Emerging Role of Nutraceuticals in Covid 19

Abstract: The global pandemic of SARS-CoV-2, claiming thousands of lives each day, has brought the world to a standstill. Such devastating and great impact of Coronavirus disease (COVID-19) is due to unexpectedly rapid spread, which did not allow for much preparedness. The scientists are working hard to come up with a vaccine, but nothing fruitful has been produced so far due to the rapid spread of the virus. Multiple drugs have been tried to target the virus, but no specific drug is there to prevent the spread of virus. Hence, we analysed the role of non-pharmacological substances such as nutraceuticals, probiotics and dietary supplements in reducing the susceptibility and mitigating the symptoms of COVID 19. In current scenario, when there is dearth of specific antiviral agents, theses substances could prove to be great importance due to their easy availability and no known side effects if administered in large doses. Scientific evidence has also suggested the beneficial role of bacterial and molecular products on immune response against the viruses. They could also regulate the inflammatory response and prevent endothelial damage. However, due to lack of specific data, rigorous clinical trials should be conducted to confirm the beneficial role of these supplements, probiotics and nutraceuticals in this period of crises.

Keywords: SARS-CoV-2, virus, supplements, probiotics and nutraceuticals.

INTRODUCTION

Since December 2019, Coronavirus Disease (COVID 19) has created a global health crisis. It is known to be caused by SARS-Cov-2, a single stranded RNA virus 2 which has approx 79% genomic similarity with bat derived SARS like CoV suggesting that it has passed from Bats to humans via some unknown intermediate and the first case was detected in Wuhan province of China [1]. The World health organization (WHO) declared it a pandemic on 11 March 2020 [2]. The suggested mode of transmission is mainly via Human-to-Human contact, through droplet released from an infected person. The clinical course of the disease may range from asymptomatic cases to severe pneumonia. However, the common clinical features are fever, dry cough, myalgia, anosmia, dyspnea and anorexia which may rapidly progress to respiratory distress. In severe cases, Acute respiratory distress (ARDS), Shock, Metabolic acidosis, disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS) may develop [3]. As of September 2020, there are total of 30 million positive cases globally with 5 million cases of COVID 19 in India itself and has claimed 9 million lives worldwide so far [4].

It has led to an extreme emergency situation with an overwhelmingly large number of cases in a short span of time. To curb the pandemic, worldwide large number of researches are going to discover a vaccine against COVID 19, however nothing fruitful has been produced yet. There is also no specific treatment available for it. Currently, the patients are mainly managed symptomatically by preventing the inflammation and supportive care with Oxygen supplementation and ventilatory support in severe cases [1]. Multiple drugs ranging from antibiotics and antimalarials to antivirals and corticosteroids have been tried so far, but only remdesivir out of all antivirals, has been found to be effective in shortening the recovery period of hospitalized patients [5]. Chloroquine (CQ) and hydroxy chloroquine (HCQ), which gained so much attention has shown mixed benefits. It was found that the HCQ could reduce the viral load in 6 days of administration from an infected person. The clinical course of the disease may range from asymptomatic cases to severe pneumonia. However, the common clinical features are fever, dry cough, myalgia, anosmia, dyspnea and anorexia which may rapidly progress to respiratory distress. In severe cases, Acute respiratory distress (ARDS), Shock, Metabolic acidosis, disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS) may develop [3]. As of September 2020, there are total of 30 million positive cases globally with 5 million cases in India itself and has claimed 9 million lives worldwide so far [4]. Another drug, tocilizumab, which is an antibody targeting Interleukin-6 (IL-6) receptors is still under investigation [8].
Since many drugs are still under the trial, there is a paucity of specific pharmacological therapy against COVID 19, non-pharmacological substances such as nutraceuticals, which are isolated nutrients, herbal products, diets and dietary supplements. These are known to strengthen the defense mechanisms by their anti-inflammatory and anti-oxidant properties and could be utilized to build up the immunity. These are the bioactive substances present inside the food, which includes nutrients such as Zinc, vitamin D and C, Curcumin and also some biologically active non-nutrient molecules such as Polyphenols and probiotics. The major advantage of using these foods derived molecules is that they are readily available, accessible, natural and usually with low or no toxicity and could get approved easily [10]. Some of these substances are already being used for many chronic illnesses and cancers, but there still no specific studies and sufficient data regarding their usefulness in COVID 19. However, we will try to review their possible beneficial role in SARS-CoV-2 infection.

**MATERIAL AND METHODS**

This review was designed keeping in mind the best review practices. The PubMed was searched for articles on nutraceuticals, probiotics and diet supplementation for the prevention and treatment of COVID 19. Studies reporting on in vitro, in vivo, or human studies were selected and study subjects, interventions and outcomes were systematically analyzed.

**Pathogenesis**

The Coronavirus disease is caused by SARS-CoV-2 virus, which is a ss RNA virus [1]. The virus enters the human body through the ACE 2 receptors which are distributed in different tissues and organs, forming the basis of multiple organ failure in patients of COVID 19 [11].

Initially, the virus enters the mucous membrane in upper respiratory tract via nasal or pharyngeal epithelium or enters directly to lower respiratory tract and infect bronchial and alveolar epithelial cells through the ACE 2 receptors expressed in lungs. At this stage, the virus may enter the bloodstream from lungs resulting in viremia [12]. The virus then affects other organs expressing ACE2 such as blood vessels, heart, GI tract and kidneys. GI tract may be involved directly by oral route as well through ingestion of virus. In severe cases, pulmonary involvement along with systemic inflammation may develop. The inflammatory process may culminate into a cytokine storm affecting other organs of the body [13].

Immune responses, innate and adaptive plays a crucial role in fighting off the invading virus or may induce the cytokine storm while invading the virus, responsible for immune-pathological damage in patients with coronavirus disease [14]. The patients at the risk for the unfavourable outcomes include old age, high body mass index (BMI), male sex, and those with underlying co morbidities such as hypertension, obesity, diabetes, chronic respiratory disease, cardiovascular disease, chronic kidney disease and obesity [15]. It was suggested that the SARS-CoV-2 virus binds to the ACE2 under the conditions of low cytosolic pH [16]. Low cytosolic pH is found under certain conditions such as diabetes, hypertension and old age, thus increasing the chances of acquiring the infection [17].

**NUTRACEUTICALS**

Endothelial dysfunction has been found as a result of chronic respiratory infection, majorly due to systemic inflammatory response and also due to oxygen stress. Endothelial dysfunction predisposes to increased platelet aggregation and increased coagulation [18]. In severe cases of COVID 19, due to the widespread pulmonary inflammation, there is development of haemorrhage and microthrombi. This predisposes the patients to intravascular coagulopathy [19]. Also, as a result of widespread systemic inflammation, there is release of inflammatory mediators such as interleukins, cytokines, tumor necrosis factors. These inflammatory mediators further lead to the endothelial injury by contributing to the clotting and thrombosis [20]. In addition to the inflammation, the oxidative stress also exposes to the hypercoagulation and thrombosis, particularly NOX2 derived ROS [21].

Thus, inflammation and oxidative stress act in synergistic manner and propagate a vicious cycle leading to the athereogenic plaque formation. Nutraceuticals, such as vitamin C, A, E, along with some minerals such as Zn, Cu and polyphenols, by maintaining proper redox homeostasis could be helpful in preventing the plaque formation.

**ZINC:**

Zinc is an essential micronutrient, involved in cell growth. It also plays a role in metabolic processes and immune system. It is also known to be a co factor for various enzymatic processes [22]. It is important for the differentiation, proliferation, maturation and proper functioning of lymphocytes and regulates the immune response [23]. Zinc deficiency has been found to increase the susceptibility of infectious and inflammatory disorders. It also plays a role in proper functioning of natural killer cells, thereby mounting an immune response against tumors and viruses [24].

It was found that the supplementation with zinc sulphate at 20mg/day for 5 months was associated with reduced mortality in case of acute lower respiratory tract infection [25]. Decreased levels of zinc have been found to result in impaired macrophage phagocytosis, thus further impairing the immune response [26]. Zinc is also involved in viral recognition with the help of zinc-finger protein ZCCHC3, which binds the viral RNA and detects
the intracellular viruses by activating the retinoic acid inducible gene-1 (RIG-1) like receptors. This further activates the antiviral genes leading to an antiviral response [27]. In normal physiological state, zinc is found bound to intracellular metallothionein proteins, which has some antiviral properties. Metallothionein sequesters the zinc from viral metalloproteins and facilitates the antiviral signalling. Zinc supplementation augments the metallothionein expression, thus further augmenting the antiviral signalling pathway [28]. Some studies have also suggested that increased intracellular zinc levels could disturb the viral replication of RNA viruses such as influenza, polio virus, SARS-CoV-2 [29]. Velthuis et al. conducted an enzymatic study using a recombinant RNA dependent RNA polymerase (RdRp) purified from E.coli and found that the zinc directly inhibited the SARS-CoV-2 RdRp elongation and reduced the template binding[29].

Approximately, 20% of the world population has low levels of zinc. The zinc deficiency has been found to be associated with diminished antibody production, altering the immune system. There is also reduced production of cytokines by mononuclear cells, reduced chemotaxis and disturbed respiratory burst of the neutrophils [30]. Taking in consideration the antiviral, immunomodulatory and antioxidant properties, zinc supplementation could reduce the severity of COVID 19 infection, there by preventing the development of complications. Chloroquine, which was used initially for the treatment of COVID 19, acted as a zinc ionophore by allowing the zinc entry inside the infected cell. However, its use was soon discontinued due to its toxicity profile [31].

POLYPHENOLS:

These are the compounds present in the plant foods. They are known to have antiplatelet and anticoagulant effect. They reduce platelet aggregation and suppress the thrombin activity [32]. They also exert beneficial effect by downregulating the NADPH oxidase and thus reducing the oxidative stress [33]. Some polyphenols also have anti-inflammatory properties, by modulating the cytokine production and increases the pro inflammatory gene expression [34].

It includes:

Resveratrol: It is a polyphenolic compound synthesised by plants in response to UV rays, viruses, fungi and toxins. It is present in Red vine, berries, nuts, etc [35]. It has shown some beneficial effects against certain diseases such as certain malignancies, cardiovascular and respiratory diseases [36]. It is known to have anti-inflammatory, antioxidant and antiviral effect. Resveratrol is an agonist to sirtuin deacetylase SIRTI, which is a regulator of multiple metabolisms. SIRTI inhibits the apoptosis and activates the cell cycle by deacetylating the Trp53 [35]. It was found in one of the studies that the inhaled resveratrol protected the mice from accelerated aging. It also maintained the lung structure, prevented DNA damage in parenchymal cells and prevented the loss of lung function [36]. Taking into the consideration all these effects, it could be used as prophylactic agent to curb the deterioration of lung structure and function. However, since no enough data is available yet, it is still under the trials.

Curcumin: It is a bioactive phenolic compound, extracted from the rhizomes of Curcuma longa. It is most commonly used spice in Asian countries, commonly known as Turmeric. Since ancient times, it has been exploited for its anti-inflammatory properties and has shown beneficial effects in arthritis, inflammatory bowel disease. Antimitagenic and antimicrobial properties have also been described for curcumin [37]. It also posses’ antiviral properties against several viruses such as influenza virus, HIV, hep A and Zika virus. It basically inhibits the viral entry into the cell, prevents viral replication and viral protein expression and stimulates the production of interferons and cytokotins. It binds to the receptor binding domain of the viral spike protein and blocks the host cell receptors, i.e. ACE2 in case of COVID 19 [38]. It also suppresses the production of certain cytokines such as IL6, IL8, TNF α and thus could prevent the cytokine storm associated with the severe COVID 19 infection [39]. Also, owing to its anticoagulant properties due to inhibition of platelet aggregation, it could also prevent the DIC in SARS-CoV-2 and could serve as a potential treatment option [40].

Hydroxytyrosol: It is also a phenolic compound, found in the olive tree leaves and olive oil. This compound is known for its antioxidant, anti-inflammatory and antiviral properties [41]. Its most important property is removal of reactive oxygen species, thereby preventing the oxidative stress. At the intracellular level, it has shown scavenging properties against superoxide anion, hydrogen peroxide and has shown to reduce the production of these anions in experimental models [42,43]. It can also modulate the pro inflammatory transcription factor NF-kB, which is known to control the expression of many genes involved in the production of cell adhesion molecules, chemokines, cytokines, interleukins etc [44]. Thus, by reducing the oxidative and inflammatory response, it can serve as a good adjuvant therapy along with antiviral drugs in COVID 19.

VITAMIN C

Vitamin C is water soluble vitamin, which helps in collagen synthesis, protects against oxidative damage and maintains proper functioning of many enzymes by acting as a cofactor. Human beings lack an enzyme L-glucolactone, essential for the synthesis of vitamin C. Hence, it must be provided externally through the diet [45]. Vitamin C is essential for innate and adaptive immune system. It also plays an essential role in maintaining the epithelial and endothelial barrier function, maintains vasodilation and reduces the
production of pro-inflammatory mediators [46]. A deficiency of Vit C leads to poor wound healing and scurvy [47].

The redox properties of Vitamin C have been utilized in treatment of known cancer patients. Many studies have shown Tumour regression, longer survival periods and better quality of life in patients receiving Vitamin C supplementation than in patients receiving only chemotherapeutic drugs and conventional anti-cancer regimes. [48,49]. The antioxidant property of Vitamin C has also been used in clinical trials against Viral diseases. In certain in-vitro experiments Vitamin C has been found to be active against Virus in presence of copper or iron [50]. Ascorbic acid is found to achieve high concentrations inside macrophages and lymphocytes [51]. With addition of Vitamin C lymphocyte proliferation, oxidative death and phagocytic activities were found to increase [52].

Following a Viral infection, phagocytes are activated in the body with formation of free radicals and reactive oxygen species (ROS). ROS damages the host cells and tissues. In RSV infection in children it has been found that production of ROS causes inflammatory damage to the lung tissues [53]. Antioxidants have been found to reduce these injuries and tissue toxicities through mechanism of free radical scavenging [54]. Vitamin C is a scavenger of free radicals and generates other antioxidants like tocopherol and tetrahydrobiopterin [46]. Utilizing this property, trials have been run in patients of common cold and Herpes Zoster Virus. Though considerable reduction in post herpetic neuralgia and pain was observed in the group receiving IV Vit C, no significant effect was found in prognosis of common cold [55,56].

In certain experiments, using Glunolactone knockout mice, it was found that the knockout mice have higher chance of infectivity and morbidity after exposure to H1N1 influenza viruses [57]. In another experiment, H3N2 influenza virus was inoculated into the noses of Gulo knock out mice and higher mortality was recorded than in normal mice [58].

The mechanism behind mortality in COVID 19 is thought to be generation of excess cytokine and induction of oxidative stress leading to ARDS and Multi organ failure. The virus after entering the body, induces a cytokine storm which causes membrane damage of the endothelial cells and infiltration of neutrophils [59]. This is also substantiated by the fact that COVID 19 patients show an increase in levels of hsCRP and IL6, which are the inflammatory markers [60]. The antioxidant properties of Vitamin C can be utilized in reduction of this cytokine storm and oxidative stress and thereby preventing the complications associated with the COVID 19 infection [61]. Administration of Vit C has shown to decrease levels of IL6 through a mechanism that blocks release of IL6 induced by Endothelin 1 in humans in earlier studies [62]. These properties may be used in treatment of Covid19. Vit C has already been used for the treatment of SARS-CoV-1 outbreak, which occurred in 2003 [63,64].

Large doses of IV Vitamin C has been proven to be efficient in ARDS caused by influenza virus. There are case reports showing remarkable improvement in lung conditions following a high dose of IV Vitamin C in patients of ARDS caused by influenza virus [65].

Keeping the above in mind, Vitamin C can be used in prophylaxis and trial of reduction of cytokine storm in late stage of severe COVID 19 disease.

**Vitamin D**

Vitamin D is a fat soluble vitamin, well known for its role in bone metabolism and absorption of Ca, Mg and Phosphate. It can be taken through the diet in the form for of vitamin D2 (ergocalciferol) or it is produced by the action of sun on the skin in the form of vitamin d3 (cholecalciferol). However, the active form of vitamin D is 1,25-dihydroxycholecalciferol (calcitriol) [66]. The deficiency of Vitamin D has been found to be associated with various pathologies such as cancer, inflammation, depression, immunological disorders, osteoporosis etc. [67]. It acts via a nuclear receptor and influences the immune and inflammatory responses by regulating the gene expression.

It has been established that Vitamin D prevents from the respiratory infections via many mechanisms [68]. The receptors for it are expressed in respiratory epithelial cells and in respiratory system macrophages. Under the influence of Vitamin D, there increased production of catelicidin from the macrophages. Catelicidin, by destructing the structure of various viruses such as influenza A, prevents the infection [69].

Vitamin D also modulates the inflammatory responses by affecting the immune mechanism. It upregulates the NF-κB inhibitory protein, thus inhibiting the NF-κB production. NF-κB is responsible for the production and mobilization of inflammatory mediators (GM-CSF, IL-5, IL-6, VCAM-1, ICAM-1) and results in an amplified inflammatory response and tissue damage [70,71]. Vitamin D, by maintaining the integrity of cellular barrier strengthens the immune function [72]. Due to its role in mitigation of inflammation and maintaining the immunity, the role of vitamin D has been studied in various respiratory infections. A meta-analysis which took into consideration 25 Randomized controlled trials, found that administration of vitamin D could reduce the risk of acute respiratory tract infections [73]. In one of the retrospective study, it was found that the elder men with comorbid condition and with lower levels of Vitamin D were at more risk of acquiring COVID 19 infection [74]. Certain epidemiological studies have also studied the role of vitamin D deficiency in onset and
severity of respiratory infections and the risk of development of severe lung damage [75].

Based on the above-mentioned evidences, it is necessary to evaluate the role of usefulness of Vitamin D supplementation in COVID 19 patients. It should be evaluated on a large scale since no data regarding the dosage, mode of administration and safety profile is available with respect to COVID 19.

**PROBIOTICS**

COVID 19, like other structurally similar Coronaviruses, bind to host ACE2 receptor with a spike glycoprotein. Following binding to host receptors, it brings about inflammation and injury to lung tissue [76]. ACE2 is expressed on alveolar epithelial cells, and on epithelial cells of trachea, bronchi, alveolar macrophages and monocytes. ACE2 receptors are also found in colon and ileum on the luminal surface of differentiated epithelial cells or enterocytes. In the intestine, ACE2 receptors regulate gut microbiota and homeostasis of dietary amino acids. ACE2 receptors have also been found to be involved with susceptibility of colitis. Few studies have shown altered gut microbiota in ACE2 mutants [77].

During the SARS-CoV outbreak in Hong Kong, 2003, evidence of viral replication in intestine was also found, along with in lung tissues [78]. COVID 19 is found to be genetically similar to the other SARS like viruses, particularly in the binding domains [79,80]. Hence, we could explore the role of intestine in COVID19 infection and pathogenesis. It is a known fact that a percentage of COVID19 patients present with intestinal symptoms along with the usual respiratory symptoms and fever.

During the beginning of the pandemic, studies conducted in Zhejiang province, China showed 11.4% of patients have diarrhea, vomiting or other GI symptoms [81]. There are existing Case studies in Wuhan Children’s hospital where children presented only with acute gastroenteritis, with absence of any respiratory symptoms and on testing, were found to be COVID19 positive [82].

A large number of diverse bacteria, fungi and few viruses colonize our intestinal mucosa, vagina, eyes, skin and respiratory system. In intestine, colon harbours the maximum number of commensal bacteria or ‘intestinal flora’, now called ‘intestinal microbiota’. A portion of our diet is composed of fibres or complex carbohydrates, which after reaching the intestine are acted upon by these bacteria, producing many different metabolites having 1 to 6 C atoms. Most common metabolite produced are Short chain fatty acids like butyrate, acetate, propionate. These play an important part in keeping the intestinal epithelial barrier intact, cell proliferation and host immune regulation [83]. The most common species producing SCFA in the gut are Bacteroides, Bifidobacterium, Streptococcus and Provoetella. These molecules also stimulate anti-inflammatory processes in the host [85,86]. The exposure of gut mucosa to microbes since birth up to first few years of life train naïve cells of the immune system, helping to develop immune tolerance [86].

There are also studies showing the existence of a gut-lung axis, with exchange and interaction of microbes and immune regulatory molecules between the two organs. Metabolites, mostly SCFA produced in the gut, enter the bloodstream and control immune mechanisms in brain and lungs also [87]. Few mice experiments have been conducted to explain the underlying mechanism in this phenomenon. It has been found in one experiment that L. acidisactobacillus reuteri, Clostridium orbiscindes, Lactobacillus crispatus and Enterococcus faecalis help resisting respiratory infections in C57BL/6 mice, possibly through extracellular signalling by Nod2 and GM-CSF in alveolar macrophages [88].

In view of the above, we can explore the uses of probiotics in modifying disease progression in COVID 19. A probiotic is live microorganisms, which is provided to the body through food and exert a beneficial effect on the host. The most common portal for probiotic have been yoghurt which is often loaded with Lactobacillus, Saccharomyces and Bacillus [89].

There are some RCTs showing benefits conferred by Probiotics on Ventilator associated Pneumonia patients. Patients of VAP were provided with Bifidobacterium, L. casei and galactooligosacharides supplementation. They showed better prognosis than in the group supplied with placebo [90]. In double blinded RCTs conducted among infants, low incidence of AURTIs was found in groups receiving probiotics in diet. Incidence of upper respiratory tract was found to be low though no significant difference in severity was found [91].

A study in China showed presence of Clostridia spp. was negatively correlated with presence of inflammation and disease severity in COVID19, while presence of Ruminococcus was positively correlated [92].

COVID 19 infection is associated with cytokine storm, an increase in levels of CRP and IL6, IL12, TNF alpha. The anti-inflammatory roles of bacterial products of diet fibre can be utilized in reducing levels of these, thereby reducing tissue toxicity and damage in COVID 19 [93,94]. Probiotics can bind to the virus and disrupt virus-host attachment [95].

Currently, probiotics are not a part of any treatment protocol against COVID 19, but they may improve the over all response of the patient by their ability to modulate the systemic inflammatory and immune response.
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