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Research Article

Orthomolecular Medicine Against COVID-19: Getting Prepared for Future Pandemic Recurrence

Tomy Muringayil Joseph[1], Anoop Kallingal[2], Akshay Maniyeri Suresh[3], Debarshi Kar Mahapatra[4], Józef Haponiuk[1], Sabu Thomas[5] and S Mohammad Sajadi[6]*

[1]*Department of Polymer Technology, Faculty of Chemistry, Gdańsk University of Technology, Poland*

[2]*Department of Pharmaceutical Technology and Biochemistry, Faculty of Chemistry, Gdansk University of Technology, Poland*

[3]*Laboratory of Bacterial Genetics, Faculty of Chemistry, Gdansk University of Technology, Poland*

[4]*Department of Pharmaceutical Chemistry, Dadasaheb Balpande College of Pharmacy, Nagpur, Maharashtra, India*

[5]*International and Inter University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, India*

[6]*Department of Nutrition, Cihan University-Erbil, Kurdistan Region, Iraq*

***Corresponding Author:** S Mohammad Sajadi, Department of Nutrition, Cihan University-Erbil, Kurdistan Region, Iraq.

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Abstract

In Jan 2022, Christopher JL Murray wrote a paper entitled "COVID-19 will continue but the end of the pandemic is near" (Lancet, 399, 417-419, 2022). He concluded that "After the omicron wave, COVID-19 will return but the pandemic will not." After almost 6 months from that time, we experience new waves of the COVID-19 pandemic. Therefore, understanding solutions for COVID recurrence are indispensable. Vaccines, masks, sanitizers, and social stimulants are preventative measures, but maybe new variants of COVID-19 happen. Almost three years after COVID-19 outbreak, we still are not able to find a universal solution; beside some side-effects of vaccines are documented. In fact, poor nutrition may have an adverse effect on the immune system, leading to an inflammatory response, potentially explaining the higher risk of symptoms from infection with SARS-CoV-2. Nourishing the immune system with the nutrients gives the ability to fight against viral invasions in the human body. The possible existence of similar epidemic diseases impacts people all over the planet. This study concentrates on the benefits of nutrients such as vitamin D, vitamin C, and zinc and the impact of weather humidity on COVID-19 to get prepared for future cases in advance.

Keywords: Micronutrient; Pandemic; Vitamins; Zinc; Flavanoids; COVID-19; Medicine

Introduction

Coronaviruses are a family of viruses that cause respiratory tract diseases in mammals, including humans and animals. It is a broad family of viruses that may cause it from a regular cold to Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), pneumonia, and now COVID-19 [1-3]. The

coronavirus was discovered in 1937 in bronchitis-infected birds and is responsible for 15 to 30 percent of common colds [2-6]. For the past 70 years, scientists have found that the coronavirus is commonly associated with rats, dogs, cats, turkeys, horses, pigs, and livestock. The ability to transmit these viruses from animals to humans was classified under the zoonotic category [7]. The majority of the members in this group will affect the airways in the host organism and create symptoms like dry cough, shortness of breath, aches, chills, and hypoxia. Severe cases of the condition are likely to result in pneumonia, kidney failure, and sometimes even death. COVID-19 is a significant lung infection causing unforeseen problems worldwide; SARS-CoV-2 is a coronavirus causing issues nowadays. Each type differs from the others by having one or more genetic variations. We have experienced the delta (B.1.617.2) variety, but the omicron variant (B.1.1.529) with highly mutable hits has recently been addressed as threatening than previous by the World Health Organization (WHO) [8].

Various medical, social, and engineering methods have been proposed to face the COVID-19 outbreak that consists of therapy, prevention, detection, prediction approaches. Technology has brought light in the fight against the COVID-19 global pandemic event through the decentralized and on-demand manufacture of different personal protective equipment and medical devices. During the COVID-19 outbreak, researches on diverse medical equipment and devices were designed and developed by using synthetic and natural polymers, polymer nanocomposites, polymer conjugates, enzymatic modifications and recognition on the structure and properties, functionalized nanoparticles, prodrug polymeric nanoconjugates encapsulating gold nanoparticles, biopolymer-based membranes, Biosorbents, flexible and portable DNA, which are unavoidable materials in the healthcare sector for the protection, disinfection, and immunization applications [9-15]. Synthetic polymers have been successfully applied for the design and fabrication of diverse face masks, shields, anti-viral coatings, as well as diagnostic kits. Natural polymers having great features such as biodegradability and environmentally friendly, including sodium alginate, chitosan, cellulose, and gums have been shown a critical role in the fabrication of personal protective equipment, immunosensors, and anti-viral spray for control and fight against COVID-19. Such achievements and advancement in recent research demonstrate the advantage to help contain the spread of emerging infectious diseases such as COVID-19 [14-22].

The treatment given to COVID patients is still experimental. There are three main factors in the treatment of COVID19. 1) antiviral drugs to reduce viral load, 2) use steroids to prevent cytokine syndrome, which adversely affects the lungs, and 3) drugs to prevent blood clotting. Health experts recommend that the number of covid sufferers not be considered life-threatening but rather a growing problem [23]. As soon as COVID arrives, there is a way of going into treatment with a cocktail of drugs (a combination of several drugs). The fact is that there is still no hundred percent effective drug. At the same time, there are some lessons to be learned from this year and a half of the experience. Such studies should be used in the treatment of this challenging situation. Uncontrolled drug usage that does not prove effective will do more harm than good. It is essential what medication is given and at which time. Premature delivery or late delivery can be dangerous. Initially, it was thought that the only complication was a lung infection caused by an infection. However, difficulties in the lungs and the arteries have been reported. Medications such as heparin are given to prevent this. This drug should not be continued in people who are usually COVID free. However, people with artificial heart valves and DVT (deep vein thrombosis) may be given heparin if needed, even after the covid is released. If the person does not have autoimmune diseases like rheumatoid arthritis or others, those who get rid of COVID should not take corticosteroid drugs [24].

It is essential to consider the immune system's role during pandemics. Diet, supplements, and good hygiene practices can strengthen the immune system. WHO recommends that people adopt a healthy lifestyle to have a better chance of fast recovery. The immune system requires proper nutrition to function correctly. Maintaining a balanced healthy diet is the best way to ensure a healthy immune system, and a healthy body needs vitamins and minerals to work properly. In addition to providing a summary of the evidence for orthomolecular drugs, this review discusses how these nutrients may be used to prevent and treat COVID-19. We sought to gather information on vitamins and Zinc for respiratory infections, including COVID-19, and determine whether supplementation with Zinc is required when vitamins alone are insufficient to treat these infections.

Colder temperatures render our bodies more susceptible to the common cold, pneumonia, and related diseases. Many health professionals believe that as the weather gets warmer, more people spend more time inside, which helps transmit viruses. Expectations often suggest that the immune system works a little more efficiently in warmer than in colder weather. Research from 2014 looked at various viruses and how they propagate in the cold versus warm

weather at different humidity levels. In one report looking at the transmission of the influenza virus, researchers crammed guinea pigs into a chamber and subjected them to various environmental tests. Low relative humidity of 20 to 35 percent was the most suitable for infection, although high humidity levels of 80 percent prevented transmission. They also noticed that when guinea pigs were housed at 5° C, translation awkwardness happened more often than when they were kept at 20° C. At a temperature of 30° C, no transmission is observed at all. Low relative humidities induced by indoor heating and cold temperatures are preferred for influenza virus dissemination (Relative humidity and temperature affect influenza virus transmission) [25].

People can get runny noses without getting a cold during the winter months, so if they have a cold and this running nose, such infections may be transmitted more quickly through the secretions that come from the nose. So people sometimes rub their noses without washing them, shaking other people, or rubbing objects, and then more people contact them. So that is another explanation why viruses propagate more quickly in the winter. Rhinoviruses are responsible for 40% of contagious colds [26]. The coronavirus is the second most frequent source of a cold. This novel Coronavirus, also known as the SARS-CoV-2, is unlike any other coronavirus. It has been shown that rhinoviruses replicate more rapidly in colder conditions, implying that you can catch a cold faster if you are out. The same is likely valid with coronavirus. It is possible that people would spend more time indoors during the winter months for a mixture of any of the above five reasons, such as cooler temperatures and lower humidity. Cold weather triggers runny noses and improves the development of our immune system. This mix of factors probably explains why Kohl's flew and covid-19 are more prone to develop infections in the winter when it is colder.

In humans, no drug has yet been approved to treat coronavirus infection. Various treatment regimens are available worldwide, but none of them are effective in eradicating the corona virus. Research into potential treatments began in January 2020, and several antiviral drugs are already in usage. Although it may take years to develop completely new drugs or vaccine, many of the drugs being tested have already been approved as development indications for other antiviral medcation. Antivirals being tested include chloroquine, darunavir, galidezivir, interferon beta, LIG, and others. RNA in the virus Dependent RNA polymerase (or non-structural protein- nsp12) is responsible for making the viral RNA in human cells. Therefore, the antiviral drug Remdesivir, which blocks this chemical fire, is being used for the treatment of COVID-19. For future pandemics, there is concern about inability or slow reaction to pandemic because of not learning lessons from current case, i.e. COVID-19. As we learned, COVID-19 can be controlled by vaccinations, masks, sanitizers, and social stimulants are preventative measures. Acceleration and scaling up of new medications are important to create greater resilience for critical healthcare systems to better prepare for similar future shocks or a possible coming wave of the current pandemic. In this regard the present review focused on the advantages of vitamins as well as the effect of weather humidity on COVID-19, in order to prepare for upcoming cases.

Biological properties

Genomics and proteomics

SARS-CoV-2 is a 100 nm enveloped virus with a mass of around one femtogram and a positive-sense linear single-strand RNA of roughly 29,800 base pairs. Nonstructural proteins account for two-thirds of the genome, while structural proteins account for one-third. Membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins are the four primary structural proteins that make up the virus. The spike protein, a modular structure with two subunits termed S1 and S2, is the most notable antigen on the virus's surface. With increasing species diversity, S1 plays a more vital role. The S2 subunit is more protected and has a function in virus membrane fusion. The virus's primary and specific target in generating diagnostic kits and medications is the receptor-binding domain (RBD) sequence of the spike S1 subunit, through which the virus attaches to the receptor. Over 5000 papers are looking at the virus's whole genomes and mutations. According to these data, 1100 nucleoids have experienced point mutations. According to reports, there are mutations in various virus gene areas, which have increased the level of amino acid residues to roughly 12 nucleotides. This virus has a modest mutation rate of approximately 106/site/cycle, compared to 3*106/site/cycle for comparable viruses such as influenza. The existence of proofreading enzymes endonuclease and exonuclease and the RNA-dependent RNA polymerase enzyme (RdRp) are the leading causes of these mutations.

The closest genome structures to SARS-CoV-2.23, 24 are Bat coronavirus (RATG13) and Penguin coronavirus, respectively, with 96 percent and 91 percent similarity. New varieties have emerged, which have been documented since the onset of the epidemic and are caused by heritable SARS-CoV-2.25 mutations. These variants are given in table 1 in the following order: variant of concern (VOC),

variant under monitoring (VUM), and the variant of interest (VOI). In SARS-CoV-2, Jackson and colleagues found signs of recombination. Four of the eight recombinant-origin viruses found in their investigation demonstrated signs of onward transmission.

Viropathology

The virus enters the cell via superficial phospholipids during cell fusion. The virus's incubation period is roughly 10 hours, followed by a 10-12 hour assembly process, after which the 103/cell virus lyses the cell and causes infection. The binding of SARS-CoV-2 to human cellular receptors is substantially more potent than the binding of other viruses of the same family to these receptors. A protease cleavage site is formed by inserting 12 nucleotides between the sequences of S1 and S2. This cleavage site is unique to the SARS-CoV-2 virus and impacts its pathogenicity.

Virus receptors

The intramembrane protein angiotensin-converting enzyme 2 (ACE2) cell receptor plays a hemostatic role in balancing the effects of ACE on the cardiovascular system. When a virus attaches to ACE2, it causes endocytosis, which reduces the amount of surface ACE2 on endothelial cells, disrupting the balance between ACE and ACE2 and increasing angiotensin II levels. Angiotensin II is a vasoconstrictor that increases inflammation by activating enzymes including disintegrin and metalloprotease 17. (ADAM17). In addition to ACE2, several receptors for SARS-CoV-2 entrance have been identified, including the coronavirus-like NL-63. CD209L (also known as L-SIGN and CLEC4M) and CD209 (also known as DC-SIGN) are two cell adhesion receptors that belong to the immunoglobulin family. Type II alveolar cells and lung endothelial cells overexpress CD209L, while dendritic cells (DCs) and tissue-dwelling macrophages express CD209. Basigin, also known as CD147 or EMMPRIN, is another viral receptor (extracellular matrix metalloproteinase inducer). This immunoglobulin-like membrane glycoprotein acts as a ligand for viral spikes. The specificity of inhibitory medications (anti-receptors) has based on the spatial epitopes of these surface glycoproteins in the discussion of blocking receptors.

Virus immunopathology

The SARS-CoV-2 virus's similarities to other viruses in its family suggested that the immunopathogenic response resulting from host-pathogen contact would be similar. In the fight against SARS-CoV-2, a lack of an appropriate immune response can alter the severity of the disease. In less than 20% of patients, significant symptoms such as acute respiratory distress syndrome, lung organ loss, respiration, and shock occur, and less than 2.4 percent die. The immune system's failure to prevent and regulate the immunological response can cause several illnesses. Cytokine storms are caused by immune cells overproducing pro-inflammatory cytokines (such as interleukin-1 [IL-1], IL-2, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha [TNF-alpha]) and chemokines (CXCL10 and CCL2). The second mechanism found in these patients, similar to MERS, is lymphopenia, particularly T cell decrease, which can occur under several circumstances. The virus's origin, age, immune system function, and the existence of chronic disorders caused by an imbalance in pro-inflammatory and anti-inflammatory cytokines are all significant influencing factors. Viral proteins, directly and indirectly, induce the production of these cytokines and stimulate their signaling pathways (especially S and N proteins). Knowledge of the disease's immunopathogenesis can influence the selection of prospective targets for boosting immune response.

Host immune response

There are two types of host immune responses. The innate immune response plays a critical role in safeguarding or failing viral reactions in the first category. Innate immune cells like neutrophils and monocytes-macrophages recognize single-stranded RNA (ssRNA) or double-stranded RNA of these viruses as pathogen-associated molecular patterns via the cytosolic RNA sensor (RIG-I/MDA5) as intracellular or endosomal RNA receptors (TLR3 and TLR7) pattern recognitions. There are two types of host immune response. In the first category, the innate immune response plays a critical role in safeguarding or failing viral responses. Innate immune cells like neutrophils and monocytes-macrophages recognize single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA) of these viruses as pathogen-associated molecular patterns via the cytosolic RNA sensor (RIG-I/MDA5) as intracellular or endosomal RNA receptors (TLR3 and TLR7) pattern recognitions.

Pathogen immune evasion strategies

Most viral proteins, particularly M, N, and S, can suppress the host's innate antiviral response by blocking the type I IFN signaling pathway. On the other hand, limiting antigen presentation by lowering the expression of MHC-I and II (major histocompatibility complex I and II) is another way for the virus to evade the adaptive immune response. Other potential immune evasion strategies include immunological fatigue, viral alterations, and immune deviation.

Prevention and treatment with micronutrients: Orthomolecular medicine

Orthomolecular medicine (Synonyms: Important Drugs, Nutrition, Micronutrient Medicine) is a sort of alternative medicine that utilizes nutritional supplements to sustain human health. Linus Polling, an American biochemist and two-time Nobel laureate, chose the term in 1968 because it clearly illustrates the basic concept of vital drugs. Optimal dosage and combination of nutrients protect and support the organism from diseases and also help to prevent age-related issues. It maintains health by changing the therapeutic concentration of substances typically contained in the human body and are essential for good health.

Orthomolecular medicine is based on the understanding that the human body requires many micronutrients (vital substances) in the proper ratios for the healthy and smooth functioning of all cell mechanisms and organs [27]. Micronutrients are physiological substances found in the human body to maintain health and vitality. The body can make these, but they must be consumed through food. Vitamins, minerals, trace elements, essential fatty acids, essential amino acids, secondary plant nutrients, and other essential substances are among these crucial substances (micronutrients). Therefore, the concentration of micronutrients ensures optimal health care when all the substances in the body are adequate.

On the other hand, inadequate supply (of vital nutrients) - for example, poor food quality and nutrition can lead to macro or micronutrient underpinnings due to an individual surplus requirement (essential nutrients). A shortage of macro and micronutrients may be detected via clinical laboratory testing. Another measure is a critical nutritional analysis. It helps determine individual macro or micro-nutrient requirements, considering all living conditions like diet, consumption of stimulants, sports, previous illnesses, and long-term medications. The dilatory sources of these essential nutrients are provided in (Table 1).

Nutrient	Sources	RDA or AI (adults > 19 years)
Vitamin A	Retinol (liver, dairy, fish), carotenoids (carrots, sweet potatoes, spinach)	700-900 mcg
Vitamin D	Sunlight, milk, fish oil	600-800 IU
Vitamin E	Sunflower seeds, almonds, wheat germ	15 mg
Vitamin K	Leafy greens, soybeans, pumpkin	90-120 mcg
Calcium	Milk products, leafy greens, broccoli	2,000-2,500 mg
Phosphorus	Salmon, yogurt, turkey	700 mg
Magnesium	Almonds, cashews, black beans	310-420 mg
Sodium	Salt, processed foods, canned soup	2,300 mg
Chloride	Seaweed, salt, celery	1,800-2,300 mg
Potassium	Lentils, acorn squash, bananas	4,700 mg
Sulfur	Garlic, onions, Brussels sprouts, eggs	None established
Iron	Oysters, white beans, spinach	8-18 mg
Manganese	Pineapple, pecans, peanuts	1.8-2.3 mg
Copper	Liver, crabs, cashews	900 mcg
Zinc	Oysters, crab, chickpeas	8-11 mg
Iodine	Seaweed, cod, yogurt	150 mcg
Fluoride	Fruit juice, water, crab	3-4 mg
Selenium	Brazil nuts, sardines, ham	55 mcg

Table 1: Sources and recommended intakes of the micronutrients.

Getting enough vitamins and minerals is essential for overall health and may even aid in disease prevention. This is owing to the fact that micronutrients are involved in almost every process in the body. Furthermore, some vitamins and minerals may function as antioxidants. Antioxidants may fight against cellular damage connected with some diseases, including cancer, Alzheimer's, and heart disease, and help enhance the immune system. The National Research Centre's alternative medicine section has established dietary guidelines for natural micronutrient supplementation in people with COVID-19. These suggestions are based on the National Institutes of Health's dietary supplement fact sheets. As shown in table 1, appropriate levels of micronutrients should be provided.

Immunonutrition is the process of modifying the immune system by altering dietary ingredients. Because of the pro-inflammatory state of ARDS, it has long been thought that raising the number of antioxidant substances in the body would be advantageous. Furthermore, boosting lymphocyte, macrophage, and neutrophil activity by supplementing with nutrients such as glutamine has

been advantageous. Nutrient supplementation has been shown to improve the clinical outcome in various patients, including those who are critically ill [28]. A variety of commercially accessible enteral and parenteral formulas with a mix of immunonutrients are available. Antioxidant vitamins, trace minerals, vital amino acids, fatty acids, and gamma-linolenic acid are the most common.

The data on the positive effects of immunonutrition in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is contradictory and frequently skewed. According to clinical investigations, patients with ARDS had decreased baseline plasma levels of beta-carotene, retinol, alpha-tocopherol, and total radical antioxidant capacity. Compared to a control group that did not receive supplementation, this might be corrected following four days of feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants. However, no clinical consequences were documented. Eicosapentaenoic acid, gamma-linolenic acid, and antioxidants were studied on patients with severe sepsis and septic shock, and mortality, ventilator-free days, and intensive care unit-free days are found to be significantly reduced. Despite these findings, the data from those studies' systematic reviews and meta-analyses are less encouraging. There was no significant reduction in all-cause mortality and no increase in the number of ventilator-free or intensive care-free days in a pooled analysis of the six controlled studies included in a systematic evaluation of enteral immunomodulatory diets in patients with ALI and ARDS. However, the two trials suggested that people with the highest mortality risk-benefit. A Cochrane review published in 2019 revealed ten studies involving 1015 ARDS patients who were randomly assigned to omega-3 fatty acid and antioxidant treatment. There was no decrease in overall mortality. It's been suggested that the number of days spent on ventilators and in intensive care units was lowered. Others have recognized the importance of immunonutrition during the current SARS-CoV-2 pandemic, with the development of guidelines for early nutritional supplementation of people infected [29]. There has been little reported work on this during the pandemic. The 'immunonutrition diet' is heterogeneous in many dietary supplements trials, consisting of numerous vitamins, minerals, and fatty acids given together, making it difficult to determine the potential usefulness of each vitamin, as detailed below.

Role of vitamins in COVID defense

Vitamins are essential for optimum health, although they are required in much lesser quantities than macronutrients such as carbohydrates and fats. They are necessary for numerous everyday body processes, including cell reproduction and development, but crucial for cell energy processing (Figure 1). According to a new report, vitamins A, D, and K could be essential in the battle against the coronavirus. According to researchers at the University of Bristol in England, these vitamins will prevent the spread of the COVID virus. However, the viral spike protein of the coronavirus binds to these vitamins, limiting their efficacy. According to, linoleic acid may attach to a specific portion of the spike protein of the virus. The researchers began testing various substances following the study to see similar results. According to a report published in the Journal of the German Chemical Society, dexamethasone, a medication used to treat COVID, has similar effects on viruses. According to the findings, vitamins A, D, and K may help decrease the incidence of viral infections. On the other side, Obesity also boosts the probability of COVID infection. Vitamin D is most prone to accumulate in the adipose tissue when it dissolves in fat. It also decreases vitamin D supply in obese individuals. COVID is less prone in people who take cholesterol-lowering statins [30]. Even if COVID arrives, their recovery time would be restricted. The effect of the COVID outbreak is even more significant in populations and countries with elevated levels of vitamin deficiency.

Figure 1: Role of various vitamins in the body and their dilatory source.

Vitamin A

By structural definition, vitamin A is an all-trans-retinol, retinol with an E- (also known as trans) geometry on all four exocyclic double bonds (Figure 2). Retinoids, a name created in the

mid-1970s, refer to natural and manufactured chemical species having similar structural appearances and with or without biological component/activity, the biological species being vitamin A. Vitamin A would then be classified as a natural retinoid species. Retinoids are usually obtained from food in preformed retinoids or provitamin A carotenoids. Retinoic acid has been discovered to be the most active retinoid. The binding mechanism of retinoic acid to its retinoid X counterpart has been revealed to influence the transcription of approximately 500 genes. These can be found in various animal foods, including meat, fish, and eggs. Carotenoids are more commonly found in fruit and vegetables in the form of alpha/beta/gamma carotene; -carotene contributes to the orange color of food and is frequently connected with carrots and sweet potatoes. These provitamin carotenoids are transformed into retinoids in the body [31]. The action location is in the tissues, where both retinol and -carotene are oxidized to retinal and retinoic acid, which are required for vitamin A's diverse biological functions. Retinol is esterified to retinyl esters and stored in the stellate cells of the liver. Vitamin A's oxidative ability has been a source of much controversy, claiming that it is both antioxidative and prooxidative.

Gene transcription, vision maintenance and health (in the form of retinal), epithelium and membrane modulation (from the skin to mucus to teeth), bone metabolism, and antioxidative characteristics are only a few of the biological roles of retinoids. It does, however, play a significant function in immune system modulation. Many studies show that vitamin A is essential in some immunoregulatory mechanisms, despite its exact involvement being unknown. Vitamin A has been shown to enhance T-lymphocyte proliferation (through an increase in IL-2) and their differentiation, particularly into regulatory T cells. This has been used as an adjuvant to vaccine usage in babies to increase antibody response to tetanus, diphtheria, measles, influenza, rabies, and malaria.

Vitamin A's pulmonary, immunomodulatory, and antibacterial functions may be critical in the fight against viral infections, including COVID-19. From a pulmonary perspective, retinoic acid has linked to regulating the development of ARDS by affecting alveolar macrophage production of IL1- and IL-1 receptor antagonists and neutrophil infiltration. Furthermore, in animal investigations, a combination of retinoic acid and simvastatin showed enhanced pulmonary regeneration and remodeling, implying that vitamin A-dependent pathways may partly mediate oxidative damage and the lungs' regenerative potential. The role of vitamin A in viral infections may also be relevant. *In vitro*, retinoids are linked to establishing the innate immunity against the measles virus via an interferon-mediated mechanism that protects bystander cells against a further round of viral replication. Animal studies using inactivated bovine coronaviruses have found that dietary supplements increase the effect of antibody responses to the vaccine in feedlot calves, and lower levels of vitamin A in chickens with viral infections are linked to an increased rate of epithelial tissue damage. These findings are consistent with clinical investigations related to reduced vitamin A levels to increased host vulnerability to influenza and SARS-CoV in numerous illness models. Oral supplementation of vitamin A and a plethora of other antioxidants are currently being explored in the treatment of COVID-19 due to its pulmonary and immunological roles [32].

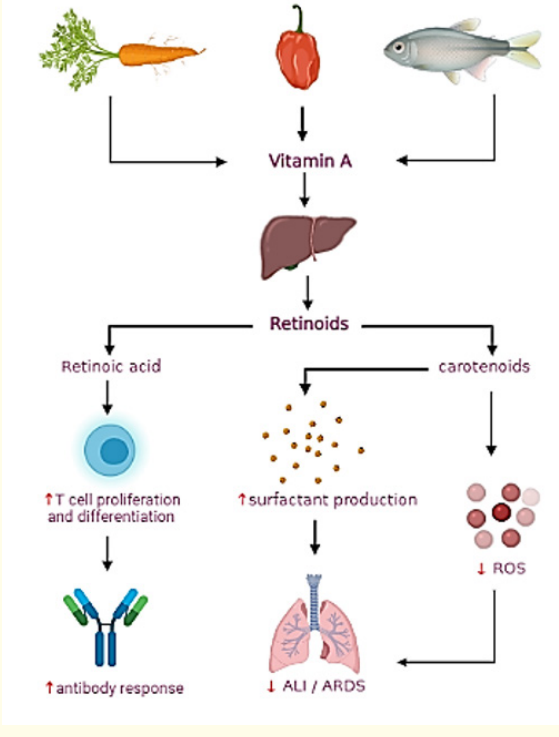

Figure 2: Effect of vitamin A on the immune system.

Vitamin B

B vitamins (B1, B2, B3, B5, B6, B7, B9, and B12) are a group of water-soluble vitamins that perform vital functions in cell metabolism. Although chemically distinct, they can coexist in the same foods, such as meat and plant-based sources. B12 is significantly found in meats like turkey, tuna, and liver, whereas folate is pri-

marily found in plant-based foods like legumes (pulses or beans), greens, nuts, whole grains, potatoes, bananas, chili peppers, tempeh, and yeast. They are also found in modest amounts in unprocessed carbohydrates, whereas processed carbohydrates, such as sugar and white flour, have decreased vitamin B levels, commonly compensated for by supplementation. A vitamin B complex is a dietary supplement that contains all eight of these nutrients. According to research, the Vitamin B complex appears to influence cytokine/chemokine production and mediate interactions with immune cells engaged in pathophysiological pathways and inflammation. Vitamin B1 (thiamine), like other B-complex vitamins, functions as a coenzyme in its phosphorylated forms, aiding glucose, fat, and protein metabolism and contributing to the body's energy production. Its lack in the neurological system could limit the ability to manufacture fatty acids and cholesterol, both of which are required for membrane function. Vitamin B1 deficiency in the brain causes overexpression of pro-inflammatory mediators such as IL-1, IL-6, COX-2, and TNF-, which cause neuronal cell death and neuroinflammation in the central nervous system (CNS), leading to Wernicke's encephalopathy and irreversible dementia of Korsakoff's syndrome. Vitamin B2 (riboflavin) has immunomodulatory properties, and deficiency increases the expression of pro-inflammatory genes. Niacin, a B3 amide, inhibits NF-B activation and decreases TNF, IL-6, and IL-1 in activated alveolar macrophages [33]. Similarly, because of its effects on pro-inflammatory cytokine expression, vitamin B7 (biotin) is considered an immunoregulatory vitamin.

The coronavirus polyprotein encodes two proteases, 3-C-like protease (M-pro) and a papain-like protease (PL-pro), that have previously been used as therapeutic targets in the SARS and MERS coronavirus outbreaks. The accessible crystal structure of the SARS-CoV-2 protein M-pro was used in a recent study to analyze existing approved medications to see whether they may be repurposed to attack COVID-19. Another computational study looked at chemicals that are predicted to bind strongly to M-pro in SARS-CoV-2 and found that folate can create strong hydrogen bonds with active site residues, suggesting that it could be used as a treatment method [34]. These computational screening techniques may make it possible to conduct targeted medication testing utilizing cell-based assays and clinical trials, with niacin (B3), folate (B9), and B12 being potential candidates. These technologies are especially crucial in the COVID-19 pandemic, where there are currently no targeted therapies and only a few successful treatment choices.

Vitamin D

Typically, our bodies do not produce vitamin D until exposed to sunlight. If we live in a colder environment, we might be an anomaly. Most of us do not get enough sunshine to create enough vitamin D during winter. So, if we do not get enough sunlight during the winter months, we will need to supplement our diet with vitamin D because we will have low vitamin D amounts if we do not. Vitamin D is essential for bone and muscle health and helps control calcium levels. It also plays a part in immune system control, but its exact mechanism remains unclear. So, why is this significant in terms of the common cold and flu and the possibility of COVID-19? Vitamin D does not seem to have much impact on viruses. However, it affects how our immune system responds to pathogens like viruses. Micronutrients have a vital function in the immune system and might have a good influence on COVID-19 [35]. Antioxidants promote the metabolism of interleukin-2 and the activity of natural killer cells and lymphocytes. Vitamin D has a crucial role in tight junction protection, viral killing, and the production of cathelicidin and defensins, all of which aid in respiratory tract protection. It also minimizes the risk of cytokine storm by lowering the production of pro-inflammatory cytokines. The effect of vitamin D on the immune system is represented in figure 3. However, limited sun exposure in the hospital or home may exacerbate vitamin D deficiency.

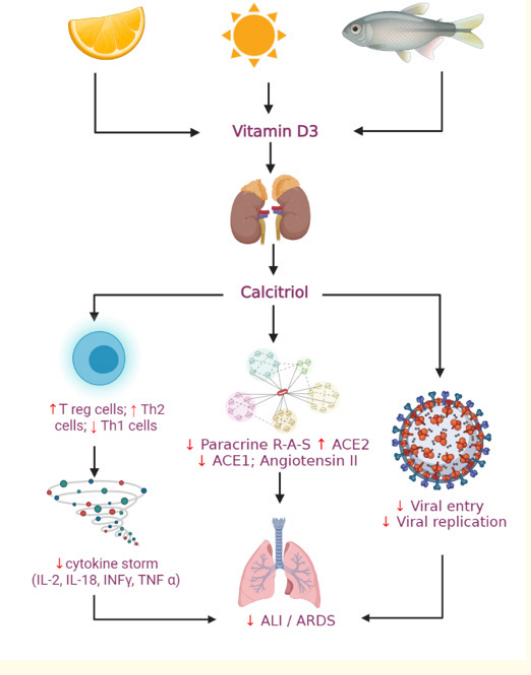

Figure 3: Effects of vitamin D on the immune system.

A systematic review, published in a British medical journal in 2017, looked into several different surveys, merged all of the findings from some of those studies, then evaluated and interpreted the statistics into one large study [36]. This meta-analysis analyzed over 25 randomised control studies with over 11,000 participants who took vitamin D. This investigation discovered a correlation between low vitamin D levels and an increased risk of respiratory infections. It also found that supplementing with vitamin D on a regular or weekly basis provided the most value to those who were vitamin D deficient. Those with more extreme vitamin D deficiency improved the most, specifically blood levels below ten and G's per ml. If they took vitamin D supplements, their chances of getting a lung illness fell by half. It was also discovered that daily vitamin D supplementation had several positive impacts on both participants. It was also found that consuming large doses of vitamin D daily would not have significant advantages, even though they were deficient. The main takeaway here is that vitamin D must be taken regularly to be safe. With a sample size of over 11,000, these findings were statistically substantial. The easiest thing to do about vitamin D is to see a doctor and check our vitamin D levels. Vitamin D supplementation is available if levels are poor. The amount of vitamin D may accomplish this in our food or by consuming a vitamin D supplement. The amount of vitamin D to be taken can be discussed between the patient and the doctor. Not all will have their vitamin D levels tested due to realistic constraints. A piece of good general advice is to take 800 to 1,000 IUs every day or every other day. It is implausible that anyone consuming that dosage every day would develop Vitamin D toxicity [37]. Although, as previously said, it is a substantial generalization in which we will go into greater depth. All of us also understand that too much vitamin D may be harmful. Vitamin D is one of four fat-soluble vitamins processed in the body more quickly than non-fat soluble vitamins. This is important since keeping it in the body increases the risk of harmful effects. As a consequence, high consumption is not a positive idea. Some brands of vitamin D, as well as other vitamins, are more reliable than others.

What is vitamin D supplementation? Even before COVID-19, second countries were taking the issue seriously, as shown by a study from the University of Helsinki, Finland, titled "Vitamin D fortification of fluid milk products and their relation to Vitamin D consumption and Vitamin D status in empirical studies." There are many separate nations, each with its solution. It is optional in Finland to add fortification to their rice, but as it turns out, everybody does it, so that it will be obligatory in Norway. In Sweden, it is purely voluntary. It is needed in Canada. It is, though, optional in the United States. Consequently, certain fluid milk, acidified milk, cultural milk, and even yogurt producers contain vitamin D in their products. However, according to one of the commentators on the Irish longitudinal report on aging's difficulty regarding Vitamin D in their study, Ireland lacks a structured Vitamin D nutritional scheme.

These are the clinical procedure recommendations from the Endocrine Society, released in 2011. 'evaluation treatment and prevention of vitamin D deficiency: an endocrine society clinical practice guideline' [38]. The report suggested oral vitamin D intakes for patients at risk of vitamin D deficiency. The study shows that, unless we are a kid, the upper limit for supplementation with vitamin D monitoring is 4,000 foreign units per day for someone over the age of eight. So, what precisely is it that they are talking about? What is the frequency of the event? What role does vitamin D toxicity play? To better understand this, we look at another research from Poland published by Frontiers in Endocrinology 'Vitamin D toxicity-a clinical perspective' [39]. The endocrine society and the institute of medicine have also reported that vitamin D toxicity is exceedingly rare and that concentrations of 25 hydroxyvitamin D must typically reach 150 nanograms per milliliter or 375 nanomoles per liter to this paper. Not just that, but there must be an improvement in calcium consumption, which we feel is appropriate due to the rarity of the disease. Some categories of people should be cautious about supplementing with vitamin D, such as patients with sarcoid or other granulomatous diseases and renal problems. However, we see a role for supplementation, particularly during this winter season when COVID is rampant. We cannot say how much vitamin D to take on an individual basis.

Vitamin C

Vitamin C is a water-soluble vitamin that is important for immune system health. Its precise role is unknown. However, it does tend to enhance the part of white blood cells. We did not know it was also required for iron absorption, and iron deficiency can render an individual more prone to infections in general. However, the average daily recommended dose of vitamin C for adults is 75 to 120 mg from food and supplements. A cup of orange juice or a slice of orange produces between 80 to 90 mg, and kiwi fruit or a pair of sweet peppers have much more. As a result, obtaining a sufficient amount of vitamin C solely by diet is relatively easy. According to Vitamin C supplements help relieve cold symptoms. However, mythology fails to stand up to statistical scrutiny for the most part.

Taking vitamin C to cure a cold was ineffective in most trials. According to one significant test, people who took a very high dose of 1,000 mg of vitamin C at the start of the cold got stronger quicker, but subsequent trials could not replicate these results. There is currently no evidence for prescribing that people take Vitamin C supplements before or after catching a cold. So, even at elevated levels, vitamin C supplementation does not seem to shield people from the symptoms of coronaviruses. Vitamin C given intravenously is currently being looked at COVID-19 patients in China who acquired pneumonia as part of the technique, which is being advertised on numerous websites and social media [40].

As a consequence, those outcomes are still pending. However, getting more vitamin C than we need will trigger GI distress and even little diarrhea. Sometimes a little too much will induce kidney stones and cataracts. So, before further trials prove that vitamin C supplementation effectively avoids or cures respiratory diseases, including the common cold, flu, and now COVID-19, it is best to avoid it.

The biological functions of both the innate and adaptive immune systems are influenced by vitamin C. It is believed that vitamin C works as an enzyme cofactor for several biosynthetic and gene-regulation enzymes, which adds to its immune-modulating capabilities. In addition, vitamin C is a powerful antioxidant protecting the body against endogenous and exogenous oxidative damage. Among its various effects, vitamin C induces neutrophil migration to infection sites, enhances phagocytosis, increases oxidant production, and destroys bacteria. The immunological effects of vitamin C are described in figure 4. It also protects host tissue from severe damage by increasing neutrophil apoptosis and macrophage clearance while lowering neutrophil necrosis and NETosis.

Vitamin C is needed to develop blood vessels, muscles, collagen, and cartilage in the human body. It is therefore essential for the body's immune system to function correctly. In addition, vitamin C has antioxidant effects. This vitamin aids in the body's defense against toxic free radicals (Related to cardiovascular disease and cancer). Vitamin C also assists in the processing of iron in our bodies. Since our bodies may not contain vitamin C, we must obtain it from food. The vitamin C-rich vegetables and fruits are Lemons, bananas, berries, peas, onions, lettuce, broccoli, spinach, and sprouted grains. The recommended regular dosage for women is 75 mg, and for men, it is 90 mg [41].

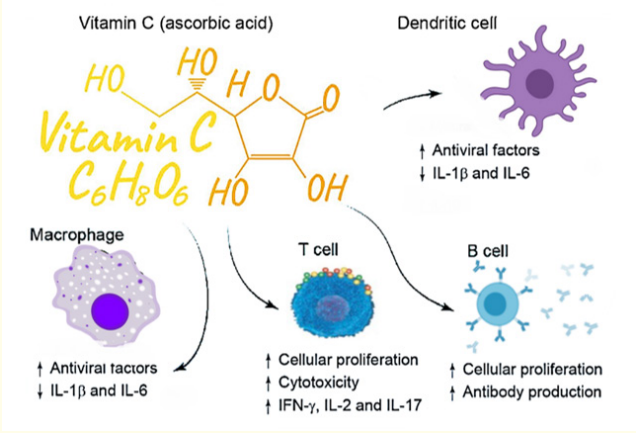

Figure 4: Effect of vitamin C on the immune system.

Vitamin C is usually known to be healthy. There are, however, several side effects correlated with the dosage. Possible side effects are nausea, vomiting, heartburn, esophagitis, bowel obstruction, diarrhoea, insomnia, exhaustion, and headache. However, what exactly has been said? First, locals believe allopathic medication is toxic and should be cast into the sea; the mega specialist facility would have proper checkups and therapies. Then remind the locals that COVID does not need medicine and that Vitamin C is adequate. What would we do if our vitamin C levels were low? Allow it to be. There are several advantages. However, this is not to be associated with the COVID procedure.

Vitamin E

Vitamin E is a fat-soluble molecule with eight isoforms, four tocopherols, and four tocotrienols. It is a lipid component of biological membranes. Only -tocopherol meets the human vitamin E requirements, and the other isoforms are not interchangeable. The primary source in the human diet differs depending on the isoform, with -tocopherol mainly found in nuts like almonds and hazelnuts, legumes like peanuts, avocados, and sunflower seeds.

The liver metabolizes, regulates, and excretes vitamin E, absorbed through the small intestine. Vitamin E, in the form of -tocopherol and, to a lesser extent, tocotrienols, is converted by the liver into chylomicrons [18], which are further transferred to lymphatic tissues. Although -tocopherol is the most biologically active isoform, some evidence suggests that tocotrienols have a potent antioxidant effect in rat models in neutralizing peroxyl radicals

and lipid peroxidation; however, due to their low bioavailability, tocotrienol isoforms have received less than 3% of research. The immunological effects of vitamin E are described in figure 5.

COVID-19, like most viral respiratory infections, prefers immunocompromised people, people with chronic illnesses, and the elderly. Immunosenescence is the age-related weakening of the immune system. Vitamin E has been shown to improve T lymphocyte-mediated immune function in response to mitogens and IL-2 and neutrophil and natural killer function, which decreases with age [42].

As a result of COVID-19, one of the primary pathogenic mechanisms that drive the biology of ARDS is oxidative stress. Excessive lipid peroxidation and biological membrane failure occur from a dramatic shift in the oxidant-antioxidant balance. The pathological effects reported in the most severely impacted are diffuse alveolar destruction, hyaline membrane development, and pulmonary edema. Vitamin E use has been shown to reduce superoxide generation, perhaps shifting the balance back in favor of antioxidants. Antioxidant deficiency has also been linked to increased genetic changes that promote the virulence of coxsackievirus, influenza virus, and two RNA viruses, including COVID-19, in animal models. Vitamin E supplementation may improve vaccination efficacy in those most vulnerable in our culture, as seen by increasing tetanus antibody titers [43] as worldwide efforts shift toward vaccine development. The biological effects of vitamin E are based on highly complicated pathways, and if the epidemic progresses, more research may be conducted to uncover the possible benefits.

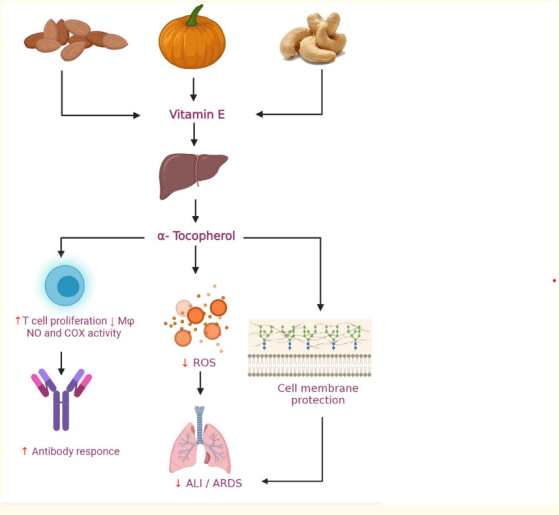

Figure 5: Effect of vitamin E on the immune system.

Zinc and COVID

Zinc has long been touted as one of the most effective treatments for cold symptoms, and it was also discovered to be connected with COVID-19. The impact of Zinc on the intensity and length of cold symptoms has produced mixed findings. Some study shows that sync will cut the size of a cold in half, while others find little impact. Another research discovered that the form of item consumed influenced the outcome, with zinc gluconate lozenges containing 13 milligrams of Zinc reducing the time of colds. Zinc acetate lawson jizz did not include five to eleven milligrams of Zinc. Zinc has already been shown to suppress coronavirus replication in cells in a lab sample, but not this novel coronavirus. (*In vitro*, Zn^{2+} prevents coronavirus and artery virus RNA polymerase development, and zinc ionophores prohibit these viruses from infecting cells.) However, no proof that was utilizing sing lozenges will eliminate this novel Coronavirus at this point. More testing is required to see if a Zinc will help people get rid of colds. Excessive Zinc injection may also trigger copper deficiency and interfere with antibiotic absorption [44]. The usage of sync nasal gels or swabs has been attributed to a lack of scent that may be acute or irreversible (Figure 6).

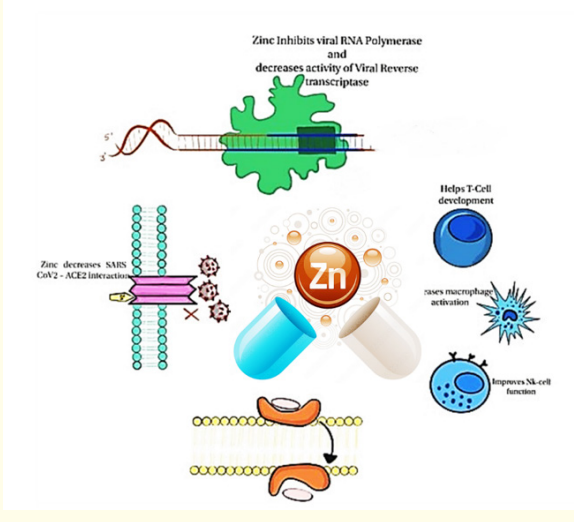

Figure 6: Role of Zinc in various biochemical events.

There are many herbs that has been used to manage cold symptoms [45]. Taking such herbal medications for cold symptoms has been shown in several trials to reduce the duration and intensity. However, these findings were of poor quality, and subsequent higher-quality research has shown a slight advantage of doing so.

In terms of herbs and vitamins, it is impossible to speak for most supplements that have clinical backing since most have not been thoroughly researched for efficacy, side effects, and dosage. In comparison, the FDA does not explicitly control the production of herbs and supplements. As a result, when opposed to prescription and non-prescribed drugs, there is a greater degree of uncertainty in terms of potency, purity, and protection.

All is concentrating on strengthening immunity after the COVID outbreak. Because of this, many consumers are rushing to purchase drugs without a doctor's order or a prescription. Vitamin C and zinc tablets are the two most common among these. Vitamin C and Zinc are thought to help avoid COVID and help people who do have it heal rapidly. However, recent evidence shows that they might not be as successful in fighting COVID as commonly believed. According to a reports suggested in jama network open, Vitamin C and Zinc have little impact on COVID cure and symptom prevention. The researchers looked at 214 COVID patients in Ohio and Florida as part of their study. They were given higher doses of vitamin C and Zinc than average. They were then compared to patients who did not take any vitamin C or zinc supplements. Fever, shortness of breath, cough, runny nose, lack of taste, and weakness were the six conditions used to equate patients. The research discovered that vitamin C and zinc supplementation did not improve immunity right away and had little impact on the ten days it takes a COVID patient to heal [46].

Vitamin C and Zinc are two beneficial nutrients for the human body. They are also capable of fighting fungus. This explains why these medications treat colds, coughs, and other persistent illnesses. However, according to experts, this is precisely what is happening with COVID. Excessive vitamin C and zinc consumption in preventing COVID may trigger gastrointestinal symptoms, dry mouth, and bloating. Excessive zinc use can also contribute to opioid and painkiller overdoses. A regular vitamin C requirement for an adult is 65-90 mg. In addition, an adult male requires 11 mg of Zinc per day, whereas an adult female requires 8 mg. More of these may trigger complications if consumed in large quantities. As a result, health authorities advise against taking vitamin C and zinc supplements without seeing a specialist [47].

Flavanoids and their application to prevent COVID-19

Flavonoids are compounds found in fruits, vegetables, and whole grains. They have antioxidant and anti-inflammatory properties and can prevent disease. Flavonoids are a phenolic compound of natural origin, also known as vitamin P, which has many pharmacological properties that work in the human body and can bring numerous health benefits - they already have more than eight thousand substances in this group. Studies point to the antioxidant capacity of flavonoids - they can react with a variety of free radicals (accelerating premature aging), thus forming stable compounds and slowing down cell aging. Mention may also be made of anti-inflammatory, vasodilating, analgesic, and anti-cancer (see research on the importance of eating vegetables against cancer here), anti-hepatotoxic, antimicrobial, and antiviral activities. Research shows that the human immunodeficiency virus, which causes AIDS, shows resistance to certain flavonoids against proteins from HIV (this does not mean that flavonoids have anti-HIV activity - always use contraceptives. No research has yet been done on the exact amount of flavonoids a person should consume. This is due to the lack of information about its distribution in the diet. Still, this amount is estimated to vary from 26 mg to 1 g per day, depending directly on the diet and consumption of specific sources [48]. Therefore, there are no recommendations for the daily consumption of these substances. Flavonoids have already aroused interest in academia and have become the subject of numerous studies, but there are still many features to be found behind these compounds. Many flavonoids prevent viral, bacterial, and fungal infections, most explored in basic and clinical studies. From the beginning of the pandemic, thousands of compounds have been reported to be effective against COVID prevention. Most of them are inhibit the viral entry in our cells by blocking an interacting receptor and viral proteases. In studies, flavonoids have been shown to have potent inhibitory effects against targets that are vital for viral entry and replication, including Mpro, RBD of the S protein, RdRp, and the human ACE-2 receptor and TMPRSS2 (Figure 7).

Discussion and Recommendations

This article evaluated the possible role and mechanism of action of vitamins, Zinc, and flavonoids in a corroborative manner. Although there is currently no conclusive and specific evidence from completed randomized controlled trials to show the role of vitamin supplementation in the fight against COVID-19, there is strong scientific evidence based on studies of vitamin physiology, pharmacology, and their role in clinical studies of infection and ARDS to suggest a role for vitamins in the fight against this global pandemic. Disease models involving low vitamin A levels and increased host susceptibility to influenza and SARS-CoV have motivated researchers to look into the link between vitamin A supplementation and

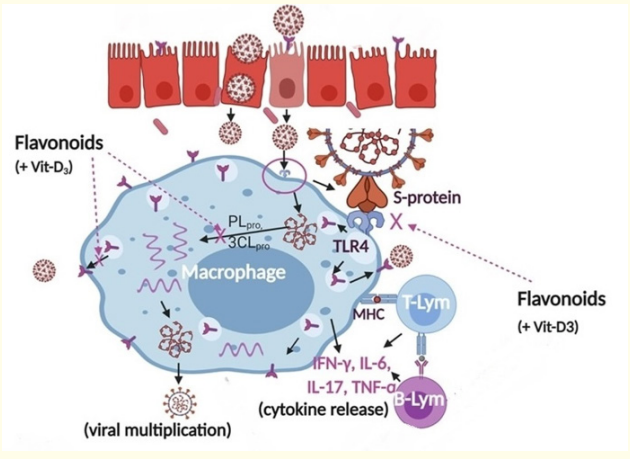

Figure 7: Role of flavonoids in COVID prevention.

COVID/COVID-like viruses. Vitamin C may be beneficial in COVID-19 due to its potential function in reducing upper respiratory tract infections, antioxidant capabilities, and use as a high-dose intravenous treatment in ARDS and sepsis. The RCTs that are now being conducted could show that this vitamin has a role in intensive care. The MATH+ protocol was announced in April 2020 by the Front Line COVID-19 Critical Care (FLCCC) Working Group, which includes vitamin C in its multimodal therapy strategy. Intravenous methylprednisolone, high-dose intravenous ascorbic acid, full-dose low-molecular-weight heparin, and optional treatment components (thiamine, Zinc, and vitamin D) were included in the protocol. This is an early intervention program aimed at reducing COVID-19 hyperinflammation. According to anecdotal evidence, the early supply of MATH+ (within 6 hours of admission) has reduced the need for mechanical breathing and improved mortality rates in North America and China. The FLCCC working group reported two deaths among 100 patients treated with the MATH+ regimen, but they did not compare their findings to a control group. These findings are impressive, but more research and clearly defined criteria are needed before this medication can be recommended for broad use. Vitamin D is currently the vitamin garnering the most attention due to the link between disease severity and populations at risk of vitamin D insufficiency, such as the elderly and black, Asian, and minority ethnic (BAME) populations. There is growing and current evidence to suggest a method through which this vitamin may play a significant role in the fight against COVID-19, including its link to the pulmonary renin-angiotensin system. Vitamin D's medicinal potential has already piqued the interest of scientists and doctors, as indicated by a growing number of clinical trials and academic papers. The interest has even reached the government, with the United Kingdom now recommending vitamin D supplementation for those from minority ethnic groups, the elderly, and those who are restricted to their homes. However, assessments of blood calcifediol concentration and COVID-19 risk conducted by the UK Biobank contradict previous evidence and official recommendations. Even though BAMEs had lower calcifediol levels, the study failed to find a link between calcifediol and COVID-19 infection after controlling for relevant confounders.

Although it would be inappropriate to suggest that vitamins are the panacea for the coronavirus pandemic, there is growing evidence that they may serve a role in either prevention or supportive therapy in established respiratory illnesses and intensive care settings. Even if this translates to a need for careful deficiency repair rather than ordinary mass supplementing, the physiology, pharmacology, and basic science underpinning vitamins A through E alludes to possible benefits that warrant further exploration and completion of clinical trials. Given the as of yet unexplained predisposition for the elderly and BAME communities to have the most severe outcomes, the current and emerging guidance to supplement at-risk populations with vitamin D is justified, exacerbated by the fact that an increasing number of people will be confined to live indoors during the COVID-19 pandemic's lockdown period. However, caution is required when recommending vitamin supplementation on a broader scale: Hypervitaminosis, especially of the fat-soluble vitamins A, D, and E, can have serious consequences. Hypervitaminosis, it should be noted, is nearly entirely the result of consuming too many vitamin supplements rather than vitamins obtained through traditional dietary and physiological sources.

During these unique times, the importance of keeping a vitamin-balanced diet appears prudent and applicable to the overall population. We expect well-designed clinical trials to offer the evidence needed to assess if the clinical utility of vitamins matches the promise of their antioxidative, antibacterial, and immunomodulatory characteristics in the near future.

Conclusion

There has been a lot of discussion regarding which vitamins and nutritional supplements can help treat the virus or lower the danger of getting Covid-19 ever since the outbreak started. According to Joan Driggs, vice president of content and thought leadership at

IRI, "Vitamins and supplements, right now in particular, are viewed as a small measure of control that people have over their life, in a really uncertain time". The supply of micronutrients (essential Nutrients) helps the body avoid micronutrient deficiencies and keeps us protected from many other diseases by boosting the immune system in our body. In addition, it alleviates the risk factors and associated symptoms of aging. According to the meta-analysis and retrospective studies, the decreased micronutrient level may be linked to an increased risk of COVID-19 infection. More research is needed to determine the effect of these micronutrients and the necessity of supplementation on the disease outcome. In addition, it alleviates the complaints and associated symptoms of aging. This might result in improvements in disease outcomes and outlook. To address this conjecture and overcome the hurdles in our present understanding of the role of micro and macronutrients in supplemental treatment in patients with COVID-19, prospective clinical trials are necessary. In this regard, the present review shed light to the importance of maintaining a well-balanced diet to improve overall health, boost immunity, and reduce the risk of infectious and chronic diseases in individuals to prevent future pandemic.

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Availability of Data and Material (Data Transparency)

Data are available as per request.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author Contributions

TMJ: Conceptualization, Methodology, Formal analysis, Writing - original draft. AK: Writing - review and editing. AMS: Writing - review and editing. DKM: Writing - review and editing. JTH: Supervision, Writing - review and editing. ST: Supervision, Writing - review and editing. SMS: Supervision: Supervision, Writing - review and editing.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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