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ANTICIPATION OF NATURAL HONEY IN FIGHTING AGAINST NOVEL CORONAVIRUS: PHARMACOLOGIC AND THERAPEUTICAL STUDY

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ABSTRACT

Honey is a natural food product produced by honey bees. Ancients have known it as a precious God-donated commodity. Thus, almost in all societies, extensive literature is available about the importance of honey on the treatment. Honey is physically an offensive and jelly material with no particular color. Chemically, it reflects the complex mixture of both organic and inorganic substances such as proteins, sugars, pigments, minerals, organic acids, etc. Historically, it is being used for the treatment of several diseases before the advent of modern medicines. Scientific literature demonstrated the importance of honey in medicinal uses. It has a wide range of antibiotics, antiviral, and antifungal activities. Honey halts the growth of microbes and destroys by different pathways, such as higher pH values and enzymatic reactions. A strong focus has been found on honey's virucidal effect on many enveloped viruses, such as HIV, herpes simplex virus, influenza virus, and varicella-zoster viruses. It is also helpful to the host immune system, increased co-morbidity, and antiviral activity for individuals diagnosed with COVID-19 which is triggered by an enveloped SARS-CoV-2 Virus. In this study, the positive impacts of honey, and the ingredients present in honey associated with antiviral, antibacterial, and antifungal activities are outlined and established a relationship of honey for COVID-19 treatment. The presented information will benefit the health officials and individuals in taking honey as the preventive remedy for the COVID-19 pandemic. Even so, *in vivo* and *in vitro* studies must further required to evaluate the influence of honey on SARS-CoV-2 treatment and/or improvement of the host immune system.

Keywords: SARS-CoV-2, Natural Honey, COVID-19, Coronavirus, Viral infection, Flavonoids.

1. Introduction

The first confirmed case of pneumonia was found in China at the beginning of December 2019 which is now emerged as the pandemic 2020. The responsible pathogen is now identified as a novel enveloped ssRNA beta-coronavirus and named as COVID-19 by the World Health Organization (WHO)[1,2].COVID-19, the newly identified disease, which was spreading rapidly throughout Wuhan at Hubei province, across other provinces in China and continues to spread around the world, and turned into severe pneumonia with acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3].SARS-CoV-2, a member of the beta coronaviruses, is a single-stranded (ss) positive sense and enveloped RNA virus. The major structural component of SARS-CoV-2 includes spike protein (S), membrane protein (M), and envelops protein (E) (**Figure 1**). The entry of the virus into host cells is facilitated by the S proteins. The S1 subunit binds with host cell surface angiotensin-converting enzyme 2 receptor, and the S2 subunit is involved in membrane fusion between the virus and the host cell[4].

The WHO has announced the COVID-19 outbreak a global pandemic on March 11, 2020. Globally, as of August 19, 2020 (06:00 GMT+6), there have been 21,989,366 confirmed cases of COVID-19, including 775,893 confirmed deaths, and 216 countries, areas, or territories with COVID-19 cases, reported to WHO[5]. Common symptoms of COVID-19 include fever, fatigue, dry cough, lymphopenia, dyspnea, etc[6]. Multi-organ failure, pneumonia, and acute respiratory distress syndrome are the most prevalent cause of death for infected individuals[6].It spreads primarily through the droplets or direct touch, blood, and the respiratory tract become compromised[7,8]. Regardless of the news of the outbreak, nature and death causes are still uncertain. However, the severity of the symptoms is supposed to be lethal for patients with underlying medical conditions, older people, and postponed hospital referral[9,10,11].

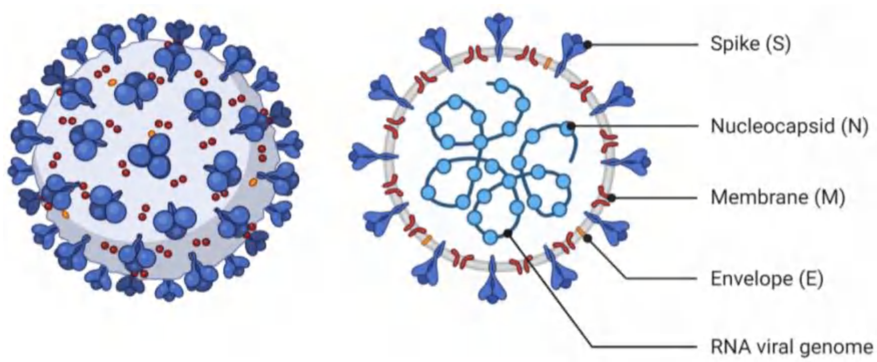

Figure 1. Structure of SARS-CoV-2

There are number of medicines is being used as a clinical trial for covid-19 treatments[12]. But an effective medicine for proven use is yet to approve. In this case, herbal and natural medicines can be an alternative selection. Traditional Chinese Medicine (TCM) is being used for covid-19 treatment in China [13].Since early times, honey has been used to treat infectious diseases, including diseases caused by viruses, bacteria, and fungi.It is produced from the bees of the *Apis* genus collecting honeydew and nectar for use, such as carbohydrates (mainly sugars) consumed in favor of muscle activity and metabolism or preserved as long-term food resource[14,15].Although there are different types of honey from various producer bees, the chemical compositionof 100 g of the commonly consumed honeys include approximately 25.4–28.1% glucose, 35.6–41.8% fructose, 64.9–73.1% carbohydrates,16.9–18% water, 1.8–2.7% maltose, 0.23–1.21% sucrose,and 0.50–1% proteins, vitamins, amino acids, and minerals [16].It found that plant secondary metabolites phenolic compounds are foundin honey with diverse chemical structuresincluding phenolic acids and polyphenols (e.g., flavonoids).

Despite the variability in the chemicalcomposition of honeys, the most abundant flavonoids are apigenin, quercetin,galangin, genistein, luteolin, chrysin,pinocembrin,kaempferol, and pinobanksin, while the most abundant phenolicacids are gallic acid, chlorogenic acid, syringic acid, vanillic acid, p-coumaric acid, p-hydroxybenzoicacid, and caffeic acid[16]. For this reason, honey has attracted researchers' attention as a supplementary and alternative medicine as a natural product[17]. Though honey contains several compounds that have potential action against bacteria, fungi, and viruses as wellbutit remained to be studied whether honey could be a therapeutic alternative for the regulation and/or treatment of COVID-19. Present study is focused on antimicrobial, antibacterial, antifungal, and antiviral properties of honey and its potential use in covid-19 treatment.

2. Antimicrobial properties

Honey has been used since prehistoric times to cure infections.Antibacterial properties of honey have been associated with a variety of factors, including hydrogen peroxide (H_2O_2), high osmolarity, moderate pH,aromatic acid, and phenolic content (a glycoprotein present in honey along with Maillard reactions, which include the interplay between carbohydrate reduction and the use of amino acids or proteins)[18,19,20,21,22]. Recent findings have shown that COVID-19 individuals experience secondary bacterial co-infections, such as bacterial pneumonia and fetal sepsis[23]. Also, a relatively similar viral infection is accompanied by a secondary infection[24]. Bacterial co-infection was observed in 12%-19% of cases of H1N1 pneumonia and influenza-infected persons with other serious illnesses[25]. In this study, it is outlined the potentially decisive role of honey and its ingredients in antibacterial, antifungal, and antiviral activities, and thereby correlate honey for treating the COVID-19 (**Table 1**).

2.1Antibacterial properties

Honey has been used for a long time for its antibacterial features by the traditional practitioners and herbal medics[26,27]. In 1892, the Dutch scientist Bernardus Adrianus van Ketel first demonstrated Honey's antibacterial effects[28]. Ever since, different studies showed that honey has large-scale antibacterial activity, even though the potenciesof the different kinds of honeyare varied against Gram-positive and Gram-negative bacteria[29,30]. Honey also offers a favorable environment to facilitate rapid cure producing white blood cellsto liberate interleukins and cytokines[31,32].The antibacterial activity against clinical bacterial isolates of theMRJP1 honey glycoprotein is recently reported as well[22].These findings indicate that the honey glycoprotein structure is the lead structure that carries antibacterial activity. Honey MRJP-containing glycoproteins, therefore, have sufficient features to be used as a novel antibacterial candidate for medication[22].

Furthermore, it was explained that the antibacterial property of the various kinds of honey is associated with its geographical origin, its botanical source, harvesting time, and processing and storage conditions[33,34].Although this beneficial effect of honey as an antibacterial agent has been recognized, but its functionagainst pathogens is still unclear.Numerous studies aimed to explore the relationships between bacterial cells and honey, especially with manuka honey, which one of the top usefulkinds of honey. Such results validated that the function of the honey affects the bacterial size (long or short cells), cell division (unequal division), motility, morphology, nucleic acid damage, surface (irregular), and lysis, depending upon the bacterial species [35,36,37,38,39].

2.2Antifungal properties

Antifungal features of honey have been demonstrated recently[40]. This property of honey was documented against *A.flavus*, *M. gypseum*, *A. niger*, *P. chrysogenum*, *Saccharomycessp.*, and *C. albicans*by preventing biofilm production and exopolysaccharide shifts[40,41].Sugars, hydrogen peroxide, phenols, dicarbonyl-methylglyoxide, even high osmolarity and low pH have been correlated for the anti-film activities of honey, whether alone or in combination with different substances[42,43].

2.3Antiviral properties

Antiviral studies of honey are minimal. Honey prevents viral replication and/or virulence activitiesby the action of its ingredients, including flavonoids, ascorbic acid, nitric oxide, compounds from nitric oxide, copper, and hydrogen peroxide[44]. Manuka honey has been reported useful against the influenza virus.It isshowed potent virucidal effects by inhibiting influenza viral replication[45]. However, clover and manuka honey were found as potential antiviral agents against the varicella-zoster virus through an experiment where melanoma cells (malignant) from human was used[46].

Additionally, antiviral activities of honey documented against herpes simplex virus-1 (HSV-1)*in vitro* by using Vero cells[47,48], and against rubella virus *in vitro* by using kidney cell cultures isolated from the monkey[49]. It is also demonstrated that the antiviral effects of flavonoids against HSV and coxsackie B, while quercetin and rutin display against HSV, syncytial, poliovirus, sindbis viruses[50].

Table 1. Potential mechanisms of antimicrobial properties of honey

Antimicrobial properties	**Mechanisms of action**	**References**
Antibacterial properties against Gram-positive and Gram-negative bacteria	i) Producing white blood cells to liberate interleukins and cytokines ii) Reducing hydrogen peroxide, sugar osmolarity, and pH	29,30 18,19

Antifungal properties	Inhibit biofilm production and exopolysaccharide shifts	42,43
Antiviral properties	Prevents viral replication and/or virulence actions	45

3. Potential roles of honeyto stopSARS-CoV-2

Honey contain flavonoids[51], andpotent inhibitory effect of certain flavonoids against human immune-deficiency virus (HIV,a positive sense, ssRNA virus) is a subsequent field of research of particular concern.To date, the disease outbreak of HIV-1 strainand its enzymes have been actively engaged in mostof the investigations.Baicalin inhibits HIV-1 infection and replication, as demonstrated *in vitro* studies[52,53].Moreover, numerous flavonoids are documented as inhibitors of HIV-1proteinase[52,53].Implemented antiviral action mechanisms are including viral polymerase inhibition, viral nucleic acid binding, or viral capsid protein binding inhibition[54].Several studies have documented that flavonoids have antiviral effects, for example, antiviral potentials against HSV, poliovirus, respiratory syncytial virus, and Sindbisinfection[54]. Both the flavonoid hesperidin and rosmarinic acid from plant extracts, which are also reportedto be found in honey[55], have shown potential to inhibit SARS-CoV-2 3CLpro in a study-basedcomputational analysis[56]. Interestingly, the analysis showed that hesperidin was the only naturalcompound that can bind to the RBD of S protein, and thus it could neutralize ACE2 and spike-RBDbinding[57]. Thus, honey contains hesperidin could have a potential effect in blocking the adhesion ofth

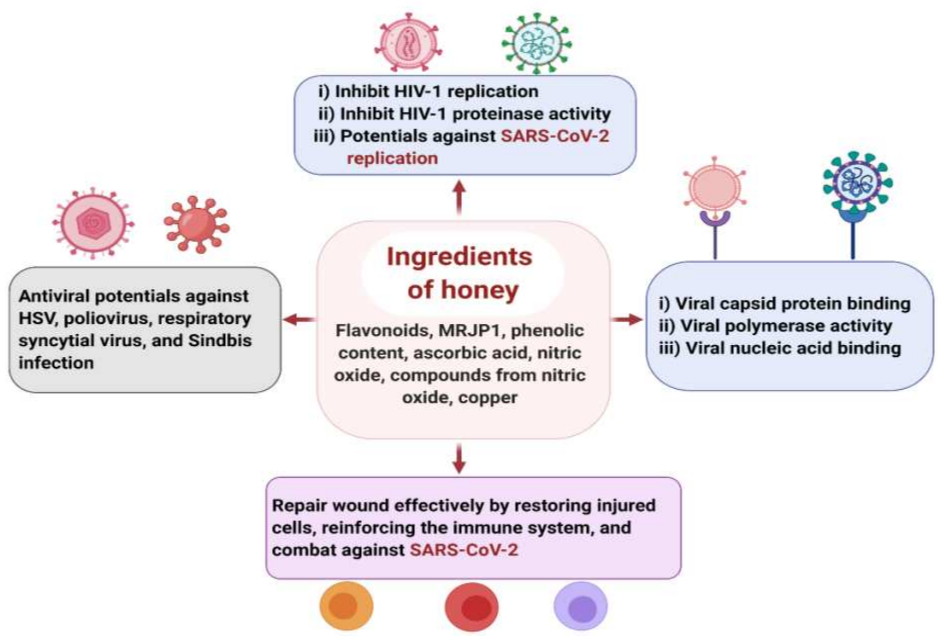

Figure 2. Possible roles of honey against SARS-CoV-2 infection

Additionally, the presentation of COVID-19 and flu viruses, i.e., influenza viruses, is adjacent. In other words, they cause respiratory problems, from asymptomatic diseases or mild diseases to severe conditions and death[58]. A recent study demonstrated that Manuka honey has a potent high activity to treat influenza viruses by efficient inhibition of the influenza viral replication process *in vitro*[58]. Combined use of honey and Nigella sativa has improved symptoms, viral clearance and mortality in COVID-19 patients[69].*In silico* analysis of phenolic chemical compounds from honey showed that caffeicacid, caffeic acid phenethyl ester (CAPE), galangin, and chrysin have good potential to inhibit theviral 3-chymotrypsin-like cysteine protease (3CLpro) enzyme, and thus inhibit viral replication[60].At a concentration of 500 µg/mL, honey showed highest antiviral activity against HSV in vitro with adecrease in viral load at a concentration of 100 µg/mL[61]. Furthermore, honey is shown to be effectiveupon the topical use to treat recurrent skin lesions caused by

HSV[62]. It is reported thatthe severity of COVID-19 infection correlates withlymphocytopenia, and patients who died from COVID-19 had lower lymphocyte counts compared tosurvivors[63]. These data suggest that lymphocyte-mediated antiviral activity is poorly effectiveagainst COVID-19. Despite lymphocytopenia, evidence for an exaggerated release of pro-inflammatorycytokines (i.e., IL-1 and IL-6) has been reported in the course of acute respiratory syndrome in COVID-19infected patients, aggravating the clinical course of the disease[64]. Therefore, honey is anticipated toplay a vital role in boosting the immune system as a supportive treatment for patients infected withCOVID-19, and also for preventive measures for healthy individuals.As reported earlier, the antiviral activity of honey due to its virucidal components may destroy many enveloped viruses, and may even have a possible suppressive effect on SARS-CoV-2 (**Figure 2**).

4. Conclusion and Future Direction

Several studies have shown that honey has enhanced immune function, antiviral, antibacterial, antifungal properties, and facilitates the healing and scavenging of recurrent ulcers and harmful free radicals[39].As mentioned by the national health institution, a phase-3 clinical trial of natural honey (among 1000 participants) for COVID-19 is also started(estimated study start date: April 15, 2020;estimated primary completion date: December 15, 2020; estimated study completion date: January 15, 2021)[65].It is expected that there will be a significant outcome after the clinical trial. Moreover, honey plays possible roles in many enveloped viruses, including influenza and HIV, which have been confirmed already. Honey can also repair wound effectively by restoring injured cells, reinforcing the immune system, and fighting viruses, bacteria, and fungi.Synergistically, honey combinations with other rich natural products (such as cinnamon,ginger, and garlic) have shown stronger antimicrobial and immune booster activities[66,67]. So there is an option to discover therapeutic for diseases in combination of honey with other ingredients.

The potential of honey with its anti-inflammatory properties may benefit the later stage of COVID-19 infection. However, it needs to be noted that honey is also capable of inducing pro-inflammatory cytokines such as IL-1, TNF, and IL-6, associated with the systemic disease of COVID-19 infection[68], render its antiviral potential to be cautiouslyapproached.Besides, until now, no significant adverse effects of honey on the human body are reported.This review will help to revisit the potential therapeutic potential of honey by enhancing antiviral, antifungal, and antibacterial properties in the battle against COVID-19.Moreover, we strongly recommend *in vitro*as well as*in vivo* studies to investigate fundamental research into the effects of honey on the replication and/or host immune system of SARS-CoV-2.

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6. Conflicts of Interest

The authors declare no conflict of interest.

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