Chapter

The Role of Complementary and Alternative Medicines in the Treatment and Management of COVID-19

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Abstract

Interception of coronavirus disease 2019 (COVID-19) into our life and its rapid global expansion, humanity has succumbed to a vulnerable position. COVID-19 is proclaiming millions of lives, underscores the urgent need for more effective therapeutic interventions. This disease created catastrophe and developments of new drugs and vaccines take a long duration. Hence, scientists and medical society turned their heads towards different approaches of treatment, referred to as complementary and alternative medicine (CAM) for eradicating the deadly virus. Ayurveda, herbal medicines, nutritional supplements, naturopathy, and yoga are some of the CAMs which have emerged as a ray of hope in these times. The understanding of the COVID-19 pathogenesis and its impact on immunity will progress the effective management of this lethal infectious disease. The host immune response has an elementary function of defense against the majority of infectious diseases including COVID-19. This chapter focuses on the utilization of various CAMs (Ayurveda, yoga, herbs, phytochemicals and nutritional supplements) in COVID-19 treatment. An additional attempt has been made in this chapter on the potential of CAMs to assist in improving immunological reactions against infections and thus may be an efficient approach in the prevention and/or management of severe acute respiratory syndrome coronavirus 2 infections.

Keywords: COVID-19, SARS-CoV-2, Complementary and Alternative Medicines, Innate immunity, Adaptive immunity, Micronutirents

1. Introduction

The coronavirus disease 2019 (COVID-19) proclaiming millions of lives, is an infectious respiratory disease affecting the lungs. COVID-19 is devastating mainly in patients of old age and with co-morbidities like obesity, cardiovascular complications etc. COVID-19 is caused by recently recognized coronavirus termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. COVID-19 outbreak was instigated in December 2019 from the Wuhan city of China, which is rapidly spreading worldwide and badly impacted the entire world [2]. The COVID-19 pandemic is currently the prevalent world health crisis and a daily large number of new cases is reported around the world [3, 4]. By June 24, 2021, the mortality rates raised to 3.9 million among 180 million confirmed cases of COVID-19. Currently, the world healthcare system is in severe crisis due to the constant and varied challenges created by COVID-19. Initially, due to the lack of understanding regarding novel coronavirus and vaccines or any treatment for the COVID-19, governments officials globally implemented various non-pharmaceutical interventions (NPIs), such as the utilization of masks, social distancing, hand-washing, remote working, closures of schools and colleges, restrictions on public gatherings, fourteen days quarantines, for the slow transmission of the disease [5]. These measures are found to be effective in mitigating the number of cases [6, 7], however, they lead to a considerable impact on the social, economic [8] and psychological wellbeing of the society [9].

Government's professionals, pharmaceutical companies and professionals in the health care system are taking great efforts to manage and combat the disease across the world. To alleviate the burden on society, a massive effort is being made by health care professionals worldwide to develop and get access to different vaccines [10, 11]. Vaccination has been started around the globe after a year of the first reported cases of COVID-19 [12]. Vaccines were developed and have been found successful in decreasing the number of patients affected with COVID-19 as well as the severity of the disease, however, it is not completely avoiding the risk of being affected with COVID-19. Additionally, new strains of coronavirus are also gradually identified. Recently it is found that novel coronavirus is having various mutations. This means that there are slight changes in the genetic composition of the virus. The Delta-plus variant is a mutated version of the Delta variant (the virus that wreaked havoc in the second wave). Delta plus is considered highly infectious. The virus can potentially dodge immune response, vaccines and antibody therapies. However, more research has to be done in this context. Few cases have been recorded in some states of India. The Government official has classified it as a Variant of Concern (VOC). There is no certainty regarding delta plus and the current numbers cannot determine any particular trend. Certain vaccines work against the Delta Plus variant, but they show 3 to 8 times less efficacy as compared to other variants. There are no conclusive reports about these variants but we should not keep our guards down [13, 14]. The United States Food and Drug Administration (U.S. FDA) approved the antiviral drug, remdesivir (Veklury), for treating COVID-19 affected patients requiring hospitalization. Remdesivir approved to be administered in the health care setting or hospital that is efficient enough of affording acute care comparable to inpatient hospital care. This approval of using remdesivir for treating COVID-19 does not include the entire population rather it is only approved for hospitalized patients who are adults and pediatric (≥12 years of age) with a bodyweight of at least 40 kilograms [15]. Moreover, health care systems are facing huge difficulties in combating the enormous demands of medicines and vaccines. Thus, providing additional therapies for preventing and curing the disease is an important step in combating this pandemic. Currently, the worldwide impetus is unabated, and a third wave is also predicted.

India and China are known for their rich history of traditional medicine [16]. Indian households are being considered as a hub of natural products, consisting of a plethora of pharmacologically active ingredients inspired by the traditional medication system (Ayurveda) [16]. Complementary and alternative medicines (CAMs) have emerged as a ray of hope in these times [17]. The following book chapter focuses on 'the role of CAMs in the prevention, treatment and management of COVID-19'.

2. Pathogenesis of COVID-19

The recently identified SARS-CoV-2 is a new member added into the family of β-coronavirus with earlier known members like Severe Acute Respiratory Syndrome

Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which results in severe pulmonary pneumonia and potentially deadly acute respiratory distress syndrome (ARDS). The large population of COVID-19 patients is asymptomatic. Six prominent symptoms include dry cough, malaise, fatigue, fever, dyspnea, secretion or sputum among various clinical manifestations noticed in patients infected with SARS-CoV-2. The gastrointestinal symptoms consist of vomiting, anorexia, and diarrhea in the patients affected with COVID-19. Pathogenesis of COVID-19 is classified into three discrete clinical phases based on the cells/tissue being infected. These three phases include asymptomatic state, upper and conducting airway response and hypoxia, ground-glass infiltrates and progression to ARDS. In Phase, I of asymptomatic state inhaled SARS-CoV-2, bind to the receptor present on the epithelial cells i.e., angiotensin-converting enzyme-2 (ACE-2) on the nasal cavity and begin reproducing [18]. There is local propagation of the COVID-19 virus and an inadequate innate immunity in the asymptomatic stage. In phase II, there is an occurrence of the upper airway and conducting airway infection. In this phase or stage, there is a robust immune response when the virus migrates and propagates down the conducting duct and along the respiratory tract. Epithelium of the upper and conducting airway infected virally results in the release of cytokines [19]. During this phase, clinical manifestations are observed. Predictions and monitoring of the subsequent course of the disease may be improved by determining the host immune responses. In most of the patients infected with SARS-CoV-2, the infection will be mild and mostly limited to the upper and conducting airways [20]. These patients do not require hospitalization and may be monitoring of patients at home with conventional symptomatic treatment will be adequate [19]. In the third stage or phase III, there will be ground-glass infiltrates, hypoxia and progression to ARDS. Typically, around 20% of the patients infected with SARS-CoV-2 advance to the severe stage and develop pulmonary infiltrates and ARDS. In this stage, the virus reaches and infects the gas exchange unit of the lungs i.e., alveolar type II cells mainly in the subpleural region of lungs [21]. Once the virus reaches the type II alveolar cells self-replicating pulmonary toxins are released and it results in apoptosis and cell death [22]. This in turn causes diffuse alveolar injury, with a few multinucleated large cells and a fibrin membrane rich in hyaline [23, 24]. Extensive scarring, fibrosis, and various kinds of ARDS may occur from aberrant wound healing. Improvement requires epithelial cells regeneration and robust innate and adaptive immune responses. Patients with older age or co-morbidities are at greater risk due to weakened capacity to repair the damaged epithelium and deteriorated immune response against the virus. In the elderly, the mucociliary clearance is also reduced and this allows propagation and rapid spread into the gas exchange unit of the lungs [25].

3. Interaction of virus with the immune system

Manifestations of COVID-19 is extremely heterogeneous, with a wide clinical spectrum varying from asymptomatic infection through mild upper respiratory and conducting airways infection, to severe pneumonia leading to fatality [24, 26]. Recognizing the machinery for the virus invasion into the host body and its interaction with the host immunity will facilitate the prevention and treatment of the COVID-19. Infection with SARS-CoV-2 has two distinct clinical phases: primary and secondary inflammatory phases. The primary phase involves the invasion of viral in the host and its replication and the inflammatory phase involves exaggerated host immune response towards the virus. Augmented host immune response eventually results in fast and uncontrolled deterioration and worsening of respiration and ultimately emerges the need for hospitalization [27, 28]. SARS-CoV-2 is a lower respiratory tract virus and enters the host through a specific receptor i.e., ACE-2, resulting in pneumonia in severe cases. It chiefly consists of four structural proteins including nucleocapsid polymer, small envelope glycoprotein, membrane glycoprotein and spike polymer, as well as numerous accessory proteins. Spike protein projected from the surface of the virus is responsible for the attachment with ACE-2 assists the invasion of viruses into the host cells [29]. ACE2 is mainly expressed on the lung, kidney, intestine and epithelial cells of blood vessels. It is worth mentioning that spike protein is considered as the potential target in the vaccination against COVID-19. The innate and the adaptive immunity pathways are two pieces of machinery of the host immune system against foreign pathogens [30]. To effectively deal with and rapidly control the spread of viral infection, the innate immunity activates and concomitantly stimulates the adaptive immunological reactions. The innate system is the first-line defense against the pathogen which comprises of external defense mechanism (e.g. epithelial cells or the mucous membranes in the nasopharynx, lung, gut, periodontium and skin), nonspecific phagocytic leukocytes (macrophages and neutrophils) as well as serum proteins [30, 31]. Adaptive immune build up in a long time includes a specific response i.e., production of protein molecules known as antibodies that react with the antigens of infectious agents to eradicate the virus and to forbid progression of the disease to severe stages [32]. The host immune system via frequently interacting innate and adaptive mechanisms defends against external pathogens. Better management and prevention of disease requires timely identification of disease as well as its influence on the immune system. The disease complexity is further noticeable when it is reported variability in susceptibility to severe infection and mortality in certain sections of the population. However, earlier literature reported that the viral infection alerts immune system operations and influences immunoglobulin levels, antibody generation, phagocytosis, lymphocyte transformation etc. [33]. Similarly, SARS-CoV-2 also impacted the innate and adaptive immunity of the host.

3.1 Impact of SARS-CoV-2 on innate immunity

It has been reported in numerous studies that interleukin-6 (IL-6) is upregulated in patients affected with SARS-CoV-2 [24]. IL-6 is chiefly produced by monocytes or macrophages. IL-6 employs immune mediators and results in the cytokine storm, which cause tissue damage and uncontrolled systemic inflammation [34]. Moreover, inflammatory cytokines including chemokines, interferon-gamma (IFN-γ), IFN-γ induced protein 10 (IP-10), tumor necrosis factor (TNF-α), interleukin-10 (IL-10) and monocyte chemoattractant protein-1 (MCP-1) are observed to be augmented in patients affected with COVID-19 [24]. Lactate dehydrogenase is a marker of pyroptosis and is also found to be augmented in patients affected with COVID-19, and is considered to be correlated with the severity of the disease as well as the rate of mortality. Innate immune response was observed to be activated in COVID-19 patients, but unsuccessful to commence robust interferon (IFN) responses. The deficient of IFN responses could probably result in insufficiency in confining the viral load and viral infection at the initial stage of disease progression [34]. There is limited literature regarding the mechanisms underlying the SARS-CoV-2 induced mitigation of IFN responses. Macrophages play important role in immune responses against viral infection. ACE2 receptors are found to be expressed on the surface of macrophages [35]. This leads to increased susceptibility of macrophages to SARS-CoV-2 infection. This signifies that macrophages may serve as a possible reservoir of the COVID-19 virus [36].

3.2 Impact of SARS-CoV-2 on adaptive immunity

Stimulation of the innate immunity subsequently activates the adaptive immunity. Thymus cells (T cells) and bone marrow- or bursa-derived cells (B cells) are key players in adaptive immunity. Effector T cells mediate cellular response against the virus by either directly killing the cells infected with the virus or by discharging regulatory and pro-inflammatory mediators. B cells mediate the humoral responses by producing neutralizing antibodies (NAbs). The released NAbs in turn obstruct the interaction between the spike protein of SARS-CoV-2 and ACE2 expressed on the surface of the cell membrane and thus block the invasion of the virus into the host cell. On the contrary, the virus-specific antibodies interact with complementary receptors expressed on the exterior of the host cell and thus assist the entrance of the virus into the host cells. This is termed antibody-dependent enhancement (ADE) [37]. The NAbs titer is reported to be associated with disease severity [38]. However, there is a range of levels of NAbs among various patients, demonstrating the individual variation in immune responses towards viral infection. Cellular immunity is another intend of the adaptive immune system is against viral infections including the cluster of differentiation 4 (CD4) and the cluster of differentiation 8 (CD8) positive T cells. CD4 and CD8 are glycoproteins that serve as a co-receptor for the T-cell receptor (TCR). CD4+ T releases cytokines, which help cytotoxic T cells and B cells. On the other hand, the CD8+ T cells after being activated eradicate the infected cells. Depletion as well as the exhaustion of peripheral CD4+ and CD8+ T cells are reported in COVID-19 patients [39]. This depletion and exhaustion of T cells may be due to the augmented level of IL-6 in COVID-19 patients [40].

4. Management of COVID-19 with the use of complementary and alternative medicines (CAMs) endorsement

Complementary and Alternative Medicine (CAM) is an umbrella term for a broad range of substances and treatments which consist of a cluster of a variety of medic and health care supplies, orders, and actions not characterized under the conceptual framework of medicines. The definition of CAM throughout the literature is not consistent. However, the National Centre for Complementary and Alternative Medicines (NCCAM) of the National Institute of Health (NIH) defines CAM as "a group of diverse medical and health care systems, products, and practices that are not currently fall under the category of conventional medicine"(NCCAM, 2002) [41]. CAM is utilized either as an alternative or adjuvant therapy of conventional treatments.

The inclination towards using CAM in and around the world, both in terms of prophylactic as well as therapeutic strategies against problems related to health, has been augmented recently [42]. CAM is an extremely broad area that consists of all health beliefs, values, practices, as well as methods exterior to the streamlined present health care system [43]. These are further classified into five important categories by National Center for Complementary and Integrative Health (NCCIH). The first category includes alternative medical systems/whole medical systems (homeopathy, traditional Chinese medicine, ayurvedic medicine), the second category includes biologically-based therapies (probiotics, minerals, vitamins, phytochemicals, whole diets and functional foods, animal-derived extracts, amino acids, proteins and fatty acids), the third category includes manipulative and body-based methods (chiropractic, osteopathic manipulation, reflexology and massage), the fourth category includes mind–body therapies; healing techniques based on mind–body therapies (art, praying, meditation, dance, music) and finally the fifth category includes energy-oriented treatments or energy therapies or (therapeutic touch, Qi gong, healing touch) [44].

Greater than 80% of the population around the globe utilizes CAMs. The foundation of the National CAM-Center leads to a significantly augmented number of CAM-related basic research and clinical trials based on CAM therapies. Approximately 30% of the adult population of the U.S. [45] and 10–40% of Europe [46] use CAM. It is predicted that the market per annum for herbal remedies, consisting of raw materials and herbal products will expand by 15% and 5% respectively. The global market for the herbal drug is projected to be $62 billion, which is likely to rise to $5 trillion by 2050 [47]. Herbal remedies for boosting the immune system are consumed in several countries across the globe to uplift health, endorse the body's defense against various infectious as well as prohibit and cure several infectious diseases [48]. In this section, several examples of CAMs projected for preventing and curing diseases are elaborated.

4.1 Methodology

Databases such as PubMed, Scopus, Embase, Google Scholar, Web of Science, and Cochrane were searched without time limitation to find relevant articles exploring the impact of CAM in COVID-19. The terms and words searched included "COVID-19", "SARS-CoV-2", "CAM", "micronutrients", "phytochemical", "Ayurveda", "extract", "essential oil", "herbal medicines", "In vitro", "In vivo", "clinical trial" etc.

4.2 Ayurveda and yoga as the prophylactic and adjuvant therapy of COVID-19

To develop a preventive and curative intervention for COVID-19, the Ministry of Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH), Government of India (GoI), formulated an interdisciplinary AYUSH research and development task force and guidelines for initiating, monitoring, coordinating efforts and conducting clinical studies of diverse traditional medicines against COVID-19 [49].

Visualizing the severity and infectivity of COVID-19, the Ministry of AYUSH, GoI recommended certain immunity boosters like lukewarm water, Kadha, (an ayurvedic preparations containing curcumin, ginger, cumin seeds, fennel seeds, cloves and honey) and homeopathic medicine 'Arsenic Album 30C' [50]. Ayurveda defined NPIs in addition to pharmacological as preventive measures in combating COVID-19. NPIs recommended by the Ministry of AYUSH include sadvritta (Sad means 'good' and vritta means 'regimen'), healthy lifestyles, enough sleep, adequate physical activity, avoidance and isolation from infected persons [51]. Certain medicines suggested by Ayurveda include turmeric (*Curcuma longa*), garlic (*Allium sativum*), Ajwain or Carom (*Trachyspermum Ammi*) as a disinfectant for the prevention of COVID-19 [52].

The nose, mouth and eyes, are the main entry portals for the droplets consisting of the virus, SARS-CoV-2. Before reaching and final attack on the lungs, the virus stays in the nose and throat region for hours. The virus is coated with fatty acid which helps in adhering the virus to the moist mucosal layers and thus facilitates its entrance into the host cells by attaching to definite receptors [53]. Ayurveda mentioned various interventions that interfere in these entry portals [54] for virus invasion to the lungs by improving the innate immunologic response of the mucus membranes. These measures work as "physiological masks" or "local prophylaxis" for obstructing the viral invasion. The common recommendation for respiratory diseases written in Ayurvedic texts [55] includes consumption of hot food, hot water, steam inhalation, gargling, local applications and herbal decoctions with medicated water. These may be useful for relief in mild cases [53]. Ayurveda recommended drinking hot and warm water for improving the digestion of Ama. Ama is a pro-inflammatory mediator of weaken metabolic disorders and is associated with augmented susceptibility to infections [56].

Warm oils and liquids are employed as mouth rinses (Kavala) or gargles (gandusha) to thoroughly clean the mouth and throat [57]. The oily decoctions coat the mucosa as biofilm as well as rinse the oral cavity, tonsillar area, and pharynx. These decoctions also have supplementary benefits of antioxidant, immunomodulatory, and antimicrobial [58]. It is well known that host mucosal immunity plays a vital role in controlling infectious agents [59]. Literature regarding Yoga advocates Jala neti which implies rinsing of the nasal passage with saline water [60]. Randomized controlled trials (RCTs) reported the effectiveness of saline water in upper respiratory infections [61].

4.3 Herb/phytochemicals

Herbal products are consumed in various countries across the globe. Literature suggests immune-boosting properties of these herbal materials which endorse the normal resistance ability of the body against infectious pathogens and to raise health, and as well as to cure and to prohibit diverse infectious diseases [48]. Curcumin, a polyphenolic compound isolated from turmeric, which is a commonly used food colorant and spice [62], can augment the antibody reaction even if it is consumed at reduced doses [63]. Additionally, literature shows that curcumin has a promising affinity for protein binding towards SARS-CoV-2 and thus directly inhibit the invasion of SARS-CoV-2 into target cells [64]. The ability of curcumin in improving various disease conditions is attributed partially to its capability to modulate the immune responses [63]. Numerous reports show that curcumin can alter the proliferation as well as the activation of T cells [65, 66]. Additionally, curcumin has the potential of regulating the response and growth of various immune cells like natural killer (NK) cells, B cells, T cells, dendritic cells (DCs), macrophages and neutrophils [63]. Glycyrrhizin, an active phytochemical moiety found in liquorice was observed to be efficient in comparison to commonly used anti-virals in mitigating the replication of SARS-CoV as well as inhibiting its adsorption and penetration [67]. A recent in-vitro study also showed that glycyrrhizin is a potential inhibitor of SARS-CoV-2 replication by hindering the viral main protease (Mpro) [68]. Molecular docking study showed two phytoconstituents Somniferine and Withanoside V from Ashwagandha (*Withania somnifera*) [69, 70], Tinocordiside [70] and berberine [71] from Giloy (Tinospora cordifolia) and three active ingredients i.e., Vicenin, Ursolic acid and Isorientin 4'-O-glucoside 2″-O-p-hydroxybenzoagte isolated from Tulsi (*Ocimum sanctum*) [70] may have an antiviral effect against novel coronavirus via potentially inhibiting Mpro of SARS-CoV-2.

4.4 Nutritional supplements

Recently conducted studies show that suboptimal intake of micronutrients and inadequate nutritional status can lead to poor immunity and consequently affect the severity of infections. Nutritional supplements emerge to reinforce the immune system. Micronutrients consisting of a variety of vitamins (A, D, C, E, B6, B12, folate) and minerals (iron, zinc, selenium and copper) are engaged in various stages of the immune responses against foreign pathogens. A study conducted in the United Arab Emirates (UAE) confirmed the association of low levels of vitamin

D3 (25(OH)D3) (<12 ng/mL) with severity and death due to COVID-19 [72]. Another study shows that hospitalized COVID-19 patients receiving vitamin D3 (calcifediol) in contrast with those not consuming vitamin D3, was significantly linked with a lesser rate of mortality during the initial thirty days of hospitalization [73]. Supplementation with vitamin D at high-dose may be well-tolerated, effective, and readily accessible for the management of COVID-19 [74]. One report showed that intake of a high dose of vitamin D has significantly reduced the inflammatory markers (neutrophil/lymphocyte ratio, ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), IL-6 associated with COVID-19 without any side effects [75]. A study confirmed that deficiency of vitamin D is correlated with severe lung injury, disease prolongation and risk of mortality, in COVID-19 patients [76]. Another study shows that combination therapy of vitamin D with vitamin B12 and magnesium in geriatric patients with COVID-19 was correlated with a considerable decline in the proportion of patients with clinical deterioration and requiring intensive care support and oxygen support [77]. Vitamin D was found to modulate innate and adaptive immune systems [78, 79]. It augments the innate immune responses while attenuates the adaptive immune responses [78]. Vitamin D metabolites directly target the adaptive immune cells [80] and it is an important part of intricate features that control the immune response against infection [81]. These findings necessitate examining the level of vitamin D in pediatric as well as geriatric persons to maintain it at optimum levels for the prevention of SARS-CoV-2 infection.

In addition to the consumption of higher doses of vitamin D3, previously it was also stated that coronavirus pandemic can be considerably controlled by the utilization of high amounts of vitamin C. Significantly low levels of vitamin C in patients affected with COVID-19 were found and daily supplementation of 100 mg/kg is highly recommended [82]. A high dose of intravenous vitamin C might repress cytokine storms associated with COVID-19, and facilitate improving pulmonary function and lessen the risk of ARDS associated with COVID-19 [83]. As SARS-CoV-2 was found to affect the host immune system, it seems crucial to boost the natural immunity and antioxidant capacity to lessen the effect of any virus infection. Vitamin C is known for its ability to activate the immune system. Therefore it seems promising to administered vitamin C concomitantly with other medications to cure the infection in acute conditions. The ingestion of vitamin C orally up to the daily threshold of bowel tolerance seems to be effective for the majority of persons. However, intravenous administration of vitamin C is suggested for serious cases. On the other side, there are certain reports, claiming that the overstimulation of immune cells in COVID-19 leads to cytokine storm which ultimately causes lung injury following pneumonia. Certain clinical investigations also suggested that intravenous administration of vitamin C in high-dose can be a safe and effective choice for the management of COVID-19 infection in its early stages. Even though previous literature recognized and approved the antiviral activity of vitamin C, but its impact has not been studied widely and, limited information is available on its effect on coronavirus. Moreover, some studies show that adjunctive intravenous administration of vitamin C for the treatment of infection in critically ill COVID-19 patients was unable to reduce the rate of mortality, ventilator settings, the requirement of vasopressor, etc. [84]. Therefore although vitamin C is vital for lessening the inflammatory response and assists in boosting the immune system of the host, there is a lack of substance to support that utilization of vitamin C at a high dose can be successful in the prevention or management of COVID-19. Moreover, as Therapeutic Goods Administration (TGA) [85] declared that more studies are required for any recommendation for utilizing intravenous vitamin C in the management of COVID-19. In addition to vitamin C and vitamin D3, it was reported that vitamin K antagonist regular use was correlated with augmented mortality in hospitalized elderly patients affected with COVID-19 [86].

Studies show that treatment with zinc as adjuvant therapy was appeared to be feasible and safe for the management of COVID-19. However, the infusion of zinc causes limited infusion site irritation on the periphery [87]. Zinc supplement was found to be efficiently clear the SARS-CoV-2 from the nasopharynx in a lesser time than other symptomatic therapy [88]. Zinc cation (Zn^{2+}) coupled with zinc ionophores pyrithione and found to inhibit RNA polymerase of coronavirus and thus block the replication of the virus [89]. Additionally, zinc also mitigates the invasion of the virus by escalating the cell membrane stability as well as stimulate interferon-alpha (IFN-α) and IFN-γ formation and attenuate tumor necrosis factor (TNF) and mononuclear cells [90]. Apart from zinc, iron also plays a vital component of enzymes involved in the stimulation of immune cells, lower levels of iron was found to influence severe symptoms associated with COVID-19. Selenium contributes to adaptive immunity by boosting the production and development of antibodies. Lack of selenium can lessen antibody production, compromised cellular immunity, attenuated the cytotoxicity of NK cells, and decreased response to vaccination. Oxidative stresses alter the viral genome from a mildly pathogenic form to a highly virulent form of the virus in the host. Selenium is a known anti-oxidant. Hence selenium with vitamin E and a cluster of certain enzymes scavenges the free radicals and lessens the oxidative stress and thus as a result, the adjuvant therapy of selenium may be considered for the treatment of COVID-19 infection [91].

5. Limitations

Literature shows that people who either have positive attitudes towards CAM or those who consume CAM are unwilling to comply with conventional therapy, most prominently the vaccinations and to follow the official COVID-19 guidelines [92–98]. It has been reported that the optimistic attitudes towards CAM are correlated with negative attitudes towards vaccination is not evidence-based but because of an underlying outlook on health or perhaps a reluctance to stick to conventional therapy [93–95]. Those who utilize CAM perceived CAM as a natural, safe approach to improve the host immunity, while vaccines are considered as a risky option [94]. Additionally, both anti-vaccination attitudes and higher utilization of CAM are correlated to the poor trust of individuals towards the healthcare system or medical authorities [92].

6. Summary/conclusion

It is apparent from the above findings, that the understanding of the COVID-19 pathogenesis and its impact on immunity will progress the management of this lethal infectious disease. As per the earlier studies, the host immune response has an elementary function of defense against the majority of infectious diseases including COVID-19. In this chapter specifically attempt has been made on the utilization of various NPIs, herbs, phytochemicals and micronutrients which has the potential to assist in the prevention and/or management of SARS-CoV-2 infection. Thus utilization of CAMs may be an efficient approach in improving immunological reactions against infections. Moreover, the consumption of vitamins and minerals was observed to be favorable in improving the immune system and its function. Although, certain clinical studies reported the success of CAMs in the treatment, prevention and management of COVID-19, additional studies through clinical analysis as well as consumers' experience on CAMs are essential to draw strong conclusions in the success of utilization of CAMs for treatment, prevention and management of COVID-19.

Conflict of interest

"The authors declare no conflict of interest."

Abbreviations

ACE-2	Angiotensin-converting enzyme-2
ADE	Antibody-dependent enhancement
ARDS	Acute respiratory distress syndrome
AYUSH	Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy
B cells	Bone marrow- or bursa-derived cells
CAM	Complementary and Alternative Medicine
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
COVID-19	Coronavirus Disease 2019
CRP	C - reactive protein
IFN	Interferon
IFN-α	Interferon alpha
IFN-γ	Interferon-gamma
IL-6	Interleukin 6
IL-10	Interleukin-10
IP-10	IFN-γ induced protein 10
LDH	Lactate dehydrogenase
MCP-1	Monocyte chemoattractant protein-1
MERS-CoV	Middle East Respiratory Syndrome Coronaviruses
Nabs	Neutralizing antibodies
NCCAM	National Centre for Complementary and Alternative medicines
NCCIH	National Center for Complementary and Integrative Health
NIH	National Institute of Health
NPIs	Non-pharmaceutical interventions
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
T cells	Thymus cells
TGA	Therapeutic Goods Administration
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
U.S. FDA	United States Food and Drug Administration
VOC	Variant of Concern

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