

Literature Review: Nutraceuticals And Covid-19

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ABSTRACT

Coronavirus disease 2019(COVID-19) was declared as a global pandemic by World Health Organization on 11th March 2020. It is caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) which affects both humans and animals and causes chronic respiratory distress and affects the immune response of the host, later leads to serious comorbidities. The SARS-CoV-2 infection has caused and is proceeding to cause, significant human torment. Recent researches on finding potential therapeutic agents for fighting the virus has shed light on specific agents known as Nutraceuticals. Current studies have shown that certain nutraceutical products have antiviral roles which act either by directly acting against the viral particles or by acting as immunity boosters. The sales and distribution of dietary supplementations and nutraceuticals have expanded during the pandemic due to their apparent immune-boosting and antiviral properties. In the current situation, COVID-19 has forced a new set of contests for the individual to maintain a healthy diet. Supplementation with nutraceutical products like vitamin C, vitamin D, omega 3 polyunsaturated fatty acids, probiotics, and zinc as they have the ability of immune-boosting, antiviral, antioxidant, anti-inflammatory effects. Though, well-controlled clinical trials are vital to confirm these findings. "Let food be thy medicine and medicine be thy food."- Hippocrates

Keywords: Nutraceuticals, COVID-19, SARS-CoV-2, Respiratory Syndrome, Pandemic.

I. INTRODUCTION

China was first made aware of the infectious disease in Wuhan on December 31, 2019, and World Health Organization (WHO) on March 11, 2020, named the contamination a pandemic.^[1] From that point forward, research centres across the globe have been working together to foster antibodies and helpful therapeutic agents for fighting this novel Coronavirus. The Severe Acute Respiratory Syndrome coronavirus 2

(SARS-CoV-2) infection is proceeding to significant human torment. It belongs to a group of viruses called the 'coronaviruses'. The virus can infect both humans and animals. The immune response gets affected, severe respiratory distress (cytokine storm), and eventually death.

In recent years, there has been development in logical interest in nutraceuticals, like which these supplements in food sources improve health and wellbeing. Dr. Stephen DeFelice authored the expression "Nutraceutical" from "Nutrition" and "pharmaceutics" in 1989.^[2] Nutraceuticals can be separated, utilized for food enhancements, or added to food sources. They are items, which other than sustenance additionally administered as medication. A nutraceutical is a substance or product which is having a physiological advantage or gives security against ongoing infection and disease and is used to prevent several chronic diseases, improve quality of life and expectancy. Recent studies have shown that certain nutraceutical products have antiviral roles which act either by directly acting against the viral particles or by acting as immunity boosters. The sales and distribution of dietary supplements and nutraceuticals have expanded during the pandemic due to their apparent immune-boosting and antiviral properties.^[3] Some of these nutraceutical products include vitamin C, vitamin D, omega 3 polyunsaturated fatty acids, probiotics, and zinc which have exhibited potential prophylactic and therapeutic values for preventing treatment of COVID-19 patients.

NUTRACEUTICALS IN COVID-19

VITAMIN C

Vitamin C, a water-soluble vitamin, plays a crucial role in multiple physiological responses within the physical structure.^[4] In the current scenario, COVID-19 has forced individuals to maintain a healthy diet, appropriate intake of zinc, iron, and vitamins A, B 12, B6, C, and E is essential for the preservation of immune function.^[5]

COVID-19 and its complication like cytokine storm may result in multiorgan failure, respiratory failure, and immune overactivity in which interleukin -6 (IL-6) and endothelin -1 (ET-1) play an important role.^[6] Vitamin C (Vit c) can bring down these kinds of activities and other inflammatory mediators in several inflammatory conditions, and is therapeutically favourable in COVID-19 hypertensive and/or diabetic obese adult patients. Vit C being economic and relatively safe; preferably an oral low dose 1–2 g/d, may be useful prophylactically. And in cases of severe COVID-19, a very high-dose regimen^[7] or moderate dose of IV Vit C with other nutrients 1.5 g ascorbic acid IV every 6 hours, plus 200 mg IV thiamine every 12 hours may be beneficial, suggested by an International Pulmonologist Consensus Groups.^[8]

The immune response against viral infections as the T-lymphocytes and Natural Killer (NK) cells inhibit reactive oxygen species production and modulating the cytokine network in systemic inflammatory syndrome. It elevates immunity by reviving interferon(IFN) production, lymphocyte proliferation, and strengthens the neutrophil phagocytic capability. Furthermore, studies have manifest that reduces the chance of infection.^[9] Vitamin C is currently under clinical trials; expected to provide more definitive evidence.^[10]

Vit C is one of the main constituents of water-soluble vitamins which tends to construct a well-built immune system. The daily recommended dietary allowance for Vit C is 90mg/d for males and 75mg/d for females.^[11] Within the respiratory tract, it's an efficient anti-inflammatory and anti-allergic agent; supplementation of Vit C has been verified as an effective therapy for the treatment of certain respiratory diseases, including rhinitis, chronic rhinosinusitis, and therefore the cold^[11] It is effective in sepsis as it reduces mortality and length of stay in ICU, hospitals.^[9] Although VitC normally exhibits low toxicity, taking >2 g of Vit C per day may cause adverse gastrointestinal events including abdominal pain, diarrhea, and/or nausea,^[12] it is inordinately excreted within the urine, it can contribute to the formation of renal stones.^[4]

VITAMIN D

Several studies show that Vitamin D (Vit D) has been linked to immunological regulation in the body. Ultraviolet B(UVB) radiation interacts with 7-dehydrocholesterol in the skin to form Vit

D3. Vit D3 or oral Vit D is converted to 25-hydroxyvitamin D(25(OH)D) in the liver and subsequently to calcitriol (1,25(OH)2D), a hormone metabolite, in the kidneys or other organs as needed.^[13] Calcitriol's most well-known role is to assist regulate serum calcium levels, which it performs in a feedback loop with parathyroid hormone (PTH), which has a variety of activities in the body.

Several studies have looked into how Vit D reduces the incidence of viral infections. As a result, the conversion of 25(OH)D to active 1,25-dihydroxy vitamin D [1,25(OH)2D], which is catalyzed by the Vit D-activating enzyme 25-hydroxyvitamin D-1-hydroxylase(CYP27B1), determines the target cell function of Vit D. By attaching to the nuclear Vit D receptor (VDR) and working as a gene regulator, the 1,25(OH)2D generated in this way acts as a steroid hormone.^[14] This vitamin exhibits anti-infective properties due to its capacity to promote the synthesis of certain peptides with potent antibacterial properties (cathelicidin or LL37 protein). Cathelicidins have direct antibacterial activity against a wide range of bacteria, viruses, and fungi, including Gram-positive and Gram-negative bacteria, enveloped and non-enveloped viruses, and fungi.^[15] Vit D boosts cellular immunity by lowering the cytokine storm triggered by the innate immune system. In response to viral and bacterial infections, the innate immune system produces both pro-inflammatory and anti-inflammatory cytokines, as seen in COVID-19 patients.^[16] 1,25(OH)2D3 reduces T helper cell type 1 (Th1) responses by largely suppressing the synthesis of inflammatory cytokines interleukin -2(IL-2) and interferon-gamma (INF- γ) modulating adaptive immunity.^[17] Antioxidant genes (glutathione reductase and glutamate-cysteine ligase modifier subunit) are also enhanced by Vit D administration^[18] which also helps in treating and preventing COVID-19 infection. The studies recommend using 10,000 International Units (IU) per day of Vit D3 for a few weeks to rapidly enhance 25-hydroxy-vitamin D levels, then switching to 5000 IU/day to avoid infection and spread of COVID-19.

FOLIC ACID

Folic acid (FA) is a type of B vitamin a common synthetic food additive found in spinach, broccoli, asparagus, dried beans, lentils, peas, and oranges. FA helps the body produce and maintain new cells, prevents changes to DNA that may lead

to cancer, and is also used to prevent neural tube defects.^{[19] [20]} To process it, after it is absorbed in the intestine which is a very well organized process, it first needs to be condensed to dihydrofolate (DHF) and posteriorly into its effective form tetrahydrofolate (THF).^{[21][20]} Recent studies have revealed that FA can disable the furin endoprotease.^{[19] [22]}

Furin is a protease enzyme, involved in the stimulation of precursor proteins by cleavage on a single or paired basic deposit.^[23] This endoprotease is vital for the SARS-CoV-2 virus to penetrate its host cell, by sequence-specific cleavage of the spike protein. Certain studies found that FA inactivates protease3-chymotrypsin-like protease(3CLpro), which is essential in the replication of all coronaviruses.^[24]

The furin is an essential protein for the activation of coronavirus thus, focusing on furin protein appears to be a chance for the infection treatment. Thus, furin inhibition can have a considerable role in the prevention of COVID-19 infection progress. A recent study announces the capability of FA to interact and inhibit furin proprotein which will restrict the access of COVID-19 spikes to furin and inhibit the cell entry and subsequently turn-over of the virus.^{[24][25][26]} Folic acid is stable over an extensive range of temperatures and pH values, and it holds its ability to bind to the folate receptor after conjugation with drugs or diagnostic markers.^{[25][26]} Hence, may also help to prevent or alleviate the respiratory contribution related to COVID-19.^[19]

ZINC

Zinc is an essential mineral that is found in higher concentrations in the body than any other trace element except iron. Zinc serves a variety of purposes. Zinc is required for the operation of numerous enzymes; it is also required for the function of some cellular mediators; it aids in the maintenance of the cell membrane, and it affects in vivo and in vitro lymphocyte apoptosis.^[27] Supplements come in a variety of forms, including zinc picolinate, zinc acetate, and zinc citrate, and can be taken orally as a tablet or lozenges. T-helper (Th) lymphocytes are where zinc has the most impact on the immune system. Th lymphocytes are divided into two types: Th1 and Th2. The deficiency of zinc in the cell causes an imbalance between Th1 and Th2, favouring Th2.^[28] Zinc supplementation helps in the elimination of the imbalance between Th1 and Th2

by significantly increasing interferon-gamma (INF- γ) which is released from peripheral blood mononuclear cells, where INF- γ has antiviral and immunoregulatory properties which help in treating SARS-CoV-2 infection.^[29] Zinc is beneficial to the respiratory mucosa because it appears to increase ciliary beat frequency, resulting in improved mucociliary clearance; additionally, this element aids in the inhibition of the replication of some viruses, such as influenza and rhinoviruses, and thus may be effective in inhibiting the replication of SARS-CoV-2.^[30]

OMEGA 3 FATTY ACIDS

Polyunsaturated fatty acids (PUFAs) such as omega-3 fatty acids (FAs) are prevalent in nature and belong to the Generally recognized as safe(GRAS)category of supplements. The largest source of omega-3 FAs in the human diet is fresh fish, particularly oily fish including mackerel, salmon, herring, flounder, and cod. Omega-3 fatty acids boost macrophage function by secreting cytokines and chemokines, increasing phagocytosis, and activating macrophages through polarization. Nuclear Factor- Beta (NF-B) is known to be down-regulated by omega-3 fatty acids. The transcription factor NF-B is thought to be involved in cell signaling that triggers the innate immune system's inflammatory response. According to the study, fish oil boosts antiviral response by producing interferon (IFN), which inhibits virus replication.^[31] Multiorgan failure, which is caused by immune system hyperactivity and cytokine storms, is one of the leading causes of death in individuals infected with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Omega-3 fatty acids are known to produce fewer pro-inflammatory cytokines, increasing omega-3 fatty acid intake through diet or supplementation may help to reduce viral entry, improve immunological function, and reduce severity in COVID-19 patients.^[32]

PROBIOTICS

Supplementing with probiotics may help to minimize COVID-19 morbidity and death. Pourhossein M, et al. conducted a systematic assessment of probiotics efficacy against viral illnesses, finding that more than 20 strains enhanced anti-inflammatory interleukins(ILs) and antibody production against viruses.^[33] SARS-CoV-2 infection can be influenced by the human microbiota, which plays an important role in immunomodulation. Microbiota may take part in

COVID-19 susceptibility, progression, and severity, according to current research. Probiotics help the immune system develop and mature by modulating innate and adaptive immunological responses. Toll-like receptors (TLR), nuclear factor kappa B (NF- κ B), mitogen-activated protein kinase (MAPK), and c-Jun NH₂-terminal kinase (JNK) pathways are all activated by probiotics, which regulate host-pathogen interactions.^[34] Probiotics help to prevent cytokine storms by enhancing innate immunity while avoiding the exaggeration of adaptive immunity, which is under pressure to respond rapidly to viral attacks. The reduction of inflammatory cytokine responses by probiotics may help to decrease both the severity and recurrence of ARDS, making probiotics an appealing supplement.

MISCELLANEOUS PRODUCTS

Certain other agents are also found useful in the prevention and treatment of COVID-19.

They are curcumin, cinnamaldehyde, selenium, lactoferrin, quercetin, allicin, piperine, propolis,^[35] etc. Lactoferrin, which is a protein that is normally found in milk and helps in the regulation of immunity. Studies found that lactoferrin can inhibit viral entry and viral replication of murine coronavirus and pseudo-type SARS-CoV. Lactoferrin as adjuvant therapy for COVID-19 is now being investigated in clinical trials.^[36] Quercetin is a dietary flavonoid that is found to have anti-inflammatory, anti-allergic, anti-hypertensive, and anticancer properties. Few studies have proven quercetin's antiviral potential, highlighting its impact on the influenza virus, H1N1 and H3N2.^[37] There are only a few clinical studies that support the use of quercetin in the treatment of COVID-19. Resveratrol, a plant compound that exhibits anti-inflammatory, antioxidant, anti-platelet properties have also proven useful in the treatment of COVID-19. Recent clinical trials make evident the in-vitro inhibition of SARS-CoV by resveratrol.^[38] Hesperidin, Vitamin K, Vitamin A supplements are also clinically proved useful for the prophylaxis and treatment of COVID-19 besides their specific health benefits.^[39]

II. CONCLUSION

Most of the countries around the world are into developing vaccines and several drugs being evaluated against COVID-19, but still, researchers are not sure about the extent of safety and efficacy of the vaccine. Markedly there is no specific drug

of choice against COVID-19.^[35] The discovery of new antivirals for COVID-19, as the pathogenesis of COVID-19, is extremely intricate,^[40] will be a significant challenge and requires considerable time and effort^[35]. Thus, it is important to pay more attention to our food habits.^[41] Nutraceuticals so far, had a remarkable stretch in the treatment of COVID-19 as they have the ability of immune-boosting, antiviral, antioxidant, anti-inflammatory effects.^[40] Grossly, supplementation of vitamin C, vitamin D, and zinc, etc, maybe a plausible method. Ensuring an adequate intake of nutraceuticals to uphold optimum immune function, which may also possess an immunomodulatory effect thus may be effective against viral infection.^[42] Though, well-controlled clinical trials are vital to confirm these findings. The role of nutraceuticals and like compounds might have a crucial role in handling this pandemic situation.^[43] "Let food be thy medicine and medicine be thy food." - Hippocrates

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