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Possible Potential Effects of Honey and Its Main Components Against Covid-19 Infection

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Abstract

Coronavirus disease 2019 (COVID-19) is a viral pneumonia that is spreading rapidly worldwide. The main feature of this disease is a severe acute respiratory syndrome and caused by coronavirus 2 (SARS-CoV-2). There are several unknowns about the pathogenesis and therapeutically treatment of COVID-19 infection. In addition, available treatment protocols have not been effective in managing COVID-19 infection. It is proposed that natural anti-oxidants such as lemon, green tea, saffron, curcuma longa, etc. with high flavonoids like safranal, crocin, crocetin, catechins, resveratrol, calebin A, curcumin have therapeutic potential against viral infections. In this context, honey and its main components are being investigated as an option for patients with COVID-19. The present study may indicate that honey and its main components inhibit the entry of the virus into the host cell and its replication as well as modulate the inflammatory cascade. This review provides basic information for the possible potential effects of honey and its main components for fighting with SARS-CoV-2.

Keywords

COVID-19, SARS-CoV, SARS-CoV-2, acute respiratory distress syndrome, honey, viral infection

Introduction

Coronaviruses (COVs) are related to the group of RNA viruses that cause mild to severe respiratory diseases. SARS, MERS, and COVID-19 viruses are known as lethal type of coronaviruses. The coronavirus disease 2019 (COVID-19) is characterized by severe acute respiratory syndrome following exposure to coronavirus2 (SARS-CoV-2). This disease was observed in Wuhan, China, during the time of first and spread rapidly throughout the world.[1] So far, physicians have been unable to find a suitable treatment regimen for COVID-19 infection, and preclinical and clinical studies on the subject are very limited and have not been able to suggest a more appropriate treatment. Various anti-viral drugs are used for the viral infection, which are directed against the virus or human cells. The protease inhibitors ritonavir and lopinavir (anti-HIV drugs) are used in COVID-19 infected patients. Other anti-viral drugs for human coronaviruses are Remdesivir, Umifenovir (Arbidol), Lamivudine (3TC), nucleoside analogues, neuraminidase inhibitors, Disoproxil and Tenofovir.[2] Antibody therapy is also recommended for patients with COVID-19. However, none of these drugs has not yet been confirmed for the treatment of

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COVID-19-infected patients. Numerous studies have focused on the effect of natural products against infectious diseases.[3] The popularity of natural compounds is linked to their positive and effective impacts, low cost and very low toxicity.[4] Natural products have long been used for medical purposes, especially in traditional medicine in Asian countries such as China and India.[5] In recent years, researchers have focused on the effectiveness of these agents (as anti-oxidant, anti-inflammatory, anti-infective, anti-carcinogenic etc.) in combining various infectious diseases due to resistance of pathogenic microbes to available vaccines and antibiotics. Natural products can modulate the sensitivity of the host to pathogens.[6] Some natural products have been investigated to consider them as alternatives drugs for the treatment of infectious diseases based on their experimental results. Furthermore, these compounds may be able to increase the efficacy of chemical drugs and vaccines in infectious patients. It has been shown that most of them act against infectious diseases through similar mechanisms of chemical drugs.[7] Medicinal plant extracts and honey are the main sources that can be effective against various infections and inflammatory diseases.[8] Honey is a naturally occurring product that has been used as a traditional medicine in many countries since ancient times. Numerous studies reported that honey exerts therapeutics effects against diabetes, cardiovascular diseases and neurological deficits as well as against diseases of the respiratory, urinary and gastrointestinal tract.[9-13] It has also been found that honey and its main ingredients can be effective against infectious diseases and also healing in wounds and burn injury.[14] There is strong evidence that honey with potential anti-oxidant and anti-inflammatory activities can be effective in various ways against viral infectious diseases. In addition to attenuating oxidative damage induced by pathogens, it also helps to strengthen the immune system. The anti-viral activity of honey and its main constituents is also related to their modulatory effects on various molecular targets involved in cellular signaling pathways such as apoptosis and inflammation. In addition, honey and its main constituents can modulate signaling cascades which are necessary for virus replication and attachment.[15] Indeed, it has been found that honey and its main constituents can alter the viral structure of the surface protein and membrane proteins, which leads to an inhibition of virus entry into the cell.[16] Although many studies have been conducted on the anti-viral effects of honey, this beneficial effect of honey and its main constituents against coronaviruses is not understood. This review focuses on the potential therapeutic effects of honey and its main constituents against coronaviruses.

Characteristics of the Honey Composition

Honey consists of water, sugars, enzymes, amino acids, flavonoids, organic acids, phenolic acids, minerals, vitamins, and volatile compounds. Several characteristics of honey including color, flavor and aroma are related to the honeybee species, the type and origin of flowers, climate and weather conditions and the processing, packaging and storage of honey.[17]

Sugar is the main component of honey (90-95%), consisting of 75% monosaccharide (fructose and glucose) and 10 to 15% disaccharides (sucrose, turanose, maltose, maltulose, isomaltose, nigerose, kojibiose, trehalose) and trisaccharides (melezitose and maltotriose), trisaccharides (melezitose and maltotriose) and very small amounts of other sugars.[18] Moreover, proteins are found in the honey including mostly free amino acids and enzymes and with the exception of glutamine and asparagine. Most of the amino acid present in honey is proline. In addition, the honey also contains aspartic acid, glutamic acid, histidine, glycine, glutamine, b-alanine, a-alanine, threonine, arginine, tyrosine, c-aminobutyric acid, methionine, valine, cysteine, leucine, isoleucine, phenylalanine, tryptophan, lysine, ornithine, asparagines, serine and alanine are present in honey.[19]

According to scientific reports, organic acids are present in all honeys at about 0.57% and cause slight acidity and electrical conductivity in the honey and influence the color and taste of the honey. The organic acids are created during the transformation of the nectar into honey or are extracted directly from nectar. Some organic acids in honey include aspartic acid, butyric acid, citric acid, acetic, formic acid, fumaric acid, galacturonic acid, butyric acid, formic acid, gluconic acid, glutamic acid, glyoxylic acid, glutaric acid, 2-hydroxybutyric acid, α-hydroxyglutaric acid, malonic acid, lactic acid, pyruvic acid, isocitric acid, α-ketoglutaric acid, malic acid, methylmalonic acid, quinic acid, propionic acid, shikimic acid, 2-oxopentanoic acid, tar-taric acid, succinic acid, and oxalic acid, however Gluconic acid is the most important acid in honey.[20]

Honey consists of small amounts of vitamins, including vitamin B[thiamine (B1), riboflavin (B2), pantothenic acid (B5), biotin (B8 or H), nicotinic acid (B3), pyridoxine (B6), and folic acid (B9)] and vitamin C. The low pH-value of honey has no influence on its vitamin substances. Vitamin C is present in various types of honey and is responsible for its anti-oxidant effect. Vitamin B2, B3, B5, B9 and vitamin C are water-soluble vitamins in honey.[21]

Macro and micro elements including magnesium, potassium, sodium, iron, calcium, phosphorus, iodine, manganese, lithium, zinc, cadmium, cobalt, nickel, barium, copper, chromium, silver, arsenic, selenium, and those observed in honeys. The amount of mineral components in honey varies between 0.04% and 0.2% in light and dark honeys. Some heavy metals such as lead, cadmium, arsenic, and mercury are toxic and they should not exceed the maximum residue levels. The measurement of toxic elements in honeys is necessary for human health.[22]

Phenolic compounds in honey are divided into phenolic acid (non-flavonoids) and flavonoids (flavones, flavanols, flavanones, isoflavones, chalcones and anthocyanidin). Phenolic acids are present in forms of hydroxybenzoic acid and hydroxycinnamic acid in honey. Hydroxybenzoic acids in honey consistof þ-hydroxybenzoicacid, syringicacid, salicylic (2-hydroxybenzoate), vanillic acid, ellagic acid and gallic acid.[23] Various flavonoids such as vanillic acid, syringic acid, caffeic acid, þ-coumaric acid, ferulic acid, kaempferol, quercetin, chrysin, pinobanksin, myricetin, pinocembrin, galangin,

ellagic acid, chlorogenic acid, rosmarinic acid, 3- and 4-hydroxybenzoic acid, hesperetin, gallic acid and benzoic acid have been found in honey[17] (Table 1).

Volatile compounds are formed which determine the taste of honey and may vary according to nectar, processing conditions, origin and storage. Over the 400 different volatile compounds have been found in honey, belonging to C13-norisoprenoids, monoterpenes, sesquiterpenes, benzene derivatives and to a lower content of alcohols, terpenes, esters, ketones, fatty acids, and aldehydes.[24]

Virological Characteristic of SARS-CoV-2

Coronaviruses are a single-stranded RNA genome coated with glycoproteins. The coronavirus genera are composed of α, β, γ and δ that the virus related to COVID-19 belongs to β-coronavirus.[25] This novel β-coronavirus has 88% similarity to the sequence of 2 bat-derived SARS-like coronaviruses.[26] This virus also named "SARS-CoV-2" by the International Virus Classification Commission.

The genome of SARS-CoV-2 is similar to the genome of typical coronaviruses, which contains at least 10 open reading frames (ORFs). Almost 66% of viral RNA is translated into 2 large polyproteins, which are ORFs (ORF1a/b). Other 34% of viral RNA codes for 4 major structural proteins, including spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins.

SARS-CoV-2 enters the cell via the angiotensin-converting enzyme 2 (ACE2) as a receptor.[27] The attachment of the to host cell receptors is necessary for the occurring infectious diseases. SARS-CoV-2 originated in bats[28] and then adapted to human ACE2 cell. Further information on receptor binding of coronaviruses may help in the management of coronaviruses infection.[29]

COVID-19 Pathogenesis

The symptoms of patients with COVID-19 are similar to SARS-CoV and MERS-CoV infections, which include fever and chills, Sore throat, nonproductive cough, smell and taste loss, fatigue, dyspnea, myalgia, normal or reduced leukocyte counts, pneumonia, cardiovascular and neurological disease.[30] However, our knowledge of the pathogenesis of COVID-19 is very limited, and the similar mechanisms of other coronaviruses help us to find unknowns about COVID-19.

The S protein of the coronavirus is involved in the enternalization of the virus into host cells.[31] The envelope spike glycoprotein of SARS-CoV-2 attaches itself to ACE2 as its cellular receptor.[28] The SARS-CoV enters the cells by direct membrane contraction between the virus and cell membrane and by clathrin-dependent and -independent endocytosis.[32] After viral entry into the cells, the genomic RNA of this virus is extruded into the cytoplasm to translate the viral proteins, and the virus then replicates. The new form of envelope glycoproteins penetrates organelles such as endoplasmic reticulum or golgi, and forms the nucleocapsid in vesicles; the vesicles then bind to the cell membrane to extrude the virus.[33]

Although the antigen presentation of SARS-CoV-2 is very effective to understanding the pathogenesis, prevention and treatment of COVID-19, it is not clear, and information on SARS-CoV and MERS-CoV may help us to identify the antigen presentation of SARS-CoV-2. The antigen presentation of SARS-CoV was mainly related to MHC I,[31] and somewhat to MHC II and antigen presentation of MERS-CoV infection was related to MHC II. The antigen presentation can activate the humoral and cellular immunity, leading to the production of IgM and IgG. It has been found that for patients with SARS-CoVs serum levels of IgG antibodies increase over a long period of time and play a protective role.[34] In patients infected with SARS-CoV-2, the number of $CD4^+$ and $CD8^+$ T cells in peripheral blood significantly decreased while high level of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) was found when it was highly activated.[35]

Acute Respiratory Distress Syndrome (ARDS) is the common cause of death in patients with COVID-19, associated with the release of cytokine cascade, including pro-inflammatory cytokines [tumor necrotic factor (TNF), interferons (IFNs), interleukins (ILs)] as well as CC chemokines (CCLs).[36] Serum levels of IFN-α, IL-6, CCL5, CXCL8, and -10 are increased significantly in patients with severe SARS-CoV and Middle East respiratory syndrome (MERS)-CoV infection compared with the mild form of the diseases.[37] The pro-inflammatory cytokines can cause ARDS and organ failure which lead to death in patients with severe status.[1]

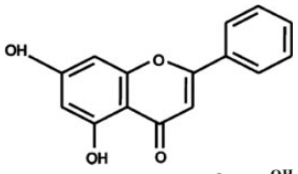
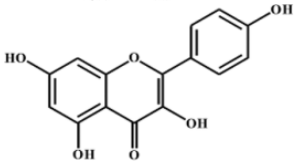
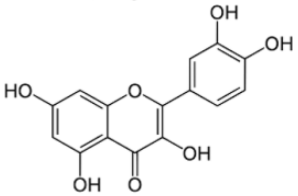
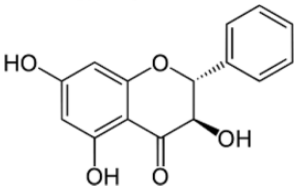
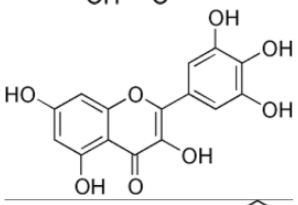
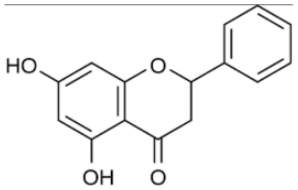
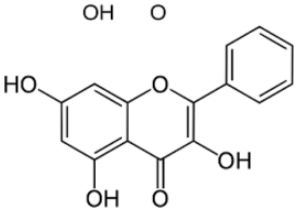
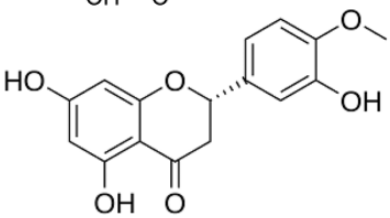
Potential Effect of Honey and Its Main Components Against Viral Infectious Diseases

Numerous studies have pointed to the therapeutic effects of honey and its main components against various viral infectious diseases. Honey and its main components could combat against Herpes zoster,[38] rubella,[39] influenza,[40] herpes disease,[41] respiratory syncytial virus,[42] AIDS,[43] immunodeficiency virus,[44] viral hepatitis,[45] gingivostomatitis,[46] rabies,[47] rhinoconjunctivitis[48] and COVID-19.[49] The mechanisms of antiviral properties of honey and its main components is very vast and unknown.[42] The anti-viral activity of honey and its main components is usually associated, similar to other natural products like resveratrol, calebin A or curcumin with anti-oxidant, anti-inflammatory, anti-resistance and anti-apoptotic effects by modulating cellular signaling pathways such as MAPK, NF-κB, Nrf2, etc.[50-58] In addition, these agents also have direct effect on the structure of the virus, such as the interaction of honey and its major components with structural and/or non-structural proteins in the virus or binding to target receptors on the virus.[58]

Effect of Honey and Its Main Components on the Virus Cell Cycle

More information about viral replication in the host cell may help to develop novel anti-viral agents that target viral replication and limit drug resistance in the virus. Viral replication

Table 1. Chemical Formula and Structure of the Most Important flavonoids and Phenolic Acids in Honey.

Main components	Chemical formula	Chemical structure
Flavonoids		
Chrysin	C15H10O4	
Kaempferol	C15H10O6	
Quercetin	C15H10O7	
Pinobanksin	C15H12O5	
Myricetin	C15H10O8	
Pinocembrin	C15H12O4	
Galangin	C15H10O5	
Hesperetin	C16H14O6	

(continued)

Table 1. (continued)

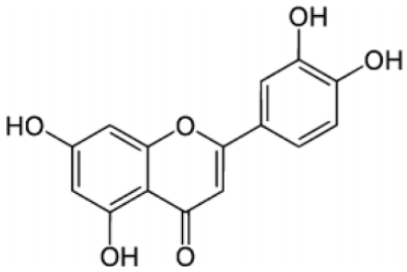
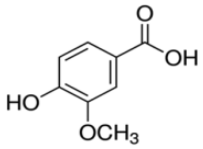
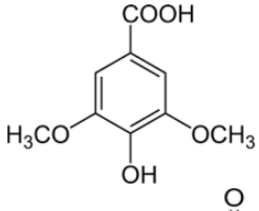
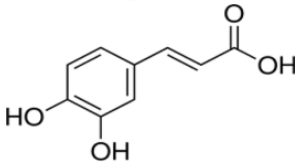
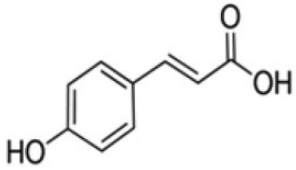
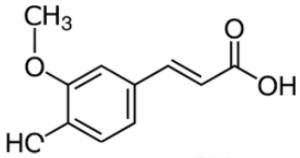
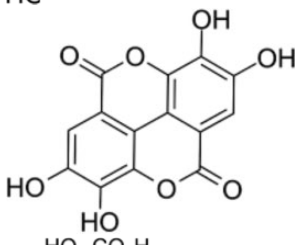
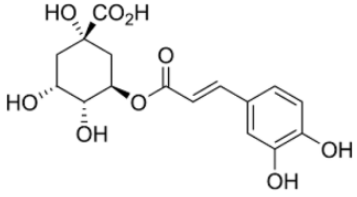
Main components	Chemical formula	Chemical structure
Luteolin	C15H10O6	
Phenolic acid		
Vanillic acid	C8H8O4	
Syringic acid	C9H10O5	
Caffeic acid	C9H8O4	
þ-Coumaric acid	C9H8O3	
Ferulic acid	C10H10O4	
Ellagic acid	C14H6O	
Chlorogenic acid	C16H18O9	

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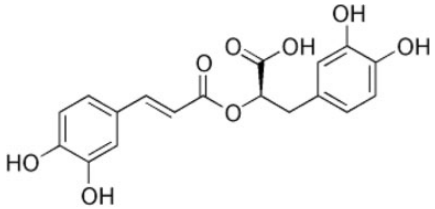
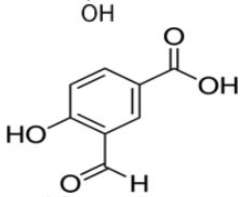
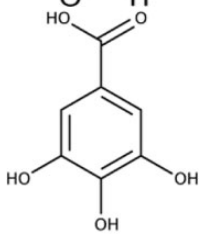
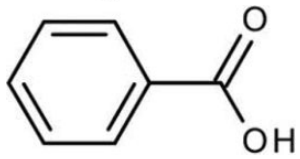
Table 1. (continued)

Main components	Chemical formula	Chemical structure
Rosemary acid	C18H16O8	
3- and 4-Hydroxybenzoic acid	C9H8O3	
Gallic acid	C7H6O5	
Benzoic acid		

takes place in 3 stages: first step involves the attachment of the virus to host cells, penetration and decoating, the second step involves the replication of the viral genome, transcription and translation and last step is viral assembly.

One mechanism underling the anti-viral action of honey and its main components is interruption of the proteins necessary for viral attachment and entry into host cells.[59]

In this regard, it has been pointed out that honey interrupts the disulphide bonds in the HA receptors, which leads to inhibition of the attachment of the influenza virus attachment to the host cell surface.[40]

Influenza hemagglutinin protein HA and the coronavirus spike protein are 2 major members of the class I fusion protein family.[60] SARS-CoV spike protein is necessary for the binding of the virus to the host cell receptor ACE2. Interestingly, it has been reported that chrysin (400 μM) showed a loose inhibition on the interaction of S protein with ACE2[61] and ACE2 and 3C-like protease (3CL pro) are recognized as the targets for anti-viral drugs Furthermore, Kaempferol and quercetin showed a high affinity to SARS-CoV-2 3CL hydrolase.[62] Kaempferol and quercetin were able to attach to ACE2 and modulate signal pathways including prostaglandin-endoperoxide synthase 2 (PTGS2), caspase 3, B-cell lymphoma 2 (Bcl-2), and Kaposi's sarcoma, which are associated with herpes virus infection, measles, hepatitis C, human cytomegalovirus and Epstein–Barr virus infection.[62]

Viruses are encoded for the ion-selective channels in the membrane of the infected cell,[63,64] and once these channels are activated, they are released in the cell and replicate.[65] Ion channel inhibitors can block virus production and allow the infected cell to potentiate its immune system.[66,67] The open reading frame 3a (ORF3a) of SARS-CoV encodes for an ion-permeable channel.[66,67] Indeed, it has been shown that flavonoids can trigger ion channel and inhibit virus release.[66,67] It was suggested that kaempferol is suitable as an agent for 3a-channel proteins of coronaviruses.[66,67]

Moreover, it has been reported that chrysin inhibited viral replication by blocking viral RNA replication and viral capsid protein formation without cytotoxicity (52). The modulation of molecular signaling pathways is one of the main targets for anti-viral drug. In this context, it was pointed out that kaempferol inhibits the replication of the influenza virus by to inducing the opposite cell-autonomous immune responses by regulating mitogen-activated protein kinase (MAPK) signaling pathways.[68] In addition, it was observed that kaempferol and quercetin can inhibit the replication of SARS-CoV-2 by targeting on phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PIK3CG) and E2F1 (E2F Transcription Factor 1) via modulating Phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway. Furthermore, quercetin and kaempferol inhibited SARS-CoV-2 replication through

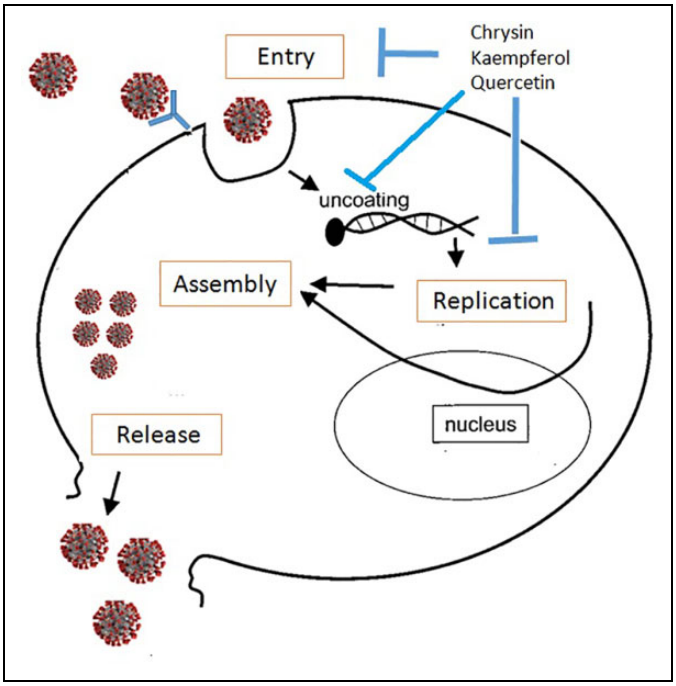


Figure 1. Effect of main components of honey on the cell cycle of corona virus. Main flavonoids present in honey such as chrysin, quercetin and kaempferol may be effective against corona virus by inhibiting virus entry, invasion and replication.

modulating of kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway[69,70] (Figure 1).

Effect of Honey and Its Main Components on the Viral Proteases

Lysosomal proteases are involved in coronavirus entry by cleaving coronavirus surface spike proteins and inducing the contraction of host and virus membranes.[71] Further, quercetin has been found to have protective effects against murine coronavirus by inhibiting H^+-ATPase of the lysosomal membrane and preventing removal of the virus coating. In addition, quercetin inhibited the ATPase of multidrug resistance-associated proteins, thereby increasing the bioavailability of anti-viral drugs.[72] The structure of main protease of the coronavirus is similar to that of *SARS-CoVMpro*, its RNA genome is approximately 82% similar to that of *SARS-CoV,* which belongs to the genus of *betacorona virus*.[73,74]

M^{pro} (3-chymotrypsin-like cysteine enzyme) is necessary for the processing of polyproteins by *SARS-CoV-2*.[75,76] Furthermore, 6 compounds present in honeybee and propolis have been found to have anti-viral activity against COVID-19 through strong binding affinity to main protease (M^{pro}) and viral replication.

It has been shown that chrysin could bind to amino acid residues (SER-46, THR-24 and THR-26) of the main protease of COVID-19 through hydrogen bond with 2.4, 2.6, 2.1 Ao, and also caused strong electrostatic interaction of the phenyl ring (HIE-41) with 3.8Ao (78). Galangine could interact with 2 amino acid residues (SER-46, THR-24) and electrostatic interaction with HIE-41 in the main protease in COVID-19. In addition, caffeic acid could interact with the main protease of COVID-19 via its hydroxyl group bound with 2 amino acid residues (GLN-189 and HIE-164) of the receptor by hydrogen bond with 2.0, 2.8Ao, and electrostatic interaction with (HIE-41) with 4.1 Ao..[77]

Effect of Honey and Its Main Components on the Inflammatory Response in Patients With COVID-19

Alveolar cells in patients with COVID-19 stimulates immune cells to release secrete cytokines and chemokines that are involved in recruiting additional immune cells to the lesion site. The activated immune cells can disrupt the virus by secreting inflammatory cytokines and phagocytosis. However, the excessive immune responses induce cytokine cascade in the lungs of patients with COVID-19. The cytokine cascade blocks the airways and increases vascular permeability, leading to edema and hypoxia. In addition, it has been found that quercetin and kaempferol to suppress the release of cytokines and to reduce immune responses and inflammatory mediators through modulating TNF, NF-κB pathways, PI3K/Akt, MAPK, T-cell, B cell, Ras and apoptosis signaling pathways, leading to inhibition of the coronavirus adsorption and replication.[46,59,78-81]

Moreover, kaempferol and quercetin also affect PTGS2, heat shock protein 90 alpha family class B member 1 (HSP90AB1), microsomal prostaglandin E synthase-1 (mPGES-1), Leukotriene A4 Hydrolase (LTA4 H), nitric oxide synthase (NOS2), TNF and IL-6, resulting in inhibition of coronavirus invasion and replication.[72,82]

It has been reported that IFNs have a major role in the control of COVID-19 infection. This virus could inhibit the induction of interferon in humans. In addition, it has been found that the main components of honey can increase the serum levels of interferon-gamma (IFN-gamma). Table 2 contains a summary of articles on the mechanisms of the main components of honey against coronavirus.

Potential Effect of Honey and Its Main Components on Vital Organs Complications of Coronavirus

Coronaviruses are able to stimulate several inflammatory mediators, which leads to various organ dysfunctions including ARDS. Honey and its main components have anti-fibrotic activity by reducing the expression of inflammatory mediators involved in lung infection. It has been found that honey lowers levels of prostaglandins (PG) E2,[8] PG2a,[83] thromboxane B2[84] and increases nitric oxide end products. These properties could help explain some biological and therapeutic properties of honey, particularly as an anti-bacterial agent or wound healing.[46] Moreover, it is suggested that honey could be effective against human respiratory syncytial virus (RSV) by inhibition

Table 2. Main Mechanisms of Controlling Coronavirus by the Main Honey Components.

Honey or its main components	Target	Effect	Reference
Chrysin	-S protein with ACE2 -3-chymotrypsin-like cysteine enzyme	Inhibition of virus entry in to host cells and virus replication	52,61,77
Kaempferol	- SARS-CoV-2 3CL hydrolase -ORF3a of SARS-CoV - PI3K-Akt, JAK/STAT, MAPK signaling pathway - COX-2, TNF, mPGES-1, AKT1, MAPK1, JUN, IL-6, CASP3, EGFR, IL1B, NOS2, PTGS2, HSP90AB1, mPGES-1, LTA4 H	Inhibition of the virus adsorption, invasion and replication	62,66-70,72,78-82
Quercetin	- SARS-CoV-2 3CL hydrolase -H+-ATPase of the lysosomal membrane -PI3K-Akt and JAK/STAT signaling pathway -PI3K-Akt, JAK/STAT, MAPK signaling pathway -COX-2, TNF, mPGES-1, AKT1, MAPK1, JUN, IL-6, CASP3, EGFR, IL1B, NOS2, PTGS2, HSP90AB1, mPGES-1, LTA4H	Inhibition of the virus coating, adsorption, invasion and replication	69,70,72,78-82
Galangin Caffeic acid	3-chymotrypsin-like cysteine enzyme	Inhibition of the virus adsorption, invasion and replication	77

viral replication.[42] Pulmonary fibrosis is a serious consequence of COVID-19 infection associated with ARDS. Furthermore, COVID-19 may affect the respiratory system and cause ARDS to secrete inflammatory mediators related to pulmonary fibrosis such as transforming growth factor beta (TGF-β) and IL-1β. Indeed, chrysin could inhibit the cellular inflammatory response by improving the NF-κB signaling pathway and fibrotic response in a rat model of viral-induced acute lung injury.[85] In addition, chrysin reduced inflammation, collagen deposition, malondialdehyde (MDA) levels in the lung in an experimental model of bleomycin-induced pulmonary fibrosis.[86] Furthermore, it has been shown that kaempferol reduced pulmonary inflammation and fibrosis in the experimental model of silicosis.[87]

In some patients with COVID-19, pulmonary edema was observed accompanied by a decrease in the activity of the epithelial sodium channels and the ion channel of the E-protein on the pulmonary epithelial cells.[88] In addition, chrysin inhibited alpha-naphthylthiourea (ANTU)-induced pulmonary edema in the animal model through regulating inflammatory responses and oxidative/nitrosative stress.[89] Moreover, cardiovascular disturbances may occur in patients with COVID-19 due to the systemic inflammation. It has been shown that honey reduced the degree of infiltration of inflammatory cells and to preserve the morphology of myocardial fiber in heart attack model.[90] In a rat model, chrysin has been found to have a protective effect on myocardial fiber structure in isoproterenol-induced acute myocardial infarction.[91]

Chrysin modulated the hemodynamic and ventricular functions in isoproterenol-induced acute myocardial infarction in a rat model through decreasing oxidative stress and also by reversing arterial ligation and peroxisome proliferator-activated receptor gamma (PPAR-γ) inhibition. Treatment with chrysin also led to an improvement in receptor for advanced glycation end-products (RAGE), inhibitor of nuclear factor kappa B (IKK-β) and nuclear factor kappa B (NF-κB) expressions and TNF-α levels. More interestingly, chrysin exerts cardiovascular protection by reducing apoptosis indices.[91-95]

The connection between COVID-19 and kidney damage is not clear. However, it was found that some patients with COVID-19 infection showed signs of kidney damage without previous history. There is some evidence linking COVID-19 infection to kidney damage: 1) the ability of coronavirus to attach to kidney cells and enter to the cell, 2) the decrease in blood oxygen, 3) the induction of systemic inflammation, 4) the formation of clots in the bloodstream that can block the blood vessels in the kidney. In addition, honey and its main components may be effective for kidney inflammation associated with COVID-19 treatment. It has been reported that rosmarinic acid improved blood pressure by inhibiting angiotensin-converting enzyme activity in 2-kidneys 1-clip model in rats.[96] Further, chrysin showed an inhibited therapeutic effect against adenine-induced CKD in a mouse model of focal cerebral ischemia/reperfusion injury by suppressing the NF-κB signaling pathway.[97] It was suggested that clot formation in small and large blood vessels may be major factor in organ failures and death from COVID-19 and that inhibition of clot formation may be effective against organ failures and death from COVID-19.[98] In this context, *in vitro* and *in vivo* assays confirmed the inhibitory effects of honey and its main components on platelet aggregation and blood coagulation.[99-106] For example, the *in vitro*, *in vivo*, and *ex vivo* models showed the anti-thrombotic and anti-coagulant effect of quercetin.[103] Indeed, several studies have reported that quercetin decreased, similar to other natural polyphenols (resveratrol, curcumin, ginkgo biloba and bilberry) diastolic pressure by potentiating eNOS activation, nitric oxide production[107,108] and the activity of thrombin, formation of fibrin clots and blood clotting through modulating the coagulation cascade.[103]

Quercetin and apigenin were found to decrease collagen- and Adenosine diphosphate (ADP)-induced aggregation in platelet-rich plasma for 2 weeks in healthy volunteers.[104]

Moreover, rosmarinic acid exerted a mild anti-thrombotic effect though inhibiting platelet aggregation and fibrinolytic activity in anesthetized rats with tight ligature in the inferior vena cava below the left renal vein.[105]

The anti-thrombotic effects of caffeic acid was investigated on cerebral arterioles and venules of mice by intravital microscopy and also *in vitro*. Furthermore, caffeic acid was able to inhibit platelet-mediated thrombosis by the activating of p38, extracellular signal-regulated kinases (ERKs) and c-Jun N-terminal kinases (JNKs) and led to an increase in cyclic adenosine monophosphate (cAMP) levels and a decrease in the expression of P-selectin and integrin αIIbβ3 activation.[106]

Potential Effect of Honey and Its Main Components on Interaction Coronavirus With Nrf2 Signaling Pathways

Nuclear factor erythroid 2-related factor 2 (Nrf2) dependent antioxidant genes expression is markedly reduced in COVID-19 patients. Nrf2 stimulators may inhibit the replication of SARS-CoV2 and also related inflammatory genes expression.[109] Previous studies indicated the Nrf2-mediated antioxidative effect of honey and its main components in various diseases. In this regard, it was found that honey stimulated the Keap1/Nrf2 signaling in the epidermis and induced epidermal barrier recovery.[110] Honey significantly improved hypertension via stimulation of Nrf2 in the kidney of hypertensive rats.[111] In murine macrophages exposed to the lipopolysaccharides (LPS), *Carthamus tinctorius* L. honey induced the expressions of Nrf-2/Heme Oxygenase-1 (HO-1), leading to inhibition of inflammation.[112] Chrysin ameliorated the neutrophils infiltration and other lung pathological damages through modulation of oxidative stress dependent Nrf2 pathway in lungs of rats exposed to carrageenan.[113] Chrysin, luteolin and apigenin protected rat primary hepatocytes against oxidative stress through modulating Nrf2 signaling pathway.[114]

Regarding to stimulatory effects of honey on the Nrf2 signaling, this natural agent can potential effect to combat against SARS-CoV2.

Conclusion and Remarks

The current study provided several pieces of evidence based on the potential effects of honey and its main ingredients against the corona virus infection. We focused on the modulating effects of honey and its main components on the molecular targets suitable for the treatment of coronavirus infections. The present study indicated that honey and its major components could be considered against COVID-19 infection because of their ability to regulate the molecular targets involved in the attachment and entry of this virus into the host cell and its RNA replication. Honey and its major components may also regulate cellular signaling pathways including oxidative stress, inflammation and apoptosis.

Honey and its main components may also be effective against pulmonary edema and fibrosis in COVID-19 infection due to their anti-fibrotic and immunomodulatory effects. In addition, systemic inflammation is one of the major threats in patients with COVID-19, which can be suppressed with honey and its main components. The inhibition of systemic inflammation by honey and its main components is attributed to their therapeutic effect on kidney, lung and cardiovascular damage in COVID-19 Infection. One of the main potential benefits of honey and its main components is its anti-thrombotic effects. In addition, it has been suggested that clot formation in patients with COVID-19 infection causes organ damage and eventually death. Since honey and its main components can inhibit the stimulation of molecular signaling pathways underlying coagulation and inflammation, they may be helpful in severe patients with COVID-19 as an adjunct to improve the cytokine cascade.

Although the safety of these compounds is approved in both animal models and human, but the low bioavailability of these compounds may reduce their efficacy. It is therefore, necessary to develop a new formula with high oral bioavailability.

Overall, the current study indicates that honey and its main components have potential implications for the preventing and treatment of coronavirus infection, including COVID-19. Till now, no clinical trial or case study have published on the protective effects of honey against COVID-19. According to our knowledge, there are some registered clinical trials including NCT04345549, NCT04323345, NCT04468139, NCT04347382 that are doing study to evaluate the effect of honey in patients with COVID-19 .

Therefore, clinical trials should be done to confirm or reject the efficacy of honey and its main components in patients with COVID-19 infection.

Abbreviations

3CL pro	3C-like protease
ACE2	angiotensin-converting enzyme 2
ADP	adenosine diphosphate
AKT	protein kinase B
ANTU	alpha-naphthylthiourea
ARDS	acute respiratory distress syndrome
Bcl-2	B-cell lymphoma 2
cAMP	Cyclic adenosine monophosphate
CCLs	chemokines
COVID-19	coronavirus disease 2019
COVs	coronaviruses
E2F1	E2F Transcription Factor 1
ERKs	extracellular signal-regulated kinases
HO-1	heme Oxygenase-1
HSP90AB1	heat shock protein 90 alpha family class B member 1
IFNs	interferons
IKK-β	nuclear factor kappa B
ILs	interleukins
JAK/STAT	Janus kinase/signal transducer and activator of transcription
JNKs	c-Jun N-terminal kinases

LPS	lipopolysaccharides
LTA4H	leukotriene A4 hydrolase
MDA	malondialdehyde
MERS	middle east respiratory syndrome
mPGES-1	microsomal prostaglandin E synthase-1
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOS2	nitric oxide synthase
Nrf2	nuclear factor erythroid 2-related factor 2
ORF3a	open reading frame 3a
PG	prostaglandins
PI3K	phosphatidylinositol 3-kinase
PPAR-γ	peroxisome proliferator-activated receptor gamma
PTGS2	prostaglandin-endoperoxide synthase 2
RAGE	receptor for advanced glycation end-products
TGF-β	transforming growth factor beta
TNF	tumor necrotic factor

Authors' Note

F.A., M.S., and S.S. designed study. All authors contributed to the collection of data, to the writing of the manuscript, and to designing tables and figures. S.S. and M.S. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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