



## Review article

## Prospects of honey in fighting against COVID-19: pharmacological insights and therapeutic promises



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## ABSTRACT

Honey and its compounds are drawing attention as an effective natural therapy because of its ability to attenuate acute inflammation through enhancing immune response. Several studies have proved its potential healing capability against numerous chronic diseases/conditions, including pulmonary disorders, cardiac disorders, diabetes, hypertension, autophagy dysfunction, bacterial, and fungal infections. More importantly, honey has proved its virucidal effect on several enveloped viruses such as HIV, influenza virus, herpes simplex, and varicella-zoster virus. Honey may be beneficial for patients with COVID-19 which is caused by an enveloped virus SARS-CoV-2 by boosting the host immune system, improving comorbid conditions, and antiviral activities. Moreover, a clinical trial of honey on COVID-19 patients is currently undergoing. In this review, we have tried to summarize the potential benefits of honey and its ingredients in the context of antimicrobial activities, some chronic diseases, and the host immune system. Thus, we have attempted to establish a relationship with honey for the treatment of COVID-19. This review will be helpful to reconsider the insights into the possible potential therapeutic effects of honey in the context of the COVID-19 pandemic. However, the effects of honey on SARS-CoV-2 replication and/or host immune system need to be further investigated by *in vitro* and *in vivo* studies.

## 1. Introduction

Recently encountered world pandemic coronavirus disease 2019 (COVID-19) is a serious concern worldwide [1]. It is anticipated that, during the end of the year 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified in Wuhan city of Hubei Province of China [2]. Due to its easily transmissible nature, the disease has spread to almost 210 countries in the world within a short period. That is why it has been declared as a world pandemic by WHO on 11<sup>th</sup> March 2020 [3]. As of 17<sup>th</sup> June 2020, 8,322,910 people are suffering from this viral infection and the number of deaths is 447,959 [4]. Before the COVID-19 pandemic, two other viruses were belonging to the same genus caused severe infection in the form of pneumonia [3, 5]. All three of these viruses can cause fatal injury to older and immune-compromised people while younger people with a strong immune system are normally

considered out of danger with the exception of comorbid conditions. The SARS-CoV-2 readily triggers infection in several body parts including the lung, cardiovascular system as well as liver [5]. It's a matter of concern that no proper treatment has been introduced yet [6]. Therefore, strategies that boost the immune system could be effective to alleviate the complications associated with COVID-19 [7, 8, 9].

The use of chemo drugs comes with several problems including multidrug resistance and side effects which prompt us to think about other alternatives like natural products for reducing the unavoidable side effects [10, 11]. Human has been using plant and its several derivatives as treatments for various types of diseases [12, 13]. In recent years, honey has got the attraction of researchers for combatting efficiently against these difficulties of chemo drugs [14]. Honey contains several compounds including sugars, organic acids, amino acids, phenolic compounds, vitamins, and minerals [15]. This is the reason why honey has

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been studied for a long time in animal and human models to observe its antioxidant potency [16, 17]. It has proved its potency in several therapeutic properties including immunostimulatory, antibacterial, anti-inflammatory, wound healing, antiulcer, antidiabetic, anticancer, antiviral, and antifungal [18, 19, 20]. It reduces the level of triglycerides (TGs), very-low-density lipoprotein (VLDL), and systolic blood pressure in experimental animals [21]. Reduced acute respiratory distress symptoms have been noticed when honey is ingested daily [22].

A recent *in silico* approach showed that honey may inhibit SARS-CoV-2 proteases and some compounds of honey may be able to bind SARS-CoV-2 protease, but this has still to be validated experimentally [23]. Methylglyoxal (MGO) modification might be involved in SARS-CoV-2 replication [24]. MGO is a component of manuka honey that can inhibit enveloped virus growth [25]. However, whether honey might be a therapeutic choice for controlling and/or treating the COVID-19, remained to be investigated. In this review, we summarized all promising beneficial roles of honey and its ingredients in the context of antimicrobial activities, numerous chronic diseases, and host immune signaling pathways and thereby tried to make a correlation of honey for the treatment of COVID-19.

## 2. Methods

A literature search was performed using PubMed, Scopus, and Google that includes all original research articles written in English on beneficial effects of honey against various pathophysiological conditions. Searching was conducted before April 2020 using various keywords including honey, inflammation, oxidative stress, bacterial infection, viral infection, and so on. Figures were generated using [BioRender.com](https://www.biorender.com), online software.

## 3. Pharmacological effects of honey

Several studies have observed honey and its active compound(s) on human physiological systems. Various *in vivo* or *in vitro* studies have also been performed to utilize its antimicrobial activities. However, the exact mechanism of protective effects of honey in case of viral infection has not been properly established yet. The recent studies on the protective effects of honey against immune dysfunction, anti-inflammatory effects, diabetes, hyperglycemia, cardiovascular disorders, and bacterial, fungal, and viral infections have been summarized and discussed in Table 1. We also tried to make a correlation of therapeutic effects of honey on COVID-19 as all of these above mentioned physiological disorders/comorbid conditions found to be associated with the high fatality rate of SARS-CoV-2 infected individuals [26].

### 3.1. Oxidative stress

Oxidative stress is the imbalance between oxidative products and antioxidants that leads to cell damage. Oxidative stress has a role in several diseased conditions including neurological disorder, cancer, aging as well as endocrine illness [27]. It also has a main role in the pathology of virus invasion by inducing inflammatory damage which consequently exaggerated immune response, commonly known as a cytokine storm. A buildup in immune cells infiltration and release of their activating compounds or cytokines occurs during cytokine storm [28]. Influenza viruses harm the lungs in presence of inflammatory signals is an example of this event. This is done by producing reactive oxygen species (ROS) which helps the influenza virus to cause infection [29].

Macrophages and neutrophils are known to produce a significant amount of ROS. The increased oxidative stress level has a role to play in pulmonary injuries including acute lung injury (ALI) and acute

**Table 1.** Effects of honey on various pathophysiological conditions.

Models	Source of honey	Effects of honey on mechanisms involved	Ref.
Bacteria	Manuka Honey	- Lowering pH, osmotic effect of sugars, and H <sub>2</sub> O <sub>2</sub> - Inhibition of biofilm activity against <i>Escherichia coli</i> O 157:H7	[14, 84, 100]
Fungus	Commercial honey (Nigeria)	- Prevention of biofilm formation and making changes to exo-polysaccharide - Synthesis of hydrogen peroxide in water-diluted honey could be the possible reason	[14, 87]
Virus	Manuka Honey	Interruption in viral transcription, and translation	[25]
Rats	Tualang Honey	Decreased glucose level in type-2 diabetes mellitus	[19]
Rats	Tuscany honey	- Reduced formation of fats and proteins in diabetic rat - Inhibition of alpha-glucosidase activities	[69]
Rats (liver cells)	Tuscany honey	Suppressing PTP1B while encouraging alteration in serum lipid profiles and expression of insulin receptor	[69]
Rat	MGO	- Reduced wound size - Increase urine osmolarity, osmolar clearance, creatinine clearance, and free water clearance	[101]
Human	Natural honey	Prevention of platelet aggregation, extend APPT, PT, and TT while decreasing amount of fibrinogen in platelet-poor plasma	[78]
Human (peripheral blood)	European honey bee ( <i>Apis mellifera</i> )	Mitogenic effect on both B- and T lymphocyte	[49]
Rat (breast cancer)	Tualang Honey	Increase IFN- $\gamma$ and IFNGR1 at serum level	[48]
Human	Manuka Honey	- Reduction of IL-8/CXCL8, IL-1 $\beta$ , MMP-9, and TNF- $\alpha$ release while increasing IL-10 and IL-1ra release from the neutrophils - Reduction in neutrophil extracellular trap formation (NETosis)	[102]
Human	Manuka Honey	Increase the concentration of cytokines	[52]
Influenza B virus	MGO	Inhibition of influenza B virus replication by MGO	[92]
Human	MGO	Induction of cell death by autophagy and inhibition of the ROS-derived Akt/mTOR signaling pathway	[103]
Mouse	MGO	Increase in MCP-1 and TNF- $\alpha$ in RAW264.7 macrophages	[104]

Interleukin-IL, Monocyte chemoattractant protein-MCP-1, Matrix metalloproteinase 9- MMP-9, Partial prothrombin time (APTT), Prothrombin time (PT), Thrombin time (TT), *Interferon-gamma*- IFN- $\gamma$ , Interferon-gamma receptor 1-IFNGR1, TNF- $\alpha$ - Tumor Necrosis Factor  $\alpha$ , MIC- Minimum Inhibitory Concentration, Methylglyoxal -MGO, Protein tyrosine phosphatase 1B -PTP1B, Neutrophil extracellular trap formation- NETosis.

respiratory distress syndrome (ARDS) [30]. There are several viruses including coronaviruses, influenza viruses that can cause deadly lung damage and can be fatal from ARDS [31]. Increased oxidative stress in ARDS takes place due to the fast liberation of free radicals and cytokines which results in cellular injury, organ failure, severe hypoxemia, uncontrollable inflammation. All of these are harmful to the alveolar-capillary barrier and can cause death [32]. In a recent study, it has been found that the time to cause infection by SARS-CoV-2 is more than 14 days. In a study, it was found that almost 93 % of patients (27 out of 29) showed elevated hypersensitive C reactive protein (CRP) which is a known marker for inflammation and oxidative stress [33].

Honey has proved its antioxidant activity by preventing several acute and chronic diseases which include diseases related to inflammation, diabetes, cardiovascular, and cancer [14]. Moreover, phenolic acids of honey protect humans from hydrogen peroxide-induced oxidative DNA damage in lymphocytes [16]. Along with phenolic acids and flavonoids, several other compounds (such as sugars, proteins, amino acids, carotenes, organic acids, and other minor components) present in honey have shown antioxidant activity for a longer period [34]. Consumption of 1200 mg/kg honey can increase both levels of antioxidants such as glutathione reductase,  $\beta$ -carotene, vitamin C in healthy human subjects [35]. While possible mechanism that could be involved in flavonoids substrate action for hydroxyl, metallic ion chelation, superoxide radical actions, hydrogen donation, free radical sequestration, is not known yet [36]. Though the antioxidant effects of honey have been established in a structured manner, there are several unknown aspects yet to be found.

### 3.2. Immune responses and inflammation

Human innate and adaptive immune systems might play protective roles against SARS-CoV-2, as no therapeutic intervention has been introduced. Angiotensin-converting enzyme-2 (ACE-2), a receptor of SARS-CoV-2 has been found on various cell surfaces including lungs, heart, kidney, and arteries [37]. The attempt of seizure of healthy cells by this virus generally stimulates different cells in the human body such as macrophages, natural killer cells, T-cells, B-cells, neutrophils, and dendritic cells. These are the classical antigen-presenting cells (APCs) that conduct the killing process of SARS-CoV-2 [38,39]. Toll-like receptors (TLRs) which are also commonly recognized as pathogen recognition receptors are suspected to be a helper for SARS-CoV-2 entry [38]. Stimulation of immune responsive cells occurs when a virus enters the body. APC for SARS-CoV-2 occupy the virus and provide co-stimulation for specific B and T cell proliferation via human leucocyte antigen (HLA) [39]. This is identified by T cell receptor (TCR) which ultimately turns into helper T cells (CD4+) and cytotoxic T cells (CD8+). CD8+ directly attacks virus-infected cells while CD4+ activates several immune responsive cells such as CD8+ T cells, natural killer (NK) cells, and memory T cells [40, 41]. B cell differentiation is stimulated by cytokines which come from helper T cells. IL-2 produced by T-cell is involved in ERK1/2-prompted plasma cell differentiation [42]. Along with plasma B cell, memory B cell creates a direct link with SARS-CoV-2. With the help of this link, antigen-specific antibodies produced by plasma B cells kill SARS-CoV-2. Some of the B cells may form memory and thereby providing a protection system to fight against future invasion [40].

According to a recent study, the adaptive immune response can target viral structural proteins like spike glycoprotein, envelop protein, and others, indicating that humoral immunity (antibodies) may mediate protection against SARS-CoV-2 [43]. Innate and adaptive immunity against SARS-CoV-2 is provided by B and T lymphocytes which are activated by dendritic cells [44]. IFNs and granzymes secreted by cytotoxic T cells (CD8+ cells) can activate NK cells to kill SARS-CoV-2 by showing cytotoxicity towards virus-infected epithelial cells thus inducing apoptosis [44, 45]. Cytokines and chemokines produced by neutrophils and macrophages can increase CRP levels which are c3a and c5a that possess antiviral activity [46].

Honey may activate T-lymphocytes, B-lymphocytes, and neutrophils which ultimately produce cytokines such as interleukin-1 (IL-1), and interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [47]. Honey also increases the serum levels of IFN- $\gamma$  and IFN- $\gamma$  receptor 1 (IFNGR1) in breast cancer in rats [48]. As IFN- $\gamma$  has an affinity to viral spike glycoprotein, nucleocapsid protein, and membrane protein, it may aid in targeting SARS-CoV-2 [43]. Honey has shown a cell dividing (mitosis) effect on both B- and T cells. This proves that it might have a role in inducing an adaptive immune response against SARS-CoV-2 infection [49]. Nigerose, a sugar derived from honey is reported as immune stimulatory [50]. A variety of honey including Manuka, Royal jelly, Pasture, and Nigerian Jungle honey can increase the mediators of immune responses such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and apalbumin 1 production [51, 52, 53]. In humans, honey provides beneficial effects by increasing the levels of ascorbic acid, glutathione reductase, minerals, and immune cells such as eosinophils, monocytes, and lymphocytes. At the same time, it decreases immunoglobulin E, ferritin, and enzymes including creatinine kinase, aspartate transaminase, lactate dehydrogenase, and alanine transaminase. It also decreases levels of different enzymes of liver and muscle and fasting blood sugars [35]. These shreds of evidence suggest that honey may be able to give protection against SARS-CoV-2 but proper validation through *in vitro* and *in vivo* experiments is required.

Anti-inflammatory effects of honey have been studied where it has shown its potency in form of cell culture model, animal model as well as in clinical trials [54, 55]. In a recent study, it is proved that MGO, a component of Manuka honey effectively senses bacterial invasion by producing mucosal-associated invariant T cells (MAIT cells). It is known that MAIT cells can effectively regulate a diverse range of immune responses which includes antimicrobial defense as well. In human monolayer cells, MGO has significantly increased MAIT cells *in vitro* [56].

Commonly known inflammatory markers such as mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF- $\kappa$ B) can induce other inflammatory factors such IL-1 $\beta$ , IL-6, IL-10, lipoxygenase 2 (LOX-2), cyclooxygenase-2 (COX-2), CRP, and TNF- $\alpha$  [57]. A study reported that honey may be a perfect suppressor agent for these two markers [58]. Several components of honey act as suppressors of pro-inflammatory enzymes, as well as stimulate the process of repairing damage which may prove honey a potential agent against disease [59].

### 3.3. Autophagy

Autophagy is known as "self-degradation", is a highly conserved catabolic process that governs a cell to remove long-lived proteins, lipid, unwanted or damaged cells, and impurities, thereby helping to recover healthier cells, the process is aided by autophagosome formation and its merging with lysosomes to destroy the selected molecule [60]. Therefore, if the human body ought to fight against a deadly virus like SARS-CoV-2, a strong immune system is must needed which involves several immune responses including autophagy [38]. Fatal viruses like SARS-CoV-2 can decrease the action of autophagy but several compounds can induce autophagy to fight against these types of viruses, therefore this immune response can be considered as a tool to fight against COVID-19 [9,61].

Natural honey is supplemented with flavonoids (kaempferol, catechin, and quercetin) and polyphenolic acid (caffeic acid and gallic acid) which have been found to show anticancer activity. One of the flavonoids present in honey i.e. quercetin has been found to inhibit proteasomal activity and mTOR signals, and promote substantial autophagy [62].

### 3.4. Diabetes

Diabetes and unrestricted glycemia are some of the main reasons behind death due to infection by several viruses including influenza A (H1N1), SARS-CoV, and MERS-CoV [63, 64, 65]. In a study with SARS-CoV-2 infection, hyperglycemia was found to be a causative agent for death in more than half of the cases [66]. In 2003, confirmed

individuals of SARS-CoV showed transient impairment of pancreatic islet cells through hyperglycemia [67].

In a clinical trial with streptozotocin-induced diabetic rats were subjected to honey for evaluating the antidiabetic effect. In that study decreased glucose level in type-2 diabetes mellitus has been observed [19]. Honey has been shown to participate in reducing glucose, fructosamine, and glycosylated hemoglobin serum concentration [68]. Honey can show glycemic control through suppressing protein tyrosine phosphatase 1B (PTP1B). At the same time, it also can encourage alteration in serum lipid profiles and expression of the insulin receptor in liver cells [69]. Honey and quercetin can raise the level of expression of protein kinase B (PKB) which is also called by Akt while reducing phosphorylation of insulin receptor substrate 1 (IRS-1) at serine, NF- $\kappa$ B, and MAPK [70]. Honey significantly increased high density lipoprotein (HDL) and reduced hyperglycemia, TGs, VLDL, non-HDL cholesterol, coronary risk index (CRI), and cardiovascular risk index (CVRI) in diabetic rats [71]. When a dose of 1000 mg/kg is administered, it can significantly develop glycemic control and hyperlipidemia [71]. Therefore, it can be predicted that honey can show a hypoglycemic effect.

### 3.5. Cardiovascular disorder and hypertension

A study with 150 positive individuals of COVID-19 showed 7% of death exhibited due to myocarditis with circulatory collapse, meanwhile, 33% myocarditis contributed towards the final severe outcome [72]. Honey is proved for its long-term cardiovascular benefits as well as short-term antiarrhythmic effects [73]. A decreased rate of cardiovascular disease is often associated with flavonoids for example anthocyanin and vitamins including niacin ( $B_3$ ). Both of these present in honey which makes it a potential therapeutic against cardiovascular disease [68, 74, 75, 76, 77]. Another study showed that honey can prevent platelet aggregation, extend partial prothrombin time (APTT), prothrombin time

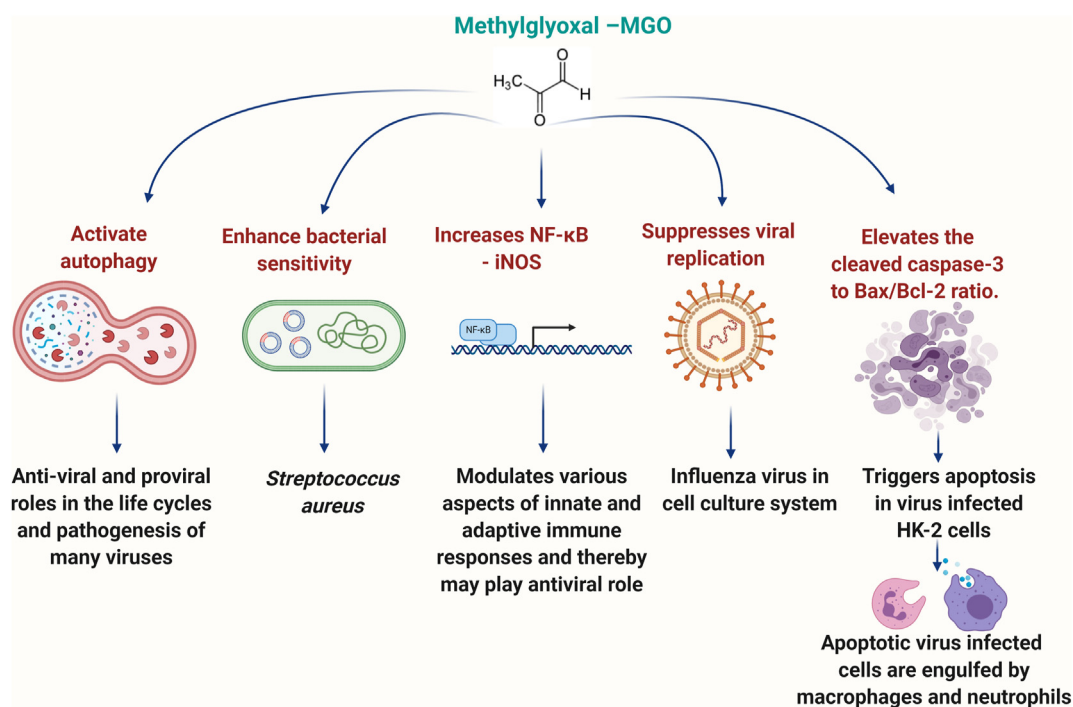
(PT), thrombin time (TT) while it may decrease the amount of fibrinogen in platelet-poor plasma [78].

### 3.6. Microbial infections

Honey is considered as an ancient remedy which is used by mankind for a long time. This ancient method of therapy is now under investigation because of modern therapeutic agents are failing. Honey has been pointed out as a drug and ointment dated back to 2100-2000 BC whereas in much later time Aristotle (384-322 BC) described honey as “good as a salve for sore eyes and wounds” [79]. Recent studies reported that COVID-19 patients are prone to develop secondary bacterial coinfections such as bacterial pneumonia and sepsis which is a fetal threat [80]. Viral infection followed by secondary infection's contribution to death is surprisingly equal [72]. Bacterial coinfections in between 12%-19% are common in H1N1 influenza and pneumonia infected individuals with other serious illnesses [81]. A typical marker for inflammation and infection is the neutrophil-lymphocyte ratio (NLR). This indicates that bacterial infection comprises pneumonia. Besides, severe SARS-CoV-2-infected individuals were found with elevated NLR. This is the characteristic of a potentially critical condition [31, 82].

#### 3.6.1. Antibacterial properties

Honey provides a favorable environment that promotes healing quickly. At the same time, the antibacterial properties of honey can speed up the healing process by producing white blood cells (WBC) to increase the pro-inflammatory cytokines including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [52,83]. Several shreds of evidence showed that honey may act as an antimicrobial agent through lowering pH, osmotic effect of sugars, and  $H_2O_2$  levels. All of these works against pathogenic bacteria including *Streptococcus typhi*, *Staphylococcus aureus*, coagulase-negative *Streptococcus*, and *E. coli* [14, 84]. The bacterial growth might be inhibited through urease



**Figure 1.** Roles of MGO in modulating cell signaling pathways, host immunity, and antiviral activity. MGO induces autophagy through activating AMP-activated protein kinase (AMPK) [105, 106]. Autophagy and autophagy associated proteins might play anti-viral and proviral roles in viral replication and pathogenesis [107, 108]. NF- $\kappa$ B and iNOS could be activated by the treatment of MGO in retinal pericytes [109]. NF- $\kappa$ B associated proteins regulate cell survival, division, and proliferation thereby modulates various aspects of innate and adaptive immune responses [110]. Besides, NF- $\kappa$ B activation may contribute to the antiviral immune pathway [111]. MGO effectively inhibits the influenza virus replication in the cell culture system, can induce apoptosis by inhibiting c-FLIPL expression through decreasing of p65 [92,112]. Influenza virus-infected apoptotic mouse cells were engulfed by macrophages and neutrophils which proved the involvement of the apoptosis process in antiviral innate immune mechanism [113].

regulation by the MGO and its precursor dihydroxyacetone (DHA) [14]. However, Wang *et al.*, 2012 demonstrated that honey showed its antibacterial effect by direct killing of bacterial cells by its bactericidal components and disrupting the bacterial quorum sensing (QS) [85]. In the case of cystic fibrosis (CF), manuka honey might play potential roles against deadly lung infections caused by antimicrobial-resistant respiratory bacteria [86].

### 3.6.2. Antifungal properties

The fungicidal property of honey has been proved against *P. chrysogenum*, *A. niger*, *M. gypseum*, *A. flavus*, *C. albicans* as well as *Saccharomyces* species. Honey can prevent biofilm formation and makes changes to exopolysaccharide [14, 87]. Honey ensures the decrement of the cell surface in biofilm which takes towards the death of biofilm by manipulating the cell membrane of fungus [88].

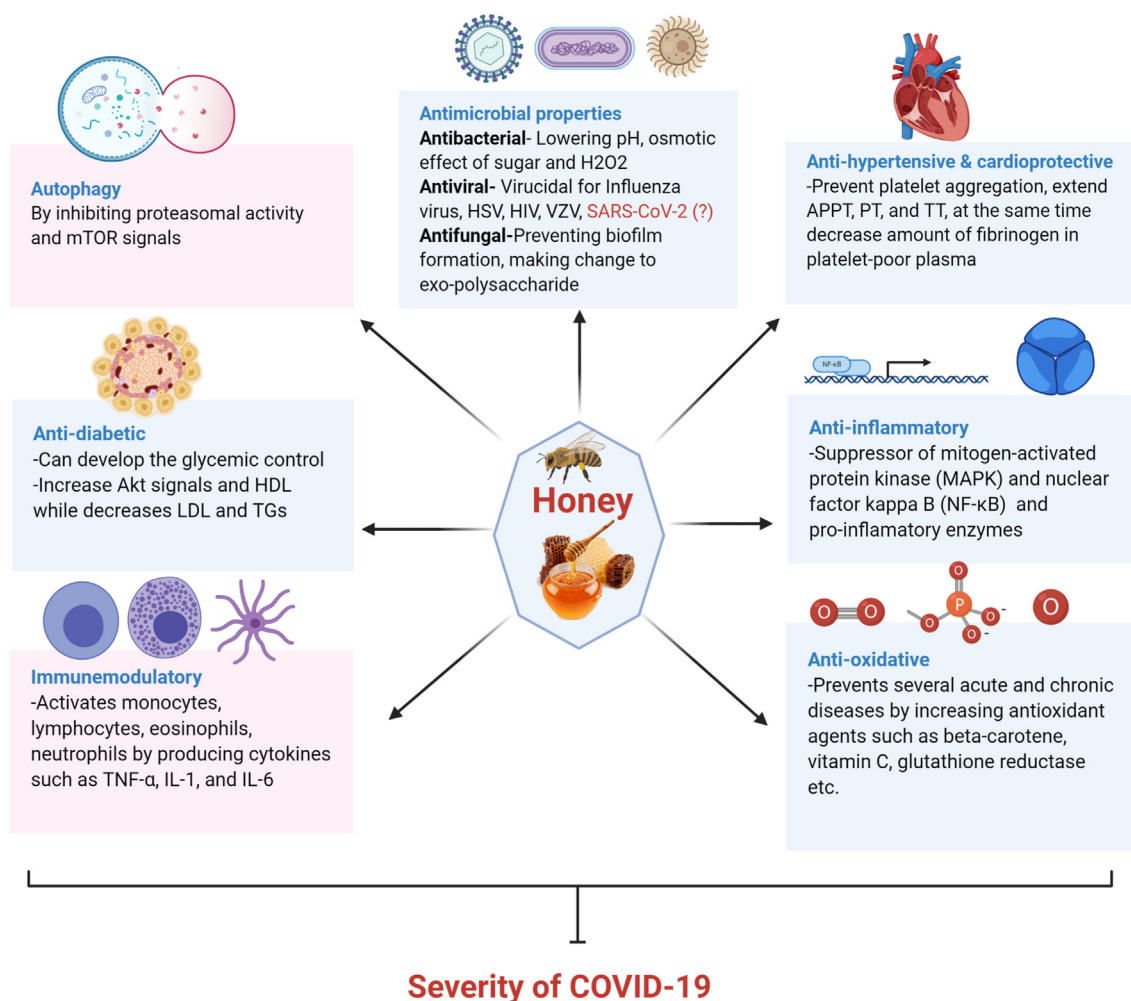
### 3.6.3. Antiviral properties

Infections and the formation of a wound are generally promoted by viral nature [89]. Due to the presence of several compounds such as MGO, copper, ascorbic acid, flavonoids, nitric oxide,  $H_2O_2$ , and its derivatives, honey can suppress viral growth by inhibiting viral replication and/or virucidal activity [25]. In some studies, honey has proved its potency against several RNA and DNA viruses i.e. influenza virus, varicella-zoster virus (VZV), rubella, herpes simplex virus (HSV), and has

proved that it can be a potential antiviral agent [18, 25, 90, 91]. Shahzad A *et al.*, 2012 demonstrated that both manuka and clover honey inhibit the VZV growth in human malignant melanoma cells (MeWo) but the exact mechanism has not been clarified [18]. Another study reported that MGO, one of the major compounds of manuka honey, showed sensitivity against both influenza B and influenza A viruses proving its virucidal activity [25, 92]. Moreover, the synergistic effect of manuka honey with the anti-influenza A viral drugs zanamivir and oseltamivir has been reported and MGO is useful for the drug-resistant virus isolates [25, 92]. Therefore, these studies suggested that enveloped viruses might be sensitive to the virucidal ingredients of honey (Figure 1).

## 4. Possible roles of honey against SARS-CoV-2 infection

SARS-CoV-2 is an enveloped and positive-sense single-stranded RNA virus [93]. As discussed above, several enveloped viruses might be killed by the virucidal ingredients of honey therefore it might also have a potent suppressive effect on SARS-CoV-2. Cell death is triggered by viral infection through draining lymphocytes which can be tackled by antioxidants. This proves that there is a relation between antiviral and antioxidant actions [94]. Honey has a broad spectrum of antioxidant effects as described, it can be said that honey might act as protective agents for patients infected with viruses like influenza or corona. But to prove this, clinical trials and proper experiments are needed. The SARS-CoV-2



**Figure 2.** Possible mechanisms involved in the pharmacological effects of honey on COVID-19. Honey activates the immune system, suppresses mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF- $\kappa$ B), and pro-inflammatory cytokines. It initiates autophagy by inhibiting proteasomal activity and mTOR signals. Besides, honey has anti-inflammatory, antimicrobial, and antidiabetic effects. As comorbidities increase the severity of SARS-CoV-2 infection, honey can be proved beneficial as well in developing comorbidities situation in SARS-CoV-2 infected individuals.

infected individual having a cytokine storm might be tackled with honey's antioxidant property along with increased IFN- $\gamma$  level [2, 48, 95]. Various micronutrients have been found to be essential for immunocompetence especially plant-derived polyphenols are very important to reduce the release of inflammatory cytokines [68]. In a case study, it has been observed that a polyphenol-rich environment effectively stimulated the activation of the local immune system and the mechanisms involved in tissue repair. As honey is rich in these bioactive compounds, it can be concluded that honey might have a possible role in alleviating the pain of SARS-CoV-2 infected patients [96]. Therefore, it is hypothesized that honey might be beneficial for SARS-CoV-2 infected patients through several major mechanisms such as direct virucidal properties, regulating/boosting host immune signaling pathways, and curing and/or improving comorbid conditions (Figures 1 and 2). Besides, based on the previous results of several studies, honey may act as a preventive agent against hyper-inflammation caused by SARS-CoV-2.

## 5. Current status and future directions

The COVID-19 has been discovered at the end of 2019 and currently, it is a pandemic threat of international concern. Currently, there are no targeted therapies effective against COVID-19. However, many vaccines are undergoing clinical trials and a couple of drugs are going through repurposing schemes [6]. A phase-3 clinical trial of natural honey for the treatment of COVID-19 has also been started as mentioned by the National Institute of Health [97]. It is already proved that honey plays a potential role against several enveloped viruses. Besides, honey acts as an antagonist of platelet-activating factor (PAF) which is involved in COVID-19 [98,99]. Therefore, we can say that honey may have a protective/beneficial effect on COVID-19. A lot of studies have been done to prove that honey is a potential natural medicine that can fight against several chronic diseases including diabetes, hypertension as well as autophagy. Also, honey can heal wound quickly by repairing damaged tissue, boosting up the immune system, and fight with the virus, bacteria as well as fungus. However, so far without some minor issues, there is no report of the serious harmful effect of honey on the human body. This review will be helpful to rethink the insights of possible potential therapeutic effects of honey in fighting against COVID-19 by strengthening the immune system, autophagy, anti-inflammatory, antioxidative, antimicrobial, antidiabetic, anti-hypertensive as well as cardioprotective effects (Figure 2). However, basic research on the effect of honey on SARS-CoV-2 replication and/or host immune system need to be investigated by *in vitro* and *in vivo* studies.

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### Author contribution statement

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The authors declare no conflict of interest.

## Additional information

No additional information is available for this paper.

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