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Prospects of Nutritional Interventions in the Care of COVID-19 Patients

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Abstract: The novel coronavirus diseases 2019 (COVID-19) has unfolded an unprecedented worldwide public health emergency with disastrous economic consequences. Around 12 million coronavirus cases have already been identified with over half a million death. Despite numerous efforts by government as well as international organizations, these numbers are still increasing with a surprising rate. Although urgent and absolutely necessary, a reliable therapeutic or vaccine is still elusive and this status quo may remain for an uncertain period of time. Taken that into account, boosting up adaptive immunity through nutritional interventions may help subside this epidemic and save many lives. This review focuses on the nexus between a balanced diet and adaptive immunity, particularly, how poor diet may lead to compromised immunity resulting in susceptibility to the viral infections. Additionally, we discuss how nutrients (vitamins, minerals, trace elements) could be used as a tool to modulate immune response and thus impede viral infections. The study also summarized nutritional recommendations to combat COVID-19 in different countries and territories and dietary sources of those key nutrients. Moreover, different nutritional intervention strategies based on different age groups, physiological and medical conditions were also included, and the challenges of nutritional interventions towards the care of COVID-19 patient were also discussed. Since the availability of a drug or vaccine is still uncertain, a balanced diet or nutrient therapy could be used as a robust strategy to combat COVID-19. Thus, we hope this review may help to make an informed decision with regard to diet choice both at individual level as well as clinical settings.

Keywords: Macronutrients; Micronutrients; COVID-19; SARS-CoV-2; Immunity; Complications;

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Background

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by a newly emerged coronavirus which was first detected in Wuhan, China during December 2019 [1]. Within a few days, several patients from Wuhan, China were admitted to the hospital, whereas most of the patients showed symptoms of pneumonia [2]. Now, it has been spread around 215 countries with its pandemic notion [3]. As a consequence of rapid transmission, WHO declared a public health emergency of international concern (PHEIC) alarm on January 30, 2020. Coronavirus is not newly appeared, rather in 2003, the severe acute respiratory syndrome (SARS) outbreak appeared in another state of China (Guangdong, southern China) for 8000 cases and resulted in 800 deaths in 26 countries and characterized as SARS CoV. Later on, in September 2012, MERS-CoV (Middle East respiratory syndrome coronavirus) associated deaths were reported in 858 cases. The disease, novel coronavirus (2019-nCoV) transmission occurred due to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [4,5]. Mathematical modeling analysis estimated the basic reproductive number R_0 of the SARS-CoV-2 in the range of 2.24 to 3.58 with mean incubation period of 6.4 days [6,7].The R_0 higher than 1 implies that the transmission can occur continuously causes an epidemic or pandemic if left uncontrolled. Even though the mortality rate is much lower than that of SARS (10.87%) and MERS (34.4%), the highly contagious SARS-CoV-2 confirmed cases around the globe after 6 months of emergence is alarming [8,9]. Immunocompromised people such as elderly ones, underrepresented minorities and the ones with pre-existing comorbidities are in the high risk groups of infection[22]. Moreover, like SARS and MERS-CoV, SARS-CoV-2 coronavirus presumed to escape human immune detection at initial stage of infection and may dampen the immune function. The vaccine trials for SARS-CoV-2 are going on with some positive results in some developing and developed countries but a certified vaccine is not available yet. In this context, enhancing the body's immune system to combat the disease till launching of an effective vaccine is necessary. However, in an organism, the immune system is a key performer that compromises defense not only for the common diseases and health complications like abnormal cell development and cancers, arthritis, allergies, but also from pathogenic infections by bacteria [10] and viruses including novel coronavirus (COVID-19). The immune defense system uses numerous plasma proteins (blood proteins, Immunoglobulin G (IgG), hemopexin (heme-binding protein) to modulate the immune response [11]. Besides, great nourishment is fundamental to a strong immune system and malnutrition is the most common cause of immunodeficiency worldwide [12,13]. However, diet is a particular selection of food and drink which is regularly consumed by a person to improve one's physical condition to prevent or treat a disease. A balanced diet ensures proper nutrition

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(carbohydrate, protein, fat, fiber, vitamins, and minerals) which is essential to strong immunity [14]. There is no alternative to a balanced diet to keep ourselves physically and mentally fit. However, immunity is the capability of the organism to fight the attack of microbes and harmful substances [15]. Lack of a balanced diet, poor socioeconomic conditions, health complications, irregularity in lifestyle, environmental problems all together lead to poor diet followed by compromised immune systems (Figure 1) which ultimately results in an increased risk of infection by pathogens [16]. Hence, taking a healthy diet, ensuring proper nutrition, and maintaining social distance can be the best way as preventive methods to win the battle against the SARS CoV-2. Several researchers are more focusing on the modification of diet to treat the deadly COVID-19 worldwide. Nutritional intervention can work well in this regard to save people from unexpected deaths. Therefore, this review attempted to know about functional foods with antiviral properties to increase immunity against viral infection against SARS CoV-1 and other RNA viruses to focus on the solution for COVID-19.

Global needs of nutritional interventions towards the COVID-19 pandemic

Since its emergence in Wuhan, the COVID-19 infection is spreading alarmingly through infecting a huge number of people with fatality rate of 0.05% till date around the world. Although the viral transmission was supposed to be linked with the trade animals in market, there is no conclusive evidence of animal association to date with the COVID-19 infection [17]. However several reports confirmed human to human transmission of this virus through respiratory droplets or close contact with the affected one [18,19]. Asymptomatic viral shedding has caused more severity of this contagious disease leading to high risk of infection [20]. The elderly peoples are more prone to infection compared to the young ones due to shrinkage of naïve T cells for prolonged antigen encounter [21]. Moreover the peoples havingco-morbidities with diabetes, hypertension and other cardiovascular and cerebro-vascular diseases are more likely to be affected severely [22,23,24,25]. SARS-CoV-2 virus can be latent for about 2-14 days in the host leading to non-severe symptomatic infection to acute respiratory distress syndrome (ARDS) with high viral load [26,27]. The virus enters into the body by binding its spike protein with angiotensin-converting enzyme 2 (ACE2) cell receptor predominantly found in the respiratory cells [28]. Type I IFN (IFN-I) response and its downstream cascade plays crucial role in counteracting the viral replication by inducing the adaptive immune system to produce antibody and memory cell. SARS-CoV viruses can block the IFN induction leading to the dysregulation of the immune system which results in cytokine storm and

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eventually death [29]. Hypercytokinemia or cytokine storm is reported in severe cases patients in China. As there is no effective treatment available for the disease, boosting immune response in the preliminary asymptomatic stage is crucial, and for that the person need to be in good health.Long time and consistent healthy dietary pattern is the key determinant of sound health. On the contrary, unhealthy diet and lifestyle promotes the development of non-communicable diseases like diabetes, cardiovascular disease and chronic respiratory disease which has negative impact on prognosis of COVID-19 [30]. An ideal nutritional condition is the prerequisite for regulating the oxidative stress and inflammatory process which ultimately have impact on immune system [31]. Nutrition deficiency resulted in different complications which act as negative prognosis factor in COVID-19 patients. Low pre-albumin level in circulating blood marks malnutrition, which demonstrated to predict the prognosis of COVID patients to the acute respiratory problems leading to the ventilation [32]. Lymphocytopenia, a malnutrition marker, has been observed severely in non-survivor patients till death than the survivor one. Obesity which is caused by consumption of foods high in saturated fat, sugars and carbohydrate has link to high mortality and increase risk to influenza-related complications. Obese and obese like diabetic patient exhibits weaker immune response during antigen presentation due to reduced macrophage activation and cause increased susceptibility to viral infection [33]. So, the nutritional interventions could be an efficient strategy to boost up the overall immunity or health conditions of normal people who further could be able to combat against COVID-19 infection.

Viral susceptibility and common complications associated with nutrient deficiencies

The immune system comprises two lines of defense. They are innate immunity and adaptive immunity [34]. Innate immunity is the rapid immunological, non-specific mechanism to protect the host from an invading pathogen [35] whereas adaptive immunity is the antigen-specific mechanism against virus infection [36]. The virus interaction with the host and spreading strategy of the virus decides the immune response of a patient [37]. The viral antigens can be present in various parts of the body depending on the spreading route and infection stage in the patient. Besides, the host has diverse immune defense functions (humoral immunity through IgA and cell-mediated immunity can eliminate local viral infections). Humoral immunity stimulates B lymphocytes to produce viral antigen-specific antibodies [38,39]. Virus recognition by leukocytes of virus-infected cells, cytokines (growth factors that are secreted by certain cells of the immune system) production is stimulated by the virus-infected cells or the virus [40]. Few cells like natural killer (NK) cells, cytotoxic T

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lymphocytes, and macrophages can identify and kill virus-infected cells. Helper T cells can also identify virus-infected cells and produce numerous essential cytokines [41,42]. Cytokines produced by monocytes (monokines), T cells, and natural killer cells (lymphocytes) play vital roles to regulate immune functions and develop antiviral immune functions [43] (Figure 2). However, the nutritional status of a person has an impact on immune cell metabolism and function [44].

Besides, sufficient intake of carbohydrates helps maintain stable blood sugar levels and reduces the body's stress response by modifying the undesirable mobilization of immune cells [45]. Moreover, the severity of protein deficiency affects the mechanisms of primary lymphoid organs (bone marrow, thymus) leading them to generate B and T cell repertoires and reduces the generation of IL-6 and TNF-Alpha by bone marrow cells [46,47]. Vitamins and minerals help optimizing the innate immunity through development, differentiation and chemotaxis of innate cells; activating macrophage and neutrophils killing property and producing antimicrobial proteins. These nutrients also have pleiotropic effect on adaptive immunity and foster the immune function via antibody production and memory cell generation [48].Deficiency of nutrients, whether they are macronutrients (carbohydrates, protein, fat) or micronutrients (vitamins, minerals, trace elements) can lead to impaired immune systems [49] and can increase the risk of bacterial and viral attack [50,51,52]. Moreover, inadequate macronutrients or selected micronutrients, especially vitamins and the minerals magnesium, iron, zinc, selenium can lead to clinically significant immune deficiency and infections in humans [53]. For example, vitamin C deficiency had been reported for susceptibility to respiratory infections like Pneumonia [54]. Similarly, low level of 25-hydroxyvitamin D, a major vitamin D metabolite have found association with acute respiratory tract infection [55].On the contrary, different micronutrients can be achieved from our daily food which can help reduce inflammation, improve immunity due to their antiviral activities [56,57,58]. Vitamins and minerals help optimizing innate immunity by production, differentiation and chemotaxis of innate immune cells and activating macrophage. Common health complications associated with nutrient deficiencies were enlisted in the Table 1 [59-75].

Food nutrients with antiviral activities suggested for COVID-19

Nutrients are classified into two major groups such as macronutrients and micronutrients. Macronutrients include carbohydrates, protein, fat and dietary fiber which are needed in larger

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quantities (g). They are energy-providing nutrients and regulate life processes (growth, development, repair of tissues). Micronutrients are minerals and vitamins which are required in very tiny amounts [76,77]. But together both are extremely important for the normal body functioning in the organism [78,79]. They are involved in triggering many important biochemical reactions [80,81,82,83]. However, micronutrients are getting attention all over the world during the COVID-19 pandemic for its ability to alter the susceptibility to infection [84,85,86]. Cytokines (certain cells secreted substances that affect other cells) lead to inflammation through damaging the lining of the lungs, leading to pneumonia. Vitamins and cytokines modulate immunity and inflammation. Immunity involves vitamins renovate the capability of some cells to produce certain cytokines that affect the mechanism of immune cells [87]. Vitamin E is indispensable to get rid of chronic viral infections [88]. Different water-soluble vitamins like vitamin B complexes, vitamin C, and fat-soluble vitamins (Vitamin A, vitamin D, vitamin E), different trace elements (Zinc, Magnesium, Iron, Selenium) have been proved to show the satisfactory effect on enhancing human immune response. Adequacy of iron can protect from the respiratory tract infections in severely critically infected coronavirus patients. Essential fatty acids such as omega-3 fatty acid that modulate immune function by its action on inflammatory response [89]. Magnesium is associated with the immune system in both innate and acquired responses. It acts as a cofactor for participation in immunoglobulin synthesis and antibody production. Magnesium is the most overlooked electrolyte, although it has an enormous role in immune function [90].Hence, the good nutritional status of the host plays a crucial role to deal with different infectious diseases [91]. Therefore, proper nutrition must be ensured to deal with unexpected infections with people who are vulnerable or who are already attacked by a novel coronavirus. If through diet, the daily required amount of different nutrients are not met, different processed food, and fortified with different nutrients can be a solution. Literature studiesfound a significant role of some food nutrients to tackle a few harmful RNA viruses including SARS viruses through boosting up immunity, and these were presented in the Table 2 [92-100].

Nutritional intervention strategies during COVID-19 pandemic

Nutritional intervention is a planned action that could be implemented to bring out a beneficial alteration in nutrition-related behavior; health condition for a person, a target groupora group of people playing a key role to combat deadly diseases like coronavirus disease [107]. During the coronavirus pandemic outbreak in China, initially, the aged individuals were infected mostly. Although at the very beginning of the COVID-19 outbreak, there was a lower rate of infection among

 doi:10.20944/preprints202007.0533.v1

infants and neonates, gradually, through mutation the virus has been changing the genetic material, attacking infants and causing deaths over time. Development of immune responses varies among different age groups along with gender, physiological conditions and activities [108]. The older malnourished adults are more likely to have inferior health outcomes, longer hospital stays, and increased mortality rate. Therefore, the effective defensive strategies to promote good nutrition among older populations are desired [109,110]. A study showed how meticulously the aging, immunity, virus infection mortality rate are interlinked in human body [111]. The innate, immature, and adaptive immune system, which matures and acquires memory, goes into a decline in adulthood followed by the risks of various kinds of infection [109]. However, vitamin C, vitamin A, vitamin D, Zinc, Iron, Magnesium, vitamin b-12 are using to treat coronavirus patients worldwide with a hope of saving million lives. Literature searches found the application of nutritional interventions (mostly of vitamin C and vitamin D) in few countries like China, Italy, the USA and Iran, and some other countries are also taking into accountthe application of those nutrients on coronavirus patients seriously (Table 3) [112-120].

However, there are three types of nutritional intervention: dietary approaches, fortified, supplementary. Modification of diet might be one of the best approaches. Due to the safety, cost-effectiveness and efficiency for assisting human immune system to combat against COVID-19, dietary supplementation is getting worldwide attention. In a recent RCT study in USA, a decrease in mortality rate was observed when 167 patients with sepsis-related ARAS were given 15 mg/day IV vitamin C [121]. In a multi-nominal logistic regression model, a retrospective study conducted on 212 people in Philippine showed a significant association of serum vitamin D status with COVID-19 patients clinical outcomes [122]. People who are more prone to Influenza or COVID-19, should take 10,000 IU/d vitamin D3 doses for a several weeks to increase serum 25(OH) D concentrations, followed by 5000 IU/d [123]. Vitamin E, being an antioxidant, it can reduce the rate of inflammation [124].Optimum level of vitamin E is indispensable to get rid of chronic viral infections [125]. Therefore, vitamin E must be taken in an adequate portion on a regular basis to reduce the possibility of being infected by SARS CoV-2. But, unfortunately, vitamin E got little attention from medical practitioners as a potential nutritional therapy for COVID-19. Vitamin B-complexes also have enormous role to treat COVID-19. Vitamin B3 treatment significantly inhibited neutrophil infiltration into the lungs with a strong anti-inflammatory effect during ventilator induced lung injury. Blood coagulation is observed in COVID-19 patients leading to deaths [126]. Iron rich food along with vitamin B6 rich food is equally important. Around 70% Iron found in hemoglobin, which carries oxygen to different cells in human body [127]. Vitamin B6 can introduce a new insight to treat

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COVID-19 patients. Perhaps, among COVID-19 patients, due to their lower oxygen level, they sometimes face critical phrase [128]. In that case, to level up their oxygen level, consuming functions as a cofactor in hemoglobin synthesis [129]. If our body faces vitamin B6 deficiency, it will directly hamper the hemoglobin synthesis leading to decrease oxygen level in human body. In severe cases, it is one of the main reasons behind million deaths. Vitamin B6 rich could be an alternative solution in that case.In contrast, deficiency of selenium can be the cause of the mutation of innocuous strains of RNA viruses (Influenza virus, Coxsackie viruses) to heavily pathogenic strains [130]. But there is no credible study is done on Selenium to ensure its impact on SARS-CoV-2.Zinc deficiency associated with cardiovascular dysfunction, obesity, diabetes, cancer and age related complications may be considered as a useful treatment due to its antiviral activity and regulation of inflammatory response [131]. Albeit, till to date, no randomized control trial has done to depict the real impact of Zinc on coronavirus patients. However, SARS CoV-2 interferes heme metabolism in human body through attacking 1-beta chain of hemoglobin and finally capturing porphyrin resulting in Iron deficiency [132]. Deficiency of iron has been acknowledged as a remarkable reason behind the development of recurrent acute respiratory tract infections [133]. As a matter of fact, adequacy of iron can play a vital role in the improvement of respiratory tract infections in severely critical infected coronavirus patients. In china, a cohort study of old age people showed positive feedback as most of the patients' demands for oxygen support or intensive care support were reduced [134]. Still, a randomized control trial including a large population is needed to observe the true benefits of those nutrients combination on COVID-19 patients. Supplementation can be applied for adults if their dietary components cannot meet the Recommended Dietary Allowance (Table 4) [135-159].

Challenges towards the nutritional interventions during COVID19 pandemic

During every pandemic, people all over the world witnessed economic, social and mental pressure from country level to individual level due to sharp decline in GDP growth rate including a drop in domestic economic activity, a decline in exports of clothing and a fall in remittances from Bangladeshi living in abroad. Those factors have huge impact on health sector and research as well. No valid medicine or vaccine is yet discovered to treat SARS CoV-2 infected people. Moreover, the quarantine during the pandemic induces binge eating which results in weight gain. Prolonged stay at home reduces physical activity and exposure to sun leading to low vitamin D in the body. In that case, modification of diet is the best approach to tackle this pandemic. To counteract the negative

 doi:10.20944/preprints202007.0533.v1

impact of reduced physical activities, people should refrain themselves from multiple meals a day with a long overnight fast. Avoiding refined sugar and balanced consumption of protein, seeds and vegetables will be helpful to modulate the immune function to fight against inflammation. Older people need to take more protein than the young ones and it is recommended to take at least 1.0g/kg body weight to maintain muscle mass which may increase in presence of chronic illness.Supplementation strategy with vitamins and minerals should be implemented to overcome the malnutrition of aged ones due to inability of ingesting adequate energy with food. But the saddest part is, without income, it is almost impossible to ensure proper nutrition and healthy lifestyle. Several countries around the world used certain nutritional supplementations in clinical settings to assess their true impact on COVID-19 patients. Unfortunately, all of those trials were predominantly carried out in hospital setting with small sample size which followed a cross-sectional prospective design. The first step to battle against COVID-19 is to successfully identify the Corona positive cases. In least developed countries like Bangladesh, even the medical technologists are not enough trained to collect sample in a right way to symbolize the true positive Coronavirus cases, which is one of the biggest challenges. Some essential nutrients for instance- vitamin A, D,E, zinc, vitamin B complexes were used against Avian Coronavirus, Bovine Coronavirus, SARS-CoV and MERS [160], which were mostly responsible for the epidemic occurrences in the past few decades. During the COVID-19 pandemic, a very few of them have been trialed clinically on hospitalized patients, but their biggest limitations were their small cohort and lack of randomized control trials due to lack of funding, time consuming and expensive. Albeit, all of those nutrient supplement trials should be conducted in a large scale to bring out the true exposure and outcome effects. In a word, the main gaps are mostly correlated to lack of diversified research designs with a priority on both laboratorial and hospital based studies. In a densely populated as well as developing countries like Bangladesh, it is more challenging to improve health sector overnight and increase Corona tests and isolate the positive cases as there is always an economic pressure on the underdeveloped and least developed countries.

Conclusion

Nutritional interventions play a central role in boosting up immunity among all aged groups and thus prevent infections. In many cases, a single nutrient deficiency is associated with compromised immunity and increased susceptibility to infections whereas multiple nutrients deficiency may lead to

 doi:10.20944/preprints202007.0533.v1

more complex and serious health complications in human body. Dietary modifications such as reduced carbohydrate intake and consuming a small amount of fat in diet than the recommended dietary intake may promote immune system resulting in reduction frequency and severity of infectious diseases. Therefore, dietary strategies could serve as a therapeutic tool to reduce the morbidity and mortality rate caused by COVID-19. In this review, we have accumulated the evidence of different dietary strategies to combat COVID-19. In this work, we have found a great consensus that both individual nutrients as well as a combination of multiple nutrients could be supplemented to modulate the severity of COVID-19 at individual level. Furthermore, a community level as well as country level dietary guidelines for at risk populations may help to modulate the trajectory of COVID-19 pandemic both at national and global level. This current work could be used as a resource for different nutrients and their functions, dietary sources and recommended intake for different age groups.

Author Contributions Statement

SA, FRB and MH initiated this topic and together designed the manuscript structure. THE supported data collection and analysis. SA, FRB and MH finalized the manuscript. SA and FRB two authors contributed equally.

SA=Sabiha Alam

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Declaration of Competing Interest

The authors have declared no conflict of interest.

Footnotes

The authors did not receive any fund for this study. They reviewed the literatures to get a good insights in food linked to micronutrients and immunology and to deliver the understanding for human welfare as immediate action in response to COVID 19 pandemic situation.

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Table 1: Common health complications associated with nutrient deficiencies

Nutrients deficiency	**Consequences** **Immunity involved (II)/ Health issues (HI)**	**Ref.**
Vitamin A (antioxidant)	II) Impairs of innate immunity HI) Increases mortality in infants and children	[59]
	II) Impairs antibody responses HI) Increases different health complications	[60]
Vitamin B complexes	II) Impairsimmune function	[61]
Vitamin B6 (cofactor of hemoglobin synthesis)	HI) Hampers the hemoglobin synthesis that lead to decrease in oxygen level in the human body.	[62]
Vitamin C (Antioxidant)	II) Boosts up immunity	[63]
Vitamin D	II) Induces Cathelicidins as well as Defensins ; reducesthe replication rate of viruses and decline the concentration of pro-inflammatory substances (cytokines)	[64]

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Vitamin E (Antioxidant)	II) Reduces the rate of inflammation and retard physical and mental growth in children	[65] [66]
Magnesium (Electrolyte)	II) Impairs innate and acquired immune responses, Cofactor for participation in immunoglobulin synthesis	[67][68] [69]
Iron	II) Impairs of immune cells proliferation and maturation and a particular response to infection HI) IntroducesCognitive and behavioral problems in children,development of recurrent acute respiratory tract infections	[70][71][72]
Zinc (Antioxidant)	II) Impairs the outgrowth and activation of T lymphocytes, B lymphocytes, antibody production (specifically Immunoglobulin G) eosinophils concentration, HI) Retards fetus growth by causing the recurrent abortion in pregnant women	[73][74]
Selenium	II) Responsible for the mutation of innocuous strains of RNA viruses (Influenza virus, Coxsackie viruses) to heavily pathogenic strains HI) Accountable for recurrent abortion in pregnant women	[75]

Table 2: General supportive and key food items to stimulate human immune system

Nutrition Interventions	**Susceptible viruses**	**Major Food groups**			**Ref.**
		Plant origin	**Animal origin**	**Others (Processed food and nutrient supplementation)**	
Fat-soluble Vitamin A	Measles virus, Human Immunodeficiency Virus (HIV), Avian Coronavirus	Orange and yellow vegetables,fruits,broccoli, most dark green vegetables, spinach	Eggs, cod liver oil, beef liver	Fortified skim milk	[92]
Water-soluble Vitamin B complexes	MERS-CoV; Ventilator-induced Lung Injury	Brown rice, legumes, sunflower seeds and nuts, fruits (bananas, citrus fruits), dark leafy	Red meat, poultry, fish, eggs, salmon, liver and other organ meats,milk, cheese, oysters,	Cheese, yogurt, nutritional and brewer's yeasts, fortified cereal	[93]

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		vegetables	mussels, pork		
Vitamin B6	HIV	Bread, whole grain cereals (brown rice, oat meal), vegetables, Soybean, potatoes, banana, spinach, seeds, carrot	Pork, fish, poultry (Chicken, turkey), eggs, milk, beef liver, beef	Vitamin B6 can be used as dietary supplement	[94]
Vitamin C	Avian Coronavirus; Lower respiratory tract infections	Citrus fruits, broccoli, cauliflower, sweet potato, strawberries, tomatoes, papaya	Beef liver, oysters, pork liver, eggs	Vitamin C tablets can be taken as a supplementation	[95]
Vitamin D	Bovine Coronavirus	seaweeds, oat, soy milk, cereal,	Marine fish, beef liver, cheese, egg yolk, milk, shrimp, mushrooms	Cheese, fortified soy milk, fortified cereal, Vitamin D tablets can be taken as a supplementation	[96]
Vitamin E	Coxsackie Virus, Bovine Coronavirus, HIV virus	Vegetable oils, nuts, seeds, green leafy vegetables	Marine fish, octopus, goose meat	Vitamin E fortified oil, Vitamin E capsule can be taken as a supplement	[97][98] [99]
Omega-3 polyunsaturated fatty acids (PUFA)	Influenza virus, Human Immunodeficiency virus	walnuts, canola oil, spinach, soybeans	Marine fish, shrimp, oysters,	Omega-3 fatty acids can be used as supplements	[100]
Magnesium		Green leafy vegetables, fruits (banana, avocado), nuts, seeds, legumes, peas, spinach, oatmeal	seafood (Salmon, mackerel, tuna), shrimp, egg, milk, beef, chicken,	Magnesium pills	[101]
Iron	Viral mutations	Legumes, pumpkin seeds, nuts, oats, brown rice,	organ meats, beef spleen, pork liver, clams, egg	Dark chocolate, meanwhile Iron the tablet can be taken as a	[102]

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		spinach, beans, potatoes	yolk, shrimp	supplementation	
Zinc	Measles virus, SARS-CoV	nuts, sesame seeds, pumpkin seeds, soybeans whole grains	Meat, shellfish, dairy products, eggs, poultry	Cheese, dark chocolate, cocoa powder	[52]
Selenium	Influenza Virus, Avian Coronavirus; Viral mutations	Almonds, pumpkin seeds, sunflower seeds, whole wheat bread	Fish, eggs pork, beef, chicken, turkey		[103]
Tannins	Influenza Virus	Tea (Green Tea, Oolong Tea, Black Tea, Puer Tea), berries, walnuts	Not available in animals	wine, chocolates	[104]
Essential oils	reducing flu virus (RNA virus) activity in vitro	carrot seed, cinnamon bark, clove bud, sweet orange, eucalyptus, rosemary, and orange, lemon	Not available in animals	Essential oils are available as supplements	[105] [106]

Table 3: Current status of nutritional intervention strategies for COVID-19 patients

Nutritional Intervention	Nutrient Type	Applied Nutrients	Mode of Actions against COVID-19	Referred Countries	Ref.
Dietary approach and supplementation	Micronutrient	Vitamin C	1)Inhibit cytokine storm through reducing inflammation rate 2) Reduce respiratory tract infection	China, Italy, USA, Iran, Bangladesh	[112] [113]
Dietary approach and supplementation	Micronutrient	Vitamin D	1)Vitamin D tablets can be taken to reduce mortality rate 2)Suppress cytokine storm in human body	China, France, Italy, USA, Germany, Iran, South Korea, Philippine, Indonesia	[114] [115] [116]
Dietary approach and	Micronutrient	Zinc	Hypothesized to treat COVID-19	University of Melbourn	[117]

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supplementation			patients with it due to its antiviral activities and modulation of immune response	proposed for the world first trial	
Combined supplementation	Micronutrients	Magnesium, Vitamin B12, Vitamin D	Reduce patients' demands for oxygen support and intensive care support	China	[118]
Oral Supplementation	Macronutrient (Protein)	High dose oral and/or IV Glutathione	Reduces respiratory symptoms	New York, USA	[119]
Food supplementation	Micronutrients	Copper, Iodine, Selenium, Zinc	Immune enhancers towards SARS CoV 2	Egypt	[120]

Table 4: Nutrient recommendations of COVID-19 patients based on different age groups and physiological conditions

Target groups	Complications	Recommendations	Health Benefits	Ref.
Pregnant and lactating women	Iron, zinc, calcium, vitamin A, vitamin D, and folic acid deficiency	Protein, Zn, Ca, and folate-rich food. Supplementation is prohibited for infants.	Reduces infection in child by increasing the immune response	[135] [136] [137] [138]
Puberty	During fetusdevelopment enormous hormonal changes occur which are associated with sexual maturation	Nutritional balance is linked to hormonal balance and can be achieved through improved family food behaviors	Introduces long term immunity	[139][140] [141][142]
Adults	prone to viral infections due to the hormonal imbalance, and	Vitamin D	Anxiety, and depression can be reduced	[143][144][145]

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	non-communicable disease			
Old	Depletion of zinc status	Zn supplementcan be taken into account to build immunity	Blocks the replication of SARS CoV-2	[146] [147]
	Lower oxygen level	Iron-rich food along with vitamin B6 rich foodshould be consumed in proper portion	Assists to level up oxygen level	[148]
	Lower level of Vitamin D	Omega-3 along with Protectin D1, vitamin D and calcium, vitamin E, magnesium, folate can be supplemented as they all are interlinked to each other and increase vitamin D status	Reduces mortality rate through mitigating age related complications	[149][154]. [155]
	Dietary Fibers	Soluble fibers found in oats, barley, peas, apples, citrus fruits, and potatoes as well, Chemically engineered sulfated glucans	Mitigate their constipation and shows strong antiviral activities	[150] [151][152] [153].
	Vitamin deficiencies	Supplementation through Vitamin C, Vitamin E, megavitamin D3 dose therapy	Used to treatduring SARS epidemicto stimulate immunity	[73] [147]
	Abnormal Vitamin E and Vitamin D status allow frequent infections	Vitamin D, Vitamin C, Zinc, and Echinacea in combination must be taken on a regular basis	Worked better in common cold	[156] [157]
	Others	Tannins 3 times daily as tea or from fruits	Safe and highly effective antiviral reagents	[158] [159]

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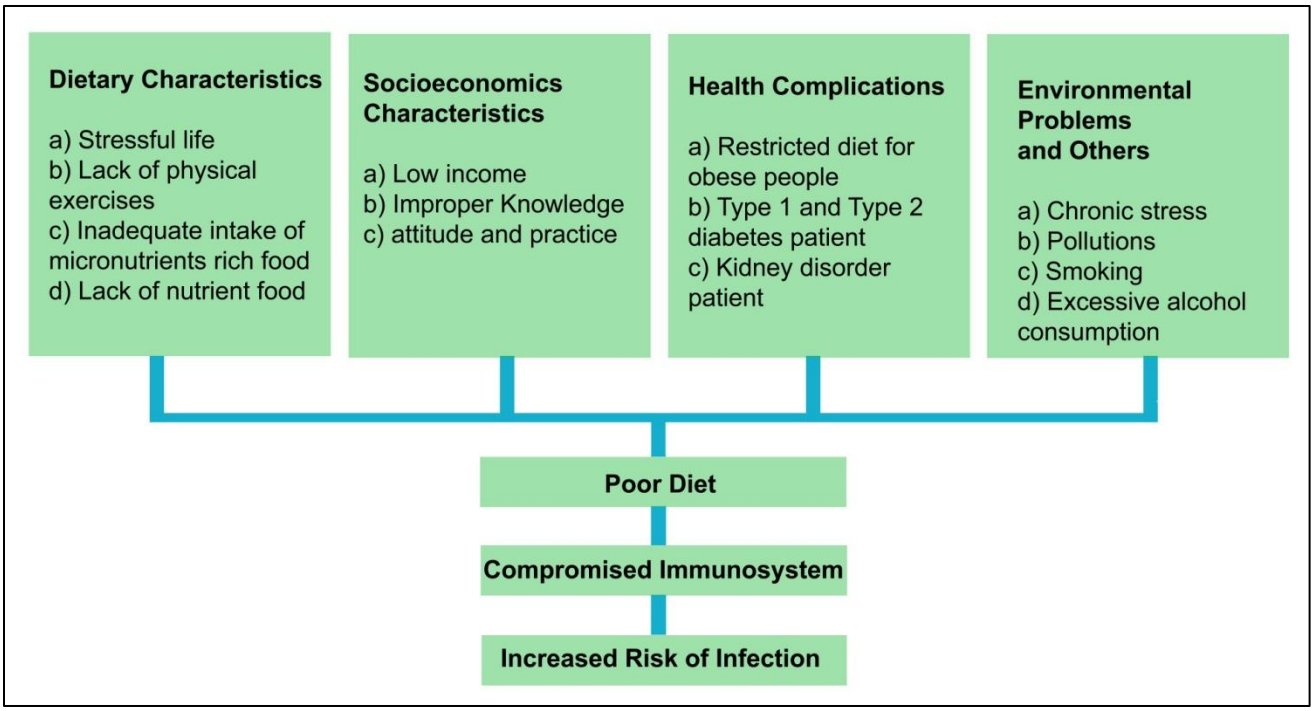

Figure 1: Leading factors towards the higher risk of infection

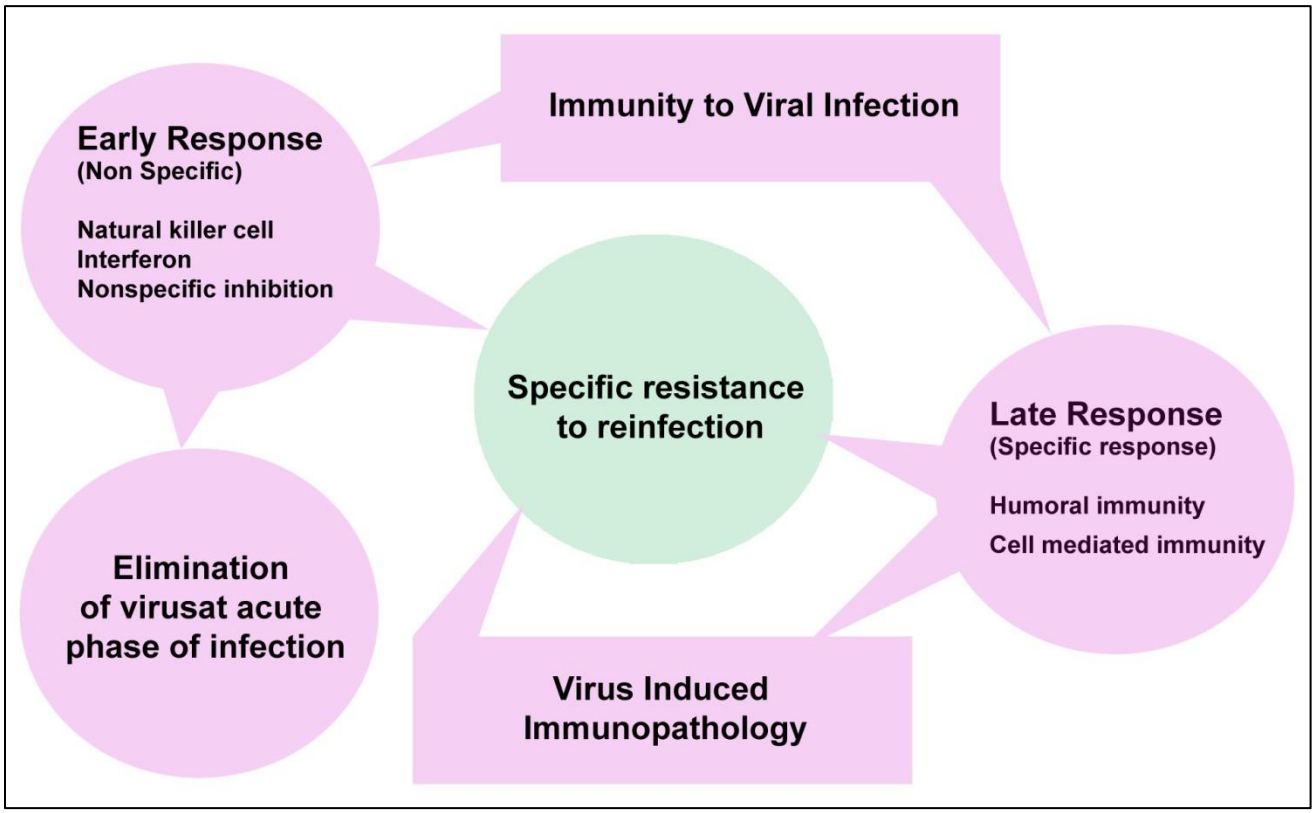

Figure 2: Associated immune response of a virus infected person