REVIEW

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Honey as Miracle Therapy for Covid-19: Literature Study

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ABSTRACT

Due to their capacity to reduce acute inflammation by increasing the immune response, honey and its constituents are gaining attention as an efficient natural therapeutic. Studies have suggested that it may be able to treat a variety of chronic illnesses and conditions, including as bacterial and fungal infections, cardiac issues, diabetes, hypertension, and abnormalities of the lungs and heart. More significantly, honey has proven to have virucidal effects on a number of enveloped viruses, including the varicella-zoster virus, herpes simplex, influenza virus, and HIV.

Honey may help patients with COVID-19, a disorder brought on by the SARS-CoV-2 enveloped virus, by boosting the host's immune system, treating comorbid conditions, and engaging in antiviral activities. Additionally, patients with COVID-19 are presently participating in a clinical trial of honey. We've attempted to condense the possible advantages of honey and its components in this review in terms of antibacterial properties, some chronic illnesses, and the host's immune system. Therefore, we have made an effort to develop a relationship with honey in order to treat COVID-19. In light of the COVID-19 epidemic, this review will be useful in reevaluating our understanding of the potential therapeutic benefits of honey. However, more in vitro and in vivo research is required to determine the effects of honey on SARS-CoV-2 replication and/or the host's immune system.

Keywords: Honey, COVID-19, SARS-CoV-2, Immune response, Viral infection.
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INTRODUCTION

The 2019 global pandemic coronavirus disease (COVID-19) is a major global health risk. By the end of 2019, Hubei province, China's Wuhan metropolis, is anticipated to have confirmed the presence of the SARS-CoV-2 virus. The disease has quickly expanded to about 210 nations throughout the world due to the ease with which it is spreadable. The WHO deemed it a global pandemic on March 11, 2020 for this reason. As of June 17, 2020, there are 8,322,910 people who have this viral illness, and 447,959 people have died as a result. Before the COVID-19 pandemic, two other viruses belonging to the same genus caused a severe infection in the form of pneumonia. With the exception of comorbid illnesses, younger persons with robust immune systems are typically thought to be unaffected by these three viruses, but the elderly and immunocompromised can suffer fatal effects. The liver, heart, and lungs are only a few of the physiological systems where SARS-CoV-2 can easily cause infection. The fact that sufficient therapy has not yet been implemented is concerning. Consequently, methods that boost immunity may be successful in reducing COVID-19-related problems.[1,2]

The use of chemotherapy treatments has a number of drawbacks, such as drug resistance and side effects, which make us consider other options, such as natural products, to lessen unavoidable negative effects. Plants and their numerous compounds have long been used by humans as remedies for a wide range of illnesses.[3,4] Researchers have become interested in honey recently since it can be used to successfully treat these problems with chemotherapeutic medicines. Sugars, organic acids, amino acids, phenolic compounds, vitamins, and minerals are just a few of the substances found in honey. This is the rationale behind the extensive research on honey's antioxidant capacity using both animal and human models. It has proven effective in a number of medicinal qualities, such as immunostimulant, antibacterial, anti-inflammatory, wound healing, antiulcer, antidiabetic, anticancer, antiviral, and antifungal.[5,6] In experimental animals, it lowers the levels of triglycerides (TG), very low-density lipoproteins (VLDL), and systolic blood pressure. When honey is consumed daily, acute reduced respiratory distress symptoms have been observed.[7]

Although this has not yet been empirically verified, a recent in silico technique demonstrated that honey can block SARS-CoV-2 proteases and that certain of its components may be able to bind SARS-CoV-2 protease. The replication of SARS-CoV-2 may be aided by the alteration of methylglyoxal (MGO).[8] Manuka honey has an ingredient called MGO that can stop the spread of an enveloped virus.[9] Honey may be a therapeutic option to manage and/or treat COVID-19, although this has not yet been researched. We attempted to establish a correlation between honey for the treatment of COVID-19 by summarizing all the promising positive properties of honey and its constituents in the context of antimicrobial activity, multiple chronic diseases, and host immunological signaling pathways.

METHODS

Using PubMed, Scopus, and Google, a bibliographic search was conducted to find all original research articles written in English that discussed the protective properties of honey against different pathophysiological disorders. Before April 2021, a variety of terms, including honey, inflammation, oxidative stress, bacterial infection, viral infection, etc., were included in the search.

RESULTS AND DISCUSSIONS

Pharmacological effects of honey

Numerous research have looked at how honey and its active ingredient(s) affect various physiological systems in people. Its antibacterial properties have also been used in a number of in vivo or in vitro research. The precise mechanism underlying honey's antiviral protective properties has not yet been sufficiently established. The results of recent investigations on the defenses of honey against bacterial, fungal, and viral infections as well as immunological dysfunction, anti-inflammatory effects, diabetes, hyperglycemia, and cardiovascular problems have been compiled and reviewed.[10]

Oxidative

Cell damage is caused by oxidative stress, which is an imbalance between oxidative products and antioxidants. Numerous illness states, including neurological disorders, cancer, aging, and endocrine diseases, are influenced by oxidative stress. By causing inflammatory damage that subsequently magnifies the immune response, often known as a cytokine storm, it also plays a significant part in the pathophysiology of virus invasion. During the cytokine storm, immune cells infiltrate more deeply and release more of their activating molecules, or cytokines. An illustration of this occurrence is when influenza viruses harm the lungs in the presence of inflammatory signals. This is accomplished by generating reactive oxygen species (ROS), which aid in the infection process of the influenza virus.[11]

ROS are known to be produced in substantial amounts by neutrophils and macrophages. Acute lung injury (ALI), acute respiratory distress syndrome, and other types of lung injury are all influenced by elevated levels of oxidative stress (ARDS). Numerous viruses, including coronaviruses and influenza viruses, can result in deadly lung injury and ARDS. Rapid free radical and cytokine release causes increased oxidative stress in ARDS, which leads to cell death, organ failure, severe hypoxia, and uncontrollable inflammation. All of these can result in mortality because they harm the alveolar-capillary barrier. According to a recent study, SARS-CoV-2 infection takes more than 14 days to spread.[12]

The ability of honey to fight off both acute and chronic illnesses like cancer, diabetes, heart disease, and inflammatory diseases has been proven. Additionally, the phenolic acids in honey shield people against the oxidative DNA damage in lymphocytes brought on by hydrogen peroxide. Several other substances (such as sugars, proteins, amino acids, carotenes, organic acids, and other minor components) contained in honey have demonstrated antioxidant activity for a longer period of time in addition to phenolic acids and flavonoids. In healthy human subjects, consumption of 1200 mg/kg of honey can boost both levels of antioxidants such glutathione reductase, beta-carotene, and vitamin C.[13] Although the exact mechanism underlying the actions of the flavonoid substrate for hydroxyl, metal ion chelation, superoxide radical actions, hydrogen donation, and free radical sequestration are still unknown.[14] Although the antioxidant properties of honey have been systematically demonstrated, there are still a number of undiscovered characteristics.

Immune responses and inflammation

Since there is no available treatment for SARS-CoV-2, human innate and adaptive immune systems may act as barriers. SARS-receptor, CoV-2's angiotensin converting enzyme-2 (ACE-2), has been discovered on the cell surfaces of many organs, including the lungs, heart, kidneys, and arteries. This virus normally activates a variety of cells in the human body, including macrophages, natural killer cells, T cells, B cells, neutrophils, and dendritic cells as it tries to seize healthy cells. These are the traditional antigen-presenting cells (APC) that kill the SARS-CoV-2 virus. SARS-CoV-2 entrance is thought to be aided by toll-like receptors (TLRs), which are also frequently known as pathogen recognition receptor.[15] The body's immune system is stimulated when a virus enters the body. APCs for SARS-CoV-2 occupy the virus and use human leukocyte antigen to costimulate specific B and T cell proliferation (HLA). The T-cell receptor (TCR), which develops into helper T cells (CD4 +) and cytotoxic T cells (CD8 +), serves as a marker for this. While CD4 + activates multiple immune cells, including CD8 + T cells, natural killer (NK) cells, and memory T cells, CD8 + directly destroys virus-infected cells. Helper T cell-produced cytokines encourage B cell differentiation. The differentiation of plasma cells mediated by ERK1 and ERK2 is aided by the IL-2 that T cells secrete. The memory B cell forms a direct connection to SARS-CoV-2 along with the plasma B cell. 2. SARS-CoV-2 is killed by plasma B cell-produced antigen-specific antibodies with the aid of this binding. Some B cells have the capacity to develop memories, which act as a defense mechanism against future invasions.[16]

A recent study found that viral structural components such spike glycoprotein, envelope protein, and others can be targeted by the adaptive immune response, suggesting that humoral immunity (antibodies) may be a key factor in SARS-CoV-2 defense. B and T lymphocytes that have been activated by dendritic cells produce both innate and adaptive protection against SARS-CoV-2. By exhibiting cytotoxicity toward virus-infected epithelial cells and inducing apoptosis, IFNs and granzymes released by cytotoxic T cells (CD8 + cells) can stimulate NK cells to destroy SARS-CoV-2. Neutrophils and macrophages both create cytokines and chemokines, which can raise levels of CRP with antiviral activity at the c3a and c5a subunits.[17]

Honey has the ability to activate neutrophils, B lymphocytes, and T lymphocytes, which leads to the production of cytokines such tumor necrosis factor (TNF) and interleukin-1 (IL-1) and IL-6. In rat breast cancer, honey additionally raises serum levels of IFN-γ and IFN-receptor 1 (IFNGR1). IFN- may aid in the attack on SARS-CoV-2 since it has an affinity for viral spike glycoprotein, nucleocapsid protein, and membrane protein. On B and T cells, honey exerts a mitotic (cell division) action. This demonstrates that it might be involved in triggering an immune response to protect against SARS-CoV-2 infection. Nigerosa, a honey-derived sugar, is said to have immunostimulatory properties.[18] The production of TNF-α, IL-1, IL-6, and apalbumin 1 can be increased by a number of honeys, including Manuka, Royal Jelly, Grass, and Nigerian Jungle Honey. By raising levels of ascorbic acid, glutathione reductase, minerals, and immunological cells including eosinophils, monocytes, and lymphocytes in people, honey has positive effects. Immunoglobulin E, ferritin, and a number of other enzymes, such as alanine transaminase, aspartate transaminase, lactate dehydrogenase, and creatinine kinase, are all decreased at the same time. These pieces of data imply that honey may be able to provide protection against SARS-CoV-2, but adequate confirmation through in vitro and in vivo trials is required. It also decreases levels of various enzymes in the liver and muscles as well as fasting blood sugar levels.

Honey's anti-inflammatory properties have been investigated, and it has demonstrated its effectiveness in cell culture models, animal models, and clinical studies. MGO, a component of Manuka honey, has been demonstrated in a recent study to efficiently detect bacterial invasion by generating invariant mucosa-associated T lymphocytes (MAIT cells). It is well recognized that MAIT cells have the capacity to efficiently control a variety of immune responses, including antimicrobial defense. MGO dramatically boosted MAIT cells in vitro in human monolayer cell.[19]

Commonly recognized inflammatory markers like nuclear factor kappa B (NF-B) and mitogen-activated protein kinase (MAPK) can trigger additional inflammatory factors including IL-1, IL-6, IL-10, lipoxygenase 2 (LOX-2), cyclooxygenase-2 (COX-2), PCR, and TNF-α. According to one study, honey may be the ideal suppressant for these two indicators. Numerous honey constituents reduce pro-inflammatory enzymes and promote damage repair, which suggests that honey may be a potential disease-fighting agent.[20]

Autophagy

Autophagy, also referred to as "autodegradation," is a highly conserved catabolic process that controls a cell's ability to get rid of long-lasting proteins, lipids, unwanted or damaged cells, and impurities. This process is aided by the formation of autophagosomes, which fuse with lysosomes to break down the target molecule. As a result, the human body requires a powerful immune system that includes numerous immunological responses, including autophagy, in order to combat lethal viruses like SARS-CoV-2. Deadly viruses like SARS-CoV-2 can inhibit autophagy, but a number of substances can activate it to combat this sort of virus, therefore this immune response can be viewed as a tool to combat COVID-19.[21]

The anticancer flavonoids kaempferol, catechin, and quercetin, as well as the polyphenolic acids caffeic acid and gallic acid, are added to natural honey. Quercetin, one of the flavonoids found in honey, has been shown to suppress proteasomal activity and mTOR signaling and to significantly increase autophagy.[22]

Diabetes

In a clinical research, honey was administered to streptozotocin-induced diabetic rats to assess the antidiabetic impact. In this study, type 2 diabetes mellitus patients' glucose levels were shown to be lower. It has been demonstrated that honey helps to reduce blood sugar, fructosamine, and serum glycosylated hemoglobin. Honey can exhibit glycemic control by inhibiting protein tyrosine phosphatase 1B. (PTP1B). Additionally, it may encourage the modification of liver cell insulin receptor expression and serum lipid profiles. Honey and quercetin can decrease the phosphorylation of insulin receptor 1 (IRS-1) substrate in serine, NF- B and MAPK while increasing the degree of expression of protein kinase B (PKB), better known as Akt. In diabetic rats, honey dramatically decreased hyperglycemia, TG, VLDL, non-HDL cholesterol, coronary risk index (CRI), and cardiovascular risk index (CVRI), and raised high-density lipoprotein (HDL). It can develop glycemic control and hyperlipidemia considerably when given at a dose of 1000 mg per kg.[23] As a result, it is possible to forecast that honey will have a hypoglycemic impact.

Cardiovascular disorder and hypertension

A study of 150 COVID-19 positive people found that myocarditis contributed 33 percent to the final severe result, while it accounted for 7% of deaths with circulatory collapse. Both honey's short-term antiarrhythmic properties and its long-term cardiovascular advantages have been demonstrated. A lower incidence of cardiovascular disease is frequently linked to flavonoids, such as anthocyanins, and vitamins, such as niacin (B3). Honey is a potential treatment for cardiovascular disorders because it contains both. Another study found that honey can reduce the quantity of fibrinogen in platelet-poor plasma, prolong partial prothrombin time (APTT), prothrombin time (PT), and thrombin time (TT), and inhibit platelet aggregation.[24]

Microbial Infections

Honey is regarded as an old cure that has been utilized by humans for a very long period. Due to the ineffectiveness of current treatment medicines, researchers are now looking into this ancient healing procedure. Since 2100–2000 BC, honey has been used as a medicine and an ointment, and Aristotle (384–322 BC) noted that honey was "excellent as an ointment for painful eyes and sores." According to recent studies, COVID-19 patients are more likely to acquire secondary bacterial co-infections such bacterial pneumonia and sepsis, which pose a risk to unborn children. The contribution of viral infection and secondary infection to death are strikingly comparable. Between 12 and 19 percent of those with h1N1 influenza and pneumonia who also have other serious illnesses frequently have bacterial coinfections.[25]

Antibacterial Properties

A favorable environment created by honey encourages quick recovery. Additionally, honey's antibacterial qualities can hasten the healing process by increasing pro-inflammatory cytokines including TNF-, IL-1, and IL-6 by creating white blood cells (WBCs). By reducing pH, the osmotic impact of sugars, and levels of H2O2, honey can operate as an antibacterial agent, according to a number of pieces of data. All of these are effective against harmful bacteria like *E. coli, Staphylococcus aureus, Streptococcus typhi*, and coagulase-negative *Streptococcus*. The control of urease by MGO and its precursor dihydroxyacetone could prevent bacterial development (DHA). However, Wang et al. revealed that honey's antibacterial activity was manifested by directly destroying bacterial cells in order to release their bactericidal components and by interfering with bacterial quorum (QS) sensing.[26]

Antifungal

Honey's fungicidal ability has been proven effective against the fungi *Saccharomyces*. chrysogenum, *A. niger, M. gypseum, A. flavus, and A. niger*. Honey alters the exopolysaccharide and can stop the growth of biofilms. Honey manipulates the fungal cell membrane to ensure cell surface depletion in biofilms, which results in biofilm death.[27]

Antiviral properties

Several RNA and DNA viruses, including the influenza virus, varicella-zoster virus (VZV), rubella, and herpes simplex virus (HSV), have been demonstrated to be sensitive to honey in some investigations, suggesting that honey may have antiviral potential. Manuka and clover honey have been shown to prevent the growth of VZV in human malignant melanoma (MeWo) cells by Shahzad A et al. (2012), albeit the precise mechanism has not been elucidated. One of the main components of manuka honey, MGO, was found in another investigation to have virucidal activity against influenza A and B viruses. In addition, manuka honey has been shown to work in synergy with the antiviral medications A zanamivir and oseltamivir to treat drug-resistant virus isolates.[28]

Possible Roles of Honey Against SARS-CoV-2 Infection

SARS-CoV-2 is a positive-sense, single-stranded RNA virus with an envelope. As was previously mentioned, honey contains virucidal compounds that have the potential to destroy a variety of enveloped viruses. As a result, honey may also have a potent suppressive impact on SARS-CoV-2. Antioxidants can prevent cell death that is brought on by viral infection through lymphocyte discharge. This demonstrates a connection between antioxidant and antiviral effects. According to the description of honey's wide range of antioxidant properties, it can be assumed that honey may work as a protective agent for those who have viruses like the flu or coronavirus. But valid clinical trials and research are required to demonstrate this. The antioxidant properties of honey along with an increase in IFN- might be used to treat the SARS-CoV-2 sick person who is experiencing a cytokine storm. Numerous micronutrients, particularly plant-derived polyphenols, which play a key role in limiting the release of pro-inflammatory cytokines, have been discovered to be crucial for immunocompetence. An environment rich in polyphenols was found to successfully increase the local immune system's activation as well as the mechanisms responsible for tissue regeneration in a case study. Since honey contains a lot of these bioactive substances, it can be inferred that honey may help SARS-CoV-2 patients who are experiencing pain.[29] As a result, it is speculated that honey may help SARS-CoV-2 infected patients via a number of major mechanisms, including direct virucidal capabilities and control of/ stimulation of host immunological signaling pathways and treating comorbid conditions, as well as improving them. Additionally, honey can inhibit hyper-inflammatory brought on by SARS-CoV-2, according to earlier findings of various research.

CONCLUSION

A possible role for honey in the fight against several enveloped viruses has already been demonstrated. Honey also inhibits platelet activating factor (PAF), which is connected to COVID-19. Therefore, we can conclude that honey may protect or benefit COVID-19. Numerous research have been conducted to demonstrate the promise of honey as a natural treatment for a number of chronic conditions, including diabetes, hypertension, and autophagy. Additionally, honey helps speed up wound healing by rebuilding injured tissue, enhancing immunological function, and warding off germs, fungus, and viruses. However, there haven't been any reports of honey having a major negative impact on the human body, save from a few small problems. To support this review, additional research is therefore required.

AUTHOR CONTRIBUTION

All authors contributed to the idea of this review article, the writing of the article, its critical revision, its final approval, and the data collecting.

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CONFLICT OF INTEREST

There is no conflict of interest for this manuscript.

ETHICAL CONSIDERATION

None.

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