus L.*), and lingonberry (*Vaccinium vitis-idaea L*), have been identified for their inhibitory effect against the replication of both coxsackievirus B1 virus and influenza A virus through the virus cytopathic effect reduction assay in Hep-2 cells (Nikolaeva-Glomb

et al., 2014). Another berry, blackcurrant (*Ribes nigrum L.*), have been found to prevent influenza infection (Ikuta et al., 2012). The extract of this berry inhibited the replication of various viruses including respiratory syncytial virus, influenza virus, herpes simplex virus, and adenovirus in Hep-2, MDCK, A549, or hTERT-BJ1 cells by more than 50% based on the plaque reduction assay. In addition, it was demonstrated that blackcurrant not only inhibited virus proliferation in host cells, but also directly inhibited virus adsorption to host cells. The blackcurrant extract at a concentration of approximately 10% inhibited the adsorption of viruses to the cell surface by more than 95%. Another study also demonstrated the antiviral efficacy of blackcurrant against both influenza virus types A and B through the plaque formation assay in MDCK cells (Knox et al., 2003). Blackcurrant extract at pH 2.8 inactivated both influenza virus types A and B by about 99%, and blackcurrant extract at pH 7.2 inhibited the activation of these two types of influenza viruses by 95–98%. This research team conducted a fractional analysis study to find the active ingredient of blackcurrant against influenza virus (Knox et al., 2001). As a result, it was suggested that the anthocyanidin components contained in blackcurrant might regulate viral uptake into cells and virus secretion from infected cells. Elderberry (*Sambucus nigra L.*) has also displayed antiviral effect against human influenza A virus in a mouse model (Kinoshita et al., 2012). In influenza A virus-infected mice, treatment with the elderberry fraction suppressed viral replication in bronchoalveolar lavage. In addition, the levels of neutralizing antibodies specific for influenza A virus in serum and secreted IgA in feces were increased by elderberry administration. Among various berries, elderberry, in particular, has been reported in clinical studies on influenza virus. In Norway, a clinical study of elderberry for Influenza was conducted in sixty patients of various ages suffering from influenza-like symptoms (Zakay-Rones et al., 2004). These patients consumed elderberry syrup 4 times a day for a total of 5 days. As a result, the patients who received the elderberry showed relief of symptoms an average of 4 days earlier than the placebo-treated group.

Licorice

Licorice, the root of *Glycyrrhiza glabra*, is an herb that has been used worldwide as a traditional medicine due to its rich flavonoids and triterpenoids contents (Fu et al., 2005). Among the major active components of licorice, glycyrrhizin (GL) is the most studied compound concerning the antiviral activity. GL has been found to exert antiviral effects by various mechanisms. Several studies demonstrated that GL can directly target the viruses at different

stages of their life cycles. Wolkerstorfer et al. revealed that GL suppressed influenza A virus by inhibiting the entry of virus into the host cell (Wolkerstorfer et al., 2009). Researchers showed that the treatment of 2.5 mM of GL reduced approximately 50% of fluorescence-labelled influenza A in A594 and 94% in MDCK cells compared to untreated cells. However, since the study used a concentration of GL that is not physiologically relevant, it is believed that further validation is required. Another research assessed the antiviral potential against two clinical isolates of coronavirus (FFM-1 and FFM-2) and found that 4000 µg/mL of GL completely inhibited the virus replication in Vero cells, especially showing high inhibitory efficacy when treated during the adsorption and penetration steps (Cinatl et al., 2003). In addition, Matsumoto et al. confirmed that GL can interfere in the release step of HCV (Matsumoto et al., 2013). In this study, the extracellular infectivity titer of HCV-infected Huh7 cells was decreased by 57% with the treatment of 500 µM of GL while the intracellular infectivity titer was increased at the same concentration of GL. In the same study, HCV core antigens were accumulated on endoplasmic reticulum, known as the platform for viral assembly, showing that GL inhibited the release of HCV from infected cells. However, most of the concentration used in these studies appear to be too high to be achieved in actual human conditions.

GL also exhibited antiviral activity by regulating the response of the host cell. The study by Michaelis et al. reported that GL reduced influenza A virus (H5N1) replication in A549 cells at the concentration of 200 µg/mL by inhibiting H5N1-induced reactive oxygen species and activation of NF-κB, p38, and JNK, known to be relevant in H5N1 virus replication (Michaelis et al., 2011). Sasaki et al. also investigated the effect of GL on HIV replication in cultures of PBMCs from HIV-infected patients (Sasaki et al., 2002). 100 µg/mL of GL inhibited more than 90% of HIV replication in cultures of 13 out of 42 PBMC samples. GL dose-dependently increased the production of CCL4 and CCL5, indicating that GL inhibited HIV replication by inducing the expression of beta-chemokines in PBMC cultures. Another study showed that GL inhibited herpes simplex virus type 1 (HSV1) activity by inducing autophagy in host cells (Laconi et al., 2014). In this study, pretreatment with 2 mM of GL induced Beclin1, an autophagy promoter, in HeLa cells and reduced HSV1 infection by up to 98%. Licorice or its active compounds GL has been examined in multiple studies for their antiviral effect, however, due to the high concentration used, it requires further evaluation to confirm their potential use as an antiviral functional food agent.

Bacillus subtilis chungkookjang (Poly-γ-glutamate, γ-PGA)

Bacillus subtilis subsp. *chungkookjang* is a *Bacillus* mainly found in Cheonggukjang, a traditional Korean food, and is known to produce poly-gamma-glutamic acid (γ-PGA), which is known for its various bioactivities.

γ-PGA produced by *Bacillus subtilis* subsp. *chungkookjang* has been identified as having antiviral function against norovirus (Lee et al., 2018). According to the previous study, γ-PGA was shown to stimulate the production of IFN-β, inhibiting norovirus replication in RAW 264.7 cells and increasing resistance to apoptosis induced by norovirus infection. In addition, oral administration of γ-PGA in a mouse model increased the production of IFN-β levels in the serum without any noticeable effect on other inflammatory cytokines, whereas it reduced norovirus loads in the ileum. Other studies have also shown that high molecular weight γ-PGA has been reported to have antiviral function against Newcastle disease virus (NDV) (Talactac et al., 2014). High molecular weight γ-PGA inhibited NDV replication and decreased apoptosis mediated by virus infection in RAW264.7 cells. Also, high molecular weight γ-PGA treatment produced inflammatory cytokines IFN-β, TNF-α, IL-6, and IL-12 in RAW 264.7 cells. In addition, γ-PGA has been reported to have inhibitory efficacy against influenza virus infection (Kim et al., 2015b). In an influenza A virus infected mouse study, the group administered intranasally with γ-PGA for 5 days showed higher survival rates and higher production of antiviral cytokines (e.g., IFN-β and IL-12) compared to control mice. γ-PGA also stimulated NK cell and cytotoxic T lymphocyte (CTL) activity against influenza A. The effect of γ-PGA on human papilloma virus (HPV) clearance was observed in a short-term clinical study (Cho et al., 2019). The HPV clearance was confirmed in 44% of eighty-five high-risk HPV-infected patients by γ-PGA treatment once a day for 4 weeks, whereas the control group showed only 27% of HPV clearance. Taken together, γ-PGA might be a promising functional material with antiviral effects against various type of viruses, such as norovirus, NDV, influenza virus, and HPV.

Epigallocatechin gallate (EGCG)

The antiviral potential of tea and its constituents have been extensively researched. Tea including black tea and green tea (*Camellia sinensis*) has been found to improve metabolic conditions and protect against infectious diseases (Khan and Mukhtar, 2018). Among the many constituents commonly found in both black tea and green tea, studies have suggested catechins to be majorly responsible for the virus inactivating effects (Ide et al., 2016; Singh et al., 2011). (–)-Epigallocatechin gallate (EGCG) is a representative tea catechin which exhibits significant antiviral effects (Ide et al., 2016; Ohgitani et al., 2021; Singh et al., 2011).

A recent study revealed that EGCG derived from green tea significantly inactivated SARS-CoV-2 (Ohgitani et al., 2021). To verify the antiviral effects of black tea and green tea, SARS-CoV-2 were pretreated with tea extracts followed by the propagation into VeroE6/TMPRSS2 cells. Upon treatment with tea extracts, the viral titers were reduced to undetectable levels and viral infectivity of SARS-CoV-2 was significantly decreased. The active tea constituent involved and responsible for this antiviral activity was found to be EGCG. Pretreatment of 1 mM of EGCG on SARS-CoV-2 reduced the infectious activity with no effect on cell viability. Ohgitani et al. also reported that 500 μM of EGCG inhibited the interaction between the recombinant angiotensin converting enzyme 2 (ACE2) and the receptor binding domain (RBD) of the SARS-CoV-2 spike proteins and hence significantly suppressed viral attachment onto cells (Ohgitani et al., 2021). As the antiviral effects of EGCG were notable only at high concentrations, the clinical significance and applications should be thoroughly examined in future studies. The inactivation of SARS-CoV-2 by tea catechins suggests the potential use of tea for the protection and prevention of human-to-human transmission of the novel coronavirus. An in vitro study revealed that EGCG inhibits the activity of SARS-CoV-2 3CL-protease at a half inhibitory concentration (IC_{50}) of 16.5 μM (Jang et al., 2020). Chymotrypsin-like protease (3CLpro) is an essential enzyme for SARS-CoV-2 replication which is responsible for cleaving 11 sites in the polyprotein to ensure the release of individual proteins with a functional substrate-binding pocket during the maturation stage of the virus (Hegyi et al., 2002; Jang et al., 2020; Muramatsu et al., 2016). The activity of SARS-CoV-2 3CL-pro was shown to be inhibited dose-dependently in EGCG-treated-HEK293T human embryonic kidney cells. The inhibition of 3CL-pro activity and the increase in abnormal protein conformations may alter RNA replication and transmission of SARS-CoV-2. The results from these in vitro studies highlight the antiviral potential of EGCG and suggest that EGCG may be a useful natural compound for the treatment of SARS-CoV-2 infections. Further studies are required to prove whether the antiviral effects of EGCG is observed in animal models as well.

Influenza is a major cause of respiratory illness worldwide. Among the four types of influenza viruses A, B, C and D, influenza A virus is the most virulent and has been the cause of global pandemics with persistent transmission.

Since the 1918 global pandemic caused by a subtype H1N1 influenza A virus, antigenic evolution of the virus has coincided with the circulating seasonal epidemics of influenza A virus (Rambaut et al., 2008). EGCG derived from green tea were also found to be potent inhibitors of different subtypes of the influenza virus replication including A/H1N1, A/H3N2 and B viruses in MDCK cells (Song et al., 2005). EGCG was treated in MDCK cells prior to infection by A/H1N1, A/H3N2 and B viruses independently. The pre-treatment of EGCG was found to inhibit plaque formation by influenza A and B viruses and significantly suppressed virus replication in MDCK cells within 8 h of exposure. With the understanding that influenza A virus adsorbs onto chicken red blood cells and result in hemagglutination, Song et al. confirmed that EGCG also restricted adsorption of viruses on red blood cells and inhibited hemagglutination with a minimum inhibition concentration of 5–10 μM (Song et al., 2005). Kim et al. investigated the molecular mechanism of EGCG to better understand how EGCG inhibits viral activities. The antiviral activities EGCG against human influenza A (A/H1N1: TW, PR8, BB, and KR; A/H3N2: HK) and B (PNM) viruses on MDCK cells were found to target the disintegration of viral membrane integrity (Kim et al., 2013). As a result, EGCG was responsible for the loss of cell penetration capacity of influenza viruses and significantly inhibited the hemifusion process between virus particles and the cellular membrane of MDCK cells (Kim et al., 2013). Oral administration of EGCG at 40 mg/kg/day significantly reduced viral titers in influenza A virus infected BALB/c mice without any visible changes in cell morphology, cytopathic effect, or cell density (Ling et al., 2012). The oral administration of EGCG also ameliorated viral pneumonia in the lungs of the BALB/c mice model with improved survival rates of the infected mice. The antiviral effects of EGCG were comparable and almost equal to the effects of the antiviral drug Oseltamivir (Ling et al., 2012). In addition, co-administration of EGCG with influenza hemagglutinin antigen enhanced the level of neutralizing antibodies and improved protection against influenza PR8 virus lethal challenge, showing promising vaccine adjuvant effects in vivo (Cheong et al., 2021).

EGCG has also been found to interfere with the viral attachment of HIV-1 by disassembling the HIV-1 virion directly (Yamaguchi et al., 2002). Li et al. further investigated the mechanism of action of EGCG on HIV-1 and HIV-2.(Li et al., 2011). In this study, EGCG was found to significantly suppress HIV transmission by acting as an allosteric inhibitor of the reverse transcriptase of HIV-1 and HIV-2 (Li et al., 2011). He et al. studied the antiviral effects of EGCG using HepG2.117, an inducible HBC replicating cell line (He et al., 2011). EGCG significantly downregulated the mRNA levels of HBV and impaired the expression of HBV replicative intermediates for DNA synthesis. In another study, Xu et al. reveals that EGCG displays anti-HBV effects by inhibiting the transcription of HBV promoter by interacting with a nuclear receptor, farnesoid X receptor alpha (FXRα) in HBV-infected HEK 293 cells (Xu et al., 2016). These studies indicate that the antiviral mechanism of action of EGCG is to downregulate the expression of HBV antigens and reduce the transcriptional activation of HBV promoters. These results encourage the application of EGCG as a potential agent for inhibiting viral infections.

Quercetin

Quercetin, a naturally occurring flavonoid abundant in many fruits and vegetables such as onion, asparagus, and berries, has been widely studied for its diverse bioactivities (Farrand and Byun, 2017; Shin et al., 2019), among which include its therapeutic potential against viruses (Anand David et al., 2016). The antiviral potential of quercetin has been studied in vivo against various viruses including HSV, canine distemper virus (CDV), HCV and dengue virus (DENV) (Gonzalez-Burquez et al., 2018; Lyu et al., 2005; Rojas et al., 2016; Zandi et al., 2011). In particular, quercetin has shown antiviral effect against several respiratory viruses. Kumar et al. revealed that quercetin has antioxidant effects during influenza virus infection in animal study (Kumar et al., 2005). Researchers orally supplemented quercetin at a concentration of 1 mg/day for 5 consecutive days to influenza virus A (H3N2)-infected mice. Quercetin significantly restored the pulmonary concentrations of catalase, reduced glutathione, and superoxide dismutase that had been decreased after H3N2 infection. A similar in vivo study revealed that when quercetin is orally administered to H3N2 infected-mouse at a dose of 1 mg/day, it decreased both superoxide radicals and lipid peroxidation (LPO) levels in lung macrophages which are critical in the development of oxidative in the early phase of influenza virus infection (Kumar et al., 2003). Moreover, the number of infiltrating cells decreased, and protective effect was observed in lung morphology, indicating that quercetin may act as antioxidant during H3N2 infection. Also, it has been reported that quercetin treatment significantly inhibited rhinovirus (RV) load in vivo (Ganesan et al., 2012). According to the study, viral RNA levels in RV-infected mice significantly decreased at both 1- and 4-days post-infection when 0.2 mg/day of quercetin is orally administered. Quercetin also reduced RV-stimulated chemokines and cytokines (CXCL-1, CXCL-2, TNF- α, CCL2) in RV-infected mice, suggesting that quercetin suppressed RV-induced inflammatory responses. Recently, senescent cells were reported to

amplify susceptibility to COVID-19, and pathogen-induced inflammation. In this study, quercetin in combination with Dasatinib was used as a senolytic agent and was able to reduce the mortality of mouse infected with mouse hepatitis virus (Camell et al., 2021).

The antiviral effect of quercetin was also demonstrated in clinical studies. The randomized, double-blinded, placebo-controlled clinical trial on 1002 subjects was performed for 12 weeks to investigate the effect of quercetin supplementation on upper respiratory tract infection (URTI) (Nieman et al., 2010). In this study, URTI patients were supplemented with 1000 mg/day of quercetin and URTI severity and URTI total sick days decreased by 36% and 31%, respectively in middle aged and older subjects compared to placebo. In addition, a randomized, controlled, and open-label clinical study of forty-two COVID-19 outpatients revealed that daily uptake of 600 mg/day of formulated quercetin for 1 week significantly reduced the symptoms severity and negative predictors such as lactate dehydrogenase ($-$ 35.5%), Ferritin ($-$ 40%), C-reactive protein ($-$ 54.8%) and D-dimer ($-$ 11.9%) (Di Pierro et al., 2021).

Quercetin also has been reported to exert antiviral effects against ebola virus (EBOV) in vitro (Fanunza et al., 2020). In HEK293T cells, quercetin reduced EBOV replication by blocking IFN-inhibitory function of viral protein with a IC_{50} of 7.4 μM. In summary, quercetin, well known as an antioxidant, has been shown to have a protective effect against viruses.

Curcumin

Curcumin, a polyphenolic component of *Curcuma longa L.* (turmeric), has been reported as a multifunctional natural compound, positively regulating a variety of biological activities including protection against viral infections (Jennings and Parks, 2020; Mathew and Hsu, 2018; Moghadamtousi et al., 2014). The antiviral capacity of curcumin has been discovered to be effective against various types of viruses (Anggakusuma et al., 2014; Chen et al., 2010; Li et al., 2020; Pacho et al., 2021; Praditya et al., 2019; Wen et al., 2007). Curcumin appears to hinder the viral infection process through several mechanisms. First, curcumin might be able to disturb the initial steps of the viral infection process. Pretreatment of 30 μM curcumin to MDCK cells decreased the infectivity of influenza A viruses by approximately 90% (Chen et al., 2010). This study has shown that this antiviral effect occurs only in the early stages of infection, but it has not been established whether curcumin directly interacts with the virus (Chen et al., 2010). Additionally, in another investigation related to the HCV, 20 μM curcumin significantly reduced the

viral infectivity up to 90%, and the outcome was also revealed to be the result from the inhibition of the viral entrance, which was triggered by decreased membrane fluidity (Anggakusuma et al., 2014). On the other hand, curcumin might eliminate the viruses directly. A time- and concentration-dependent virucidal activity was observed when transmissible gastroenteritis viruses were exposed to 40 μM curcumin (Li et al., 2020). The α, β-unsaturated ketone groups of curcumin were described to be majorly responsible for the antiviral effects of the compound. The impairment of the viral activity by curcumin was caused by reduced membrane fluidity of the viruses (Anggakusuma et al., 2014), which might modulate both the infectivity and the integrity of the viruses. Abovementioned matters might be assessed for the future antiviral food/supplement development with curcumin.

Lactobacillus plantarum

With continuous scientific findings, probiotics have been reported to have many antiviral properties (Cryan and Dinan, 2012; Kalliomaki et al., 2001; Sivan et al., 2015; Tremaroli and Backhed, 2012). *Lactobacillus plantarum* is one of the most studies probiotic species. *L. plantarum* is a lactic acid bacteria which exists in various types of food (Arasu et al., 2016). Certain strains from this species appear to exert antiviral effects against several types of viruses (Arena et al., 2018; Huang et al., 2021; Kim et al., 2018; Liu et al., 2020; Park et al., 2013; Rather et al., 2015; Soloveva et al., 2021; Sunmola et al., 2019). According to a report, intranasal or oral treatment of *L. plantarum* strain DK119 (10^9 CFU per mouse), protected the mice from influenza A virus infection, reducing lethality, weight loss, and virion loads in the lungs (Park et al., 2013). Noteworthily, in several research studies, the cell supernatant of *L. plantarum* emerged as the key player of the suppressive activity (Huang et al., 2021; Rather et al., 2015; Soloveva et al., 2021). In one study, among the different fractions of *L. plantarum* YML009 (e.g. cell-free supernatant, heat-killed supernatant, and cell-mass), the cell-free supernatant showed the most efficient anti-influenza A activity against host cells (Rather et al., 2015). In other studies, the supernatant obtained from *L. plantarum* 8 RA 3 suspension displayed a significant inhibitory effect on viral reproduction in vitro (Soloveva et al., 2021), and the supernatant of *L. plantarum* CQ2017RC suspension repressed the replication of porcine epidemic diarrhea virus (Huang et al., 2021). Furthermore, the exopolysaccharides (EPS), one of the major components in the supernatant, was revealed to be the key active component, affecting the viral infectivity and host immune response (Huang et al., 2021). Also, the effect of EPS obtained from *L. plantarum* LRCC5310 on antiviral and immune-relieving functions has been reported

(Kim et al., 2018). EPS produced from *L. plantarum* LRCC5310 was shown to inhibit replication of rotavirus in MA104 cells. The oral administration of EPS produced from *L. plantarum* LRCC5310 relieved diarrhea score in mice inoculated with rotavirus, indicating that *L. plantarum* EPS might act as an antiviral postbiotic factor. Collectively, *L. plantarum* might be applied for the development of a promising antiviral candidate.

Conclusion

In this review, we summarized food materials and food-derived compounds reported to possess antiviral effects against SARS-CoV-2, Influenza A viruses, HIV, or HCV (Table 1). The consumption of functional foods such as red ginseng, chlorella, *L. plantarum*, EGCG, quercetin, curcumin, berries, and licorice appears to exhibit potential inhibitory activities against viral infections by enhancing host immunity, suppressing virus-host cell interaction, or/ and preventing the viral replication cycle. Further studies on human applications and identifying their mechanism of

Table 1 Food components with antivirus function

Food components	Type of virus		Key mechanism of action	Model	References
Red Ginseng	Influenza A	H1N1	Increase activation and proliferation of NK and CD3 + T cells	In vitro	Kim et al. (2016)
			Mitigate H1N1 virus lytic gene expression	In vitro	Yoo et al. (2012)
		H3N2	Increase expression of antiviral cytokine IFN-γ	Animal	Yoo et al. (2012)
		H5N1	Increase expression of antiviral cytokines IFN-α and IFN-γ	Animal	Park et al. (2014)
		PR8	Increase influenza virus-specific IgA antibody production	Animal	Quan et al. (2007)
			Increase Th1 and Th2- type cytokine expression		
	HIV-1		Increase CD4 + T cell proliferation and delayed progression of resistant HIV-1 mutations	Animal	Sung et al. (2005, 2009)
			Reduce CD8 antigen expression of cytotoxic T cells	Human	Sung et al. (2005)
Chlorella	Rotavirus		Reduce virus infectivity	In vitro	Cantu-Bernal et al. (2020)
	HCV		ALT levels improved with decreased HCV viral load	Human	Azocar and Diaz (2013)
			Reduce HCV RNA levels		
Berries	Coxsackievirus B1		Inhibit replication and proliferation of virus	In vitro	Nikolaeva-Glomb et al. (2014)
	Influenza A	PR8	Inhibit viral plaque formation and reduce viral uptake into host cells	In vitro	Knox et al. (2003)
			Increase secretion of IgA and neutralizing antibodies	Human	Zakay-Rones et al. (2004)
Licorice	Influenza A	H3N2	Inhibit entry of virus into host cells	In vitro	Wolkerstorfer et al. (2009)
		H5N1	Inhibit H5N1-induced reactive oxygen species and activation of NF-κB, p38 and JNK pathway required for H5N1 virus replication	In vitro	Michaelis et al. (2011)
	SARS-CoV-2		Suppress virus replication and penetration	In vitro	Cinatl et al. (2003)
	HCV		Inhibit release of infectious HCV particles	In vitro	Matsumoto et al. (2013)
	HIV		Increase CCL4 and CCL5 beta-chemokine production to inhibit virus replication	In vitro	Sasaki et al. (2002)
	HSV1		Induce autophagy promoter Beclin 1	In vitro	Laconi et al. (2014)
Bacillus subtilis chungkookjang	Norovirus		Increase production of IFN-β to inhibit virus replication	In vitro	Lee et al. (2018)
	NDV		Increase expression of antiviral cytokines IFN-β, TNF-α, IL-6, IL-12	In vitro	Talactac et al. (2014)
	Influenza A	H1N1	Increase production of antiviral cytokines	Animal	Kim et al. (2015a, b)
		PR8	Induce NK cell and cytotoxic T lymphocyte proliferation		

Table 1 continued

Food components	Type of virus		Key mechanism of action	Model	References
EGCG	SARS-CoV-2		Suppress viral attachment by inhibiting recombinant angiotensin converting enzyme 2 (ACE2) to virus spike proteins	In vitro	Ohgitani et al. (2021)
			Inhibit SARS-CoV-2 3CL protease activity	In vitro	Jang et al. (2020)
	Influenza A	PR8	Disintegrate virus membrane integrity and inhibit interaction between virion and cell membrane of host cells	In vitro	Kim et al. (2013)
		PR8	Increase production of neutralizing antibodies	Animal	Cheong et al. (2021)
		H1N1 H3N2	Inhibit plaque formation and suppress virus replication	In vitro	Song et al. (2005)
	HIV	1	Disassemble HIV-1 virion	In vitro	Yamaguchi et al. (2002)
	HIV	2	Act as an allosteric inhibitor of HIV-2 reverse transcriptase and suppress virus transmission	In vitro	Li et al. (2011)
	HBV		Downregulate mRNA expression and replicative intermediates of virus	In vitro	He et al. (2011)
			Target and inhibit transcription of HBV promoter	In vitro	(Xu et al., 2016)
Quercetin	Influenza A	H3N2	Reduce superoxide radicals and lipid peroxidation	Animal	Kumar et al. (2005), Kumar et al. (2003)
	Rinovirus		Reduce viral RNA level	Animal	Ganesan et al. (2012)
			Reduce production of CXCL-1, CXCL-2, TNF- α, CCL2	Animal	Camell et al. (2021)
	Ebola virus		Suppress type 1 interferon (IFN-I) signaling and inhibit viral protein function	In vitro	Nieman et al. (2010)
Curcumin	Influenza A	H1N1 H6N1	Interfere with viral infection and reduce infectivity	In vitro	Chen et al. (2010)
	HCV		Inhibit virus entry	In vitro	Anggakusuma et al. (2014), Li et al. (2020)
			Impair integrity of virus and reduce virus membrane fluidity		
Lactobacillus plantarum	Influenza A	H1N1 H5N6	Inhibit virus replication	In vitro	Rather et al. (2015), Soloveva et al. (2021)
	Porcine epidemic diarrhea virus		Inhibit virus replication	In vitro	Huang et al. (2021)
	Rotavirus		Inhibit virus replication	In vitro	Kim et al. (2018)

action could help improve personal and public health against viral diseases.

Declarations

Conflict of interest The authors declare no competing interests.

References

Anand David AV, Arulmoli R, Parasuraman S. Overviews of biological importance of quercetin: A bioactive flavonoid. Pharmacognosy Reviews. 10: 84-89 (2016)

Anggakusuma, Colpitts CC, Schang LM, Rachmawati H, Frentzen A, Pfaender S, Behrendt P, Brown RJ, Bankwitz D, Steinmann J, Ott M, Meuleman P, Rice CM, Ploss A, Pietschmann T, Steinmann E. Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells. Gut. 63: 1137-1149 (2014)

Arasu MV, Al-Dhabi NA, Ilavenil S, Choi KC, Srigopalram S. In vitro importance of probiotic *Lactobacillus plantarum* related to medical field. Saudi Journal of Biological Sciences. 23: S6-S10 (2016)

Arena MP, Elmastour F, Sane F, Drider D, Fiocco D, Spano G, Hober D. Inhibition of coxsackievirus B4 by *Lactobacillus plantarum*. Microbiological Research. 210: 59-64 (2018)

Azocar J, Diaz A. Efficacy and safety of Chlorella supplementation in adults with chronic hepatitis C virus infection. World Journal of Gastroenterology. 19: 1085-1090 (2013)

Camell CD, Yousefzadeh MJ, Zhu Y, Prata L, Huggins MA, Pierson M, Zhang L, O'Kelly RD, Pirtskhalava T, Xun P, Ejima K, Xue A, Tripathi U, Espindola-Netto JM, Giorgadze N, Atkinson EJ, Inman CL, Johnson KO, Cholensky SH, Carlson TW, LeBrasseur NK, Khosla S, O'Sullivan MG, Allison DB, Jameson SC, Meves A, Li M, Prakash YS, Chiarella SE, Hamilton SE, Tchkonia T, Niederhofer LJ, Kirkland JL, Robbins PD.

Senolytics reduce coronavirus-related mortality in old mice. Science. 373 (2021)

Cantu-Bernal S, Dominguez-Gamez M, Medina-Peraza I, Aros-Uzarraga E, Ontiveros N, Flores-Mendoza L, Gomez-Flores R, Tamez-Guerra P, Gonzalez-Ochoa G. Enhanced viability and anti-rotavirus effect of Bifidobacterium longum and *Lactobacillus plantarum* in combination with *Chlorella sorokiniana* in a dairy product. Frontiers in Microbiology. 11: 875 (2020)

Chafekar A, Fielding BC. MERS-CoV: Understanding the Latest Human Coronavirus Threat. Viruses. 10 (2018)

Chan LY, Kwok HH, Chan RW, Peiris MJ, Mak NK, Wong RN, Chan MC, Yue PY. Dual functions of ginsenosides in protecting human endothelial cells against influenza H9N2-induced inflammation and apoptosis. Journal of Ethnopharmacology. 137: 1542-1546 (2011)

Chen DY, Shien JH, Tiley L, Chiou SS, Wang SY, Chang TJ, Lee YJ, Chan KW, Hsu WL. Curcumin inhibits influenza virus infection and haemagglutination activity. Food Chemistry. 119: 1346-1351 (2010)

Cheong Y, Kim M, Ahn J, Oh H, Lim J, Chae W, Yang SW, Kim MS, Yu JE, Byun S, Jang YH, Seong BL. Epigallocatechin-3-gallate as a novel vaccine adjuvant. Frontiers in Immunology. 12: 769088 (2021)

Cho HW, Park YC, Sung MH, Park JS, Kim TJ, Seong SJ, Cho CH, Lee JK. Short-term clinical and immunologic effects of poly-gamma-glutamic acid (gamma-PGA) in women with cervical intraepithelial neoplasia 1 (CIN 1): A multicenter, randomized, double blind, phase II trial. PLoS ONE. 14: e0217745 (2019)

Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 361: 2045-2046 (2003)

Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience. 13: 701-712 (2012)

Di Pierro F, Derosa G, Maffioli P, Bertuccioli A, Togni S, Riva A, Allegrini P, Khan A, Khan S, Khan BA, Altaf N, Zahid M, Ujjan ID, Nigar R, Khushk MI, Phulpoto M, Lail A, Devrajani BR, Ahmed S. Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: A prospective, randomized, controlled, and open-label study. International Journal of General Medicine. 14: 2359-2366 (2021)

Fanunza E, Iampietro M, Distinto S, Corona A, Quartu M, Maccioni E, Horvat B, Tramontano E. Quercetin blocks ebola virus infection by counteracting the vp24 interferon-inhibitory function. Antimicrobial Agents and Chemotherapy. 64 (2020)

Farrand L, Byun S. Induction of synthetic lethality by natural compounds targeting cancer signaling. Current Pharmaceutical Design. 23: 4311-4320 (2017)

Fu B, Li H, Wang X, Lee FS, Cui S. Isolation and identification of flavonoids in licorice and a study of their inhibitory effects on tyrosinase. Journal of Agricultural and Food Chemistry. 53: 7408-7414 (2005)

Ganesan S, Faris AN, Comstock AT, Wang Q, Nanua S, Hershenson MB, Sajjan US. Quercetin inhibits rhinovirus replication in vitro and in vivo. Antiviral Research. 94: 258-271 (2012)

Gonzalez-Burquez MD, Gonzalez-Diaz FR, Garcia-Tovar CG, Carrillo-Miranda L, Soto-Zarate CI, Canales-Martinez MM, Penieres-Carrillo JG, Cruz-Sanchez TA, Fonseca-Coronado S. Comparison between in vitro antiviral effect of mexican propolis and three commercial flavonoids against canine distemper virus. Evidence-Based Complementary and Alternative Medicine. 2018 (2018)

Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, Madhur MS, Tomaszewski M, Maffia P, D'Acquisto F, Nicklin SA, Marian AJ, Nosalski R, Murray EC, Guzik B, Berry C, Touyz RM, Kreutz R, Wang DW, Bhella D, Sagliocco O, Crea F, Thomson EC, McInnes IB. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovascular Research. 116: 1666-1687 (2020)

He W, Li LX, Liao QJ, Liu CL, Chen XL. Epigallocatechin gallate inhibits HBV DNA synthesis in a viral replication - inducible cell line. World Journal of Gastroenterology. 17: 1507-1514 (2011)

Hegyi A, Friebe A, Gorbalenya AE, Ziebuhr J. Mutational analysis of the active centre of coronavirus 3C-like proteases. Journal of General Virology. 83: 581-593 (2002)

Huang S, Yu Q, Xie L, Ran L, Wang K, Yang Y, Gan L, Song Z. Inhibitory effects of *Lactobacillus plantarum* metabolites on porcine epidemic diarrhea virus replication. Research in Veterinary Science. 139: 32-42 (2021)

Ide K, Kawasaki Y, Kawakami K, Yamada H. Anti-influenza virus effects of catechins: A molecular and clinical review. Current Medicinal Chemistry. 23: 4773-4783 (2016)

Ikuta K, Hashimoto K, Kaneko H, Mori S, Ohashi K, Suzutani T. Anti-viral and anti-bacterial activities of an extract of blackcurrants (Ribes nigrum L.). Microbiology and Immunology. 56: 805-809 (2012)

Im K, Kim J, Min H. Ginseng, the natural effectual antiviral: Protective effects of Korean Red Ginseng against viral infection. Journal of Ginseng Research. 40: 309-314 (2016)

Jang M, Park YI, Cha YE, Park R, Namkoong S, Lee JI, Park J. Tea polyphenols EGCG and theaflavin inhibit the activity of SARS-CoV-2 3CL-protease in vitro. Evidence Based Complementary Alternative Medicine. 2020: 5630838 (2020)

Jang YJ, Kim JH, Byun S. Modulation of autophagy for controlling immunity. Cells. 8 (2019)

Jennings MR, Parks RJ. Curcumin as an antiviral agent. Viruses-Basel. 12 (2020)

Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P. Global trends in emerging infectious diseases. Nature. 451: 990-993 (2008)

Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet. 357: 1076-1079 (2001)

Kaufmann SHE, Dorhoi A, Hotchkiss RS, Bartenschlager R. Host-directed therapies for bacterial and viral infections. Nature Reviews Drug Discovery. 17: 35-56 (2018)

Khan N, Mukhtar H. Tea polyphenols in promotion of human health. Nutrients. 11 (2018)

Kim BR, Kim JE, Sung H, Cho YK. Long-term follow up of HIV-1-infected Korean haemophiliacs, after infection from a common source of virus. Haemophilia. 21: e1-11 (2015a)

Kim EH, Choi YK, Kim CJ, Sung MH, Poo H. Intranasal administration of poly-gamma glutamate induced antiviral activity and protective immune responses against H1N1 influenza A virus infection. Virology Journal. 12: 160 (2015b)

Kim H, Jang M, Kim Y, Choi J, Jeon J, Kim J, Hwang YI, Kang JS, Lee WJ. Red ginseng and vitamin C increase immune cell activity and decrease lung inflammation induced by influenza A virus/H1N1 infection. Journal of Pharmacy and Pharmacology. 68: 406-420 (2016)

Kim K, Lee G, Thanh HD, Kim JH, Konkit M, Yoon S, Park M, Yang S, Park E, Kim W. Exopolysaccharide from *Lactobacillus plantarum* LRCC5310 offers protection against rotavirus-induced diarrhea and regulates inflammatory response. Journal of Dairy Science. 101: 5702-5712 (2018)

Kim M, Kim SY, Lee HW, Shin JS, Kim P, Jung YS, Jeong HS, Hyun JK, Lee CK. Inhibition of influenza virus internalization by (-)-

epigallocatechin-3-gallate. Antiviral Research. 100: 460-472 (2013)

Kinoshita E, Hayashi K, Katayama H, Hayashi T, Obata A. Anti-influenza virus effects of elderberry juice and its fractions. Bioscience Biotechnology and Biochemistry. 76: 1633-1638 (2012)

Knox YM, Hayashi K, Suzutani T, Ogasawara M, Yoshida I, Shiina R, Tsukui A, Terahara N, Azuma M. Activity of anthocyanins from fruit extract of Ribes nigrum L. against influenza A and B viruses. Acta Virologica. 45: 209-215 (2001)

Knox YM, Suzutani T, Yosida I, Azuma M. Anti-influenza virus activity of crude extract of Ribes nigrum L. Phytotherapy Research. 17: 120-122 (2003)

Kumar P, Khanna M, Srivastava V, Tyagi YK, Raj HG, Ravi K. Effect of quercetin supplementation on lung antioxidants after experimental influenza virus infection. Experimental Lung Research. 31: 449-459 (2005)

Kumar P, Sharma S, Khanna M, Raj HG. Effect of Quercetin on lipid peroxidation and changes in lung morphology in experimental influenza virus infection. International Journal of Experimental Pathology. 84: 127-133 (2003)

Kwok HH, Poon PY, Fok SP, Ying-Kit Yue P, Mak NK, Chan MC, Peiris JS, Wong RN. Anti-inflammatory effects of indirubin derivatives on influenza A virus-infected human pulmonary microvascular endothelial cells. Scientific Reports. 6: 18941 (2016)

Laconi S, Madeddu MA, Pompei R. Autophagy activation and antiviral activity by a licorice triterpene. Phytotherapy Research. 28: 1890-1892 (2014)

Lee SY, Kim YK, Park NI, Kim CS, Lee CY, Park SU. Chemical constituents and biological activities of the berry of Panax ginseng. Journal of Medicinal Plants Research. 4: 349-353 (2010)

Lee W, Kim M, Lee SH, Jung HG, Oh JW. Prophylactic efficacy of orally administered Bacillus poly-gamma-glutamic acid, a non-LPS TLR4 ligand, against norovirus infection in mice. Scientific Reports. 8: 8667 (2018)

Li S, Hattori T, Kodama EN. Epigallocatechin gallate inhibits the HIV reverse transcription step. Antiviral Chemistry and Chemotherapy. 21: 239-243 (2011)

Li Y, Wang J, Liu Y, Luo X, Lei W, Xie L. Antiviral and virucidal effects of curcumin on transmissible gastroenteritis virus in vitro. Journal of General Virology. 101: 1079-1084 (2020)

Ling JX, Wei F, Li N, Li JL, Chen LJ, Liu YY, Luo F, Xiong HR, Hou W, Yang ZQ. Amelioration of influenza virus-induced reactive oxygen species formation by epigallocatechin gallate derived from green tea. Acta Pharmacologica Sinica. 33: 1533-1541 (2012)

Liu YS, Liu Q, Jiang YL, Yang WT, Huang HB, Shi CW, Yang GL, Wang CF. Surface-displayed porcine IFN-lambda 3 in Lactobacillus plantarum inhibits porcine enteric coronavirus infection of porcine intestinal epithelial cells. Journal of Microbiology and Biotechnology. 30: 515-525 (2020)

Lyu SY, Rhim JY, Park WB. Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro. Archives of Pharmacal Research. 28: 1293-1301 (2005)

Mathew D, Hsu WL. Antiviral potential of curcumin. Journal of Functional Foods. 40: 692-699 (2018)

Matsumoto Y, Matsuura T, Aoyagi H, Matsuda M, Hmwe SS, Date T, Watanabe N, Watashi K, Suzuki R, Ichinose S, Wake K, Suzuki T, Miyamura T, Wakita T, Aizaki H. Antiviral activity of glycyrrhizin against hepatitis C virus in vitro. PLoS ONE. 8: e68992 (2013)

McCune JM. The dynamics of CD4+ T-cell depletion in HIV disease. Nature. 410: 974-979 (2001)

Mercorelli B, Palu G, Loregian A. Drug repurposing for viral infectious diseases: How far are we? Trends in Microbiology. 26: 865-876 (2018)

Michaelis M, Geiler J, Naczk P, Sithisarn P, Leutz A, Doerr HW, Cinatl J, Jr. Glycyrrhizin exerts antioxidative effects in H5N1 influenza A virus-infected cells and inhibits virus replication and pro-inflammatory gene expression. PLoS ONE. 6: e19705 (2011)

Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. Biomed Research International. 2014 (2014)

Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. AIDS. 13: 1933-1942 (1999)

Muramatsu T, Takemoto C, Kim YT, Wang H, Nishii W, Terada T, Shirouzu M, Yokoyama S. SARS-CoV 3CL protease cleaves its C-terminal autoprocessing site by novel subsite cooperativity. Proceedings of the National Acadamy of Sciences of the United States of America. 113: 12997-13002 (2016)

Nieman DC, Heinz SA, Henson DA, Austin M, Jin FX. Quercetin supplementation and upper respiratory tract infection: a randomized community clinical trial. Pharmacological Research. 24 (2010)

Nikolaeva-Glomb L, Mukova L, Nikolova N, Badjakov I, Dincheva I, Kondakova V, Doumanova L, Galabov AS. In vitro antiviral activity of a series of wild berry fruit extracts against representatives of Picorna-, Orthomyxo- and Paramyxoviridae. Natural Product Communications. 9: 51-54 (2014)

Ohgitani E, Shin-Ya M, Ichitani M, Kobayashi M, Takihara T, Kawamoto M, Kinugasa H, Mazda O. Significant inactivation of SARS-CoV-2 in vitro by a green tea catechin, a catechin-derivative, and black tea galloylated theaflavins. Molecules. 26 (2021)

World Health Organization (WHO). (2020). Coronavirus (COVID-19) Dashboard. Retrieved Mar 11, 2022 from https://covid19.who.int/

Pacho MN, Pugni EN, Diaz Sierra JB, Morell ML, Sepulveda CS, Damonte EB, Garcia CC, D'Accorso NB. Antiviral activity against Zika virus of a new formulation of curcumin in poly lactic-co-glycolic acid nanoparticles. Journal of Pharmacy and Pharmacology. 73: 357-365 (2021)

Park EH, Yum J, Ku KB, Kim HM, Kang YM, Kim JC, Kim JA, Kang YK, Seo SH. Red Ginseng-containing diet helps to protect mice and ferrets from the lethal infection by highly pathogenic H5N1 influenza virus. Journal of Ginseng Research. 38: 40-46 (2014)

Park MK, Ngo V, Kwon YM, Lee YT, Yoo S, Cho YH, Hong SM, Hwang HS, Ko EJ, Jung YJ, Moon DW, Jeong EJ, Kim MC, Lee YN, Jang JH, Oh JS, Kim CH, Kang SM. Lactobacillus plantarum DK119 as a probiotic confers protection against influenza virus by modulating innate immunity. PLoS ONE. 8, e1 (2013)

Praditya D, Kirchhoff L, Bruning J, Rachmawati H, Steinmann J, Steinmann E. Anti-infective Properties of the Golden Spice Curcumin. Frontiers in Microbiology. 10: 912 (2019)

Quan FS, Compans RW, Cho YK, Kang SM. Ginseng and Salviae herbs play a role as immune activators and modulate immune responses during influenza virus infection. Vaccine.. 25: 272-282 (2007)

Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature. 453: 615-619 (2008)

Rather IA, Choi KH, Bajpai VK, Park YH. Antiviral mode of action of Lactobacillus plantarum YML009 on Influenza virus H1N1. Bangladesh Journal of Pharmacology. 10: 475-482 (2015)

Rojas A, Del Campo JA, Clement S, Lemasson M, Garcia-Valdecasas M, Gil-Gomez A, Ranchal I, Bartosch B, Bautista JD, Rosenberg AR, Negro F, Romero-Gomez M. Effect of quercetin on hepatitis C virus life cycle: From viral to host targets. Scientific Reports. 6: 31777 (2016)

Rouse BT, Sehrawat S. Immunity and immunopathology to viruses: what decides the outcome? Nature Reviews Immunology. 10: 514-526 (2010)

Ryu W-S. Molecular virology of human pathogenic viruses. Academic Press, Amsterdam (2017)

Sant AJ, McMichael A. Revealing the role of CD4(+) T cells in viral immunity. Journal of Experimental Medicine. 209: 1391-1395 (2012)

Sasaki H, Takei M, Kobayashi M, Pollard RB, Suzuki F. Effect of glycyrrhizin, an active component of licorice roots, on HIV replication in cultures of peripheral blood mononuclear cells from HIV-seropositive patients. Pathobiology. 70: 229-236 (2002)

Shang Y, Li H, Zhang R. Effects of pandemic outbreak on economies: Evidence from business history context. Frontiers in Public Health. 9: 632043 (2021)

Shibata S. Chemistry and cancer preventing activities of ginseng saponins and some related triterpenoid compounds. Journal of Korean Medical Science. 16 Suppl: S28-37 (2001)

Shin EJ, Lee JS, Hong S, Lim TG, Byun S. Quercetin directly targets JAK2 and PKCdelta and prevents UV-induced photoaging in human skin. International Journal of Molecular Sciences. 20 (2019)

Shin SH, Lee JS, Zhang JM, Choi S, Boskovic ZV, Zhao R, Song M, Wang R, Tian J, Lee MH, Kim JH, Jeong M, Lee JH, Petukhov M, Lee SW, Kim SG, Zou L, Byun S. Synthetic lethality by targeting the RUVBL1/2-TTT complex in mTORC1-hyperactive cancer cells. Science Advances. 6: eaay9131 (2020)

Shrivastava S, Ray RM, Holguin L, Echavarria L, Grepo N, Scott TA, Burnett J, Morris KV. Exosome-mediated stable epigenetic repression of HIV-1. Nature Communications. 12: 5541 (2021)

Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallo-catechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochemical Pharmacology. 82: 1807-1821 (2011)

Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, Chang EB, Gajewski TF. Commensal Bifidobacterium promotes anti-tumor immunity and facilitates anti-PD-L1 efficacy. Science. 350: 1084-1089 (2015)

Soloveva IV, Ilyicheva TN, Marchenko VY, Pyankov OV, Tochilina AG, Belova IV, Zhirnov VA, Bormotov NI, Skarnovich MO, Durymanov AG, Molodtsova SB, Filippova EI, Ovchinnikova AS, Magerramova AV, Ryzhikov AB, Maksyutov RA. Genome features and in vitro activity against influenza A and SARS-CoV-2 viruses of six probiotic strains. Biomedical Research International. 2021 (2021)

Song JM, Lee KH, Seong BL. Antiviral effect of catechins in green tea on influenza virus. Antiviral Research. 68: 66-74 (2005)

Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C. From SARS to MERS, thrusting Coronaviruses into the spotlight. Viruses. 11 (2019)

Sung H, Jung YS, Cho YK. Beneficial effects of a combination of Korean red ginseng and highly active antiretroviral therapy in human immunodeficiency virus type 1-infected patients. Clinical Vaccine Immunology. 16: 1127-1131 (2009)

Sung H, Kang SM, Lee MS, Kim TG, Cho YK. Korean red ginseng slows depletion of CD4 T cells in human immunodeficiency virus type 1-infected patients. Clinical and Diagnostic Laboratory Immunology. 12: 497-501 (2005)

Sunmola AA, Ogbole OO, Faleye TOC, Adetoye A, Adeniji JA, Ayeni FA. Antiviral potentials of Lactobacillus plantarum, Lactobacillus amylovorus, and Enterococcus hirae against selected Enterovirus. Folia Microbiologica. 64: 257-264 (2019)

Szajdek A, Borowska EJ. Bioactive compounds and health-promoting properties of berry fruits: a review. Plant Foods for Human Nutrition. 63: 147-156 (2008)

Talactac M, Lee JS, Moon H, Chowdhury MY, Kim CJ. The antiviral effect of high-molecular weight poly-gamma-glutamate against newcastle disease virus on murine macrophage cells. Advances in Virology. 2014: 301386 (2014)

Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. Nature. 489: 242-249 (2012)

Wang G, Wang J, Liu W, Nisar MF, El-Esawi MA, Wan C. Biological activities and chemistry of triterpene saponins from medicago species: An update review. Evidence Based Complementary and Alternative Medicine. 2021: 6617916 (2021)

Wat D. The common cold: a review of the literature. European Journal of Internal Medicine. 15: 79-88 (2004)

Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY, Liu HG, Lee CK, Chang ST, Kuo CJ, Lee SS, Hou CC, Hsiao PW, Chien SC, Shyur LF, Yang NS. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. Journal of Medicinal Chemistry. 50: 4087-4095 (2007)

Wolkerstorfer A, Kurz H, Bachhofner N, Szolar OH. Glycyrrhizin inhibits influenza A virus uptake into the cell. Antiviral Research. 83: 171-178 (2009)

Xu J, Gu W, Li C, Li X, Xing G, Li Y, Song Y, Zheng W. Epigallocatechin gallate inhibits hepatitis B virus via farnesoid X receptor alpha. Journal of Natural Medicines. 70: 584-591 (2016)

Yamaguchi K, Honda M, Ikigai H, Hara Y, Shimamura T. Inhibitory effects of (-)-epigallocatechin gallate on the life cycle of human immunodeficiency virus type 1 (HIV–1). Antiviral Research. 53: 19-34 (2002)

Yoo DG, Kim MC, Park MK, Song JM, Quan FS, Park KM, Cho YK, Kang SM. Protective effect of Korean red ginseng extract on the infections by H1N1 and H3N2 influenza viruses in mice. Journal of Medicinal Food. 15: 855-862 (2012)

Yun TK. Brief introduction of Panax ginseng C.A. Meyer. Journal of Korean Medical Science. 16 Suppl: S3-5 (2001)

Zakay-Rones Z, Thom E, Wollan T, Wadstein J. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. Journal of International Medical Research. 32: 132-140 (2004)

Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, Abubakar S. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virology Journal. 8: 560 (2011)

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 395: 1054-1062 (2020)

Zumla A, Rao M, Wallis RS, Kaufmann SH, Rustomjee R, Mwaba P, Vilaplana C, Yeboah-Manu D, Chakaya J, Ippolito G, Azhar E, Hoelscher M, Maeurer M, Host-Directed Therapies Network c. Host-directed therapies for infectious diseases: current status, recent progress, and future prospects. Lancet Infectious Disease. 16: e47-e63 (2016)