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Article

Impact of supplemental vitamins and natural honey for treatment of COVID-19: A review

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The main aim of the paper is to assess whether vitamin C, vitamin D, and natural honey can be administered in the course of the COVID-19 pandemic for promising in line methods with recent evidence. Both systematic literature and clinical trial identification were conducted by searching various databases. A total 58 articles and 29 clinical trials were selected wherein 11 for vitamin C, 16 for vitamin D, and 2 for natural honey were identified for analysis. The high doses of vitamin C (i.e. '200 mg/kg body weight/day, divided into 4 doses') has been found to reduce COVID-19 lung damage, various flu infections. Additionally, the high doses of vitamin C can shorten around 7.8% stay in the intensive care unit. At the same time, vitamin D can effectively protect from lung injury and acute respiratory infections whereas vitamin D deficiency severely affects 75% of the institutionalized people (serum 25(OH) D < 25 nmol/L). Meanwhile, natural honey which contains proteins (0.1–0.4%); ash (0.2%); water (15–17%) has potential antiviral effects and the ability to improve immunity. Therefore, the administration of vitamins and honey is the promising evidence-based approach for reducing fatalities, saving lives, and bringing the COVID-19 pandemic to a rapid end. It is believed that the utilization of vitamin C, vitamin D, and natural honey with the current treatment may be effective in treating COVID-19-caused fatal complications such as pneumonia. Therefore, high-level clinical studies are required on COVID-19 to administrate the effects of vitamins and natural honey.

Keywords: Vitamin C. Vitamin D. Natural honey. Lung damage. Antiviral effects.

INTRODUCTION

COVID-19 infection causes several effect with predominantly respiratory effects ranging from common cold to extreme acute respiratory syndrome (Yin, Wunderink, 2018). Due to human-to-human interaction and animal-to-human interaction, CoV transmission is a zoonotic pathogen (Li *et al*., 2020). Multiple epidemics had occurred during the last two decades. Between 2002 and 2012, about 800 and 860 people died from Severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS-CoV), respectively (Bhagavathula et al., 2020). After eight years of the MERS-CoV epidemic, the latest outbreak of the novel coronavirus COVID-19 was first identified in Wuhan, Hubei province, China, which has become a global pandemic and public health concern (Lai *et al*., 2020). The World Health Organization (WHO) announced COVID-19 as a public health emergency of international concern (PHEIC) on January 30, 2020 (Eurosurveillance Editorial Team, 2020). More than 13,616,593 cases and 585,727 deaths have been recroded in 213 countries, regions or

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territories, until 17 July 2020 (20:00 CET) (World Health Organization, 2020).

The most important and fatal clinical symptom for the COVID-19 disease was characterized as pneumonia (Hançer, Yilmaz, Yilmaz, 2020). Pneumonia causes hypoxia and leads to respiratory failure, radiologically there is a change in X-ray and CT scan. Furthermore, cytokine storm occurs among pneumonia patients. A recent study reported involvement of both lung and a clear frosted glass in radiological analysis among 98 percent patients. In addition, the complications of COVID-19 were classified as secondary infection (10 percent) and Acute Respiratory Distress Syndrome (ARDS) (29 percent). Recently, various researchers worked related to COVID-19 treatment approach (Ali, Alharbi, 2020; Cheng, 2020; Rabby, 2020; Rabby *et al.*, 2020; Rabby, and Hossain, 2020; Ilie, Stefanescu, Smith, 2020; El-Sayed *et al.*, 2020; Abbas *et al.*, 2021; Abrishami *et al.*, 2021; Gao *et al.*, 2021; Kumar *et al.*, 2021; Zhang *et al.*, 2021; Zhao *et al.*, 2021) wherein the implementation of supplemental vitamins and natural honey for the treatment of COVID-19 were identified.

Most studies on vitamin and natural honey only focused on either a specific type of vitamin or natural honey. Moreover, clinical trials on vitamin and natural honey were not summarized in literature yet. This study fulfills the literature gaps by combining literature and clinical trials regarding vitamin C, vitamin D, and natural honey. Apart from these, readers of this review will be highly benefited as the review highlighted the significance of supplemental vitamins such as vitamin C, vitamin D, and natural honey to tackle the COVID-19 pandemic.

MATERIAL AND METHODS

Two search strings literature search and clinical trial search were conducted. PubMed, Google Scholar, and Scopus database were considered for literature search by using keywords "vitamin D"; "vitamin C, "natural honey", "COVID-19 and vitamin C"; "COVID-19 and vitamin D" as well as "COVID-19 and natural honey". In the meantime, ''Clinicaltrial.gov'' and ''clinicaltrialsregister.eu'' websites were considered for clinical trials by using keywords "COVID-19 and vitamin C"; "COVID-19 and vitamin D" as well as "COVID-19 and natural honey". Published articles and registered clinical trials until 2 June 2020 were considered as inclusion criteria. For the review, letter to the editor, correspondence, and short communication were not included. For clinical trials, inactive or terminated trials were not included for analysis. Meanwhile, for both cases, English language instruction was considered as inclusion criteria.

RESULTS AND DISCUSSION

After the literature search, 58 potential articles were selected based on the inclusion criteria to summarize the available literature. Meanwhile, from clinical trial database, 29 registered clinical trials were identified to analysis wherein 11 for vitamin C, 16 for vitamin D and 2 for natural honey.

Vitamin C

Vitamin C is known as 'ascorbic acid', which is a powerful antioxidant. Unstable compounds known as free radicals in living things are neutralized by antioxidants (Carr, Maggini, 2017). Antioxidants allow the regeneration of the cell itself or prevent unstable compounds to create cellular damage. Oxygen is a necessary molecule without which no living creature can survive. The cell can be damaged due to reactive oxygen species whenever an incomplete reduction of oxygen molecules occurs. If free the radicals and reactive oxygen species are created extensively in cells, it is known as "oxidative stress" (Güleşci, Aygül, 2016). Due to oxygen stress, the mitochondrial function can be affected and structural changes can be noticed in the mitochondrial membrane (Cai *et al.*, 2015). These structural changes can prevent the antiviral signal transduction, which reduces the intensity of the antiviral immune response (Koshiba *et al.*, 2011). A balance can be noticed between the antioxidants defense system of organisms known as scavengers and free radicals in the organisms that formed by physiological conditions. Due to free radicles, balance shifts occur in the disease process that causes a serious increment of oxidative stress. Moreover, COVID-19 infection is a serious oxidative stress source

for the organism. Therefore, antioxidant substances, i.e. vitamin C, which have been identified to be effective in correcting the integrity of mitochondria, are necessary for reducing oxidative stress in order to prevent cell damage (Kim *et al.*, 2016).

Receiving vitamin C affects the immune system in various ways. Antioxidant activity causes a reduction of inflammation by providing immune function improvement (Rogovskii, 2017). Meanwhile, severely infected people require larger vitamin C dosages to counteract the elevated immune response and metabolic demand associated with COVID-19 (Farjana *et al.*, 2020). COVID-19 can increase the stress reaction in the body that causes fatal consequences and severe symptoms. Due to the stress response, glucocorticoid releases excessively, which creates the production of ROS and stops the systemic suppression of innate antiviral immune response. The efficient role of vitamin C in stress and stress-related glucocorticoid release was identified in a study that remarkably reduced cell activity of natural killer and changed the T-cells balance (Cai *et al.*, 2015). Figure 1 represents the possible therapeutic efficacy of supplemental vitamin C. Improvement of iron absorption, collagen synthesis, immune function, cardio-vascular and anti-oxidant are some possible therapeutic efficacies of supplemental vitamin C (Elste *et al.*, 2017).

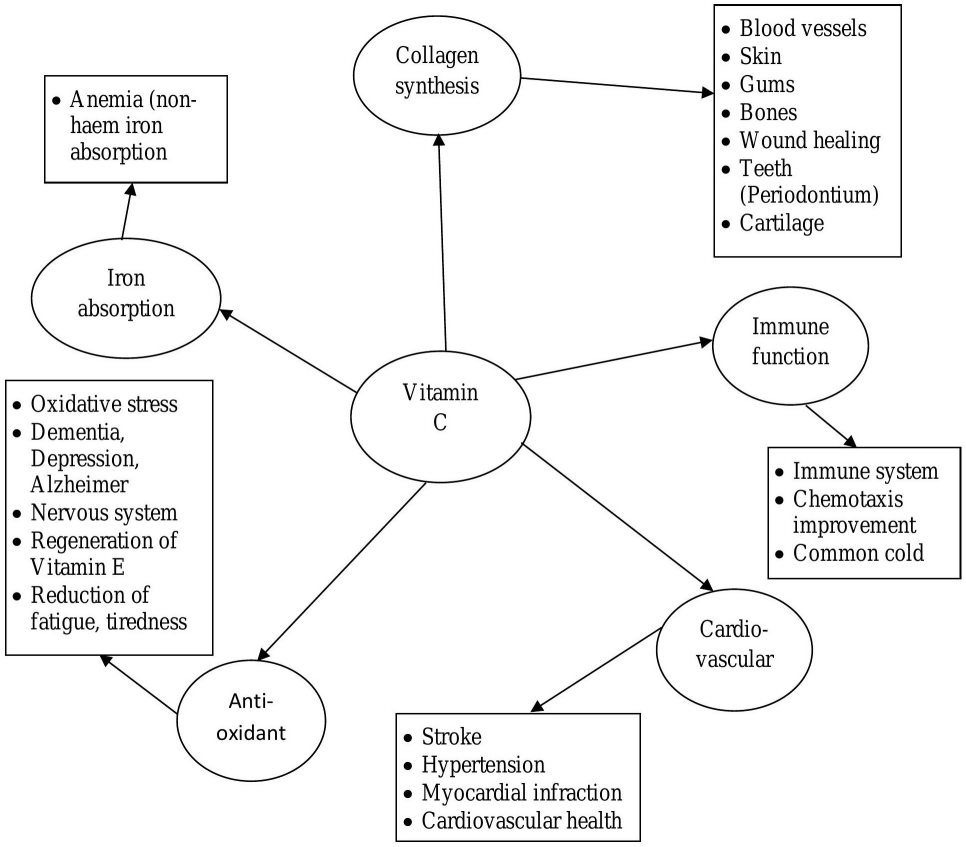

FIGURE 1 - Possible therapeutic efficacy of supplemental vitamin C (Elste *et al.*, 2017).

Till date, no particular antiviral drug or vaccine has been identified against coronavirus diseases. Different experimental applications, isolation, and symptomatic therapy were discovered for controlling the disease. Vitamin C has become an essential element in the cellular antioxidant system and it is beneficial for critical care management (Liu, Gao, Ci, 2019; Nabzdyk, Bittner, 2018).

Cytokine storms can be visible not only in viral infections but also in bacterial infections (Fowler *et al*., 2017) and the oxidative stress can increase due to cytokine storms through a non-particular and usual pathway. Meanwhile, it has been noticed that honey extract Camelyn can be non-cytotoxic, harmless, and seems to have antiviral activity against COVID-19 (Kalediene *et al*., 2021). Since a large antioxidant dose can perceive the prevention and management of oxidative stress, this process can be compatible with COVID-19 along with intravenous high-dose vitamin C depending upon three of the previous clinical studies outcome that involved 146 patients with sepsis (Li, 2018). Different high-dose intravenous vitamin C infusions (i.e. '200 mg/kg body weight/day, divided into 4 doses') can shorten around 7.8% stay in the intensive care unit (Hemilä, Chalker, 2019) along with a noticeable reduction in mortality rate (Marik *et al*., 2017). High dose vitamin C was utilized clinically for various decades and the safety of the regimen (1.5 g/kg body weight) has already been stated in a document without any notable adverse events. As effective antiviral drugs and vaccine development take time, currently, available agents, i.e. vitamin C and other antioxidants may help the mitigation of COVID-19 associated ARDS (Cheng, 2020). COVID-19 and similar types of viruses target the alveolar epithelium in order to cause the formation and increase reactive oxygen species in the vascular space. It induces the death of 4 cells and damages tight connection by disabling the activity of the sodium pump in the epithelium. Virally infected 'alveolar epithelial cells' produce cytokines for activating other 'capillary endothelial cells' and leads to neutrophil infiltration. According to one of the case studies, a patient who was 20 years old developed ARDS because of the viral infection and received treatment of 'extracorporeal membrane oxygenation' in intensive care, along with high-dose intravenous vitamin C treatment [(24 h 200 mg/kg) the total daily dose of vitamin C was divided equally into four doses and infused every 6 h] (Hançer, Yilmaz, Yilmaz, 2020). In that case, a noticeable improvement had observed from the first day of the administration of intravenous vitamin C, and after long-term ARDS, the patient rapidly recovered without fibroproliferative sequelae. Additionally, pulmonary edema could be eliminated with the help of vitamin C because it shortens the damage of alveolar epithelial cells by preventing the deposition and activation of neutrophils (Li, 2018). For mechanical ventilation time of a patient, administration of larger than the daily dose is suggested which can ultimately improve lung function. Recently, several studies related to vitamin C found beneficial effect.

Most of the vitamin C related trials are interventional, especially the 'phase 2' type. Moreover, the majority of the trials are conducting in the United States. In the observed trials, vitamin C has been utilized to access the reduction of organ dysfunction, the increment of lymphocytes activity, change of hospital mortality, the occurrence of adverse events, calculation of mechanical ventilation free days, investigation of clinical efficacy and safety, length of hospital stay, prevention of COVID-19 symptoms, reduction of COVID-19 symptoms, and protection from COVID-19. Table I represents trials related to vitamin C.

TABLE I - Trials related to vitamin C

NCT Number	Study Type	Estimated Enrollment	Primary Outcome/ Objective	Age (year)	Start Date	Completion Date	Status	Country
NCT04401150	Interventional (Phase 3)	800	Death or persistent organ dysfunction; Number of intensive care unit-free days; Persistent organ dysfunction-free days in ICU	>=18	Jun-20	Jan-22	Not yet recruiting	Canada
NCT04363216	Interventional (Phase 2)	66	Clinical Improvement; Patient status upgraded to ICU level	>=18	May-20	May-21	Not yet recruiting	United States
NCT04323514	Interventional	500	In-hospital mortality; PCR levels; Lactate clearance; Hospital stay	Child, Adult	March 13, 2020	March 13, 2021	Recruiting	Italy

TABLE I - Trials related to vitamin C

NCT Number	Study Type	Estimated Enrollment	Primary Outcome/ Objective	Age (year)	Start Date	Completion Date	Status	Country
NCT04357782	Interventional (Phase 1, Phase 2)	20	Incidence of adverse events; Incidence of serious adverse reactions; Incidence of adverse reactions	>=18 and <=99	April 16, 2020	August 1, 2020	Recruiting	United States
NCT04264533	Interventional (Phase 2)	140	Ventilation-free days; 28-days mortality; ICU length of stay	>=18	February 14, 2020	September 30, 2020	Recruiting	China
NCT04344184	Interventional (Phase 2)	200	Number of ventilator-free days; All-cause-mortality; Acute-inflammation-free days; Organ-failure-free days	>=18	Jun-20	May-21	Not yet recruiting	United States
NCT04335084	Interventional (Phase 2)	600	Prevention of COVID-19 symptoms as recorded in a daily diary; Safety as determined by presence or absence of Adverse Events and Serious Adverse Events	>=18	May-20	Aug-21	Not yet recruiting	United States
NCT04347889	Interventional (Phase 2)	1212	COVID-19 Seroconversion rate; Admission for Covid-19	>=18	April 20, 2020	December 30, 2020	Not yet recruiting	United States
NCT04395768	Interventional (Phase 2)	200	Length of hospital stay; Invasive mechanical ventilation or mortality	>=18	May 25, 2020	December 31, 2021	Not yet recruiting	Australia
NCT04326725	Observational	80	Protection against COVID-19	>=20 and <=90	March 20, 2020	September 1, 2020	Recruiting	Turkey
NCT04342728	Interventional	520	Fever; Cough; Shortness of Breath; Fatigue	>=18	April 8, 2020	April 30, 2021	Enrolling by invitation	United States
NCT03680274	Interventional (Phase 3)	800	Number of deceased participants or with persistent organ dysfunction; Number of participants with persistent organ dysfunction-free days in intensive care unit	>=18	November 8, 2018	December 31, 2022	Recruiting	Canada

Vitamin D

The deficiency of vitamin D has become a global public health issue for all age groups (Palacios, Gonzalez, 2014; MacLaughlin, Holick, 1985). However, the status of vitamin D worsens in the age group of above 70 years because of the decrement of cutaneous synthesis and sun exposure (Adami *et al.*, 2009). Moreover, vitamin D deficiency severely affects 75% of the institutionalized people (serum 25(OH) D < 25 nmol/L) (Lips, 2019). Figure 2 represents the possible therapeutic efficacy of supplemental vitamin D. Improvement in concomitant drugs, disease/organ pathology, concomitant supplements, innate immune modulation, intracellular state of metabolome, improved muscle function, modern formulation component, genetics, protect from acute respiratory infections, alleviate lung injury and weakens the capability of macrophages are some possible therapeutic efficacies of supplemental vitamin D (Zou *et al.*, 2014; Braithwaite *et al.*, 2013; Raftery, O'Morain, O'Sullivan, 2012; Helming *et al.*, 2005).

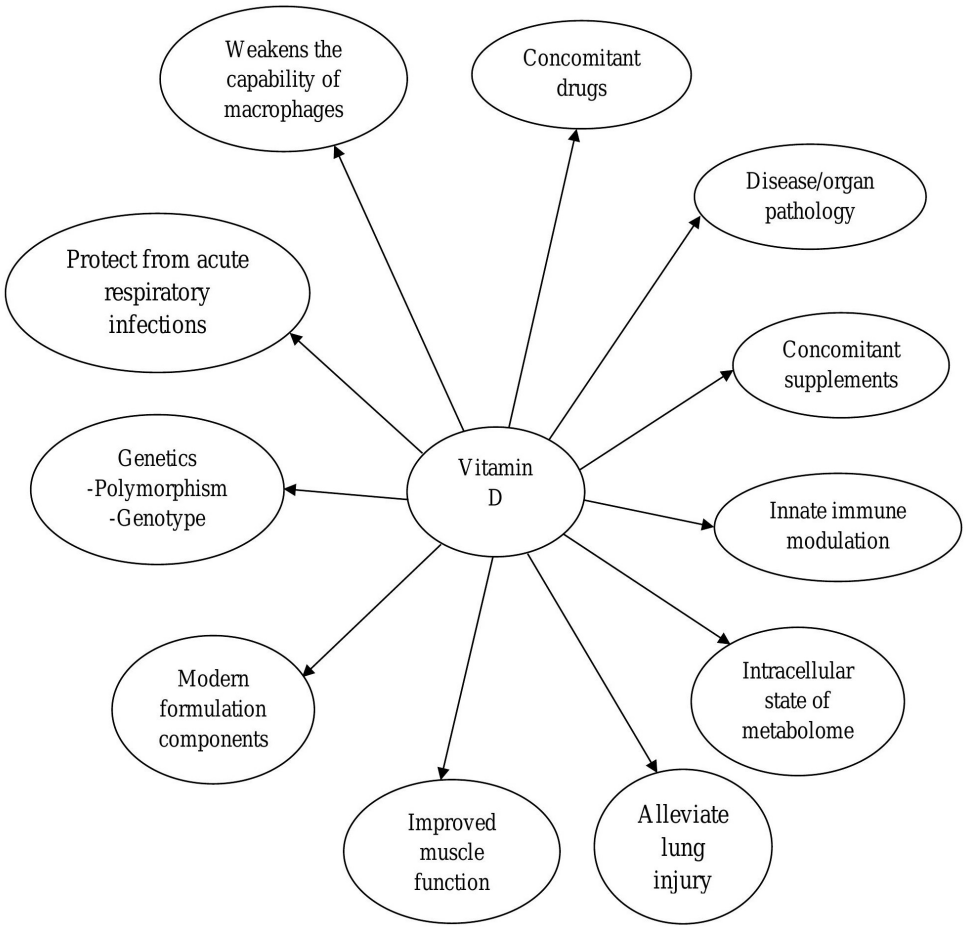

FIGURE 2 - Possible therapeutic efficacy of supplemental vitamin D (Zou *et al.*, 2014; Braithwaite *et al.*, 2013; Raftery, O'Morain, O'Sullivan, 2012; Helming *et al.*, 2005).

A meta-analysis reported vitamin D supplementation as protective and safe against 'acute respiratory tract infections' (Martineau *et al.*, 2017). Moreover, this analysis identified that vitamin D deficient patients with critical condition were highly benefitted by taking vitamin D supplements. Notable impacts was exerted on Ang(1–7)/ACE2/MasR axis with an intensified expression of Ang(1–7), MasR, and ACE2 generation by taking Calcitriol (1,25-dihydroxyvitamin D3) (Cui *et al.*, 2019). The deficiency of vitamin D was narrated by Abu-Amer, Bar-Shavit (1993). They identified that it weakened the capability of macrophages to engender macrophage-specific surface antigens, to mature, to discharge water, and to engender the lysosomal enzyme acid phosphatase. Besides, strong inhibitory action on post-infection was observed because of the utilization of vitamin D, which suggested the vitamin D as an additional therapy for the treatment of COVID-19 in the future (Ahmed, Araf, Ullah, 2021). Better outcomes can be achieved for coronavirus disease by keeping a higher ACE2 level as ACE2 helps to prevent acute lung injury effectively (Kuba, Imai, Penninger, 2006). Inductions of vitamin D receptors are influenced by various toll-like receptors (Gruber-Bzura, 2018). In COVID-19 pneumonia or illness, cytokine storm occurs due to overexpression of immune function. Vitamin D is applied to modulate the response of macrophages, which helps to prevent the release of excessive inflammatory chemokines and cytokines (Helming *et al.*, 2005). Recombinant human ACE2 protein can alleviate lung injury that is induced by H5N1 flu infection (Zou *et al.*, 2014). The consequences of the expression of ACE2 in the lungs were investigated by Xudong *et al*. The findings reported that ACE2

reduction was comparatively smaller in the middle-age group and young adults (18% and 25% for female and male respectively) while the reduction was comparatively higher in the older group (67% and 78% for female and male respectively) (Xudong *et al.*, 2006). Though disease management or approach can create variation, mortality can be a better indicator for the number of cases among the population. Noticeable crude relationships can be identified between the number of cases of COVID-19 (especially, morality) and the levels of vitamin D (Ilie, Stefanescu, Smith, 2020). The aging population is the most vulnerable group not only for COVID-19 but also for the deficient level of vitamin D. However, dedicated studies should be performed regarding the levels of vitamin D in COVID-19 patients accompanying with various degrees of severity of the disease.

The majority of the vitamin D related trials are interventional, and most of them are 'phase 2' type. Moreover, most of the trials are conducting in Spain. In the observed clinical trials, vitamin D has been applied to access the duration and severity of the disease, the requirement of oxygen therapy, discharge and death of hospitalized patients, the requirement of higher oxygen flow, the evolution of clinical and biochemical parameters, composite of morality, the reduction of severity and death, length of hospital stay, the necessity of invasive mechanical ventilation, the survival of institutionalized aged patients, the reduction of hospitalization, the recovery of COVID-19 symptoms, the improvement of prognosis of COVID-19 and the prevention of COVID-19. Table II represents trials related to vitamin D.

TABLE II - Trials related to vitamin D

NCT Number/ EudraCT Number	Study Type	Estimated Enrollment	Primary Outcome/ Objective	Age (year)	Start Date	Completion Date	Status	Country
NCT04385940	Interventional (Phase 3)	64	Symptoms recovery; Hospitalization; Blood white blood cell count (WBC)	>=17	May-20	Dec-20	Not yet recruiting	Canada
NCT04386044	Observational	1000	COVID-19 infection; Oxygen therapy for COVID-19; Discharge following COVID-19 hospitalisation; Death due to COVID-19	>=18	June 1, 2020	June 1, 2021	Not yet recruiting	United Kingdom
NCT04403932	Observational	500	Severe COVID-19	>=18	April 17, 2020	July 1, 2020	Recruiting	Spain
NCT04370808	Observational	500	Differences in vitamin D blood levels between COVID-19 patients with different degrees of disease severity; Differences in genetic variants in vitamin D-related genes between COVID-19 patients with different degrees of disease severity	>=18	Jun-20	Mar-21	Not yet recruiting	Portugal
NCT04334005	Interventional	200	Composite of cumulative death (i.e. mortality) for all causes and for specific causes; Necessity of invasive assisted ventilation; Necessity of non-invasive assisted ventilation	>=40 and <=70	April 10, 2020	June 30, 2020	Not yet recruiting	Spain
NCT04363840	Interventional (Phase 2)	1080	Hospitalization	>=18	May-20	Dec-20	Not yet recruiting	United States
NCT04351490	Interventional	3140	Survival rate in asymptomatic subjects at inclusion; Survival rate in symptomatic subjects at inclusion; Survival rate in overall subjects	>=60	Apr-20	Jul-20	Not yet recruiting	France

TABLE II - Trials related to vitamin D

NCT Number/ EudraCT Number	Study Type	Estimated Enrollment	Primary Outcome/ Objective	Age (year)	Start Date	Completion Date	Status	Country
NCT04344041	Interventional (Phase 3)	260	Number of death of any cause, during the 14 days following the inclusion and intervention; Number of death of any cause, during the 28 days following the inclusion and intervention	>=70	April 15, 2020	Jul-20	Recruiting	France
NCT04335084	Interventional (Phase 2)	600	Prevention of COVID-19 symptoms as recorded in a daily diary; Safety as determined by presence or absence of Adverse Events and Serious Adverse Events	>=18	May-20	Aug-21	Not yet recruiting	United States
NCT04394390	Observational	100	laboratory measured vitamin D levels	Child, Adult	May 1, 2020	June 30, 2020	Enrolling by invitation	Turkey
NCT04395768	Interventional (Phase 2)	200	Length of hospital stay; invasive mechanical ventilation or mortality	>=18	May 25, 2020	December 31, 2021	Not yet recruiting	Australia
NCT04386850	Interventional (Phase 2, 3)	1500	COVID-19 (SARA-Cov-2) infection; Severity of COVID-19 (SARA-Cov-2) infection; Hospitalization; Disease duration	>=18 and <=75	April 14, 2020	March 15, 2021	Recruiting	Iran
2020-001960-28	Not mentioned	70	Assess whether the group of patients receiving vitamin D supplements presents a less serious evolution of his pneumonia translated into lower mortality than patients who do not receive this supplement	>=18 and <=64	May 25, 2020	Not mentioned	Authorized	Spain
2020-002274-28	Not mentioned	60	Analyze if the administration of a single dose of native vitamin D (100,000 IU of Colecalciferol) (1 ampoule of 100,000) has an influence on the evolution of clinical and biochemical parameters of the disease	> = 18	May 19, 2020	Not mentioned	Authorized	Spain
2020-001602-34	Not mentioned	260	Evaluate the efficacy of a high dose of cholecalciferol 400,000 IU per os at one time versus a standard dose of 50,000 IU per os at once on the 14-day death rate (D14) in elderly patients	> = 70	April 10, 2020	Not mentioned	Authorized	France
2020-001363-85	Not mentioned	206	Investigate whether prophylactic treatment with daily hydroxychloroquine, vitamin D, and zinc supplementation reduces the risk of COVID-19, the severity of the disease, the hospitalization rate, and death in nursing home residents	> = 70	April 23, 2020	Not mentioned	Authorized	Denmark
2020-001717-20	Not mentioned	1008	Demonstrate that in patients ≥18 and <90 years, positive for coronavirus, newly hospitalized with or without oxygen respiratory support, conventional or non-invasive ventilation, treatment with Calcifediol will decrease the need for ventilation invasive and admissions to the Intensive Care Unit and deaths	>=18 and <=90	April 20, 2020	Not mentioned	Authorized	Spain

Natural honey

Natural honey has anti-inflammatory, anti-bacterial, and anti-oxidant properties and it is a proven remedy in the case of prophetic medicine (Yaghoobi, Kazerouni, 2013). It can effectively utilize as a wound dressing for promoting improved and rapid healing. These effects are mainly due to the antibacterial action of honey, subject to its hydrogen peroxide content, anti-oxidant content, osmotic effect, and high acidity. The utilization of honey can relieve pain in burn patients, improve wound healing in acute cases, and reduce the inflammatory response in the patients. Moreover, honey may benefit patients with COVID-19, by increasing the immune response, alleviating comorbid diseases, and acting as an antiviral (Hossain *et al*., 2021).

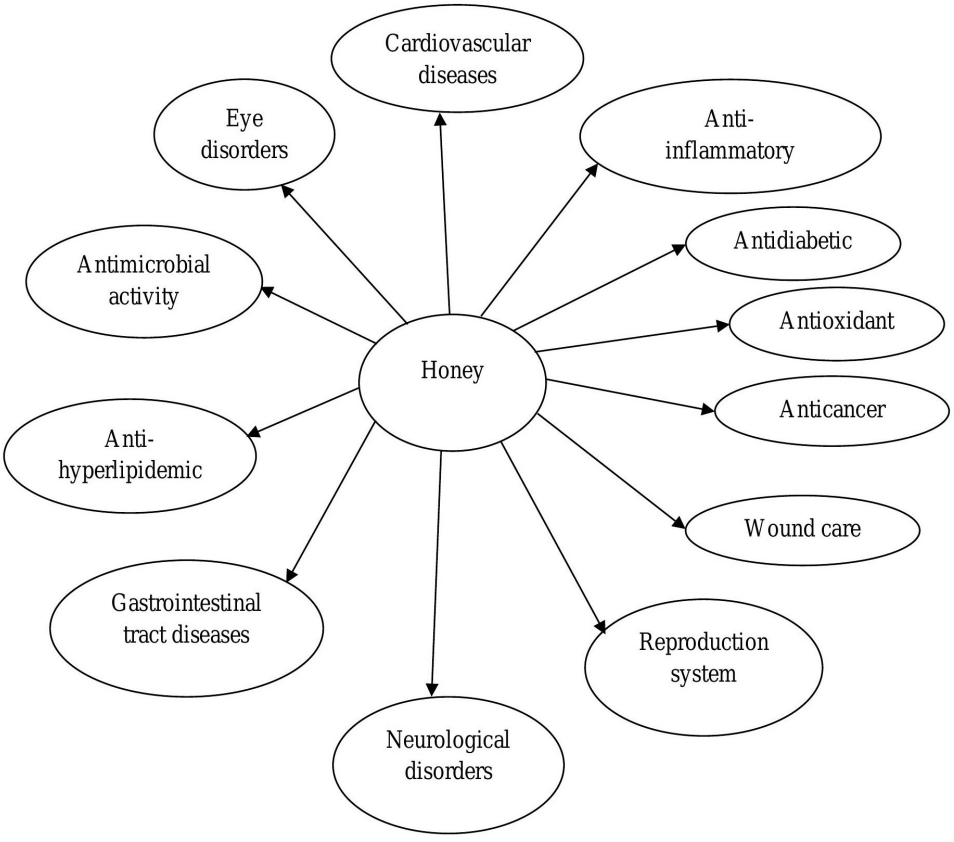

FIGURE 3 - Possible therapeutic efficacy of honey (Rao *et al*., 2016),

Honeybee products are one of the promising products because of nutrition and antiviral medicinal treatments. Propolis was identified as the best among all-natural products in various trials for treating herpetic skin lesions, particularly those related to HSV-1 (Münstedt, 2019). The utilization of honey in adult patients with frequent attacks of herpetic lesions (genital and labial) was reported (Al-Waili, 2004). A comparison was made between acyclovir treatment and topical treatment with honey where honey exhibited comparatively better results without any adverse effects over patients utilizing acyclovir who reported itchiness. The trial identified an effective topical application of honey in the pain management with other symptoms and signs of frequent lesions from labial and genital herpes. Manuka honey effectively exerted virucidal effects and inhibited the replication of the influenza virus (Watanabe *et al*., 2014). Children's herpes simplex gingivostomatitis can also be treated with honey (Awad, Hamad, 2018). Figure 3 represents the therapeutic efficacy of honey. Improvement in cardiovascular

diseases, anti-inflammatory activity, antidiabetic, antioxidant, anticancer, wound care, reproduction system, neurological disorders, gastrointestinal tract diseases, anti-hyperlipidemic, antimicrobial activity, and eye disorders are some possible therapeutic efficacies of honey (Rao *et al.*, 2016).

Honey is a globally available natural sweetener that is extensively utilized for various purposes among natural products. Moreover, clinical applications of honey have already been identified (Ahmed, Othman, 2013). Around 200 different chemical compounds of honey have been discovered (Ramanauskiene *et al.*, 2012). Honey that is obtained from the honey bee is a viscous solution containing various molecules, including amino acids and proteins (0.1–0.4%); ash (0.2%); water (15–17%); glucose and fructose (80–85%) and small amounts of vitamins, enzymes, and other substances, i.e. phenolic compounds (Rao *et al.*, 2016). Moreover, variation of the honey composition depends on the plant types from which nectar is consumed by the bees. Still, almost all honey that are globally available contain identical types of phenolic acids, including ellagic, caffeic, p-coumaric and ferulic acids; flavonoids, i.e. quercetin, pinocembrin, kaempferol, hesperetin, galangin, chrysin, and apigenin; and antioxidants, i.e. reduced glutathione, catalase, superoxide dismutase, ascorbic acid, and tocopherols. It was noticed that every component has specific medicinal and nutritional properties wherein the components behave synergistically, lending honey utility in various applications (Vit, Vargas, Valle, 2015). Moreover, honey's chemical composition and physical properties are influenced by the variations of the types of flora, geographical region, and climatic conditions. In addition, various methods were utilized in order to discriminate the entomological origins of stingless and sting bee honeys (Vit, Deliza, Pérez, 2011; Vit *et al.*, 2015) while nuclear magnetic resonance has been utilized in order to authenticate commercial honeys (Schievano, 2015).

Both of the natural honey related trials are interventional, 'phase 3' type. Moreover, the trials are conducting in Egypt and Pakistan. In the observed clinical trials, natural honey has been utilized to access the rate of recovery from positive to negative swaps, the number of days till no fever, the number of days till lungs recovery in chest X ray or CT, the requirement of days to get a positive COVID-19 PCR to negative, the HRCT/ X-ray findings of disease progression, the severity of symptoms progression, and the duration of hospital stay. Table III reveals trials concerning natural honey.

Overall, it has been found that vitamin C, vitamin D and natural honey have the capability to improve the immune system and reduce the lung damage. Therefore, fatal complication, i.e. pneumonia may be treated by these. Vitamin and natural honey were been utilized earlier for various infectious diseases which showed efficacy. Therefore, it strongly indicates that COVID-19 may also be treated with them. Moreover, many clinical trials are conducting in present related to vitamin C, vitamin D, and natural honey to identify the efficacy to treat COVID-19. The identified clinical trials on vitamin C, vitamin D, and natural honey is summarized in Table III. However, these trials can only be recommended after getting results from these trials.

TABLE III - Trials related to natural honey

NCT Number	Study Type	Estimated Enrollment	Primary Outcome/ Objective	Age (year)	Start Date	Completion Date	Status	Country
NCT04323345	Interventional (Phase 3)	1000	Rate of recovery from positive to negative swaps; Fever to normal temperature in days; Resolution of lung inflammation in CT or X ray	>=5 and <=75	April 15, 2020	January 15, 2021	Recruiting	Egypt
NCT04347382	Interventional (Phase 3)	30	Days required to get a positive COVID-19 PCR to negative; HRCT/ X-ray findings of disease progression	>=5	May 20, 2020	July 30, 2020	Recruiting	Pakistan

CONCLUSION

This review summarized and discussed the impact of supplemental vitamins and natural honey for the treatment of COVID-19 from current works of literature and clinical trials. However, the main findings of this review can be summarized as follows:

- The high doses of vitamin C was found to decrease COVID-19 lung damage, organ dysfunction and other flu infections. In addition to COVID-19 therapy, intravenous administration of vitamin C may also be useful.
- Vitamin D can effectively weaken the capability of macrophages, protect from lung injury and acute respiratory infections. Additionally, it can improve the immune system to fight against COVID-19 infection.
- Natural honey has potent antiviral effects and the ability to improve immunity. Moreover, it exerts calming effects on the tissue and prevents co-morbidities effectively. Therefore, honey may benefit patients with COVID-19, by increasing the immune response, alleviating comorbid diseases, and acting as an antiviral. It may also help to access the rate of recovery from positive to negative swaps, number of days till no fever, number of days till lungs recovery in chest X ray or CT of COVID-19 positive patients.
- This review also identified that for COVID-19 treatment, the administration of vitamins and honey may be potential to reduce fatalities, length of hospital stay, symptoms of COVID-19, duration and severity of disease as well as the requirement of oxygen flow.

Since the utilization of vitamin C, vitamin D, and natural honey with the current treatment may be effective in treating COVID-19-caused fatal complications such as pneumonia, lung injury and acute respiratory infections therefore high-level clinical studies are required to administrate the effects of vitamins and natural honey.

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