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COVID-19: Honey as a Potential Adjuvant Treatment

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Abstract

Background: This article sums up the possible impact of honey in the amelioration of COVID-19 induced recognized pathogenesis. The pandemic due to the current outbreak of COVID-19 infected thousands of individuals round the globe. The indicator of COVID-19 infection suggests that increased inflammation, oxidation, and an overstressed immune reaction are key contributor of COVID-19 pathogenesis.

Method: This overstressed immune response leads to numerous cytokine production and consequently and led to the development of severe injury in lungs (ALI)/acute respiratory distress disorder and in some conditions becomes reason of death. Honey is formed when honeybees collect nectar from various, and then process it to form the honey. It is a natural remedy to reduce the incidence of various diseases, due to its potential anti-inflammatory, anti-oxidative, immune booster, antiviral, anti-diabetic, antimicrobial, anti-proliferative, cardiovascular, neurological and gastrointestinal diseases and anti-metastatic properties. Honey has been used for the curing of bronchial asthma, throat infections, tuberculosis, thirst, hiccups, fatigue, and hepatitis and also for the ALI/ARDS treatment caused by virus or any other pathogen.

Conclusion: Doctors recommend honey as a nutritional supplement to boost the immunity of patients under critical conditions, reducing oxidative stress, inflammation, viral infections that confirm that honey may be used to combat the infection and other complications caused by COVID-19 pandemic. There are many reports which reveal that honey may be used in bacterial and viral infections such as COVID 19, however, further experimental studies are required to validate these speculations.

Keywords: Honey; COVID-19; Pandemic, antiviral; Cytokines; Inflammation

Abbreviations: COIVID-19:Coronavrus Disease 2019; CoVs: Coronaviruses; SARS-CoV: Severe Acute Respiratory Syndrome Coronaviruses; MERS-CoV: Middle East Respiratory Syndrome Coronaviruses; (IL-1β: interleukin 1β, IFN-γ : interferon γ, IP-10: interferon-inducible protein 10, and MCP-1: Monocyte Chemoattractant Protein 1, IL-4: Interleukin-4, IL-10: Interleukin-10, ALI: Acute Lung Injury; ARDS: Respiratory Distress Syndrome; DDPH :1,1-diphenyl-2-picrylhydrazyl; FRAP: Ferric Reducing Antioxidant Power; ROS: Reactive Oxygen Species; ACE-2: Angiotensin-converting enzyme-2; APCs: Antigen-Presenting Cells; MAIT cells: Mucosal-Associated Invariant T Cells; MAPK: Mitogen-Activated Protein Kinase; NF-kB: Nuclear Factor Kappa-B; LOX2: Lipoxygenase 2; PTP1B: Protein Tyrosine Phosphatase 1B; IRS-1: Insulin Receptor Substrate Kinase-1; HDL: High Density Lipoprotein; TGs,: Triglycerides; VLDL: Very Low Density Lipoproteins; CVRI: Coronary Risk Index (CRI) and Cardiovascular; APTT: Prothrombin Time; PT: Prothrombin Time

Background

Coronaviruses (CoVs) are RNA viruses that the infect mankind as well as animals; the respiratory, gastrointestinal and nervous systems are primary targets of this infection [1]. Severe acute respiratory syndrome coronaviruses (SARS-CoV) as well as Middle East respiratory syndrome coronaviruses (MERS-CoV) are causative agents of infection and dangerous, and thousands of deaths have been reported in past two decades [2]. Presently the epidemics of SARS-CoV2 was initially seen in Wuhan city of China; this extremely infectious disease has stretched in entire China and later affected other countries as well [3]. However, various anti-viral drugs and corticosteroid therapy have been used to in the treatment/control of this contiguous disease and in various points mechanical respiratory support have been applied, but specific treatment for COVID-19 is still lacking [3].

Honey is discussed in secular and religious book for thousands of years. It is a natural gift produced from the nectar of flowers by honeybees, among the main pleasant and prized natural stuffs, honey is one the main natural stuff used by humans as time immemorial. Moreover, dietary supplement value, honey is also used as a alternative medicines as well as adjuvant therapy for various clinical situations including healing of wounds and cancer as well [4-5]. In traditional medicine system i.e., Unani and Ayurveda, honey possesses potential to treat various ailments such as bronchial asthma, throat infections, and tuberculosis, thirst, hiccups, hepatitis, and eye diseases [6]. Constituents of honey are reported to be used to enhance antioxidant [7], immunomodualtory [8], antimicrobial [9], anti-inflammatory [10], anti-proliferative [11], anticancer [4], and anti-metastatic effects. It has also been reported that honey is also used an alternative treatment to control diabetes, wound healing, cardiovascular diseases, asthma, neurological [12], and gastrointestinal diseases [13]. Further, the recent studies reported that honey is used as a natural remedy against the different diseases including respiratory, cardiovascular, diabetes mellitus, nervous and gastrointestinal diseases. In the present article, information on existing therapeutic properties of honey that signifies it as a supportive adjuvant in treating COVID-19 induced pneumonia, acute lung injury (ALI) and respiratory distress syndrome (ARDS) have been compiled and described [14].

COVID-19 Pathogenesis and the Justification for using Honey

A patient suffering from COVID-19 infection (infected by SARS-CoV2) complains fever; dry cough, myalgia, fatigue, and diarrhea, however, signs are age dependent. In various conditions, it leads to the development of the serious disease and finally results to the ALI/ARDS, respiratory failure, heart failure, sepsis, and abrupt cardiac arrest within short span of time [3,15]. Investigation of samples obtained from lung of the COVID-19 infected patients having moderate of infection, revealed swallowing, proteinaceous exudates having globules, infiltration of irregular inflammatory cells as well as configuration of temperate hyaline membrane [16]. However, post-mortem examination of a COVID-19 patients suffering from rigorous ARDS, infected lung samples observed mutual/ two-sided damage in alveoli is including edema, pneumocytes, desquamation and formation of hyaline membrane [17].

However, only some cases were reported in which these pathological were observed, both in SARS and MERS induced pneumonia the pathological characteristics resembles with each other [18]. Beta–coronavirus family comprises SARS-CoVs, MERS CoVs and SARS-COV2 [15]. Recent studies evidenced that 79.0% nucleotide sequences in SARS-CoV2 matches with SARS-CoV and 51.8% same to MERS-CoV [19], point towards towering genetic homology among SARS-CoV-2, MERS-CoV and SARS-CoV. SAR-CoV and MERS-CoV infected animals, reveals considerable increase in inflammation as well as immune response might stimulate a “cytokine storm”, epithelial cell and endothelial cell apoptosis, consequently leakage from vessels, both T cells as well as macrophages shows abnormal responses, therefore induces ALI/ARD or in some incidence leads to death [20].

Genetic background can be traced from the homology and pathogenic characteristics of the infected lung, it might be expected that excessive production of cytokines occurs in COVID-19 infected persons. Haematological examination of coronavirus infected patients shows considerable elevation in interleukin 1β (IL-1β), interferon γ (IFN-γ), interferon-inducible protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1), and IL-4 and IL-10 in comparison to the patients infected with SARS virus [21]. In coronavirus infected patients, the immune responses are suppressed having hypoalbuminemia, lymphopenia, neutropenia as well as reduced CD8+T cell percentage [3,15]. Current research findings reveals that many COVID-19 infected patients, even though tested negative for viral nucleic acid test, however in patients also shows prominent inflammation level. However, co-administration of antiviral therapies and certolizumab pegol (TNF blocker) in some clinical trials might be found beneficial for COVID-19 patients [21]. In general, results available in the literature specify that foremost setback found in COVID-19 patient is elevated rate of inflammation. Therefore, it was predicted that increased inflammation, undermined immune system, and higher production of cytokines plays important role in the COVID-19 infection [21]. During initial phases of coronaviruses illness, dendritic cells and epithelial cells are stimulated, huge number of pro-inflammatory cytokines and chemokines includes IL-1β, IL-2, IL-6, IL-8, both IFN-α/ β, tumor necrosis factor (TNF), CeC motif chemokines-3 (CCL3), CCL5, CCL2, and IP-10 etc, are greatly expressed. These all cytokines and chemokines are regulated through immune system [21]. Therefore, excessive production of all cytokines as well as chemokines that contributes to the progression of disease [22,23]. T-helper-2 produces IL-10 works as antiviral agent, but during the infection of coronaviruses causes noteworthy reduction in IL-10 [24,25]. Surprisingly COVID-19 infected patients sometimes showed significant increase in IL-10 level [21], but it is now clear that this is a characteristic of COVID-19 infection. Elevated inflammatory response might be promoting the programmed death or accidental death in infected cells, and re-energizes the inflammation, followed by elevation in blood vessel permeability as well as abrupt deposition of inflammatory monocytes, macrophages and neutrophils in alveoli of lungs [26]. This ferocious circle creates a condition of intensifying the uncontrolled immune response and production of cytokines and increases that leads to terrible consequences. Excessive production of cytokine is associated with pathogenesis of coronaviruses because it corresponds with the SARS CoV experimental models. In some other cases, disconnected IFN α/β receptors or decrease in inflammatory monocytes/macrophages leads a remarkable increase in the life span of coronaviruses host

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devoid any alteration in viral load [26,27]. These two situations advocate a prospective accelerating mechanism associated with CoV-induced ALI/ARDS instead of huge viral load. Therefore, it might be hypothesized that if COVID-19 causes the similar pathogenic condition, amelioration of the excessive cytokine production through specifically targeting key steps in the process hopefully could give better results [21].

Honey possesses various biologically important properties such as antiviral, anti-inflammatory, anti-oxidative, immune booster, antiviral, anti-diabetic, antimicrobial, anti-proliferative, cardiovascular, neurological, and gastrointestinal diseases and anti-metastatic properties, anti-inflammation, antioxidant and immune boosting. Honey used as home nutritional supplement and can be used to boost the immune system under critical care conditions in patient. Honey decreases oxidative stress, inflammation, viral infections, might be used against the COVID-19 pandemic respiratory infection. Previous findings, in addition to the present summarized, provide great support towards the rationale of honey for the treatment against viral diseases. Further, various properties of honey such as anti-inflammation, antioxidant, antiviral and immunity boosting supports its capability to ameliorate COVID 19 infection (Figure 1). Various research findings reported the use of honey against the viral infection and would also be effective against the COVID 19 infected patients. However, further experimental studies are required to validate these speculations.

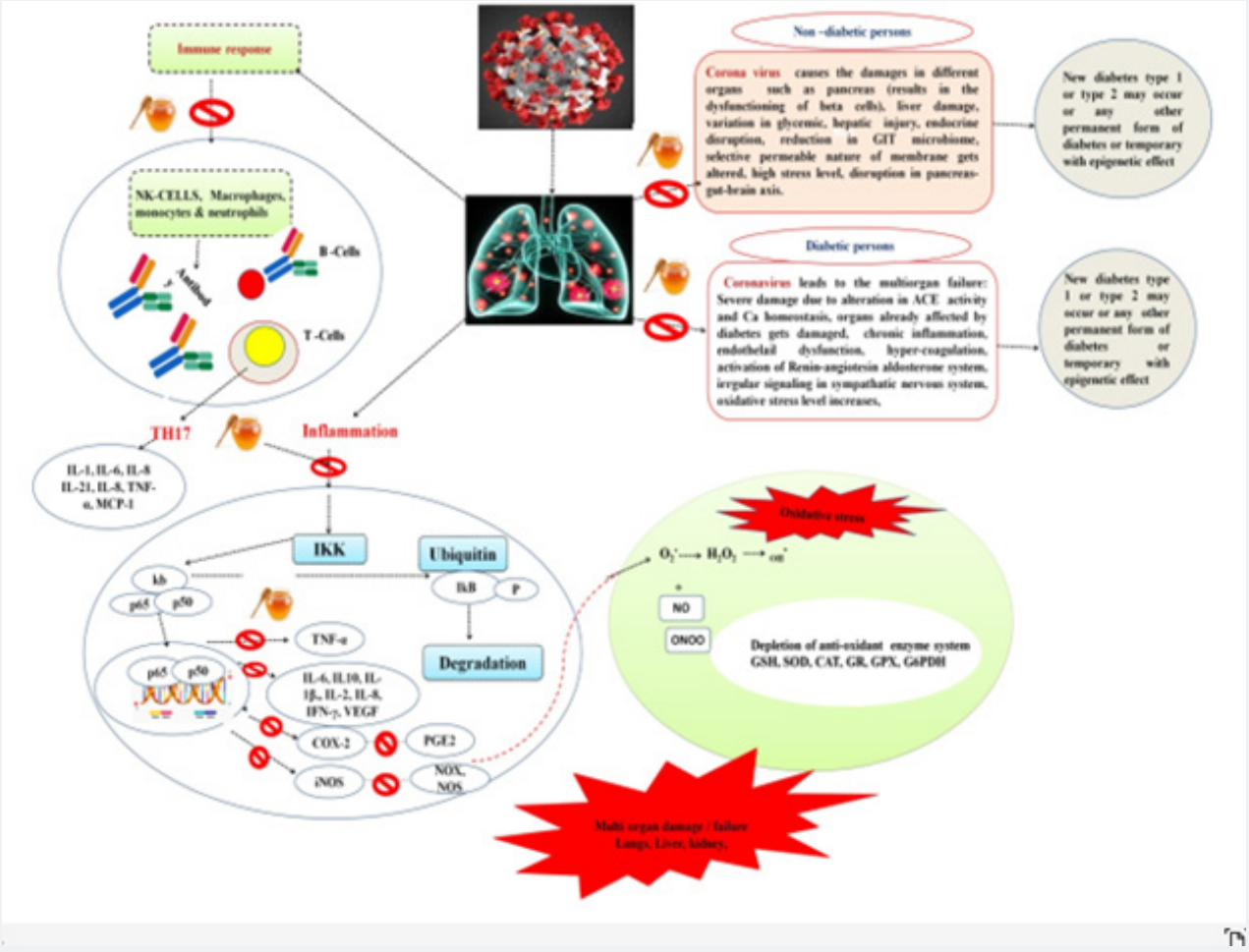

Figure 1: Various properties of honey such as anti-inflammation, antioxidant, antiviral and immunity boosting supports its capability to ameliorate COVID 19 infection.

Anti-Inflammatory Action of Honey

Iinflammation has been provokedbecause of the production of variouspro-inflammatory enzymes and cytokines (low molecular weight compounds or the enzymatic breakdown of tissues). Enzymes are mainly responsible for inflammation process includes cyclooxygenase-2 (COX-2), an isoform of cyclooxygenase (COX), which catalyses the transformation of arachidonic acid to prostaglandin. When inflammation is prolonged or excessive, it may prevent healing or even cause further damage. Drugs

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used for treatment of inflammation are having several shortfalls such as corticosteroids restrain growth of tissues and limits the immune-reaction, and the non-steroidal anti-inflammatory drugs are detrimental to cells, particularly for stomach [28-30]. Presently, various severe diseases like SARS-CoV2 can be elucidated due to the overproduction of initial response proinflammatory cytokines [tumour necrosis factor (TNF), IL-6, and IL-1β], called as the cytokine storm. It may increase the threat of vascular hyper-permeability; dysfunction in many organs and ultimately death can occur. Therefore, therapeutic investigations are mainly targeting the over production of cytokines with anti-cytokine therapies or immunomodulators [31-33]. In this context, honey may be a promising immune modulator as many research studies focus on the anti-inflammatory action of honey free from harmful side effect. Galangin and Chrysin present in honey reduce the inflammation aggravated by various chemicals. Many types of honey including manuka, gelam, Jelly bush and pasture honey has potential to activate or inhibits the secretion of some cytokines (tumor necrosis factor-α, interleukin-1β, interleukin-6) from human monocytes and macrophages, according to the type and severity of inflammation. Studies reported that during inflammatory reaction H2O2 generation stimulated by honey in turn activates the growth of fibroblasts and epithelial cells to revamp the damage caused by inflammation. This effective anti-inflammatory property of honey built it a novel therapeutic alternative to cure the respiratory infectious diseases [34-36] (Table 1).

Table 1: Showing the Anti-inflammatory activity of honey.

S. No.	Parameters	During Inflammation	Role of Honey	References
1.	Nitric oxide synthase (iNOS)	Activated	Honey controls the over-activation of iNOS pathway.	37-38
2.	Cyclooxygenase1 and cyclooxygenase-2 (COX-1& COX-2)	Activity Increases	Honey slows down the activation of COX- and COX-2.	38
3.	Prostaglandins' prostaglandin E2 (PGE2), thromboxane B2 (prostaglandin F2ά (PGF2á).	Level increases	Honey reduces the production of prostaglandin E2 (PGE2), thromboxane B2 (prostaglandin F2ά (PGF2á)	39
4.	During inflammation the level of pro and inflammatory cytokine level alters Tumor necrosis factor alpha (TNF), interleukin6 (IL6), and IL1β, by different types of honey. IL-6, and IL-1β],	Alters	1. Honey reduces the mediators of inflammatory reactions, including IL-6, IL-1β. Honey reduces the mediators of of inflammatory reaction such as TNF-α and COX-2 by weakening translocation of NF-κB into the nucleus. Therefore hinders the activation of the NF-κB pathway 2. Presence of polyphenols in honey (galangin and Chrysin) inhibits the inflammation. 3. Honey demonstrates antiinflammatory such as down reregulation of proinflammatory mediators, includes IL-1β and NF-KB.	38,40

Antioxidant Activity of Honey

Oxidative stress

Oxidative stress is the misbalance between oxidants and antioxidants that leads to cellular injuries. Oxidative stress contributes significantly in various ailments such as neurological disorder, cancer, aging and endocrine disorders [41]. Oxidative stress plays major role in the pathogenesis of invasion of virus through the induction of inflammatory damages which subsequently exaggerated immune response, general known as a cytokine storm. In cytokine storm numerous immune penetration and liberation of their triggering compounds or cytokines take place during cytokine storm [42]. Influenza viruses damages the lungs in presence of inflammatory signals are an example of this incident. This cytokine storm is occurred due to the generation of reactive oxygen species (ROS) which assists the influenza virus to cause infection [43]. Previous studies evidenced that macrophages and neutrophils are well known cells to induce generation of ROS in surplus quantities. This aggravated oxidative stress level contributes in the induction of pulmonary damages such as acute lung injury (ALI) and acute respiratory distress syndrome (ARD) [44]. There are different viruses such as coronaviruses, influenza viruses than could lead threatening lung injury and can be lethal from ARDS [45]. Elevated oxidative stress in ARDS occurs because of the rapid release of free radicals and other cytokines which consequently results in damages in cells, malfunctioning of organs, drastic hypoxemia, and un-regulated inflammation. These changes are very destructive to the alveolar-capillary barrier and leads to death [46]. Current studies reported that duration of SARS-CoV-2 infection is more than 14 days. It has been reported that in 93% patients (27 out of 29) revealed increased hypertensive C reactive protein (CRP) which is well recognized indicator for inflammation and oxidative stress [47].

Honey has been confirmed as an antioxidant potential by inhibiting different acute and severe diseases such as diseases associated with the inflammation, diabetes, cardiovascular and cancer [48]. In addition to this, honey is rich in various polyphenolics which shields the human body from the oxidative DNA damage in lymphocyte produced due to production of hydrogen peroxides [49]. Honey also contains various other

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compounds including sugars, proteins, amino acids, carotenes, organic acids, and other minute constituent which possesses the antioxidant activity for prolonged time [50]. Studies reported that intake of 1200mg/kg honey enhances the antioxidants including glutathione reductase, β-carotene, vitamin c in normal humans [51]. The prospective mechanism might be that these polyphenolic compound and other minor components are associated with hydroxyl, chelation of metal ions, neutralization of super-oxides, and donation of hydrogen ions (H+), sequestration of free radicals [52].

It has been speculated from the previous findings that excessive oxidation or oxidative stress (ROS) is likely involved inCOVID-19. "Oxidative stress" leads inequality between the generation of free radicals and activity of antioxidant enzymatic system [53,54]. Honey is a natural dietary antioxidant agent that can help to inhibit the deterioration caused by oxidizing agent (O2, OH^-, superoxide etc.). Free radicals are produced during the various metabolic processes inside the organism and leads damage in cells, physiological dysfunctions and mutation in the confirmation of DNA. Antioxidant property of honey helps to prevent the synthesis of mutagens, skin ulcers, gastrointestinal disorders, inflammatory processes etc. [55-58]. Honey possesses the antioxidant due to the presence of phenolic acid, polyphenols, Enzymes (catalase, glucose-oxidase, peroxidase), flavonoids (such as chrysin, pinocembrin, hesperetin, quercetin, apigenin, galangin, and kaempferol), Maillard reaction products and peptides, ascorbic acid, phenolic acids (such as ferulic, ellagic, caffeic, and p-coumaric acids), tocopherols, vitamins, amino acid (proline) etc might be used to reduce the oxidative burden [59-63].

It has been confirmed that honey is used as an antioxidant because its consumption prevents various acute and chronic diseases such as inflammatory, allergic, thrombotic, diabetes, cardiovascular, cancer and others [64]. These properties have been proved and measured through antiradical activity whereas ORAC assay (Oxygen Radical Absorbance Capacity), DDPH scavenging assay (1,1-diphenyl-2-picrylhydrazyl) as well as FRAP assay (Ferric Reducing Antioxidant Power) [65]. In honey not only phenolic acids and flavonoids exerts antioxidant activity but presence of sugars, proteins, amino acids, carotenes, organic acids, and other minor components present in honey contributes to antioxidant activity for a longer period of time [66,67]. Intake of 1.2g/kg honey elevates amount and activity of antioxidant agents including beta-carotene, vitamin C, and glutathione reductase in healthy humans [68]. Honey causes sequestration of free radicals, donates hydrogen ions, chelates metal ions, flavonoids steel hydroxyl and superoxide free radicals [69-75].

Immune Responses and Inflammation

Innate and adaptive immunity in human beings could protect them against SARS-CoV2, however, vaccine has been developed, but due to higher population density, it is not possible to vaccinate all the human beings simultaneously. Moreover, in some vaccinated cases it does not properly prevent the attack, or it shows other side defects. Angiotensin-converting enzyme-2 (ACE-2), a receptor of SARS-CoV2 has been found on surfaces of different cells such as lungs, heart, kidney, and arteries [76,77]. During the attack of SARS-CoV on healthy cells stimulates various cells in the human body including macrophages, natural killer cells, T-cells, B-cells, neutrophils, and dendritic cells. These antigen-presenting cells (APCs) that execute the death of SARS-CoV2 [78,79]. Toll-like receptors (TLRs) which are also generally identified as pathogen recognition receptors are suspected to be a helper for SARS-CoV2 entry [72]. Stimulation of immune responsive cells takes place when a virus invades in the body. APC for SARS-CoV2 inhibits the virus and provides co-stimulation for specific B and T cells multiplication through human leucocytes antigen (HLA) [80]. This response is recognized by T-cell receptor (TCR) which finally turns T-cells (CD4) and cytotoxic T cells (CD8). CD8 cell directly hits the virus infected cells whereas CD4 stimulates various immune responsive cells including CD8 T cells, natural killer (NK) cells, and T memory cells. Cytokines triggers the differentiation of B-cells generated from helper T-cells. The T-cell generated IL-2 are involved in the differentiation of ERK1/2-prompted plasma cells. Plasma B cells and memory B cells makes direct connection with SARS-CoV2 and the production of antigen-specific antibodies by plasma B cells kills the SARS-CoV2. Certain B cells could produce memory and thereby makes a protective shield for the future attack of the virus [82]. Recent studies reported that the adaptive immune response has ability to attack on the structural proteins of virus such as spike glycoprotein, envelope protein, and others, specifies that humoral immunity (antibodies) could protect from SARS-CoV2 attack [85]. B and T lymphocyte provides innate and adaptive immunity to fight against the SARS-CoV2 activated by dendritic cells [86]. Cytotoxic T cells (CD8+ cells) secretes IFNs and granzymes stimulates the NK cells to eliminate SARS-CoV2 by inducing cytotoxicity in virus infected epithelial cells hence inducing programmed death (apoptosis) [88,89]. Neutrophils and macrophages secrete cytokines and chemokines enhances the CRP level such as c3a and c5a that possesses antiviral activity [90,91].

Honey could stimulate T-lymphocytes, B-lymphocytes, and neutrophils which finally generates cytokines including interleukin-1 (IL-1) and interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) [92]. Moreover, honey enhances the levels of IFN-γ and IFN-γ receptor 1 (IFNGR1) in breast cancer in rats [97,98]. Because IFN-γ possesses affinity towards the viral spike glycoprotein, nucleocapsid protein, and membrane protein, it could help in attacking SARS-CoV2 [93,94]. Honey has ability in the proliferation of B- and T-cells;this reveals that it contributes in the induction of adaptive immune responses against SARS-CoV2 infection. Murosaki et al. (2002) It has been reported that honey contain nigerose (a sugar derivative) acts as immune stimulator [99]. Different types of honey such as Manuka, Royal jelly, pasture, and Nigerian Jungle honey has ability to enhance the

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moderators of immune reaction including TNF-α, IL-1β, IL-6, and albumin 1 production [100]. It has been studied that consumption of increases the levels of ascorbic acid, glutathione reductase, minerals, and immune cells such as eosinophils, monocytes, and lymphocytes in human body. However, on the other hand honey reduces the immunoglobulin E, ferritin and enzymes such as creatinine kinase, aspartate transaminase, lactate dehydrogenase, and alanine transaminase. Honey also reduces the activities of various hepatic enzymes and muscle and fasting blood sugar level [101]. According to the findings of these studies, it may be inferred that honey has ability to protect against SARS-CoV2, however deep and proper *in vitro* and *in vivo* experimentation is required. Anti-inflammatory efficiency of honey has been studied as it shows its potential has been studied under cell culture model, in animal model and in clinical trials [102]. Recently it has been studied that Manuka honey contains MGO, it effectively recognizes the invasion of bacteria by generating mucosal-associated invariant T cells (MAIT cells). These MAIT cells very efficiently control the different range of immune responses such as antimicrobial defense. It has been studied that a common inflammatory marker including mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-kB) are able to induce other inflammatory factors including IL-1β, IL-6, IL-10, lipoxygenase 2 (LOX2), cyclooxygenase-2 (COX-2), CRP, and TNF-α [103]. It has been reported that honey has potency to inhibit these two inflammatory markers. Various constituent of honey present in honey are having inhibitory effect on pro-inflammatory enzymes, activates the growth of fibroblast and epithelial cells and also activates the process of repairing of injury which could prove that honey might be a potential adjuvant treatment [104].

Immunomodulatory Effects of Honey

As we reviewed the literature, we found that when SARS-CoV2 virus invades in body, it leads to the dysfunctional immune responses such as disproportionate permeation of monocytes, macrophages and T-cells, cytokine storm, pulmonary oedema, pneumonia, uncontrollable swelling and multiorgan failure. It enhances the disease progression rapidly. Clinical reports of COVID-19 suggested a lower count of neutrophils, lymphocytes and CD8+ T cells in peripheral blood [31]. Whereas, strong immuno-reaction, initial stage of inflammation drags the virus specific T cells towards the position of infection, at the infection site T-cells eradicate the infected cells prior to the spread of virus. These strong immune respondent individuals can block viral infection by the Neutralizing antibodies and then alveolar macrophage identifies neutralized viruses and apoptotic cells. Phagocytises takes place to clear these viruses and cells. All these processes together such as removal of virus and least damage to lung, leads to the revival stage. However, in some conditions, Viruses (Corona viruses) try to reduce ability of the native immune system, the primary-line immunological reaction of individual, through decreasing the interferon response and, simultaneously replicate and undisturbed at high rate spread in the body. Altogether, these processes can cause severe damage in the body of an individual due to the dysfunctional immune responses [105,106]. The present scenario of Chinese, Italians and history of SARS-CoV have expressed individual by weaker immune reaction, especially the aged ones with comorbidity, can acquire an irregular uncontrolled inflammatory response with severe and diffused lung injury, which even becomes cause of death [107]. Honey is having complex immunomodualtory activity due to the presence of various bioactive components depends on the origin of honey from different regions. Recently, use of pleiotropic therapeutic agents having various functions, honey is one of the best natural pleiotropic agents having immune modulating activity. Now a days more attention has been given towards the honey to explore its immune boosting activity and is used to boost the immune system of patients to fight against different pathogens. Honey and its by-products are having potential to activates or slow down the production of various cytokines including tumor necrosis factor-α, interleukin-1β, interleukin-6 from human monocytes and macrophages relying on rate of inflammation. It also enhances the number of cells in bone marrow, the number of white blood cells and immune potentiating (CD4 lymphocytes, CD8 lymphocytes and Interferon-gamma). Similarly, honey either decreases or increases the generation of reactive oxygen species from neutrophils, also relies on microenvironment of inflammation [108].

Autophagy

Commonly autophagy is known as “self-eating” is a greatly conserved catabolic processes that orders a cell to eliminate long-lived proteins, lipids, discarded or injured cells, and impurities, therefore, helps the cells to recover normal health state of cells, this process if mediated by autophagosome generation and it merges with lysosomes to eliminate the selected molecule [109,110]. Hence, for fight against a life-threatening virus like SARAS-CoV2, needs a powerful immune system is requires which engages various immune responses such as autophagy [111]. Lethal viruses such as a SARS-CoV2 has potential to reduces the autophagic function, however, various compounds are able to induce autophagy to fight against these kinds of viruses, hence, this type of immune reaction can be used as a toll to fight against the COVID-19 [112,113]. Consumption of natural honey along with flavonoids (kaempferol, catechin, and quercetin) and polyphenolic acid (caffeic acid and gallic acid), evidences anticancer activity. Quercetin is one of the well-known flavonoid present in honey suppresses the proteasomalactivity, mTOR signals and supports the considerable autophagy [114].

Diabetes

Diabetes and uncontrolled glucose level are few major causes behind the death because of the infection via different viruses such as influenza A (H1N1), SARS-CoV, and MERS-CoV [115]. It has evidenced that along with SARS-CoV2 infection, hyperglycaemia has been detected as reason for death in more than half of the

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patients [116]. In 2003, it has been proved that SARS-CoV shows destruction in pancreatic islet cells via hyperglycaemia [117]. Clinical trials conducted on streptozotocin induced diabetes in rats showed that honey reverses the diabetic impediments; Honey reduces the blood glucose level in type-2-diabetes mellitus [118]. Honey contributes to the decreases the glucose, fructosamine, and glycosylated haemoglobin serum concentration [119]. This hyperglycaemic effect of honey by inhibits the protein tyrosine phosphatase 1B (PTP1B). Simultaneously, it also modulates the changes in serum lipid profiles and expression of the insulin receptors in liver cells [120]. Honey and quercetin increase the expression level of protein kinase B (PKB) also known as AKT, whereas decreasing the phosphorylation of insulin receptor substrate kinase 1 (IRS-1) at serine, NF-κB, and MAPK [138]. Honey considerably elevates the high-density lipoprotein (HDL) and decreases glucose level, TGs, VLDL, non-HDL cholesterol, coronary risk index (CRI) and cardiovascular (CVRI) in diabetic rats [121]. Administration of 1000mg/kg of honey considerably controls glucose level and hyperlipidemia [121] (Table 2).

Table 2: Potential of honey against various diseases.

Disease	Cell Line or Species	Compound Dose and Exposure Time	Effect	Reference
Chronic Asthma	Rabbit (Cytoplasm BAL fluid) + ovalbumin (OVA)	Honey (inhalation dosage form), (25 and 50%) for 5days	Decreases Number of inflammatory cells Decreases penetration of inflammatory cells Decreases thickness of the airways epithelial and mucosal regions	[111]
Chronic Asthma	BALB/c mouse+(OVA)	Chrysin, (100mg/kg) for 8 weeks	Decreases numbers of total inflammatory cells Decreases macrophages Decreases lymphocytes Decreases neutrophils Decreases serum total IgE Decreases IL-4,IL-13, IFN-γ Decreases α-SMA protein expression Akt and ERK1/2 phosphorylation inhibition	[163]
Asthma	Mouse+conalbumin	Honey, (650mg/kg for 18 days	Increases peripheral blood neutrophils	[164]
Allergic asthma	Mouse +(OVA)	Gelam honey (10, 40, and 80%) for 28 days	Decreases infiltration of inflammatory cells Decreases thickening of epithelial cells of airways Decreases number of mast cells	[165]
Pleurisy and lung injury	Rat (lung tissue)+ carrageenam	Chrysin (20 and 40 mg/kg)	Decreases MPO Decreases β-glucuronidase levels Decreases TNF-α and IL-1β levels Decreases MDA Increases GSH Increases nuclear NRF2 deposition Increases HO-1 expression Inhibits the ICAM-1 expression Suppresses expression of VCAM1	[167]
Allergic inflammation	Human mast cells (HMC-1) Rat basophilic leukemia IgE cells (RBL-2H3)	Chrysin (0.1,1, 10μM)	Cell viability----No effect Inhibits Calcium mobilization Inhibits TNF-α Inhibits IL-4 Inhibits IL-6 Decreases IkB α breakdown Decreases p65 NF-Kb translocation Decreases NF-kB luciferase activity Decreases caspases-1 activation	[168]
	Mouse+mast cell degranulator (compound 48/80)	(1-100mg/kg)	Inhibits Serum histamine release	
	Rat +anti DNP IgE		Decreases PCA reaction	
Inflammation	Murine macrophage cell line (RAW 264.7)+LPS/IFN-γ (or iNOS inhibitor 1400W)	Gelam honey (0.039-5mg/ml) for 24	Increases viability	[169]

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			Suppresses DHR-123 oxidation	
			Inhibits synthesis of peroxynitrite	
	Rat+LPS	(50mg/kg or 500mg/kg)	Suppresses the production of Peroxynitrite	
Inflammation	(RAW 264.7)+LPS	Manuka honey, (3 and 8mg/ml) for 24 h	Increases viability of cells Decreases rate of apoptosis Increases expression of caspases-3 Increases foci migration and wound closure activity Increases basal OCR values Decreases basal ECAR values Increases p-AMPK protein expression	[170]
Inflammation	(RAW 264.7)+LPS	Manuka honey (3 and 8mg/ml for 24h	Decreases ROS production Decreases deposition of NO Increases GSH content Decreases TBARS level and carbonyl content Decreases OGGI expression Increases GR, GPx, GST, CAT, SOD, Increases expression of Nrf2, Keap1 protein levels, HO-1 expression Inhibits over expression of iNOS, NF-Kb, TNF-α, IL-1β, Increases iNOS protein expression Increases TLR-4, TNF-α, IL-6, IL-10, IL-1β protein expression	[170]
Myocardial Ischemia	Rat +isoproterenol	Tualang Honey 3g/kg for 45 days	Increases GR, GPx, GST, CAT, SOD, Decreases TBARS level decreases lipid peroxidation	[170]
Type 2 diabetes	Pancreatic Hamster cells	Gelam honey and quercetin (20,40,60, and 80µg/ml)	Decreases phosphorylated JNK Decreases IKK-β Decreases IRS-1 Decreases TNF-α, IL-6, IL-10, IL-1β Increases p-Akt Decrease ROS	[170]
	(HIT-T15)+glucose	(20,40,60 and 80µg)		
Type 2 diabetes	Rat +streptozotocin	Chrysin (20, 40, and 80mg/kg)	Increases SOD, CAT and GST Decreases MDA	[171]
Dyslipidemia	Rat+diet	Honey (Malicia (1000ml/kg) for 35 days	Increases SOD activity	[172]

The persistent hyperglycemic condition leads auto-oxidation of glucose which leads to the production of reactive oxygen species which causes cellular damages, deterioration of membrane, disintegration, protein glycation, liver and kidney damages. Honey has been proved as scavenger of reactive oxygen species, decreases glucose level and ameliorates oxidative stress [122,123]. Administration of honey given to the diabetic rats decreases oxidative stress in kidneys. However, there is bit contradiction as honey is sweet and contains huge quantity of sugars; hence it could not have any hypoglycaemia effect. The interesting fact is that presence of fructose and oligosaccharides exerts hypoglycaemia effect [124]. Moreover, reduction in oxidative stress and glucose, supplementation of honey decreases the prevalence of various metabolic damages such as reduction in hepatic transaminases, triglycerides and glycosylated hemoglobin (HbA1c) as well as increased HDL cholesterol [125,126] serum fructosamine, creatinine, bilirubin. It has been reported that honey increases serum insulin level whereas as it decreases concentration of glucose and frustosamine in diabetic rats [127]. Therefore, on the basis of these findings it can be concluded that honey can be used as an adjuvant SARS-CoV-2 induced diabetic complications by ameliorating the glucose level and decreases oxidative stress.

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Cardiovascular Disorder and Hypertension

Recent studies reported that among 150 positive cases of COVID-19, 7% died due to myocarditis with circulatory collapse, whereas 33% myocarditis causes severe outcome [126]. It has been confirmed that honey is used to treat cardiovascular diseases as well as short-term antiarrhythmic effects [127]. These cardiovascular benefits of honey may be due to the presence of flavonoids such as anthocyanins and vitamins such as niacin. Therefore, presence of anthocyanins and niacin makes honey a potential therapeutic remedy against the cardiovascular diseases [127]. Some studies reported that honey stops the platelet aggregation, extend partial prothrombin time (APTT), prothrombin time (PT), thrombin time (TT) whereas it could reduce the quantity of fibrinogen in platelet-poor plasma [128] (Table 2).

Microbial Infections

From the ancient times honey is considered is used as a remedy by human beings for the treatment of various diseases. This ancient method of therapy has been now taken under consideration because recent allopathic therapeutics is failing to control the diseases. In 2100-2000 BC honey was used as a drug and ointment, however later on Aristotle (384-322 BC) explained that honey as "good as a salve for sore eyes and wounds" [129]. Current studies it has been reported that COVID-19 subjects are susceptible to develop secondary bacterial coinfections including bacterial pneumonia and sepsis which is a fetal threat [130]. Viral infection along with other secondary infections leads to death [98]. Bacterial coinfections range between 12-19% in N1H1 and pneumonia infected persons along with other serious ailments [131]. Neutrophils-lymphocyte ratio (NLR) is considered as a specific marker of inflammation. This reveals that bacterial infection constitutes pneumonia. In addition to severe SARS-CoV-2-infected subjects were found increased NLR. This is the feature of a potentially crucial situation [132,133]. These antimicrobial activities of honey is due to the presence of various compounds such as higher concentrations of sugars (decreased water activity), low pH, production of hydrogen peroxide, proteinaceous compounds, or other unidentified constituents of honey [134,135]. Nitric oxide and prostaglandin may also explain some of the activities promoted by honey.

Antiviral Activity of Honey

COVID-19 is a highly communicable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), currently, erupted in Wuhan, China and spreaded in the world. Genomic analysis of this virus showed that SARS-CoV2 is phylogenetically related by severe acute respiratory syndrome-like (SARS-like) bat viruses. Therefore, it has been assumed that COVID-19 is originated from an animal host (bat) and gets directly transferred from one human being to another. The reason behind the transmission of virus from one person to another and then into the human population, because touch with infected person, open coughing, sneezing, respiratory droplets or aerosols. These aerosols invade into the human body (lungs) by inhaling the environmental air contaminated with virus particles [136]. Till date not any antiviral drug has been approved against the COVID-19. The strong immune system of a healthy person responds actively against the coronavirus and abolishes the infection. However, imbalanced immune responses, as such, results impairment in pulmonary gas exchange of an infected person [137,138]. Literature suggests that COVID-19 and influenza viruses' infection are having similar signs and symptoms i.e., both viruses induce respiratory disease, which might cause broad range of respiratory illness from asymptomatic to chronic disease (pneumonia and severe acute respiratory syndrome) and in many instances led to death. The mode of transmission is same in both the viruses (coughing and sneezing), whereas there are some variations reported among the two viruses such as speed of transmission, secondary infection generated by infected person and mortality rate taken into consideration [140]. P8Hydrogen peroxide (H_2O_2) is one of the components in honey that contributes to the enhancement of antimicrobial activity [141]. Hydrogen peroxide has potential to inactivate the human coronavirus 229E (HCoV-229E) and influenza viruses (A and B) [142]. In addition to this H_2O_2 inhibits the infection potential of bird viruses such as H5N1, IBV, and Newcastle disease virus (NDV) [143,144]. Recent study reported that H_2O_2 has promising virucidal activity against the feline callicivirus (FCV), which causes infection in domestic cats [142].

Currently scientific community are trying to explore the therapeutic applications of honey to treat different health issues. Various studies suggested that different kinds of honey (including manuka honey & sidr honey) possess the significant antiviral activities against certain viruses like influenza virus, rubella virus, herpes simplex Virus, varicella zoster virus [143,144]. In manuka honey a potent antiviral a-ketoaldehyde compound methylglyoxal (MGO) is present which contributes significantly antiviral activity against the influenza virus. Mechanism of honey and its components, such as methylglyoxal (MGO) was virucidal against different viral diseases. Moreover, the combined activity of honey and NA (neuraminidase) inhibitors was also found to be significant against the inhibition of influenza virus replication. Various research studies reported that combination of anti-influenza drugs with manuka honey resulted in synergistic activity against the influenza virus [145,146]. Another study revealed that combination of hydrolic extract of some medicinal plants plus lemon juice and honey has been observed efficient for common flu and cold virus infections [147]. Presently, a number of clinical trials are running out on different combinations with multiple antiviral drugs, plant extracts and honey. However, not any significant recommendation comes out till now [148,149] (Table 3).

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Table 3: Showing the anti-viral activities of honey.

S. No.	Type of Virus	Effect of Honey	Reference
1.	Type 1 Herpes Simplex Virus	1. 5% of honey has been found to be having greater inhibitory effect on HSV-1.	[126]
		2. Honey ameliorates by inhibiting the secretion of prostaglandins at the lesion site.	
2.	Influenza viruses (H1N1, H5N1 & H7N9)	1. Inhibits the replication of virus. (Rutin, chyrosin, α-ketoaldhyde compound	[127-128]
		2. Jim Duke's Viroxymel (An oxymel a mixture of honey, water, vinegar, and spice, boiled to a syrup")	
3.	Rubella virus	Inhibits rubella virus infection	[128]
4.	Ebola virus	Inhibits the replicative activity of Virus	[128]
5.	Virus EC50	Manuka and clover honeys	[128]
6.	Varicella zoster virus.	Inhibits the spreading of virus	[128]
7.	HSV, syncytial virus, poliovirus, and Sindbis virus.	Quercetin and rutin present in the honey shows antiviral activity	[129]
8.	Asymptomatic Human Immunodeficiency Virus (HIV) patients	Reduces the count of CD4 cells, decreases viral load	[130]

Honey and Cough

After extensive literature review, it was observed that cough is a most common symptom among patients of COVID-19 [150]. Cough is common among all people especially in children having multi-factorial etio-pathological causes. It may be caused by bacteria or viral infections or existence of detrimental allergen in the respiratory tract. Infection in upper respiratory tract (IURTs) is one of the main prevalent causes of coughing among children. Infection in bronchial mucosa occurs by pathogenic agent either physical or chemical mediator, its counter back with an inflammation, that leads to the excessive production of inflammatory cells and mediators. Since antiquity, honey has been recommended as a potential treatment for mucus and dry cough symptoms. In some cases, it may find to be even superior over other medicines used for cough treatment [151]. Honey possesses antimicrobial and wound-healing potency, due to which honey is commonly used to treat cough and sore throat. World Health Organization, recommended honey as a treatment option for cough and sore throat. Although various common drugs are used in the treatment of cough are diphen-hydramine and dextromethorphan. It has been reported in the literature that dextromethorphan and honey obtained from buckwheat reveals equal efficacy against the treatment of cough, coadministration of Ananas comosus extract plus honey and honey alone showed improvement in the incidence of irritative cough [152-154].

Other Safety and Supportive Properties of Honey

The coordinated vascular endothelial barrier is important for the regulation of immune functions in the alveoli. Chronic inflammation as well as immune response causes apoptosis in epithelial and endothelial cells, and also elevate formation of VEGF, which initiates accumulation of serum in tissues or spaces and infiltration of immune cells. Majority of COVID-19 affected patients have history of diabetes, irregular lipid metabolism, increased blood pressure, obesity and pulmonary conditions. In case of inflammation mitogen-activated protein kinase (MAPK) and nuclear factor kappa-β (NF-κB) pathways becomes stimulated, which in turn accelerates various essential pro-inflammatory markers such as cyclo-oxygenase-2 (COX-2), lipoxygenase-2 (LOX-2), C-reactive protein (CRP), interleukins (IL-1, IL-6 and IL-10) and tumour necrosis factor alpha cytokine (TNF-α) [157]. Experimental studies suggested that honey modulates the atherosclerosis induced inflammation by inhibiting the proinflammatory markers including cytokines, COX-2, CRP and TNF-α [10-12], production of reactive oxygen species. Moreover, honey decreases the cytokine (TNF-α, IL-1β and IL-10) and NO levels but increaseshemeoxygenase-1 levels. Honey suppresses thrombin-induced ROS generation by the phagocytes. Therefore, the use of honey in COVID-19 patients ameriolerate respiratory infections and also improves general health and prevents patients' wellbeing and potential complications.

Effect of Honey on Cytokines Level in Human Body

Coronaviruses possesses very quick replication frequency, permeation of inflammatory cells as well as quick elevated responses to inflammatory proteins such as cytokines. Several reports reveals that the large secretion of interleukin (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10; CXCL10), MCP-1 (CCl2), MIP-1A (CCL3), IL-1β, IL-1ra, IL-2R, IL-6, IL-8 (CXCL8), IL-17, interferon (IFN)-γ and GM-CSF (granulocyte macrophage colony-stimulating factor) through severe COVID-19 infections Interferon (IFN)-γ, tumor necrosis factor (TNF) and IL-1 are having considerable importance in

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COVID-19 patients (Table 2). A defective immune reaction causing overproduction of pro- inflammatory cytokines and this cytokine overproduction further leads to the failure of many organs such as cardiac, hepatic and renal systems [155].

A number of investigators have reported that honey may function as an immune modulator having pro-inflammatory as well as anti-inflammatory properties, because honey stimulates or inhibit the secretion of various factors like cytokines, ROS, and MMP-9. Some major components of honey such as flavonoids may be having inhibitory action on cytokine production. Inhibition of inflammatory mediator reactions is one of the major steps in inflammation control. During healing stage of infection honey enhances the secretion of proinflammatory cytokines. In contrast to the above statement under controlled inflammation, honey helps to reduce the elevated levels of proinflammatory cytokines. During severe swelling, NF-kB activates and controls the transcription of IL-1b, IL-6, iNOS, COX-2 and TNF-a. Various studies reported that Gelam honey slow down the overproduction of pro inflammatory mediators e.g., TNF α and COX 2, by inhibiting NF κB and its translocation into the nucleus. Activation of NF κB plays very important role in the inflammation [156-162] (Table 2).

Conclusion

Coronavirus pandemic has posed threat to the entire world, it not only causes respiratory problems, but also increases the chance of other complications such diabetes, cardiac arrest, liver and kidney failure. Nature has enriched honey with various bioactive components having therapeutic potencies to combat the pathogenesis of various diseases. Among such properties immune modulation, antiviral, anti-inflammatory properties are very prominent in honey. COVID-19 that mainly causes immune suppression, inflammation and many other secondary complications and ultimately failure of organs, honey might act as potential therapeutic adjuvant to overcome the pathogenesis of COVID-19.

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