

Review article

Organic Diet as Silent Pretreatment Strategy to Boost Immune System Against SARS-CoV-2.

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**ABSTRACT**

Nowadays, world is facing the life-threatening disease SARS-CoV-2 which creates panic situation among people because of no effective treatment modality and lack of chances to get novel vaccination. In such circumstances, self-isolation and prevention to get expose to viral environment is best strategy to safe our society. Healthy and nutritional dietary measures can facilitate us to boost our immunity system against viral attacks. In this review, we discussed the importance of organic diets that can be used to fight against SARS-CoV-2 infection by improving the immune system as pretreatment strategy. We also discussed other factors that can improve immune system such as reducing the stress and inflammation, avoid smoking and toxins and doing moderate exercise daily. Meanwhile, plasma therapy is also under examination to save patient's life, and discussed in this review.

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INTRODUCTION

Coronavirus belongs to Coronavirinae sub-family of Coronaviridea family. This virus is RNA positive and is classified into four genera, Alphacoronavirus, Betacoronavirus, Gamamcoronavirus and Deltacoronavirus. Alpha and Beta coronaviruses infect the mammals while Gamma and Delta viruses infect the birds ^[1]. The virus of this family was first discovered in 1960's. However, in human it was first reported by David A.J. Tyrrell and his coworkers

during the era of cold epidemics in 1965 ^[2] and it gained much more attention of researchers when severe acute respiratory syndrome (SARS) was observed in high percentage in human being in 2003, yet it begins in November 2002 in southern china and reached Hong Kong in February 2003. This virus spread to 29 countries/regions on five continents. This virus hits many countries out of which seven Asian countries are considered as the top ten ^[3]. The virus infected 8422 people and causes 916 deaths

throughout the globe [4]. Almost 8000 cases and 774 deaths caused by SARS was reported in China [5]. The bats were considered as the ancestors of this virus [1]. SARS-related coronavirus has been categorized into alpha coronaviridea and beta coronaviridea that are produced from civet cats and bats, respectively, affects human beings while the later genera responsible to affect various kinds of birds [6,7]. Middle East respiratory syndrome coronavirus was also reported in 2012 that affects humans and camel in Saudi Arabia. Recently, in late December 2019, a novel coronavirus epidemic belong to same coronaviridae family was emerged in Wuhan, China with more than 84000 people has been infected and about 4600 people has died. World health organization named this coronavirus as COVID-19 on mid-January. Now, this virus has spread almost all over the world with more than 5.9 million people infected and nearly 364000 death reported until June 2020 [8]. The prefix "CORONA" arises from a Latin word called "CROWN" which shows the crown like appearance of its spike proteins present on its outer surface. It is basically RNA virus which acts as pathogen and shows human-to-human transmission through sneezing, touching, mouth droplets and coughing. Its size is about 80-220 nm, with spherical shape and having enclosed genome [1].

Mechanism of COVID-19 entry

Coronavirus is usually a lethal disease which infects the respiratory system of a body. Before 2003, viruses of this family moderately affected the respiratory system but now it had severe attack on the respiratory tract. The genes of corona are expressed by complex policy and reported to cause mild or severe infection both in humans and animals. Infection causes to occur when a virus gets a host, penetrate into lungs and replicates. Mainly it affects the healthy cells of the body. The genome of the virus gets multiplied inside the protective protein shell and the spikes protein present on its protective layer helps it to get the entry

in the host cell for viral activity. The virus travels within the cell membrane of host cell and reached to its nucleus, where it approaches the ribosomes which help the virus genome to multiply several times and Golgi bodies carried them to the vesicles where new virus formed from the host body and it is bud off. When we take air in the alveoli dilate like a balloon, and when we exhale alveoli contracts. Air ways carry the moisture from the mucous which is present around the trachea, bronchi, and bronchioles. Hair like cilia present around the tube continuously pushing the germ and mucous out of your body. Cells of your immune system kill the virus which enters to the body. But if the immune system is weak just in case of old aged people, it enters into your alveoli which become filled with the fluid causing it difficult for breathing. Incubation period of this virus is 2 to 14 days, and its symptoms range from mild to severe depending upon the immunity level of the host. According to a survey almost 2 to 4 percent population is at risk by this virus [9]. The schematic route of inhaling and entry to lungs is presented in Figure 1.

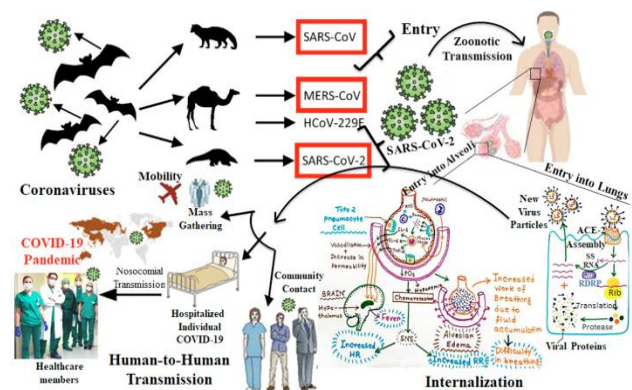


Figure 1: Schematic representation of entry, internalization and transmission of SARS-CoV-2 in host person

It is not necessary that the virus spread through the person who has clear symptoms of the disease, the other carrier person can also spread coronavirus through mouth droplets, touching, sneezing and coughing. Here, the carrier means the person having

coronavirus in his/ her body either symptomatic or asymptomatic and can transfer this virus into other person, termed as human-to-human transmission. However, it is impossible to predict that exactly how much of the current coronavirus outbreak has been fueled by asymptomatic, mildly symptomatic, or pre-symptomatic people. That's why the social distancing is far better choice than unnecessary or overcrowded public gatherings ^[10].

Diagnosis of COVID-19

The symptoms of this disease are mainly depending upon few parameters including age, sex, past medical history and most importantly diet. It is a transmissible viral infection that affects the living cells. It is ingested orally creates initially flu like symptoms with continuous temperature and the victim feels dry cough, limb pain, muscular pain with inflamed lymph nodes. It causes cold diseases of the upper respiratory tract, rarely infecting the lower airways ^[11].

In infants and young children, the infection can take a much severe course and can be associated with croup like symptoms like flu, running nose etc. It also led to asthma and in some patients, it causes bronchitis and pneumonia ^[12]. In cases of pre-existing respiratory diseases such as asthma and chronic bronchitis, these symptoms can be strengthened in both children and adults. Human coronaviruses have also been associated with disorders of the gastrointestinal system. This appears to occur only in immunologically compromised individuals, e.g. in AIDS patients, who can also have prolonged diarrhea. The presence of viral nucleic acid is examined by using polymerase chain reaction (PCR) from appropriate clinical modalities ^[13].

Current treatment strategies

Coronavirus December-2019 (COVID-19) has now become pandemic with no specific and approved therapeutic treatment with substantial mortality rate. It is critical to find new treatments with fewer side

effects, low mortality rate and high therapeutic index. To determine whether convalescent plasma transfusion may be beneficial in the treatment of critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Patients received transfusion with convalescent plasma with a SARS-CoV-2 specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immune sorbent assay [ELISA]) and a neutralization titer greater than 40 (endpoint dilution titer) that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission. In this preliminary uncontrolled case, the series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in wider clinical trials ^[14].

The mechanism of interaction of SARS-CoV-2, against immune system and the immunopathological damage to the host merit was further investigated. The successful fight back against SARS-CoV-2 was attributed mainly to traditional pavement-pounding epidemiological control measures rather than advances of modern medicine. It must also be emphasized that the immune system played a vital role in defending against SARS-CoV-2 virus, since none of the drugs employed to treat the virus or to inhibit the viral replication in vivo. Strong humoral responses have been found in most patients following SARS-CoV-2 infection, with high titers of neutralizing Abs present in their convalescent sera. The nucleocapsid (N) and spike (S) proteins of SARS-CoV-2 appear to be the dominant antigens recognized by serum Abs CD4+ T-cell responses against the N protein have been observed in COVID-19 patients and an HLA-A2-restricted cytotoxic T-lymphocyte epitope

in the S protein has been identified. It should also be emphasized that leukopenia and lymphopenia are present in other viral diseases such as measles, respiratory syncytial virus disease and sepsis the mechanism for which is also unclear. It is likely that the immune responses induced by SARS-CoV-2 infection could also cause pathological damage to the host, especially in the case of pro-inflammatory cytokines. It is also investigated that the immune system and local tissues are essential targets to future diagnosis, control and treatment of this very contagious disease [15].

Infections with human coronavirus EMC (HCoV-EMC) are related with severe pneumonia. We reveal that HCoV-EMC resembles severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in productively infecting primary and continuous cells of the human airways and in preventing the induction of interferon regulatory factor 3 (IRF-3)-mediated antiviral alpha/beta interferon (IFN- β) responses. As test systems, we used two established continuous cell line models for SARS-CoV-2 namely, Calu-3 (derived from human bronchial epithelium) and Vero (derived from the kidney of an African green monkey), and primary non differentiated HTBE cells for comparison. These cells were pretreated overnight with different amounts of human IFN- β and infected with the coronaviruses at a multiplicity of infection (MOI) of 0.01, and virus yields were determined by a TC-ID50 (half maximal tissue culture infective dose) assay. However, HCoV-EMC was markedly more sensitive to the antiviral state established by ectopic IFN. Thus, HCoV-EMC can utilize a broad range of human cell substrates and suppress IFN induction, but it does not reach the IFN resistance of SARS-CoV-2. We found robust virus replication in differentiated and non-differentiated primary airway epithelial cells, in the lung-derived cell line Calu3, and in the kidney cell lines Vero and 293, whereas the lung cell line A549 is abortively infected. In any case, treatment with IFN, which is an approved drug against a variety of viral,

malignant and autoimmune diseases appears to be a promising therapeutic option against HCoV-EMC [16].

No doubt antiviral and supportive treatments are very important in the treatment of patients with COVID-19. As Cytokine storm (CS) is relatively common in severe cases and often lead to the exacerbation, while anti-inflammation therapy may help in preventing further injury. As we know, there are a variety of anti-inflammatory medications, including non-steroidal anti-inflammatory drugs (NSAID), glucocorticoids, chloroquine/ hydroxyl chloroquine, immune suppressants, inflammatory cytokines antagonists (such as IL6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists, janus kinase inhibitor (JAK) inhibitors), suggested that tailored therapy in stage III hinges on the use of immune modulatory agents to reduce systemic inflammation before it overwhelmingly results in multi-organ dysfunction. In this phase, use of corticosteroids may be justified in concert with the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist). Intravenous immune globulin (IVIG) may also play a role in modulating an immune system that is in a hyper-inflammatory state. Overall, the prognosis and recovery from this critical stage of illness is poor and prompt recognition and application of such therapy may have the greatest yield [17].

It is an ugly fact that a significant amount of the world's population will contract SARS-CoV-2 infection with the current spreading. While specific treatment is not yet available, individual risk assessment and management strategies are crucial. The individual preventive and protective measures drive the personal risk of getting the disease. Among the virus-contracted hosts, their different metabolic status, as determined by their diet, nutrition, age, sex, medical conditions, lifestyle, and environmental factors, govern the personal fate toward different clinical severity of getting COVID-19, from

asymptomatic, moderate, and severe to death. The careful individual assessment for the possible dietary, nutritional, medical, lifestyle, and environmental risks, together with the proper relevant risk management strategies are the sensible ways to deal with the pandemic of SARS-CoV-2. The individual assessment for the possible dietary, nutritional, lifestyle, and environmental risks together with the proper risk management is considered as sensible way to deal with the pandemic of SARS-CoV-2 [18]. The effects of high cholesterol (CHOL) diet as well as corticosteroids on the toxicity of vitamin D2 (VD2) were studied in the rats. Vitamin D2 was administrated orally at dosage of 5-60 IU/ Kg, once a day, for 4 days. Due to vitamin D2 treatment showed a decrease in mortality in animals which fed CHOL. Dietary CHOL inhibited toxic responses such as a decrease growth rate following anorexia, elevated serum calcium level and calcium deposition in tissues, which were produced by a Sublethal dose of VD2 IU/ Kg. The pre-treatment of animals with the high cholesterol diet from two weeks before the first administration showed much more symptomatic relief than those given this diet after VD2 administration. While dexamethasone (DEX) and corticosterone remarkably increased the mortality after administration of VD2. Degree of toxicity of the VD2 increase by the (DEX) was correlated with degree of hypercalcemia and tissues classification. The inhibitory effects of CHOL are not likely due to activation of the CHOL corticosterone system in the adrenal gland. This study has shown that glucocorticoids increase the population of the 1, 25-dihydroxy-VD receptor in the bone cell and stimulate bone resorption by this metabolite of VD. Therefore, in the present experiments in which rats were treated with glucocorticoids plus VD2 [4] coronavirus termed SARS-CoV-2 is caused severe acute respiratory symptoms. Still no antiviral treatment has been established so far. Interferons are cytokines which

induce the synthesis of several active proteins in the cell.

In this study, we revealed that multiplication of SARS-CoV-2 in the cell culture can be strongly inhibited by pre-treatment with the interferon-beta, interferon-alpha and interferon-gamma; by contrast, these were less effective. Myxovirus resistance protein 1 (MxA) in humans is one of the most prominent proteins induced by interferon-beta. Although, no interference with SARS-CoV-2 replication was detected in Vero cells stably expressing MxA. Therefore, other interferon-induced proteins must be responsible for the strong inhibitory effect of interferon-beta SARS-CoV-2. Experiments show that the Vero cells were chosen because they are unable to synthesize interferons (IFNs) type I but are fully responsive to IFNs treatment. Therefore, any additional effects of virus-induced IFN that would bias the results can be excluded. Cells with pre-treated with the IFNs infected with SARS-CoV-2 and virus in the supernatant was determined after overnight incubation [8].

Furthermore, it has never been reported about such kind of respiratory disease earlier with wide and quick contamination abilities. Hence, SARS-CoV-2 attracts the attention of the world to publicize the awareness with control manual but unfortunately without definitive and approved treatment. For the appeal from frontline clinicians and public health professional's of 2019-nCoV infected pneumonia management, an authentications base guideline pressing needs to be developed. Thus, experts have drafted the rules with quick advice guidelines methodology and common rules of WHO guideline development; also add up the first hand data management of Zhongnan of Wuhan University. It includes guideline scheme, epidemiological characteristic, disorder screening and so on hilarious infection and community anticipation, diagnosis, treatment and control (disease nursing of 2019-nCoV).

These abrupt guidelines are suitable for doctors, nurses, management of hospitals, healthcare centers, civil persons and researchers including all people who are interested in corona virus [19].

Dietary Treatment Strategies

Vaccine is a way to boosting or to develop natural immune system to fight against diseases. It helps in building strong immune system. The presence of white cells called leukocytes in the blood helps the body to fight against incoming viruses. The substance called antibodies naturally present in blood plasma inhibit the virus growth that gets entries from outside the body and strengthen the immune system for further germs attack [4]. All diseases require their unique vaccine to activate the respective antibodies. There are many diseases which are contagious and need vaccine for their cure. The first human vaccine was developed for small pox in 1796 by Edward Jenner. It found a deadly disease which kills about 300 million to 500 million people worldwide in last century. Diseases like Smallpox, Measles, Mumps, Polio, Chickenpox, HPV, Whooping, cough, Diphtheria, can cause death. Therefore, vaccines are developed to overcome the death rate. Vaccine of some disease like Rotavirus, Hepatitis B, Whooping cough, Diphtheria, Mums, Measles, Chickenpox, Pneumococcal disease are given at childhood to create immunity against this disease. Some vaccines are also given in the adult age if one is exposed to some disease. There are some diseases like Hepatitis A, Influenza, Tetanus, Herpes zoster etc. For any infection, naturally antibodies are produced which strengthen our immune system and stopped the growth of any viral genome. Antibodies and interferons are secreted in the nasal secretion, to fight against infections [20].

At the present time there is no special vaccine is available in market for SARS-CoV-2, but the research institutions and universities are going their best to carry out research project for the development of

suitable vaccines, but the whole idea behind this research should the chemistry, biochemistry and working mechanism of coronavirus. It has been observed in many cases that some people have naturally extraordinary resistant to fight against coronavirus due to their good immune system. So, transferring the plasma of a healthy person in infected person helps him to cure. Antibodies that are present in plasma of cure patient attached to spike of corona and block its system. So, corona is not able to attack on living cell [14].

Since SARS-CoV-2 infection is seems to be harmless at all, no remarkable efforts have ever been made in last two decades to develop a vaccine. So, our focus is to develop immune system with steroids and organic diet to fight against the COVID-19. Nutrition support treatments in patients are televised for nutrition risk based on the NRS 2002 score when they are avowing to the hospital. The commend plan for patients with different nutrition risk scores are as follows: First, if the total score is <3 points, it is suggested to eat protein-rich foods (such as eggs, fish, lean meat, dairy products) and carbohydrate-containing diets. The supposed ideal energy ingestion is 25–30 kcal / (kg·d) and the protein mass are 1.5 g / (kg·d). Second, if the total score is ≥ 3 points, the patient should be given nutritional support as soon as possible. It is suggested to raise protein intake by oral nutrition supplement, 2–3 times/ day (≥ 18 g protein/ time). In order to gain the mount of 18 g protein/ time, protein powder can be added on the basis of standard whole protein preparations. Enteral nutrition tube should to be placed when the patient cannot intake supplemental nutrition by oral routine, by keeping in view the condition of patients, provide high-protein, high-vitamin, carbohydrate-containing diets (e.g. eggs, fish, lean meat, milk, etc.) for sufficient nutrition to boost physical condition [21].

Just like vaccine a good food is also very important for the development of strong immune system to fight

against virus and bacteria (fruits and vegetables like berries, citrus fruits, kiwi, apples, red grapes, kale, onions, spinach, sweet potatoes, carrots, fresh garlic and mushroom varieties like shiitake) [22]. In organic plant product, vitamin C, Carotenoids (organically grown plants like sweet, peppers and yellow plum) phenolic compounds, omega-3 fatty acids and conjugated linoleic acid (which is present milk of organically grown animals) are higher in amount than conventional plants [23]. The consumer of organic food evaluates their health status notably better than consumer of non-organic food [24].

Beta carotene gets converted to vitamin A, which is necessary for a strong immune system. It works by helping antibodies respond to toxins and foreign substances. Vitamin C rise blood levels of antibodies and helps to differentiate lymphocytes (white blood cells), which help the body to detect what kind of protection is needed. Some research has suggested that higher levels of vitamin C like ascorbic acid (at least 200 mg) reduces the duration of cold symptoms [25]. Vitamin D increases the production of a protein that "selectively kills infectious agents, including bacteria and viruses. Vitamin D also alters the activity and number of white blood cells, known as T-2 killer lymphocytes, which can reduce the spread of bacteria and viruses. One meta-analysis revealed that zinc supplements may shorten the duration of symptoms of the common cold. Probiotics and prebiotics help boost the health of the microbiome, which in turn supports our immune system. Though "Mild dehydration can be a physical stressor to the body, Women should aim to consume 2.7 liters or 91 ounces of fluids daily, and men, 3.7 liters or 125 ounces; an amount that includes all fluids and water-rich foods, such as fruits, vegetables and soups are listed in Table 1 [26].

Table 1: The intake of water-rich food supports to overcome the deficiency of following Vitamins.

Essential Vitamins	Sources
Vitamin A	Oily fish, carrots, egg yolks, sweet potatoes, cheese, pumpkin, , nuts, seeds, grains and legumes
Vitamin B6 (riboflavin)	Cereals, legumes, green leafy vegetables, fruit, nuts, fish, chicken and meat
Vitamin B9 (folate)	Green leafy vegetables, legumes, nuts, seeds, commercial bread-making flour, rice and pastas
B12	animal products, including eggs, meat and dairy, and also in fortified soy milk
Vitamin C	Oranges, lemons, berries, kiwifruit, strawberries, broccoli, tomatoes and capsicum, leafy green vegetables
Vitamin D	Mainly sunlight, but also found in some foods such as eggs, fish, while some milks and margarine brands may be fortified with it, also found in orange juice.
Vitamin E	Oranges, lemons, bananas, limes, chickpeas, berries, baked potatoes, kiwifruit, broccoli, tomatoes and capsicum, hazelnuts and Spanish Meat, chicken and fish. Vegetarian sources include legumes, whole grains and iron-fortified breakfast cereals also in seafood's.
Iron (Folic Acid)	Oysters, crab like seafood, meat, chicken, dried beans and nuts, yogurt and chickpeas.
Zinc	Nuts, especially Brazil nuts and meat, cereals and mushrooms

Immune system depends upon the nutrients to function well. Nutrients may be micronutrients as well as macronutrients. The balanced level of both is necessary for the proper functioning of immune system.

Role of Macronutrients

Macronutrients include carbohydrates, proteins, and fats. Carbohydrates are the rich source of calories. Intake of proteins and some amino acids like arginine, glutamine, taurine and sulfur containing amino acids are responsible for the immunomodulatory properties. Polyunsaturated fatty acids help for the proper functioning of the cell, also omega-3fatty acid is responsible for better immune cell function. Omega-

3 and omega-6 PUFAs helps to promote the anti-inflammatory and pro-inflammatory and helps to fight against COVID-19 [27].

Role of Micronutrients and Trace Elements

Vitamin A (retinol, retinoic acid, beta carotene) is considered as the fat-soluble vitamin. It plays an important role for the immune system to develop and function properly. This vitamin proved very beneficial for the humoral and innate immune system. Literature highlights the importance of isotretinoin (a derivative of vitamin A) whose intake suppresses the activity of angiotensin-converting enzyme-2 (ACE-2), a cellular protein serves as host protein for internalization of SARS-CoV-2 in the body. Food like carrots, spinach and sweet potato are considered as rich source of vitamin A [28, 29].

Vitamin C Literature shows the importance of vitamin C (which is known as ascorbic acid) to support the immune function and to help fight against corona virus. It is a very powerful antioxidant and enzymatic co-factor for many physiological reactions occurs in the body like hormone production and collagen synthesis etc. As COVID-19 affects the lower respiratory track, Results of the study shown that intake of vitamin C by corona patients reported less chance of getting pneumonia. Food rich in vitamin C are citrus fruits like orange, lemon, kiwi [28].

Zinc is considered very important part of white blood cells. It helps in the proper growth, development of the immune system. It is basically preventing the body against infectious diseases. Literature shows people with low level of zinc in their body are more susceptible to flu, cold, and increases the risk of HIV and HCV. Most of the nuts like almonds, cashews, milk products, red meat are rich source of zinc [28].

Copper plays a very important role in immunity by production of immune cells. Literature reported the antiviral properties of copper. As, thujaplicin-copper chelates reduced or control the replication of human

influenza virus. Copper is required by the body in small amount for the production of red blood cells, bones, for proper processing of cholesterol and for the development of babies in the womb. Food rich in copper are Lobsters, green leafy, nuts and seeds, dark chocolate [28, 30].

In case of immunity vitamin D plays a vital role. Vitamin D is very necessary for bone and mineral homeostasis. Vitamin D deficiency leads to multiple diseases. Recent study reported that vitamin D3 is an immune modulator with shows its impact on both innate and adaptive immunity. Therapies that target vitamin D3 signals provide new ways for infected and inflammatory skin diseases by affecting both innate and adaptive immune functions. There are two sources by which vitamin D can be intake i.e., by diet and the other is by direct exposure of solar UV light on the skin [31]. It is very important for our body to have strong immune system which acts as an army for our body. If our immune system is weak then there are high possibilities of flourishing the bacteria and other viruses in our body [32].

Vitamin D Sources and Importance

Immune system can be boost up by using the diet rich in vitamins, minerals. Out of all the vitamins, vitamin D is considered as one of the most important vitamins to help the body to fight against the flu and cold virus. Vitamin D helps to boost the innate immune response, which is the body's first line of defense against microbes. When the vitamin D level goes down, the ability of our body to recover from illness become weaker. Vitamin D is considered as the "Sun shines" vitamin and it also has "Antioxidant" property. Literature says that Vitamin D is not actually vitamin, but it is a prohormone which is synthesized in the body as a result of interaction between cholesterol, skin and the sun exposure. Since Vitamin D is considered as the fat soluble Vitamin, meaning that it is absorb best with the fish liver oil and other fatty foods for good absorption of it. As, vitamin

d is fat soluble so it cannot be easily excreted from the body, and its over dosage could be toxic for our body so it should be taken in a proper range. Instead of getting vitamin D from food or sunlight as during the cold months of the year, it can be taken from the supplements, but before going to supplements once should consult a Doctor because it is necessary to take it in normal range.

Dosage of Vitamin D

Most recommend dosage of Vitamin D is from 400 IU to upward to 10,000 IU but it depends upon the age, weight and other factors like absorption capacity of the body. Physician suggest that an adult should take a range from 5000 IU to 10,000 IU/ day depends upon the body weight, while children should take 1,000 IU/ day depending upon their body weight [31].

Mechanism to activate Vitamin D

Vitamin D is produced in the body as a result of immediate exposure to sunlight, but vitamin D produced by this way is actually in inactive form. There is a complete mechanism by which vitamin is converted into its active form. But there are many factors by which its production is inhibited in the body like latitude, season, use of sun block and skin pigmentation. It is actually the Melanin hormone in the body which absorbs the UV light from the sun and inhibits the production of active Vitamin D from 7-dihydrocholesterol. This inactive form of vitamin goes into the liver where it is converted into 25OH vitamin D₃, D₃ (25 D) by hydroxylation. This compound is also inactive but it is useful by measuring a person's vitamin D status in the body. This inactive compound is converted into its active form 1, 25-dihydroxy vitamin D (1, 25-D) or also called calcidiol. This action is completed in the kidney with the help of an enzyme named 1- α -hydroxylase (CYP27B1) which is stimulated by PTH. This active form 1, 25-dihydroxy vitamin D (1, 25-D) may further metabolize into the inactive form 1, 24, 25 vitamin D by the action of an

enzyme called 24-hydroxylase (CYP24). The level of vitamin D in the body is maintained by the compound 1, 25-dihydroxy vitamin D (1, 25-D) which inhibits the 1- α -hydroxylase enzyme in the kidney and stimulates the 24-hydroxylase enzymes to maintain the excessive vitamin D activity in the body.

Role of Vitamin D

This active compound 1, 25-dihydroxy vitamin D (1, 25-D) helps to maintain many functions in the body, like it acts on the intestine for the calcium re-absorption and promote osteoblast differentiation and matrix calcification. Vitamin D help to treat the infectious disease like Tuberculosis when there was no antibiotic, the patient of the tuberculosis was treated by direct exposure to sunlight, which is thought to kill the tuberculosis infection. Literature shows a link between Vitamin D and respiratory infections. A report was published in which people with low level of Vitamin D affects with the upper respiratory infections. There were also other diseases which was common due to vitamin D deficiency like bacterial vaginosis and HIV. This all thought due to low level of vitamin D in affected individual [33].

Vitamin D, Cytokines and Immune system

Our immune system works best by the help of cytokines. Cytokines are the protein cells which are released by the immune system. Cytokines are actually acted as chemical messengers in our body, passing information from one cell to other cell with the help of receptors on their head. Cytokines are of different types and can work with each other, work together or work against each other but their duty is to regulate the immune response [34]. Although the role of cytokines is positive but in a normal range, higher or lower production of cytokines in the body can lead to the weakening of immune system in our body which further leads to the effect of infection long lasting. Cytokine storm can be the result of an infection, or autoimmune condition, or many other

diseases. Cytokine storm could be life threatening and also cause the failure of multiple organs in the body [35]. Among the infectious diseases COVID-19 is one of the most dangerous and life-threatening infection the world faces these days.

Vitamin D actually controls the cytokines level in our body, study have shown that vitamin D suppresses the cytokines production in our body, also boosting our immune system and help to fight against the infection.

Vitamin D and COVID-19

Although there is only the hypothesis regarding a link between the COVID-19 and Vitamin D but Researches shown the role of vitamin D to control the cytokines storm against the Viral influenza pandemic during 1918 – 1919 [36]. Vitamin D enhances the cellular innate immunity by reducing the cytokines storm. Vitamin D can produce both pro-inflammatory and anti-inflammatory cytokines. Vitamin D reduces the production of pro-inflammatory Th1 cytokines like tumor necrosis factor- α and interferon- γ . Literature study shows there is a link between COVID-19 and pro-inflammatory cytokines, C-reactive protein, increased risk of pneumonia, sepsis, acute respiratory distress syndrome, and heart failure. When the COVID-19 viral infection hits the innate immune system, it starts to produce Th1 type cytokines which ultimately causes the cytokines storm in the body and affects the lungs thus causes pneumonia. From COV infections in case of SARS-COV and MERS-COV, there was production of Pro-inflammatory cytokines. But in case of COVID-19 there is a production of the cytokines which suppress the inflammation and thus differ from SARS-COV. There is another factor which affects the immune system is the reduction in the level of 1, 25(OH)D which is usually occur with the age. The seasonal viral infections are also due to the low level of 25(OH)D, which may result due to the rainy seasons in most of the regions. This was investigated for the influenza

virus and also for SARS-COV. Many researches have shown that the high concentration of 25(OH)D can saved the people from various diseases. The Endocrine Society recommend the supplementation of serum 25(OH)D concentration of about 30ng/mL and also 1000-4000 IU/ day of vitamin D to boost up the immunity against many diseases. In winter, when there is less sunlight, vitamin D supplementation is recommended to the people to achieve a required level above than 30 ng/ mL of 25(OH)D serum. By taking dairy and flour products one can be able to raise few levels of ng/ ml.

While taking the vitamin D supplements, Magnesium supplements are recommended. Magnesium helps to activate the vitamin D which in turn can regulate the level of calcium and phosphate in bones and also help their growth. Actually, magnesium acts as the necessary element for all those enzymes which activate the vitamin D. The level of magnesium taken should be in range of 250-500 mg/ day. Although this is a hypothesis that vitamin D help to reduce the risk of seasonal influenza and COVID-19 but many clinical trials are in progress in the hospitals on COVID-19 patients to convert this hypothesis into law [37].

Some foods that are highly enrich with vitamin D should be intake for boosting immune system against any type disease [38, 39] are listed below:

1. Salmon

It's a most famous type of fatty fish that contain large amount of vitamin D. According to the United States Department of Agriculture (USDA) one salmon contains 66% DV (daily value) of vitamin D. Hence, the quantity of DV is different in wild (124%) and farmed salmon (32%).

2. Cod liver oil

Cod liver oil is also an essential nutrient to overcome the deficiency of Vitamin D especially for those who don't like fishes. It contains almost 58% DV and 450 international units (IU) per teaspoon, which is 75 percent of a person's recommended daily allowance (RDA) of vitamin D. It also contains omega-3-fatty acid but high consumption should be avoided.

3. Canned Tuna

It is also a type of fish. Highly rich in vitamin D, Vitamin K and good source of niacin. Usually, light tuna is a healthier than white tuna which is secure to eat up to 6 ounces (170 grams) per week. It serves almost 34% DV of vitamin D.

4. Egg Yolk

It is also a good source of vitamin D provides 5% DV. Vitamin D levels in egg yolk depend on the exposure of sun and the content of food on which chicken grows. When given the same feed, pasture-raised chickens that roam outside in the sunlight produce eggs with levels 3–4 times higher.

5. Mushrooms

Mushrooms synthesize their own vitamin D by direct in-contact with the sun so its consumption should be very necessary as a source of vitamin D while by contacting with ultraviolet light it contains greater amount of Vitamin D. It produces Vitamin D₂.

6. Fortified food

So many kinds of fortified food helped in regulating the deficiency of vitamin D i.e. cow milk (nutrients like calcium, phosphorus, and riboflavin), soy milk, orange juice (lactose intolerant), cereals, oatmeal etc. These items are fully enriched with vitamin D and provide maximum 22% DV of vitamin D.

Here are some other general and useful strategies by adopting which we can boost our immune system to fight against coronavirus are listed below:

1. Reduce Stress

Maximum reduction in stress boosts the immune system. In the body central nervous system (CNS), endocrine system and the immune system are forming complex systems that interact with each other. Modulation of the immune response by the CNS is mediated by a complex network of bidirectional signals between the nervous, endocrine and immune systems. During critical stress condition different hormones from pituitary and adrenal gland are released and these hormones are captured by the receptors on white blood cells present in the immune system which affects the immunity system which leads to cause some disease and sometime they may be fatal. Just like heart attack, nervous breakdown, brain hemorrhage etc. So, it should be ensured to work with balance life. Intake of maximum water is also beneficial for reducing stress. Artificial supplements are also present in market to reduce stress conditions and relaxant the body.

2. Stay hydrated

Maximum use of water protects the body from germs of viruses and bacteria. Low amount of water inside the body decreases the saliva antimicrobial proteins important for mucosal immunity [36]. Dehydrated body causes headache, and affects kidney function and ultimately leads to illness, so to prevent from such circumstances the body should be hydrated.

3. Adequate Sleep

Sleeping is rebuilding unit in boosting our immune system. Lack of moderate sleep leads to cause many diseases, including infection, and with increased mortality. Lack of proper sleep is an important problem in the intensive care unit, and interventions have been designed to improve it. Sleep is linked with

immune function, and this relationship is partially based on the physiological basis of sleep, sleep architecture, the sleep-wake cycle, cytokines and the hypothalamic-pituitary axis. plasma levels of corticotrophin and cortisol hormones inside the body are lowest during sleep and highest during periods of wakefulness [40]. Cortisol levels are elevated when normal sleep is frequently interrupted [41]. Therefore people, including ICU patients, who are under stress, have higher circulating levels of hormones associated with the HPA axis and lower levels of sleep. Promotion of good-quality sleep can therefore be considered a primary prevention strategy for all patients [37]. By not taking enough sleeping, our body gets stressed and it hurts our immune system. If we're drinking caffeinated drinks all the time, we may not even realize just how tired we really are so the proper usage of diet also played an important role in enhancing the immunity level.

4. Healthy and Fresh Food

Intake of healthy food plays an important role in boosting the immunity potential naturally. The use of fresh fruits and vegetables are entire package of all vitamins, iron, carbohydrates etc. Organically raised diet contains more healthy and beneficial components. As organic crops contain more dry matter, vitamin C, phenolic compounds, essential amino acids and while sugar contain less nitrates and pesticides. Similarly, the processed milk contains nutritional fats, calcium, vitamins and linoleic acid. Meat which is obtained from the organically raised animals contains more content of unsaturated fatty acid and better n-6/n-3 fatty acid ratio. By taking good quality of food one can be able to fight against diseases [38]. Garlic and mint have properties of antiviral. It enhanced the immune health by stimulating protective white blood cells to fight against any incoming virus inside the body. Mint also act as antiseptic agent and fight against viral genome.

5. Consume immunity-boosting vitamins

To support our immune system, we can intake immunity supporting foods like citrus fruits, garlic, broccoli, and spinach. If our immune system is already weak, it can also be helpful to take supplement with key vitamins and minerals that may have become depleted like Vitamin C, Vitamin B, Vitamin D, and Zinc. Most effective way to get high doses of Vitamin C, Vitamin B and Zinc is intravenously (IV). Vitamins are known as the important part of our lives which helps us to improve immune system. Recently vitamin A and D got attention due to their key effect on immune system. Vitamin D is known as immune system booster which is available directly by sun light or in the form of tablets and injections. Vitamin A can be available by diet or all-trans-retinol, retinyl ester or β -carotene [42]. The natural sources of β -carotene are carrots but in their off season, supplements can be used to full fill the required demand.

6. Reduce Inflammation

Infections cause people to become sick and change their behavior. They develop fever, sleep poorly, eat less, experience difficulty with memory and learning, withdraw socially and complain of pain and fatigue. Inflammation and sickness place a burden on working memory by reducing the ability of the short-term memory register to process environmental stimuli. Sickness is as normal to infection as the fear response is to a threatening predator. Its purpose is to promote survival of the organism. Immune cells produce pro-inflammatory cytokines that act on the brain to cause sickness behavior. To reduce this effect the consumption of such foods should be reduce [43] like Sugar, processed meat, vegetable oils, and alcohol tend to be inflammatory foods so they busy the immune system, leaving other problems in our body unaddressed. That's why it can be really helpful to remove these inflammatory foods if we want a healthy immune system.

7. Avoid Smoking

Smoking is very dangerous to health and inhaling the cigarette results in severe attack on lungs via respiratory tract. The effect of smoking and tobacco on the immune system and its potential impact on periodontal health are very adverse. Smokers are 2.5 - 6 times more likely to develop periodontal disease than non-smokers, and there is evidence for a direct correlation between the number of cigarettes smoked and the risk of developing disease. Tobacco users also tend to exhibit increased severity of periodontal disease. Direct correlations between tobacco use and increased attachment loss and pocket depth and reduced bone crest height have been reported. Recent studies indicate that one potential mechanism is that tobacco use exacerbates periodontal disease because it alters the immune response to periodontal pathogens. Indeed, smokers exhibit increased numbers of peripheral blood mononuclear phagocytes which appear to be functionally compromised. Inadequate phagocyte activity could reduce the clearance of pathogens from the oral cavity and thereby facilitate the development of periodontal disease. Tobacco-exposed B- and T-lymphocytes exhibit reduced proliferative capacities which could limit the production of protective immunoglobulin against oral pathogens [44]. It also increases the blood pressure which results cardiac attacks. It also causes pancreatic cancer which ultimately leads to death.

8. Moderate Exercise

Exercise is the best things to boost immunity. But we have to be careful because too much exercise is stressful on the body and can be tough on our immune system. So just keep the other tips in mind, keep the stress low, and if we feel tired rest should be taken.

9. Avoid toxins

Toxins can be devastating for the immune system. For example, mycotoxins are notorious for destroying immunity. Many other toxins seem to have

detrimental impact on immunity as well. So, try to minimize exposure to chlorinated drinking water, pesticides, aromatic hydrocarbons heavy metals, air pollution, and food additives. Liver detoxification is essential to reduce toxins burden on our body.

10. Steroids

Natural Steroids like corticosteroids helps our immune system to fight against infection. Luckily, we are gifted with such diets which are considered as natural steroids. It includes Spinach, Banana, Asparagus, Figs, Eggs, Oyster, Quinoa, Avocado, Fava Beans, Wild oats, Olive oil, Coconut oil, Onion are also a good source for steroids production [40]. The use of such foods helps the immune system to fight against the viral genome such as flu, cough, diarrhea, anemia etc. It also maintains the blood pressure, blood sugar level, and maintain the dilate flow of blood through vessels so that every artery every vein carries the moderate blood to each part of the body. Muscular pains are also relief by strong immune system. Cardiovascular diseases are also lessened by the strong immune system. The maximum production of white blood cells in the blood plasma stops the entry of germs and protect the respiratory tract and it leads to the prevent the lung cancer [20].

As we all know the covid-19 is spreading through cough and sneezing and almost there could be up to 40,000 droplets of saliva in one sneeze travelling at a speed of over 320 km/h. If coughing throws thousands of droplets of saliva or agents of infection, sneezing is its more virulent cousin. A sneeze begins at the back of the throat, produces multiple times more droplets of saliva and generates much greater speed. Droplets coming out during a sneeze are generally smaller than those gushing out in a cough. This means they can deposit millions of viruses including novel coronavirus if coming from an infected person on to a healthy person, and thus increasing the chances of Covid-19 spread many times more. So, if our immune system should be strong enough to stop the entry of

such virus inside our body and it all can be done by already mentioned factors [45].

CONCLUSION

The conclusion is that there is no special vaccine is accessible in the trade for coronavirus. Just like vaccine a good food is also key for the development of a strong immune system to fight against virus and bacteria like fruit and vegetables (Oily fish, carrots, egg yolks, sweet potatoes, cheese, pumpkin, nuts, seeds, grains and legumes, cereals, green leafy vegetables, Oranges, lemons, berries, kiwifruit, strawberries, broccoli, tomatoes and capsicum etc.). The commend plan for patients with different nutrition risk also score. If the total score is less or it has 3 points, it evinces to eat protein-rich foods and carbohydrate-containing diets. If the total score is ≥ 3 points, the patient should be given nutritional support instantly. By keeping in view, the situation of patients, provide high-protein, high-vitamin, carbohydrate-containing diets for sufficient nutrition to boost physical condition. The vitamins like vitamin D helps to maintain many functions in the body, as it acts on the intestine for the calcium re-absorption, promote osteoblast differentiation and matrix calcification to treat the infectious disease like Tuberculosis. It actually produces both pro-inflammatory and anti-inflammatory cytokines. Our immune system works best with the help of cytokines. Cytokines are the protein cells which are released by the immune system. Vitamin D suppresses the cytokines production in our body, also boosting our immune system and help to fight against the infection. The proteins, carotenes that are present in an organic diet also help the human body by increasing the levels of antibodies as well as the production of a protein that can selectively kill the infectious agents. It also alters the activity and number of T-2 killer lymphocytes, which can reduce the spread of bacteria and viruses. By using an organic

diet, our immune system could be strong enough to stop the entry of such virus inside our body.

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Authors Contribution

All authors contributed equally in designing, data collection, assimilation and writing of this manuscript and the final version was read and approved by all authors.

Conflict of Interest

The authors declare no conflict of interest.

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