

Review Article

# COVID-19: A Review on Various Therapeutic and Nutritional Approaches

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**Abstract:** The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2, has affected the world drastically with almost every country in the world reporting cases of coronavirus. Undoubtedly, challenging situations have caused social and economic disturbances. Communities with poor hygiene practices and immunological disorders are more susceptible to this viral disease which affects the respiratory tract. Centers for Disease Control and Prevention, World Health Organization and governments of different countries have devised several strategies and regulations to minimize the spread of the virus. These include physical distancing measures, frequent hand washing and strict lockdowns in many regions of the world. Owing to its novel nature, no single specific treatment can be shortlisted for COVID-19. Alternatively, the therapeutic and nutritional approaches currently being considered have been effective in treating similar viruses in the past like SARS-CoV-1 and MERS. These approaches aim to assist and reinforce the immune response by stimulating innate and adaptive responses. This is a descriptive review - highlights all such potential therapeutic and nutritional approaches that effectively mediate the anti-inflammatory responses in patients reported with COVID-19. Since vaccination programs are in their initial stages, these approaches when used in a combination, can reduce mortality rate and ensure recovery in affected masses.

**Keywords:** COVID-19, Diet, Therapeutics, Novel Virus, Symptoms

## 1. Introduction

Viruses are infectious parasites with a genomic composition of either DNA or RNA. The viral genome can be single-stranded as well as double-stranded. Viruses are obligate intracellular parasites which imply that they need the host's cellular machinery to replicate [1]. A complete, functional and mature viral particle capable of replicating is known as viroid. It possesses a genome, a protein coat known as capsid, an envelope and a membrane that enables the viroid to attach and bind to its host cell to take control of its cellular

machinery [2]. Viruses can infect a wide variety of organisms including different species of plants, animals and even microorganisms. Some viruses are extremely specific in their binding to specific hosts based on their receptors whereas some viruses can bind to a range of species and infect them. They cannot be observed with a normal microscope because their size ranges from 50nm to 200nm [3].

### 1.1 The novel virus

As 2019 was ending, in December, numerous cases of a new respiratory ailment were reported in China. These cases emerged in Wuhan located in the province of Hubei [4]. In January 2020, the cause of this illness was known: The novel coronavirus [5]. This virus was then called SARS-CoV-2 because of its genetic and structural resemblance with SARS-CoV that was identified in the viral outbreak during the years 2002 and 2003. This virus causes a disease that is known as COVID-19 [6]. COVID-19 has affected people from almost every region of the world. At the outset, it was considered an epidemic but considering the stats from all the continents recently, WHO has announced COVID-19 to be a Pandemic that implies a global public health emergency [7]. This disease mainly affects the human respiratory system thus causing severe itching in the throat and difficulty in breathing [8]. Initially, the patients hospitalized were having pneumonia-like symptoms but the etiology of this disease was unknown [9].

This review tends to highlight the potential nutritional and therapeutic approaches that can help reduce the symptoms of COVID-19. Through this descriptive review, we will see how these therapies can play a vital role in boosting a patient's immune system.

### 1.2 Covid-19 relation with SARS, MERS and its morphology

Genome analysis of COVID-19 indicates that it structurally resembles more - SARS-CoV than MERS-CoV [10]. Although all three of these viruses i.e., SARS, MERS and SARS-CoV-2 are labelled as beta coronaviruses and are responsible for respiratory disorders. Over the last 18 years, these viruses have emerged as zoonotic diseases [11]. Coronaviruses are enveloped viruses. They can be pleomorphic or spherical in shape. Their size varies from 150nm-160nm. They have a positive single-stranded RNA genome and various nucleoproteins [12]. COVID-19 is different from other existing Coronaviruses because it possesses an additional glycoprotein with properties resembling acetyl esterase and hemagglutination [13].

### 1.3 Genome Analysis

The length of the RNA genome of coronavirus varies from 27-32kb. CoVs can be classified into the Roniviridae, Arteriviridae, and Coronaviridae families. In the year 2014, coronaviruses were classified further into four genera named as:  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  [14]. The SARS-CoV-2 that has caused acute respiratory syndrome belongs to genus  $\beta$  [15]. It is the special structure of coronavirus that enables it to infect humans and S proteins (Spike proteins) play a major role in entering humans [16]. The S protein has a trimeric structure comprising of two functional subunits. These subunits are S1 and S2. The binding with host receptors is mediated through S1 while the virus fuses with the cell membrane via S2. Between the two subunits of Spike proteins, a furan cleavage site is present. A mutation arises in this cleavage site that differentiates between SARS-CoV-1 and SARS-CoV-2 [17]. The entry in host cells by S protein of SARS-CoV-2 is mediated by ACE2 receptors of the host cell surface. These receptors are abundant in respiratory and intestinal epithelial cells of the human body thus SARS-CoV-2 can easily infect humans [18]. Notably, excessive ACE2 expression levels are observed in the lungs of smokers hence they are more likely

to be infected as compared to - non-smokers [19]. Such facts are important while designing specialized drugs for infected populations.

#### 1.4 Incubation Period

The incubation period for different viral infections is diverse. There are many factors to be taken under consideration such as type of pathogen, virulence and route of transmission [20]. CDC has made it essential for every affected person to be quarantined for 14 days without any pause. Generally, the incubation period varies from person to person depending on the immune system of the host and pathogenicity of the viral strain. A range of 2-14 days or sometimes more can be observed [21].

#### 1.5 Symptoms

Common symptoms are fever, fibromyalgia and cough albeit 50% of the infected people were observed to be asymptomatic [22]. Along with difficulty in breathing, some patients also experience nausea and loss of appetite [23]. The death rate is comparatively higher in aged people with multiple diseases and weaker immune response [24]. The COVID-19 disease conditions can be mild, moderate and severe [25]. Symptoms can vary from individual to individual. Fever may not be common in all the patients even if the condition is severe, various symptoms can be missing as shown in Table 1.

**Table 1: Common Symptoms in Different Disease Conditions Ranging from Mild, Moderate to Severe**

<b>MILD</b>	<b>MODERATE</b>	<b>SEVERE</b>
Dry cough	Dry cough	Pneumonia [26]
Mild fever	Tachypnea	Tachypnea, dyspnea [27]
Headache	Fatigue	Multiple organ failure [28]
Sore throat	Fibromyalgia	Pharyngitis, septic shock, cardiac injury [29]
Restlessness	Pharyngitis	Respiratory disease [30]

## 1.6 Acute-Respiratory-Distress-Syndrome (ARDS)

ARDS can occur under extreme conditions of COVID-19. The values for Partial pressure of oxygen (PaO<sub>2</sub>) and oxygen fraction FaO<sub>2</sub> determine the severity of ARDS. If the values are less than 100 mm Hg, then it's a severe ARDS condition. PaO<sub>2</sub> and FaO<sub>2</sub> values between 100-200 mm Hg indicate moderate ARDS while the values between 200-300 mm Hg indicate mild ARDS. Cystic changes and pleural effusion and mediastinal lymphadenopathy can be detected with the aid of a CT scan before the actual symptoms start to appear [31].

## 1.7 Diagnosis

Diagnosis of COVID-19 can proceed after the identification and isolation of the virus. Since viral isolation requires strict measures so it is only be performed in well-equipped laboratories for research purposes. To assess the presence of - virus, a nucleic acid test is performed. Various samples from Person Under Investigation (PUI) can be taken such as nasopharyngeal swabs, alveolar fluids, respiratory excretions, faeces and blood for nucleic acid testing [32]. Samples from both the upper and lower respiratory tract can be taken for nucleic acid testing. Viral RNA is identified in the samples by subjecting them to real-time fluorescence quantitative Polymerase Chain Reaction [33]. Whether the test is positive or negative, it has to be repeated various times to be certain. Another screening method to identify the presence of SARS-CoV-2 is an antibody screening method. After 7 days of viral infection, the two antibodies, IgG and IgM can be observed in the serum of the affected individual [34]. Immuno- Fluorescent Assay can be effectively used to check the presence of viral antigens in the samples. The samples taken from respiratory fluids tend to give better results because of the large amount of viral deposition in the respiratory tract [35].

## 2. POTENTIAL THERAPEUTIC APPROACHES

Various potential therapeutic approaches have been reported to be efficient in treating patients of SARS-CoV and MERS-CoV. It is therefore perceived that such drugs can possibly cure conditions of SARS-CoV-2 due to the structural resemblance. Following therapeutic approaches are described below:

### 2.1 Antiviral drugs

#### 2.1.1 Chloroquine and hydroxychloroquine

These drugs along with interferons effectively block viral entry in the host cells [36] has shown that viral replication is hindered and gradually decreased by the use of chloroquine in the human epithelial lung cells (L132). There are many speculations regarding the clinical efficacy of chloroquine and hydroxychloroquine, stating these drugs might be a potential source to cure COVID-19. However, the future prospects of these medicines rely on the clinical testing of various animal and mammalian cell lines and elaborative lab research. A combination of chloroquine with azithromycin is also under study as a possible treatment for COVID-19. Although these are antiviral drugs, their potential side effects and combinations with other drugs are grey areas that still need further research [37].

#### 2.1.2 Remdesivir, favipiravir and ribavirin

Another category of drugs simply works through a mechanism that inhibits the synthesis of viral RNA. These drugs include remdesivir, favipiravir and ribavirin. These antiviral medicines - have previously been demonstrated to inhibit viral growth and replication. Remdesivir, a nucleotide analog, has been beneficial in treating patients with Ebola virus,

Marburg virus, Hendra virus and the coronaviruses [38]. All of these viruses have a single-stranded RNA genome. Remdisivir blocks the activity of RNA polymerase and inhibits viral RNA replication [39]. Both favipiravir and ribavirin are broad spectrum anti-viral drugs used against many viral diseases. Some of these are: Ebola virus, yellow fever, chikungunya and enterovirus [40]. They are nucleotide analogue and can inhibit nucleotide synthesis either by chain termination method or by the process of mutagenesis. Furthermore, the use of ribavirin along with interferon alpha (IFN- $\alpha$ ) has proven to reduce the death rate in patients of SARS and MERS [41]. However, like other drugs, ribavirin might have damaging effects on liver and in adverse cases, - can also cause anemia therefore to render it safe for usage, further research is required [42].

### 2.1.3 Other drug combinations

Other drug combinations such as lopinavir-ritonavir and lopinavir-darunavir, viperin, emodin, and promazine can also be used to inhibit viral replication but more studies are required before being certain about these drugs. SARS-CoV-2 gains entry in the host cell via ACE2 receptor and serine 2 which is a trans-membrane protease [43]. Camostat Methylate blocks viral entry in the host cell by down regulating the spike protein responsible for viral entry. Drugs of this sort are under clinical trials before they can be used for patients of COVID-19 [44].

## 2.2 Passive immunotherapy

### 2.2.1 Convalescent plasma

Researchers and doctors are currently figuring out a potential way that can treat COVID-19 cases with minimum side effects. - COVID-19 patients - who are fortunate to recover, can potentially donate their plasma for convalescent plasma therapy [45]. Their plasma already has antibodies against the disease. Hence these critically ill COVID-19 patients who have weaker immune system can be treated with convalescent human plasma [46]. This is thought to be a potential method that can induce passive immunity. Application of this method roots back to an era where antimicrobial agents had not been discovered [47]. In the global pandemic of Influenza virus in 1918, this method was also used to reduce death rate amongst the affected populations. The donor and recipients' blood groups have to be compatible. This therapy can be beneficial in the long run but actual efficacy will be confirmed after clinical trials worldwide [48].

### 2.2.2 Monoclonal Antibodies

There are two types of immunity: Active and Passive. Monoclonal antibodies can induce passive immunity. Another possible approach to develop passive immunity in COVID-19 patients is by using man-made monoclonal antibodies [49]. As the latest research is being carried out on the molecular orientation of SARS-CoV-2, various pharmaceutical companies are aiming to develop specific monoclonal antibodies to treat the disease [50].

## 2.3 Vaccines

The innate immune response is fast and non-antigen specific and while adaptive immune response is comparatively slower but it is specific concerning its antigen. The innate immune response is aided by various guards such as skin and nasal hair that act as a shield against pathogens. Other antimicrobial agents, the complementary cascade and collection of phagocytic cells also aid innate immune response to kill pathogens particularly by identifying non-self-cells followed by inflammatory responses.[51]. Since it is a nonspecific response; therefore, adaptive immunity is more efficient in combating viruses and other

pathogens that are a threat to an organism. The adaptive immune response comprises - antigen specific cells for example the T and B cells. They can kill the infected cells and produce antibodies respectively. Adaptive immunity is known for its special trait: the immunological memory. This implies that in future, whenever the body will be attacked by the previous pathogen that attacked, the body will be quick to retaliate with already existing specific antigenic response. Vaccines work by the same principle as shown in Table 2. Too often vaccines contain dead or live attenuated pathogens that trigger body's immune response to secrete antigen specific antibodies and memory is induced for later times. Vaccines are effective ways of generating immunity but it is a time-consuming process. Some viruses mutate rapidly or have a segmented genome same as in the case of coronavirus [52].

**Table 2: A List of Vaccines Approved by the World Health Organization (WHO) [53]**

Vaccine Name	Type	Doses	Efficacy
Pfizer-BioNTech	mRNA	2 doses, 21 Days Apart	95%
Moderna	mRNA	2, 28 Days Apart	95%
AstraZeneca- University of Oxford	Adenovirus-based	2, 28 Days Apart	70%
Johnson & Johnson	Adenovirus-based	1	66% to 72%
Sputnik V Vaccine	Adenovirus-based	2, 21 Days Apart	91.4%
Sinovac Biotech	Inactivated SARS- CoV-2 virus	2, 2-4 Weeks Apart	50.38% to 91.25%
Sinopharm	Inactivated SARS- CoV-2 virus	2, 3-4 Weeks Apart	79%

### 3. NUTRITIONAL THERAPY

Keeping in mind the current situation of the world, the increasing death rate and severe health problems due to COVID-19, although several potential vaccines have already been launched in the market like Pfizer, AstraZeneca, Sputnik etc. But it will take quite some time for masses to get vaccinated against coronavirus. It has been seen that patients who were malnourished were more prone to catch the severity of this disease. [54]. Moreover,

patients with chronic or severe illness due to COVID-19, tend to have weaker immune response due to which their bodies fail to endure the ailment [55]. Many a time, the connection between immunity and nutrition is not discussed on public health forums. However, studies have shown how some vitamins and trace elements play a vital role in strengthening adaptive and innate immune responses. If their amounts decrease, the immune response is altered in a negative way. If taken in the right dosage, these vitamins and elements can reduce the risk of infection [56].

### 3.1 Vitamins and their potential applications

#### 3.1.1 Vitamin A

It is known to be a fat-soluble vitamin. Three forms of vitamin A are functionally active: retinol, retinal and retinoic acid. This vitamin actively helps the immune system to fight infective agents. Measles and diarrhea are some of the common diseases in which deficiency of vitamin A is directly responsible [57]. Studies have shown that administering the right dosage of Vitamin A can even reduce the mortality rate in patients with diarrhea and measles. Supplementation has also been seen to lower the death rate and intensity of infection in various diseases like lung diseases, HIV infection and malaria [58]. The deficiency of vitamin A in calves make them more susceptible to bovine virus as the inactivated bovine coronavirus vaccines fail to work effectively in the absence of Vitamin A [59]. Another disease that is caused by IBV which is a type of coronaviruses was found to adversely affect the chickens that had Vitamin A deficiency as compared to the populations supplemented with the vitamin [60]. Vitamin A is found to up-regulate the cells of the innate immune system hence reducing the viral infection in the body [61]. It is present in red, yellow, green- leafy vegetables like spinach, carrots, bell peppers etc. Moreover, liver or liver products are enriched in vitamin A, although there is a risk of getting too much vitamin A [62].

#### 3.1.2 Vitamin B

Another water-soluble vitamin, vitamin B also works as coenzymes. Vitamin B is further classified into eight major types. Each type has a distinct function. Vitamin B2, also known as riboflavin, supports energy metabolism in cells and its deficiency can cause health problems. Old aged people often have a deficiency of riboflavin [63]. The combination of riboflavin and Ultra Violet light has been proven effective in reducing the concentration of coronavirus in human blood plasma. Vitamin B3 has various anti-bacterial and anti-inflammatory effects [64]. However large dosage can result in hypoxia [65]. Vitamin B6 is also known as pyridoxine. It is essential for protein metabolism. It also strengthens the immune response. Vitamin B and folic acids are found in many foods e.g., peas, mushrooms, nuts and fish etc. [66].

#### 3.1.3 Vitamin C

Deficiency of vitamin C results in a disease called scurvy. Ascorbic acid, a water-soluble vitamin, works as an anti-oxidant. Vitamin C supports the synthesis of collagen in connective tissues. Vitamin C supports the immune system against coronavirus [67]. Ascorbic acid has a special property: It acts as an antihistamine agent. This property is essential to provide relief from irritation in the respiratory tract. It also provides relief from flu and runny nose [68]. It had been reported that people adequately supplemented with Vitamin C had lower risks of having pneumonia. Hence, respiratory infections can be suppressed via Vitamin C so it is speculated that it might be a potential agent in treating COVID-19 [69]. It is mainly found in citrus fruits (orange, lemon), strawberries, broccoli

and strawberries etc. Although, it cannot be stored in our body so it is needed to be taken every day in the diet [70].

### 3.1.4 Vitamin D

This lipid soluble vitamin plays an integral part in strengthening bones and severe deficiency diseases such as osteoporosis, rickets and osteomalacia can occur if intake is not adequate. The human body is capable of producing vitamin D when exposed to sunlight. In winter seasons, adults have been seen to have vitamin D deficiency because of an absence of sunlight [71]. People who work at night hours or have less exposure to sunlight also have vitamin D deficiency [72]. It contributes to the maturation of immune cells. Multiple studies at the outbreak of coronavirus pandemic demonstrated that deficiency of Vitamin D was directly proportional with the intensity and severity of the disease. Since the viral pandemic emerged in the winter months, susceptible populations were already deficient. Furthermore, the deficiency of Vitamin D is also associated with elevated susceptibility of calves to bovine coronaviruses [73]. It is present abundantly in oily fish, red meat, liver and egg yolks [74].

### 3.1.5 Vitamin E

Vitamin E is found in plant oils, nuts and wheat grams [75]. Tocopherols and tocotrienols are subcategories of Vitamin E. Free radicals have harmful effects on tissues and organs of the body. They can initiate a chain reaction causing oxidative stress. Vitamin E has an anti-oxidative effect by binding with free radicals [76]. An RNA virus coxsackievirus B3, causes infection in mice. The deficiency of this fat-soluble vitamin causes myocardial infarction [77]. Deficiency is also responsible for the severity of bovine coronaviruses in calves [78]. Some trace elements and their importance are shown in Table3.

**Table 3: A list of trace elements and their significance is given below:**

Trace elements	Significance
<b>Zinc</b>	<p>Dietary trace element, essential for adaptive and innate immune cells [79].</p> <p>Zinc is abundant in meat, dairy products and legumes [80].</p> <p>Deficiency results in increased susceptibility to infectious diseases [81].</p> <p>Zinc supplemented diet can reduce the risk of respiratory infections [82].</p> <p>Zinc can reduce viral replication in RNA viruses. Zinc and pyrothione can effectively reduce the replication of SARS-CoV[83]</p>

<b>Selenium</b>	<p>Vital for redox reactions [84].</p> <p>Deficiency can cause oxidative stress so normal pathogens can have drastic effects [85].</p> <p>Deficiency can enhance the virulence of viral pathogens [86].</p> <p>Selenium and vitamin E can assist enzymes to deal with oxidative stress in tissues [87].</p>
<b>Iron</b>	<p>Iron is essential for the host's immunity, excess iron can cause oxidative stress [88].</p> <p>Deficiency has been linked to respiratory tract infections [89].</p>
<b>Copper</b>	<p>Essential trace element, found in nuts, cereals and fruits [90].</p> <p>Prevents oxidative damage in cells and tissues [91].</p> <p>Copper deficiency can increase disease intensity [92].</p> <p>Large amounts can be toxic [93].</p>

### 3.2 Polyunsaturated fatty acids

Their structure comprises of long-chain fatty acids. They play role in assisting adaptive immune responses. They are mediators of inflammatory responses in the body. They can either halt these responses or stimulate them. Resolvins and protectins are anti-inflammatory molecules and Omega-3 PUFAs are their precursors. Omega-6 PUFAs are the precursors of pro-inflammatory molecules, prostaglandins and leukotrienes. Therefore, the body needs a balance between the types of PUFAs for a better immune response [94]. Fish and fish oils are abundant in PUFAs. The EPA and DHA trigger anti-inflammatory responses by incorporating them into cell membranes. Consequently, the eicosanoid synthesis is altered [95].

## 4. HERBAL MEDICINE

### 4.1 Chinese herbal medicine

Chinese medicine makes ample use of glycyrrhizin which is abundant in liquorice roots. Studies have shown the possibility of inhibiting SARS viral replication by glycyrrhizin. It inhibited the growth of SARS virus [96]. It was also found that the ethanol extracted from the *Scutellaria baicalensis* and it is very important component baicalein inhibit the viral replication of SARS-CoV-2 [97]. Hence Chinese medicine can also be a potential method in curing viral infection. The effectiveness of these herbal medicines can be

enhanced by coupling them with immune enhancers and better nutritional supplements to reinforce the immune system against pathogens.

#### 4.2 Echinacea purpurea

Echinacea, popularly known as “purple coneflower” is a European herbal medicine that has shown effective results towards viral infections. Extracts of *E. purpurea* consists of polysaccharides, caffeic and chicoric acids and alkylamides etc. It acts via direct virucidal activity. A study conducted by Burger et al. in the USA demonstrated that commercially manufactured products of Echinacea display more of an immunostimulatory effect than an immunosuppressor [98]. The study showed that Echinacea moderated the release of several cytokines by macrophages. So, Echinacea can serve as a potential treatment towards SARS-CoV-2 due to its virucidal characteristics. Although it still needs to undergo clinical trials [99].

#### 4.3 Curcumin

Curcumin, a member of the ginger family is an herbal plant known as rhizomatous. It is famous for its health benefits since ancient times. Some of these benefits include its anti-inflammatory and antioxidant properties. Due to these properties, it is used to treat several diseases like diabetes, cardiovascular diseases, obesity and hypertension etc. However, it can take quite some time in reducing - blood pressure [100].

### 5. Conclusions

Viral infections have always been difficult to treat and almost impossible to eradicate because viruses mutate rapidly. The COVID -19 pandemic has either killed or affected most of the population of the world, scientists, researchers and doctors all over the world are trying to find the best possible cures for this disease. So far, the approaches used to treat previous viral infections similar to SARS- CoV-2, are being considered but to generate a proper conclusion about their efficacy still needs more time. While many steroidal medicines can be a potential cure, their side effects are still unknown. Convalescent plasma therapy was used to cure Influenza patients and it was proven to be effective. Doctors and researchers are speculating that convalescent plasma can effectively help the infected patients because it already has antibodies against the viral pathogen. Currently, many vaccination programs are being carried out in different countries but their effectiveness towards new strains of COVID-19 is unknown. There is a large variation in the intensity of SARS-CoV-2. The novel virus is severely affecting people with weaker immune system so many nutritional therapies with vitamins and trace elements are being prescribed to patients to boost their immune system. Herbal medicines and extracts are also recommended in some parts of the world by health care professionals and nutritionists. All of these nutritional and therapeutic approaches aim to strengthen the immune response of the host, thereby increasing the chances of survival and recovery. In the current situation, all potential nutritional approaches can be used to treat COVID-19 but it still has not been under proper clinical trials so their harmful effects are unknown. Although if their efficacy is confirmed, these herbal medicines and extracts and therapeutic approaches may be effective towards all variants of this viral disease.

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