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## IMMUNE BOOSTING NUTRACEUTICALS

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### ABSTRACT

The consumption of specific nutrients and bioactive chemicals found in food has a significant impact on how well the human body functions in terms of immunity. These bioactive compounds' ability to prevent a variety of ailments has been well studied. Consumption of functional foods is widespread throughout numerous cultural groups. In one way or another, which offer advantages above and beyond the need for basic sustenance. Bioactive components with a variety of immunomodulation qualities, including phytoconstituents, polyunsaturated fatty acids and probiotics, are being used to create novel functional meals. These substances influence immunity by their antiviral, antibacterial and antioxidant qualities in addition to immunomodulation. The scientific community is under pressure to provide a suitable and efficient treatment for the severe acute respiratory syndrome coronavirus-2 pandemic, as there is a deadline of sorts.

### KEYWORDS

Phytoconstituents, Immunomodulation, Polyunsaturated, Plethora and Immunity.

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### INTRODUCTION

The word "nutraceutical," which is a combination of the words "pharmaceutical" and "nutrition," describes any product made only of herbs, nutrients, certain diets, processed meals, and beverages that are utilized for both medicinal and nutritional purposes. Numerous bioactive derivatives from indigestible sources, including phytochemicals, fatty acids, amino acids, prebiotics, and probiotics, as well as antioxidants, are included in nutraceutical. Numerous of them have immune-system-influencing therapeutic qualities. Nutraceuticals are divided into groups in this special issue according to their source, kind and use. The anti-cancer, anti-inflammatory,

antioxidant, and anti-lipid effects of nutraceuticals were categorized by the authors. Nutraceuticals can strengthen the immune system to fend off infections, neurological diseases, cancer and digestive issues.

### **WHY NUTRACEUTICALS?**

It is impossible for a great number of us to obtain enough nourishment from everyday foods. Second, the environment in which we live is extremely harmful due to pollution and pesticides, which interfere with our bodies' natural ability to manage it. Strengthening our immune system or using Tertian is a more rational course of action than resorting to antibiotics that have outlived their usefulness. Drugs usually have negative effects because they are not natural to the body; but, are high-quality.

### **IMMUNE – BOOSTING NUTRACEUTICALS ZINC (ZN)**

Zinc serves as a structural element, co-factor, and signaling molecule in many biological processes, making it a vital metal. In addition to its antiviral and antioxidant properties, it controls inflammatory activity. Moreover, zinc has the ability to control viral budding, fusion, replication, protein translation, and entrance of respiratory viruses. Zinc lowers the risk of developing acute respiratory infections. Zinc also speeds up the healing process and reduces the length of flu-like symptoms by two days. Zinc's anti-inflammatory, antioxidant, and direct antiviral properties make it a promising supportive treatment for COVID-19 infection. Research using a rat model demonstrates that a zinc deficit raises the production of vascular cell adhesion molecules, pro-inflammatory TNF and oxidative stress.

### **VITAMIN D (VD)**

Vitamin D is a fat-soluble vitamin that is essential for antioxidant, immunomodulation, and antiviral responses. The vitamin D receptor is constitutively expressed by the human airway epithelium, which makes vitamin D effective in preventing respiratory

infections. In addition to promoting normal mitochondrial functioning peroxidation, and protein oxidation linked to oxidative stress, VD raises the levels of the antioxidant NRF-2.

VD deficiency is associated with a higher risk of acute viral respiratory infections, according to epidemiological data, while its supplementation strengthens the body's defenses against respiratory viral infections, such as those brought on by influenza A and B, para influenza 1 and 2, respiratory syntactical virus (RSSV), and chronic hepatitis C. Despite the lack of evidence linking VD to changes in viral load or replication, studies show and preventing DNA damage, lip Vitamin D is a fat-soluble vitamin that is essential for antioxidant, immunomodulatory, and antiviral responses. The vitamin D receptor is constitutively expressed by the human airway epithelium, which makes vitamin D effective in preventing respiratory infections. In addition to promoting normal mitochondrial functioning in peroxidation and protein oxidation linked to oxidative stress, VD raises the levels of the antioxidant NRF-2.

### **VITAMIN C (VC)**

Because of its crucial function in immune function, vitamin C may offer protection against infection. This vitamin improves the capacity of different immune cells to fight infection and promotes their normal function. It has been demonstrated that taking VC supplements shortens and lessens the intensity of upper respiratory infections, including the common cold, the majority of which are thought to be caused by viral infections. The range of recommended daily doses for VC was 1 to 3g. For VC, a total of 60mg is the recommended daily amount (RDA). Vegetables, fruits, herbs, and a variety of species have been proven to be great sources of volatile carbon (VC).

It has recently been suggested, based on clinical trials, that oral is a strong antioxidant as well. As an antioxidant, it scavenges reactive oxygen species (ROS), inhibits lipid peroxidation and stops protein alkylation, protecting cells from damage caused by oxidative stress. Additionally, research has shown

that administering quercetin and VC together has synergistic antiviral, antioxidant, and immunomodulation administration of 250-500mg quercetin, 500mg VC for subjects with mild symptoms and high-risk, up to 3g VC and 500mg quercetin twice daily for 7 days in patients with ARDS (assisted ventilation/incubation), improves the overall recovery in SARS-CoV-2 patients. Consequently, taking a food supplement containing VC sources can aid in reducing inflammation and strengthening the immune system.

### **CURCUMIN**

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### **CINNAMALDEHYDE**

The chemical component known as cinnamaldehyde, which gives essential oils of cinnamon its flavor and aroma, is a naturally occurring substance. One well-known phytonutrient in medicine with anti-inflammatory qualities is cinnamon aldehyde. It was discovered that by suppressing NF-KB activation, cinnamon aldehydes reduce inflammation brought on by TNF. Additionally, research has shown that it can inhibit the production of prostaglandins (PGEs) through the suppression of endotoxin-mediated hyperexpression of TLR4 and NOD-, LPR- and pyrin domain-containing protein 3 (NLRP3) inflammasome signaling pathways by down-regulating IL-1 induced COX-2 activity, thereby reducing the likelihood of hyper inflammation in a dose-dependent manner. According to all of the aforementioned data, cinnamon aldehyde is a bioactive substance with potential anti-inflammatory properties that may help reduce lung hyper inflammation caused by SARS-CoV-2.

### **ALLICIN**

Due to its numerous nutritional benefits, garlic is a well-known plant and herb that belongs to the Allium (onion) family. It has been used for centuries. Allicin, the main thiosulfate found in fresh garlic extract, has been linked to several health advantages because of its antiviral, antioxidant, and anti-inflammatory qualities. Allicin reduces inflammation by blocking the expression of IL-1 $\beta$ , IL-8, IP-10 and IFN- $\gamma$  that TNF- $\alpha$  induces, as well as by preventing the degradation of NF- $\kappa$ B inhibitory protein I $\kappa$ B in intestinal epithelial cells (65). In activated macrophages, it suppresses the production of inducible NO nitric oxide synthase (66, 67).

Several chemicals related to garlic have demonstrated potent virucidal effects on a variety of viruses, such as the human rhinovirus, para influenza virus type 3, herpes simplex virus (HSV)-1, HSV-2, and vesicular stomatitis virus (VSV). Ajoene, allicin, allyl, methyl thiosulfinate, and methyl allylthiosulfinate are a few of the chemicals found in garlic that have viricidal activity (68, 69). The majority of the functional effects listed above were noted at doses of 200ng/ml. The majority of the biological activities of garlic were successfully induced in samples that underwent no processing, such as drying or heat induction (70). Fresh garlic extract may therefore be helpful as a preventative measure against COVID-19.

### **PIPERINE**

Black pepper is a highly valued herb among medicinal plants and has been used for a long time in many different cuisines. A prominent alkaloid of the cinnamamide group, piperine is derived from the ethanolic extract of black pepper (71). Because piperine has potent anti-inflammatory properties, it can be used to reduce hyper-inflammation brought on by COVID-19. By suppressing the expression of matrix metalloproteinases (MMP-13) and IL-6, it downregulates PGEs (71). Piperine is known to decrease LPS-induced production of IRF-1 and IRF-7 mRNA, phosphorylation of IRF-3, type 1IFN mRNA and down-regulation of STAT-1 activity. It

also increases the phagocytic activity of phagocytes, which in turn enhances innate immunity (72). Piperine suppresses the generation of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and PGE2 in BV2 cells induced by LPS, according to a small body of research on microglial cells (73).

Additionally, it was discovered to suppress human peripheral blood mononuclear cells (PBMCs) ability to produce IFN- $\gamma$  and IL-2 (74). Additionally, in the brain ischemia-reperfusion-induced inflammation rat model, piperine administration was observed to decrease the production of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , COX-2, nitric oxide synthase-2 and NF- $\kappa$ B (75). These results demonstrate the piperine's potent anti-inflammatory properties. Moreover, piperine is a strong antioxidant that guards against oxidative damage by scavenging hydroxyl, ROS and free radicals. With an IC50 of 1.82mM, it scavenges superoxide radicals and has an IC50 of 1.23mM that prevents lipid peroxidation. According to these findings, piperine has a direct antioxidant impact on a range of free radicals (76). These characteristics make piperine a promising candidate for use as a preventative or therapeutic agent to guard against the hyper-inflammation and oxidative stress brought on by COVID-19.

### **SELENIUM (SE)**

Many common foods, including corn, garlic, onions, cabbage, and broccoli, are high in selenium. It is a micronutrient that is necessary for several physiological functions as well as the immune system. Because selenium is incorporated into selenoproteins in the body, it has a biological effect. A daily intake of 100 micrograms of selenium is optimal for NK cell activity, T cell proliferation, and innate cell activities. Fosters robust immunity to pathogens and a higher response to vaccinations. Research has indicated that the administration of supplements containing selenium reduces the inflammatory response in individuals suffering from respiratory distress syndrome by reinstating

the lungs' antioxidant status and lowering levels of IL-1 $\beta$  and IL-6 (78).

Selenium supplementation suppresses pathogen-induced activation of NF- $\kappa$ B and its downstream pro-inflammatory cytokines release (79). The antiviral properties of selenium have been found to be mediated through its antioxidant effects. Selenium-deficient HIV+ patients tend to present with diminished antioxidant glutathione peroxidase activity (77). On the other hand, selenium supplementation demonstrates improved CD+ T cell counts (80) and improves glutathione peroxidase and other antioxidant selenoenzymes along with catalyze activities (81). Overall, selenium improves immunity through its non-enzymatic role acting as a co-factor for enzymes involved in critical post-transnational modifications of proteins. Because of its substantial role in suppressing inflammation and augmentation of antioxidant status and innate immunity, selenium supplementation may be useful in the fight against COVID-19.

### **Propolis**

A wide range of biological characteristics, including anti-microbial, anti-inflammatory, hepatoprotective, laxative, anti-diabetic, anti-tumor, and immunomodulation activity, are associated with propolis, which is made by honeybees (82). Flavonoids and some phenol acids, particularly caffeic acid, phenethyl esters, and artemillin C (3, 5-diprenyl-4-hydroxycinnamic acid), are responsible for the immunomodulatory effect. Additionally, acropolis increases the formation of antibodies, indicating that it might be utilized as a vaccine adjuvant. Higher quantities of propolis prevent lymphoproliferation, whereas lower concentrations have the opposite effect and promote lymphoproliferation (84). Additionally, substances found in honey propolis suppress several viruses, including influenza virus A1, herpes simplex virus, human cytomegalovirus, and denguevirus type 2 (85). Propolis has both immunomodulatory and antiviral properties, making it a viable preventive against COVID-19.

## PROBIOTICS

Probiotics that are frequently utilized include Lactobacillus and Bifidobacterium species, which are followed by Escherichia coli, Streptococcus, Enterococcus, and Bacillus. Probiotics enhance system performance and control in addition to promoting gut health (86). Nevertheless, it is unclear how gut microbial prevent respiratory tract infections by using the gut-lung axis. The gut microbiome is generally found to influence both local and systemic immune responses at distant mucosal locations, such as the lungs (87). It has been discovered that consuming Lactobacillus and Bifidobacterium helps eliminate the influenza virus from the respiratory tract (88). Probiotics increase the levels of interferon, lung mucosal antibodies, NK cell activity, and antigen-presenting cells (APCs) (89). The Lactobacillus plant arum DR7 strain is known to lower plasma per oxidation levels, affect the immune system, and has been proven to have a suppressive effect on pro-inflammatory cytokines like TNF- $\alpha$  and IFN- $\gamma$ . It also boosts anti-inflammatory cytokines like IL-10 and IL-4 (90). It has been reported that the administration of Lactobacillus acid o plus CMCC878 to mice infected with Pseudonymous aeruginosa and Staphylococcus aureus reduced lung damage by decreasing inflammation and bacterial load (91). According to a clinical study, giving resistant starch, insulin prebiotics, and other prebiotics together with Leuconostocmesenteroides 32-77:1, Lactobacillus plant arum 2,362, L. paracasei.. paracasei 19, and Pediococcus pentosaceus 5-33:3 decreased infections and the systemic inflammatory response syndrome (92). The BB536 strain of Bifidobacterium long enhances innate immunity and guards against influenza infection (93). The exact mechanism underlying their anti-inflammatory and immunomodulation actions in the lung is unknown. Probiotics generally reduce Th2-mediated responses and increase Th1 responses by modulating the NF- $\kappa$ B, MAPK, and pattern recognition receptors (PRR) pathways. This results in anti-inflammatory and immunomodulatory effects.

Additionally, they have the capacity to prevent bacterial LPS from adhering to the CD14 receptor, which reduces overall NF- $\kappa$ B activation and the synthesis of pro-inflammatory cytokines (94, 95). Probiotics can be used as prophylactics and adjuvants to fight the pathogenesis of COVID-19 because of their role in enhancing the host's innate immune response as well as their anti-inflammatory effects (87), as well as the possibility that gut involvement and enterocytes (96) can act as reservoirs of SARS-CoV-2 infection.

## LACTOFERRIN

Natural and non-toxic, lactoferrin (Lf) is a glycoprotein that has been extensively researched against several viruses, including SARS-Co, a closely related strain of SARS-CoV2. By attaching itself to either or both of the viral particles' surfaces, Lf prevents the entry of the virus. It was also reported to inhibit the spread of viruses, including HIV. As a result, it is essential for blocking the entry and spread of the virus (97). Research has indicated that it possesses immunomodulatory and antioxidant properties through the stimulation of T-cell activation, inhibition of interleukins such as TNF- $\alpha$  and IL-6 and reduction of ferritin levels (98). Additionally, it inhibits oxidative stress caused by H<sub>2</sub>O<sub>2</sub> in human umbilical vein endothelial cells (99). Moreover, zinc-saturated Lf has a stronger antiviral impact (100). At doses ranging from 100mg to 4.5g, it is mostly employed as a nutritional component in clinical research and newborn formulae.

## QUERCETIN

Well-known for its anti-inflammatory and antiviral properties, quercetin is an antioxidant. It suppresses the synthesis of IL-8 in lung A549 cells (102), TNF- $\alpha$  production in LPS-induced macrophages (101) and glial cell m RNA levels of IL-1 $\alpha$  and TNF- $\alpha$  (103). Additionally, it restricts the rat liver epithelial cells' ability to produce the enzymes lipooxygenase (LOX) and cyclooxygenase (COX) (104). Additionally, research has demonstrated that quercetin inhibits DNA and RNA viruses. It

decreases the expression of pro-inflammatory cytokines and lung inflammation brought on by rhinovirus in mice (106) and it prevents virus entrance and viral-cell fusion (105). Furthermore, it has been demonstrated that the metabolite of quercetin (4', 5-diacetyloxy-3, 3', 7-trimethoxyflavone) inhibits the replication of picornaviruses by blocking the RNA replicase complex (107). Research has also revealed that quercetin-3 $\beta$ -galactoside binds to viral protease 3CLpro and inhibits its proteolytic activity because it has a hydroxyl group (108). The supercomputer SUMMIT drug-docking screen and gene set enrichment analysis (GSEA) reveal that 85, 70 and 61% of the SARS-CoV-2 viral proteins in human cells are inhibited by quercetin, VD, and estradiol, respectively, in the setting of SARS virus infection. Based on these findings, the research also suggests that a tripartite combination of quercetin, VD, and estradiol, as opposed to a bipartite combination of VD and quercetin, may impact 73% of human genes that encode SARS-CoV-2 targets, suggesting a potent mitigation drug against COVID-19 (109). Moreover, estradiol's greater capacity than testosterone to influence human genes encoding SARS-CoV-2 targets raises the possibility of an explanation for the coronavirus pandemic's apparent higher male fatality rate (109). According to these findings, a randomized intervention clinical trial has been posted on the clinical trial website (<https://clinicaltrials.gov/ct2/show/NCT04359329>) that uses estradiol or VD as a mitigating drug. In addition, prediction models have shown that quercetin binds to the SARS-CoV-2 S-protein at the host receptor region or to the S-protein-human ACE2 interface, obstructing the virus's ability to enter cells and suggesting possible therapeutic uses (110). This prediction is in line with observations that the SARSCoV virus can be inhibited by quercetin and a structurally similar luteolin (111). Moreover, quercetin and VC together provide synergistic antiviral and immunomodulatory actions against COVID-19, according to earlier research (47). When combined, these data indicate that quercetin may have anti-SARS-CoV-2 properties

and may be repurposed as a therapeutic and preventive agent to fight COVID-19.

## CONCLUSION

Nutraceuticals include immune-boosting capabilities that include immunomodulatory, antioxidant, anti-tumor, antiviral, antibacterial and anti-fungal activities. These properties can be used therapeutically to treat a variety of pathological disorders. For millennia, natural products have been valued for their therapeutic properties. These compounds have been utilized as anticancer, gastroprotective, anti-diabetic and immune boosters in the modern period. Consequently, it may be possible to manufacture these herbs as nutraceuticals.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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