REVIEW ARTICLE

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Nutraceuticals, Immunity and their Antiviral Effects against Respiratory Viruses

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Abstract: Respiratory infections have always been a cause of significant morbidity and mortality around the world. The surge in Coronavirus disease-2019, especially in the weaker immunity groups, is more severe and disastrous. Alternative therapy for treatment or risk reduction is the need of the hour. For this review, we explored published clinical trials and papers on nutraceuticals and antiviral phytochemicals fulfilling our eligibility criteria. It is important to highlight those nutraceuticals that impact viral entry, signalling and host immune response of respiratory viruses. Their antioxidant, anti-inflammatory and immunostimulatory action can further potentiate antiviral action of pre-existing antiviral moieties. Few nutraceuticals are even found to reduce the severity of respiratory infections including the common cold. The aim of this review is to aid researchers and physicians in understanding the immunity-boosting and antiviral potential of certain nutraceuticals in respiratory viral infections.

INTRODUCTION

The lower respiratory infections caused by respiratory viral pathogens are one of the leading cause in the global burden of diseases, as found by world Health organization (WHO) in 2016. [1] Adenovirus, enterovirus, human coronavirus, human metapneumovirus, rhinovirus (RV), influenza, parainfluenza and respiratory syncytial virus (RSV) are commonly found respiratory viral pathogens. These diseases can show mild or severe symptoms such as asymptomatic upper airway infections or severe wheezing, bronchiolitis or pneumonia. [2] There have been few epidemics caused due to new strains of viruses such as Ebola, SARS, MERS-CoV and due to new variants or mutated strains of viruses e.g. influenza. These diseases have the repercussions in terms of increased mortality rate, altering morbidity of patients and potential loss of social cohesion. These factors, directly and indirectly, contribute to significant economic losses of patients and their families, society and public infrastructure. [3]

The global pandemic i.e. coronavirus disease-2019 (COVID-19) is caused due to transmission of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which basically originated in Wuhan, China. [4] The sheer speed of its global expansion and the sudden increase in the number of cases demonstrated that its capacity of diffusion is phenomenal. As of 13th May 2020, the incidence and mortality of COVID-19 are depicted in Figure 1. With a current mortality rate of about 6.8%, the new coronavirus is found to be more deadly than the typical annual flu. In India, 74,281 confirmed cases of COVID-19 were reported out of which 2415 people died. [5]

Symptomatic infections are associated with a heightened immune response in the blood. These influenza infections especially COVID-19 take a toll on the individuals' immune systems, hence strengthening the defence system is essential to fight this invasive virus. Alternative medicine and ways to prevent infection are the need of the hour. Nutraceuticals through their immunomodulating, antioxidant and anti-inflammatory actions accompanied by their antiviral properties can play a major role in fighting the infection.[6–8] Studies have reported the synergistic role of the nutraceuticals along with synthetic antiviral drugs or other nutraceuticals or phytochemicals against infections. [9–12] This review article in detail will explain the novel virus, viral and host immune response, nutraceuticals and their potential benefits in combating this infection and boosting the immune system of the host.

INFLUENZA AND SARS CORONAVIRUS

The influenza virus is the family of enveloped viruses comprising of negative-sense single-strand RNA (ssRNA) segments. The novel coronavirus i.e. SARS-CoV-2 is affecting almost 210 countries and territories, across all continents. [13] Morphologically, SARS-CoV-2 is an enveloped positive ssRNA coronavirus (Figure 2). S-glycoprotein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors of the host-serving as a precarious step for virus entry in the human body. Other proteins assist in pathogenesis and interfere with host immune response. [14] The viral M2 channel helps in membrane fusion due to an irreversible conformational change in the Hemagglutinin (HA). This facilitates the release of viral ribonucleoproteins (vRNPs) into the cytoplasm and nucleus and stimulates transcription process. Neuraminidase (NA) is an enzyme responsible for cleaving sialic acid from the cell's surface, permitting the new virion to be released from the cell and helping the virus transport in the bronchial cells. [15]

Symptoms and Diagnosis

The usual symptoms of COVID-19 infections consist of an upper respiratory tract viral infection (mild fever, cough (dry), sore throat and nasal congestion), headache, muscle pain, or malaise. These are milder while in severe cases, the high inflammation spread in the lungs is responsible for acute respiratory distress, organ failure and death. [16]

The clinical manifestations of COVID -19 by their level of severity are described in Table 1. [16]

Molecular assays, immunoassays, laboratory testing and radiographic imaging are the methods by which diagnosis of COVID-19 is carried out. [16]

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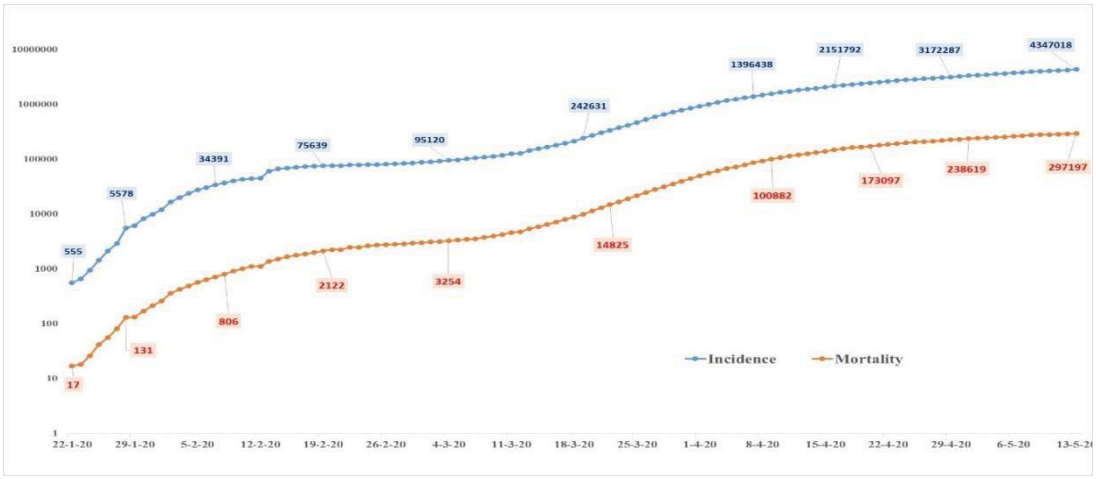

Figure 1: Overall global distribution of incidence and mortality of COVID-19 between the periods 22nd Jan 2020-13th May2020 [5]

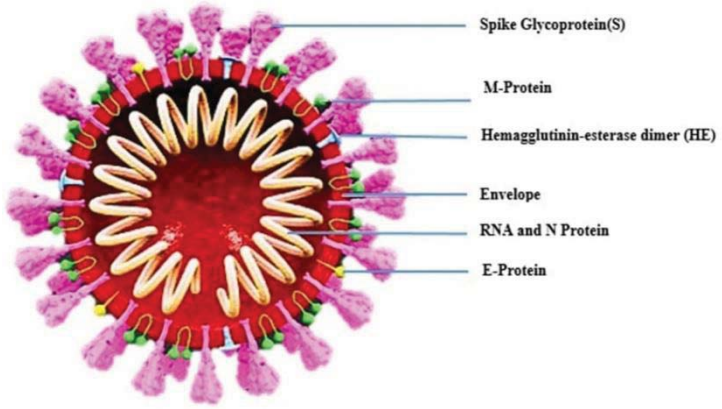

Figure 2: Morphology of SARS-CoV-2 [14]

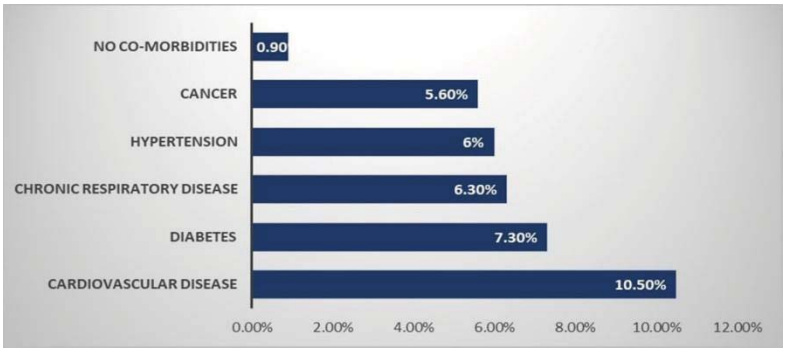

Figure 3: Overall global distribution of death rate based on pre-existing medical conditions [17]

Table 1: The Clinical Manifestations of COVID-19 [16]

Mild Disease	Severe Disease	Critical Disease
Non pneumonia Mild pneumonia	Dyspnea Respiratory frequency ≥ 30/min, Blood oxygen saturation ≤ 93%, Lung infiltrates > 50% within 24 to 48 hours	Respiratory failure, Septic shock, Multiple organ dysfunction (MOD) or failure

Risk Factors

According to the gender, the death rate in males was reported to be 2.8%, while in females it was 1.7% among the overall cases. According to the WHO statistics from China, the case fatality rate was 0.2% in the age group 10-39, 0.4% in 40-49, 1.3% in 50-59 and 3.6% in 60-69. The mortality rate of the new coronavirus soars among patients aged 70 or more with 8%but rose drastically to 14.8% for people aged between 80 or older. However, no fatalities were reported in the age group of less than 10. Several underlying conditions are reported to be associated with high fatality rates such cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and cancer (Figure 3). [17]

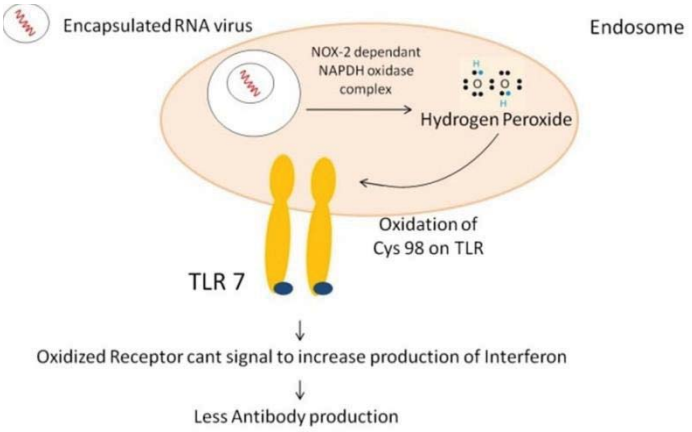

Figure 4: Changes in the mechanism of TLR7 mediated pathway of interferon production by entry of ssRNA [19]

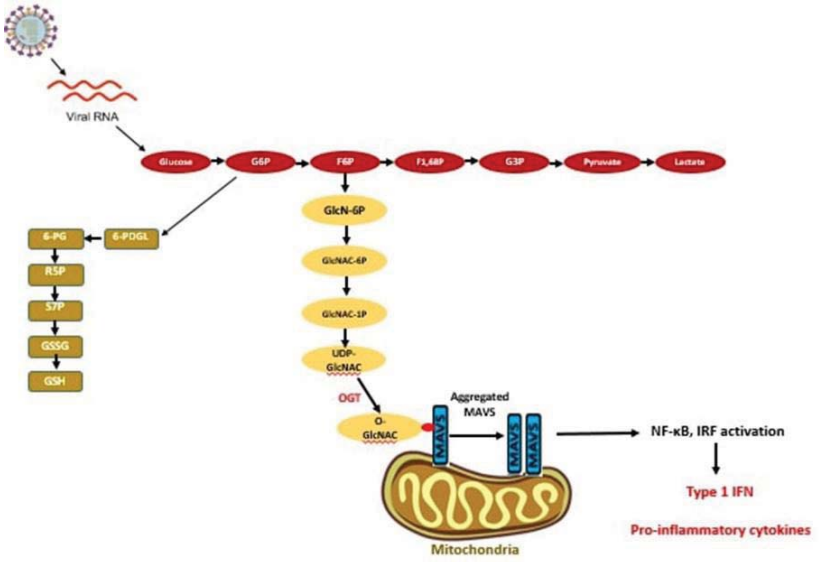

Figure 5: Effect of ssRNA on mitochondrial antiviral-signalling protein(MAVS) pathway [19]

ENTRY AND SIGNALLING OF SSRNA VIRUS

The entry of SARS-CoV-2 into the human body brings out cascades of responses from the host's immune system and from the host cells.

The Entry of ssRNA Virus in the Host Cell and Its Effect on the Response of Type 1 Interferon Production

The ssRNA alters the major intracellular pathways of host cells which have the potential to boost the type 1 interferon production.

1. Angiotensin-Converting Enzyme (ACE-2) Receptor

The entry of virus in the human body causes the cleavage of trimeric S protein (on virus' surface)into 2 subunits i.e S1 and S2. S1 is responsible for the binding of the virus to the receptor site while S2 causes membrane fusion. The receptor binding domain (RBD) of S1 gets directly bound to the peptidase domain of the Angiotensin-converting enzyme (ACE-2) receptor. ACE-2 is expressed on the oral mucosa. When the binding occurs, host proteases cut a cleavage site on S2. This is a crucial event in the process of viral infection. The physiological role of ACE-2 in the lungs is unclear, however, it provides entry to the virus in the host cells. [18]

2. TLR-7 Signalling Inhibited by NOX-2 Dependant Free Radical Production

The virus induces the superoxide formation in the host cells due to the activation of the enzyme NOX-2 dependent NADPH oxidase complexes. Furthermore, the subsequent generation of hydrogen peroxide within these endosomes leads to ectomeric oxidation of Cys98 on TLR7 that blocks natural propensity of this receptor to transmit a signal boosting type 1 interferon production(as depicted in Figure 4)Interferons are essential in the process of producing antibodies against viruses. Activation of TLR7 leads to activation of Nuclear Factor Kappa-Light-Chain-Enhancer of activated B Cells (NF-κB), a transcription factor for several types of cytokines with antiviral and proviral properties. [19]

3. Mitochondrial Antiviral—Signalling Protein (MAVS)

Mitochondrial antiviral-signalling protein (MAVS) is also responsible for activation of the transcription factor of interferon regulatory factor 3 (IRF3). In response to the RNA virus, MAVS oligomerizes and activates the production of interferons by phosphorylation. This process is carried out by O-glcNacylation of MAVS on numerous sites, which makes it vulnerable for K63-linked ubiquitination. So, the

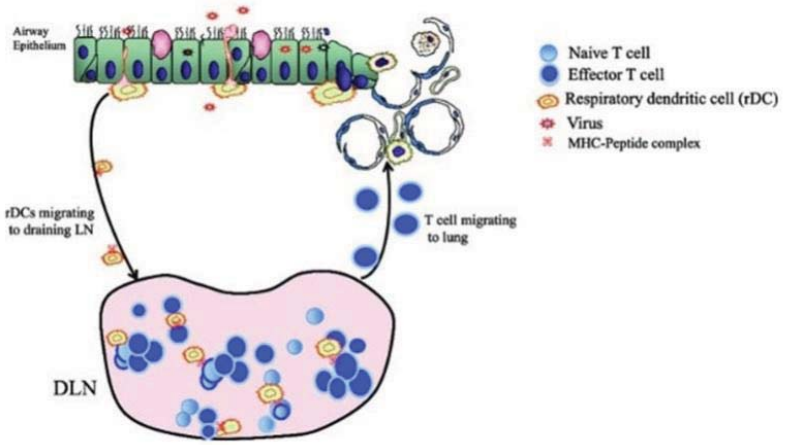

Figure 6: Response of T cells to respiratory virus infection [22]

molecules which can stimulate or suppress MAVS or increase/decrease the concentration of UDP-N-acetylglucosamine (substrate for the enzyme used in the O-glcNacylation process) could have potential to boost or deplete the production of interferon respectively (as shown in Figure 5). [19]

Immune Response

1. Innate Immunity

When COVID-19 enters into the human respiratory system, prominently in the alveolar macrophages type II cells, antigens were detected in the cytoplasm of infected type II cells, electron micrographs confirmed that secretory vesicles are filled with viruses. The concentration of virus RNAs is increased as time proceeds. These virions are expelled by exocytosis from alveolar macrophages type II cells. In response to the infection, there is a significant increase in mRNA concentrations of interferon–b and interferon–λ (IL-29) and various pro-inflammatory cytokines and chemokines. [20]

2. CD4+ Response

The entry of virus causednatural Killer (NK) cells, macrophages and plasmacytoid dendritic cells (pDC) transfer into the lungs, which further stimulated the synthesis of cytokinesand chemokines and in turn led to an inflammation storm, as found in the preclinical study. This event was correlated with T lymphocytes (CD8+ and CD4+) entry into the infection areas. The reduction in CD4+ T cells resulted in an enhanced immune-mediated interstitial pneumonitis and delayed clearance of virus from the lungs due to reduction in neutralizing antibody and cytokine production and pulmonary recruitment of lymphocytes. However, the reduction of CD8+ T cells didn't have significant effect in the depletion of viral replication or their clearance. This study proved that CD4+ T cells are critical in providing immune response against virus infections. [21]

3. T Cell-Mediated Response

Lung-resident respiratory dendritic cells (rDCs) acquire and process the respiratory virus and become activated and traverse to the draining lymph nodes (DLN). MHC/peptide complex with the virus in DLN invites circulating T cells and this interaction cause stimulation and multiplication of virus-specific effector T cells which travel to the site of infection (Figure 6). These cells produce antiviral cytokines (IFN-γ, TNF-α, IL-2), chemokines (CXCL-9, 10 and 11) and cytotoxic molecules (perforin and granzyme B). The viral replication process is inhibited by effector cytokines. [22]

POTENTIAL THERAPY

In absence of concrete treatment or prevention regimen available against SARS-CoV2 by World Health Organization (WHO), the Centre's for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), treatment regimens which included drugs such as chloroquine, lopinavir, ritonavir, were developed and practiced based on the local evidence. [23]

POTENTIAL FUTURE TREATMENT

These synthetic drugs are expensive and also associated with several side-effects. Their unavailability at the time of crisis has called for discovering and developing different measures.

WHAT ARE NUTRACEUTICALS?

Nutraceutical is a combination of two terms "nutrition" and "pharmaceutics." Nutraceuticals are the part of food or fortified food product, which not only complements diet but also has medicinal properties and help in preventing diseases/disorders. [6] They are extracted from herbal or animal sources, they provide dietary supplements (nutrients), specific diets and processed foods other than nutrition. They play a role in improving health, delaying the ageing process, preventing chronic diseases, increasing life expectancy, or supporting the structure or function of the body. These days, nutritional, safety and therapeutic effects of nutraceuticals have been emphasized in various studies. Many researchers have identified the potential of nutraceuticals against several diseases such as diabetes, atherosclerosis, cancer and neurological disorders. For example Natural antioxidants present in fruit and vegetables, including vitamins C and E, carotenoids and polyphenols (e.g. flavonoids), are currently considered to

be beneficial. [7] In a compelling article in Progress in Cardiovascular Diseases, published by Elsevier, authors Mark McCarty and James DiNicolantonio propose that certain nutraceuticals may help provide relief to people infected with encapsulated RNA viruses such as influenza and coronavirus. Authors identified certain nutraceuticals and may help to reduce the inflammation in the lungs from RNA viruses and others may also boost type 1 interferon response to these viruses, which stimulate the antibody production against viral infections. [19]

MECHANISM OF ACTION OF NUTRACEUTICALS AGAINST SARS-COV-2

Inhibiting NOX-2

Nutraceuticals which inhibit NOX2-dependant NADPH oxidase, are able to produce TLR7 mediated stimulation of type 1 interferon and antiviral antibodies. They help in enhancing the immunity against RNA viruses and are capable of inhibiting NOX2, discouraging the production of hydrogen peroxide, or assisting restoration and maintaining the original form of Cys98 in TLR7, might be responsible to increase the TLR7-mediated induction of type 1 interferon and antiviral antibodies. Phycocyanobilin (PCB) chromophore of cyanobacteria (present in spirulina), have structural similarity with bilirubin and mimic its NADPH oxidase inhibiting activity. Activation of heme-oxygenase 1 (HO-1) generates a low concentration of unconjugated bilirubin within the cell that potentially inhibits NOX2 system. [19]

Enhancing MAVS

In a preclinical study, the survival rate of mice, fed with glucosamine rich diet, was higher against influenzavirus. They demonstrated that Glucosamine regulates the concentration of UDP-N-acetylglucosamine – the substrate for OGlcNacylation in the host cells and correspondingly suppress or amplify the activation of MAVS. [19]

Antioxidant

The influenza viruses replicate themselves and modify the functions of host cells by altering intracellular redox sensitive signalling pathways. It can be either by decreasing the intracellular glutathione or increasing reactive oxygen species (ROS) production.

Antioxidant nature of nutraceuticals suppresses the virus spread in the lungs and inhibits the pro-inflammatory signalling pathway in endothelial cells. Thus, the influx of inflammatory cells is reduced. Nutraceuticals exert their antioxidant property by:

- ROS scavenging ability e.g. N-Acetyl-L-Cysteine and its pro-Drugs
- Inhibiting the superoxide formation
- Inducing the production of peroxidase enzymes which restores the cysteine site on TLR7 receptor and
- Inducing the formation of Glutathione, which is essential in maintaining the redox state and an important factor for certain peroxidases and increases the reconversion reactions of oxidized cysteine groups to the original state on TLR7 receptor. [24]

LIST OF NUTRACEUTICALS

Nutraceuticals exert antioxidant, anti-inflammatory and immunomodulatory effects that might aid control of RNA viruses including influenza and coronavirus.

Phycocyanobilin (PCB) Chromophore of Cyanobacteria (Such as Spirulina)

The chromophore phycocyanobilin (PCB), present in blue-green algae and cyanobacteria such as Spirulina, is a potent inhibitor of enzyme NADPH oxidase. It gets converted to phycocyanorubin, which mimics of bilirubin in mammalian cells. Orally administered PCB can be very well absorbed and can provide systemic antioxidant activity. The antiviral action is due to both NADPH oxidase inhibition and antioxidant properties. [19]

Phase 2 Inducers – Ferulic Acid, Lipoic Acid, Sulforaphane

Ferulic acid and Lipoic acid helps in controlling the spread of infections caused by RNA viruses by intensifying the signalling pathways of TLR7 and MAVS and evoke the proliferation of type 1 interferon. They restore the oxidised cysteine part of TLR7 receptor by escalating the synthesis of different peroxidase enzymes and induce the production of glutathione, a cofactor for certain peroxidases and a catalyst in reactions. [19] Sulforaphane reduces the inflammation which is caused by lipopolysaccharides-TLR4 complex. The concentration of lipopolysaccharides is increased by the entry of microbes into the host cells. Sulforaphane have a tendency to get attached to TLR 4 receptor. Sulforaphane-TLR4 complex inhibits LPS-TLR4 complex formation and thus inhibit the cytokine storm. [25]

N-Acetylcysteine (NAC)

It comes under thiol-based antioxidants. They exert their action by hunting down ROS and restoring it to its native state and acting as a precursor for the production of glutathione, which again is a cofactor for certain peroxidases enzymes, which reconvert the oxidised part of cysteine on TLR 7 receptor. [24]

Brewer`s Yeast Beta-Glucan

These polysaccharides which cannot be synthesized by humans have an immunostimulant action. So when they enter the human body, immune systems get triggered by these foreign compounds and take them as antigens. It evokes the innate and adaptive immunity of host cells by activating receptors such as dectin-1 receptor, the complement receptor 3 (CR3) and TLR, present on immune cells (monocytes, macrophages, neutrophils, eosinophils, dendritic cells and natural killer cells). This leads to immune action such as phagocytosis, oxidative burst and the production of cytokines and chemokines in dendritic cells and macrophage. [26]

Zinc

It has found that the morbidity of paediatric patients infected with lower respiratory infections was reduced with the provision of zinc supplements. The main

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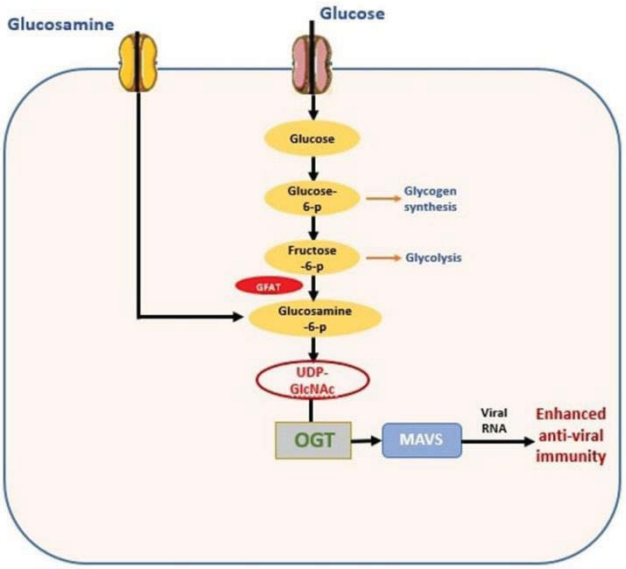

Figure 7: Mechanism of action of glucosamine [33]

mechanism of action is an alteration of the ability of cells to support viral replication. [19]

Kaempferol

The flavone kaempferol is one structural derivative of quercetin in which the catechol part of the structure is converted to phenol. It is found to be active against HIV. It inhibits the reverse transcription process and controls the virus replication process. It alters the steps when a virus is entered and inhibits the enzymes integrase and protease. [15, 27]

Luteolin

The flavone luteolin has been shown to possess antiviral properties by blocking of NA enzyme which cleaves the newly produced viruses and assists their spread. It induces carbohydrate metabolism and acts as an immunomodulator by inhibiting nuclear factor kappa B (NF-kB) and stopping the inflammatory response in macrophages and other immune cells. [15, 28]

Quercetin

Quercetin is a structural analog to luteolin, with hydroxyl at position 3 on the benzopyran ring. It inhibits the protein HA, which is essential in the fusing process of the virus membrane to host cells. Wu et al. determined through several assays that quercetin inhibits the membrane fusion process by blocking the entry of virus into the cell. Takashima et al. found that quercetin moderated the inflammation in the bronchial cells of mice (generated by administration of lipopolysaccharide) by inhibiting inflammatory factors such as TNF-α, IL-1β, IL-6 and MMP-9. [15, 29]

Apigenin

The antiviral activity of Apigenin is due to its action against cycle arrest, apoptosis, anti-inflammatory and antioxidant function. The anti-inflammatory response is due to inhibition of NF-κB or activation of B cells owing to a decrease in the lipopolysaccharide-induced phosphorylation. The oxidative stress, such as free-radical scavenging caused by the adhesion molecules, is decreased by reducing their expressions while the expression of antioxidant enzymes such as GSH-synthase, catalase and SOD is also increased so that cellular oxidative and electrophilic stress are countered. It inhibits the NADPH oxidase complex and in turn, stops the inflammatory storm. It induces the expression of the nuclear translocation of Nrf-2. Apigenin is found to inhibit metastasis and initiate angiogenesis process by associating with mitogen-activated protein kinase (MAPK) pathways. [30]

Glycyrrhizin

Glycyrrhizin exhibits antiviral property against a wide range of viruses. The mechanism of action of Glycyrrhizin is by altering the release steps while infectious Hepatitis C Virus (HCV) particles are infecting cells and by inhibiting HCV full-length viral particles and HCV core gene expression. It has immunostimulatory effect via stimulating of T lymphocytes production and is responsible for inhibiting virusinduced production of chemokine ligand10 (CXCL10), interleukin6 (IL-6) and chemokine(C-Cmotif) ligand5 (CCL5) and reducing the apoptosis caused by a virus. [31]

Caffeic Acid or Chlorogenic Acid

The mechanism of action for this chlorogenic acid is by inhibition of influenza RNA synthesis, especially via blocking virus RNA polymerase acidic the influenza. This compound has been found effective even when administered alone. It works synergistically with compounds that target sialic-acid binding sites. Lin et al. examined nine naturally occurring chlorogenic acid derivatives and observed that five of them significantly inhibited viral RNA polymerase. Ding et al confirmed the inhibition of neuraminidase activity where chlorogenic acid obstructed the release of newly formed virus particles from infected cells in surrounding tissues.[15]

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Table 2: List of Nutraceuticals with their Mechanism of Action, dosage and Source

Nutraceutical /Phytochemical	Class of drug	Mechanism of action	Virus Strain	Provisional Daily Dose per day	Source
Ferulic acid[19]	Immunomodulator	Induction of Hemoxygensase -1 (HO-1), thus increasing Type-1 Interferon response	Respiratory syncytial virus, Influenza virus	500 – 1000 mg	Bee propolis[15]
Lipoic acid[19]	Immunomodulator		Influenza A virus, Human immuno-deficiency virus (HIV)	1,200 – 1,800 mg	Spinach, broccoli, peas[6]
Spirulina[19]	Antioxidant	Structurally similar to bilirubin and mimic its NADPH oxidase inhibiting activity	Influenza virus, Herpes simplex virus (HSV)	15 g (or 100 mg PCB)	Blue-green algae
N-Acetylcysteine[24]	Antioxidant	Increases Glutathione (antioxidant)	Influenza A virus	1,200 – 1,800 mg	Supplements
Selenium[6, 19]	Antioxidant; Immunomodulator	An important cofactor for peroxidases enzymes; improve Immune function; Increase NK-cell cytotoxicity; enhance cell and humoral mediated immunity	H1N1 Influenza Virus	50 – 100 mcg	Brazil nuts, fish, red meat, eggs, grain, chicken, liver, garlic
Glucosamine[19]	Immunomodulator, Anti-oxidant	Enhance TLR3 and MAVS signalling pathway leading to activation of IFR3	HIV, HSV, Cytomegalovirus (CMV)	3 g or more	Shellfish, bone marrow, fungi.
Zinc[19, 34]	Antiviral	Inhibit viral replication	H1N1 Influenza Virus	30 – 50 mg	Whole grains, Milk products
Brewer`s Yeast Beta-Glucan[19, 26]	Immunostimulant	Evokes the innate and adaptive immunity of host	-	250-500 mg	*Echinacea, Viscum and Pelargonium.*
Kaempferol[15,27]	Antiviral	Inhibits the enzyme protease and integrase; control the viral replication process	Japanese encephalitis virus (JEV)	-	Kale, beans, tea, spinach and broccoli.
Luteolin[15,28]	Antioxidant	ROS scavenging activity	-	Effective concentration: 5-10 µM	Parsley, artichoke leaves, celery, peppers, olive oil, rosemary, lemons, peppermint, sage, and thyme
Quercetin[15,29]	Antioxidant, Anti-inflammatory	Inhibits the protein HA, responsible for membrane fusion of virions and host cells	-	-	Red (grape) wines, leaves of radish (*Raphanus raphanistrum subspecies ofsativus)* and fennel (*foeniculum vulgare*) seeds of pepper (*Capsicum annuum)*
Apigenin[30]	Antioxidant, Anti-inflammatory	ROS scavenging, NADPH oxidase inhibitor	-	-	Chamomile tea (*Matricaria chamomilla)*, leaves of parsley (*Petroselinum crispum)*, celery

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					(*Apium graveolens)* and spinach (*Spinacia oleracea)*
Resveratrol (trans-3,4,4'-trihydroxystilbene, RV) [24]	Antiviral, Antioxidant	RV decreased IL-6 production; improvement of plasma levels of interferon gamma (IFN-gamma) and NK cells and partially inhibited RSV replication in cell cultures	Respiratory syncytial virus (RSV)	>150 mg	Grape skin
Phycocyanobilin[19]	Immunomodulator, Antiviral	Structurally similar to bilirubin and mimics its NADPH oxidase inhibiting activity; inhibits viral plaque formation and reduced viral replication	Influenza virus, coronavirus.	15 g (or 100 mg PCB)	Spirulina
18β-glycyrrhetinic Acid[31]	Antiviral	Reduce the levels of viral proteins VP2 , VP6 and NSP2 after entry of virus into host cells	Rotavirus	-	Liquorice
Glycyrrhizin[31]	Immunomodulator, Anti-inflammatory	Stimulating of T lymphocytes production; Inhibits several inflammation mediators (CXCL10, IL6, CCL5)	Hepatitis C virus	-	Liquorice
Caffeic acid[15]	Antiviral, anti-inflammatory	Inhibit viral RNA polymerase and control viral replication	Influenza A virus, HSV, Polio virus	-	Coffee bean, Cocoa species
Astaxanthin[35]	Immunomodulator, antioxidant	Increases the total number of antibody-producing B-cells; Amplifies natural killer cell cytotoxic activity; Leads to increased number of T-cells; Stimulates lymphocyte [white blood cell] counts; Significantly increases delayed-type hypersensitivity response	Hepatitis C virus	-	Algae, yeast, salmon, trout, krill, shrimp and crayfish
Bioactive peptides[36]	Immunomodulator	Increase in activity of macrophages, natural killer cells (NK), release of T and B lymphocytes, modulation of cytokines release	-	10–100 mg	Bovine milk, soy, rice, oysters, cod and salmon

High Dose Vitamin C

Vitamin C is known as an anti-oxidant and enzymatic co-factor in the process of immune potentiation. Human body can't produce vitamin C, it should be acquired from dietary sources or in form of supplements. The high dose vitamin C plays dual role as a pro-oxidant for immune cells to decrease pro-inflammatory mediator expression and enhance alveolar fluid clearance and as an antioxidant to ameliorate the functions of lung epithelial cells. Several clinical trials are going on with Vitamin C. These treatment regimens suggested 50 mg/ per kg (body weight) of high-dose intravenous vitamin C for every 6 hours for 4 days with a glucose restriction. [32]

Glucosamine

It is a substrate of an enzyme UDP-GlcNAc, which mediates the o- GlcNAcylation of MAVS. This is an essential step in initiating the immune response by activating the production of interferons (Figure 7). [19]

Nutraceuticals and their mechanism of action, required dosage, activity against specific virus strain/strains and their source are summarized in Table 2.

NUTRACEUTICAL SOURCES WITH ANTIVIRAL PROPERTIES

Black Currant *(Ribes nigrum folium)*

The antiviral effect of Black Currant leaves and black currant berries was due to inhibition of EGFR phosphorylation. The compound doesn't activate NF-κB and doesn't inhibit receptor-mediated NF-κB activation. Researchers found that an extract preparation from black currant berry leaves was effective against strains in the influenza virus. In addition, the virus didn't develop resistance to the extract. [15] According to Ikuta et al., [37] the extracts of blackcurrant showed certain potency for use as a disinfectant and antiseptic agent to prevent influenza virus infection.

Jamaican Sorrel *(Hibiscus sabdariffa)*

The presence of luteolin, quercetin and chlorogenic acid give anti-inflammatory properties. The antiviral action especially against influenza viruses is due to the inhibition of HA. The abundant presence of vitamin C also strengthens the antioxidant property and immune response. [15]

Honey

The chemical constituents and their percentages varies with geographical location has a great effect on the chemical constituents and their percentages. Manuka honey from New Zealand has found to possess antiviral properties. The mechanism of action of manuka honey's effect on the influenza virus is not clear, however, they are found effective against influenza viruses and act synergistically with NA inhibitors. Inhibition of NF-κB, IκBα, COX-2 and TNF-α was found in the rat paws when mice were pretreated with Gelam honey. On exposure to UVB radiations, inhibition of IL-1β, IL-6 and TNF-α release from PAM212 keratinocytes was observed and expression of COX-2 and Prostaglandin E2 was also reduced. [15]

Bee Propolis

Bee propolis confer strong action against viruses due to the presence of several compounds such as chlorogenic acid, caffeic acid and many other compounds, including artepillin C, baccharin, 3,4,5-tricaffeoylquinic acid, isosakuranetin, p-coumaric acid, drupanin and ferulic acid.Cytokine storm (inflammatory response) induced by the influenza virus is inhibited by Bee propolis via blocking several cytokines. Researchers found that caffeic acid phenethyl ester (CAPE), a derivative of Chlorogenic acid and a constituent of bee propolis, was effective in inhibiting TNF-α, IL-8 and IκB-α in human middle ear epithelial cells when they were exposed to lipopolysaccharide. [15]

Siberian Ginseng *(Acanthopanax senticosus/ Eleutherococcus senticosus*)

Ginseng contains various pharmacologically active substances such as ginsenosides, polysaccharides, polyacetylenes, phytosterols and essential oils. Ginsenosides are considered the major bioactive compounds. It also contains syringin (also known as eleutheroside B), chlorogenic acid, caffeic acid, eleutheroside E and isofraxidin. For Siberian Ginseng extracts, they exert direct antiviral activity by inhibiting viral attachment, membrane penetration and replication, they also enhance the host immunity. Siberian Ginseng also possesses anti-inflammatory effects. [38]

Elderberry *(Sambucus nigra*)

Elderberry is a very rich source of anthocyanins, it is thought that the presence of ferulic acid facilitates the impact on the virus. Ferulic acid is a prominent metabolite that appears in plasma following anthocyanin ingestion. This extract curtails the duration of influenza 20 by 2-4 days and minimizes the severity level. [19]

Echinaforce *(Echinacea purpurea)*

It is a perpetual medicinal herb with significant immunostimulatory and anti-inflammatory properties. It enhances the respiratory activity resulting in the augmentation of leukocyte mobility and produces immunomodulatory effects via Phagocytosis activation and fibroblast stimulation. They exert their action by increasing the concentration of cyclic adenosine monophosphate (cAMP), p38 mitogen-activated protein kinases (p38/MAPK) and c-Jun N-terminal kinases (JNK) signaling, as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activating transcription factor 2/cAMP responsive element-binding protein 1 (ATF-2/CREB-1) in primary human monocytes and macrophages. [39]

OTHER NUTRACEUTICALS

Natural products provide a different perspective on the discovery of antiviral agents with excellent pharmacological effects. Few examples of phytochemicals with antiviral properties are Baicalin, Chalcones, Dammarenolic acid, Jubanines, Sennosides A, Limonoids, etc. [27]

Micronutrients such as vitamins A, D, C, E, B6 and B12, folate, zinc, iron, copper and selenium play very important and synergistic roles in the whole immune response. Micronutrients provide support to the mucosal cells in the skin or respiratory tracts by maintaining structural and functional integrity; they are also responsible for differentiation, proliferation, functioning and movement of innate immune cells (e.g. regulates number and cytotoxic activity of NK cells; the phagocytic activity of macrophages; proliferation and functions of monocytes and neutrophils). They exert anti-inflammatory, antioxidant effects and regulate the differentiation, production and functioning of T cells. They respond to the presentation of antigen and assist in antibody production and development. However, the daily treatment dosage of micronutrients, which is essential for providing immune function, is usually higher than the recommended daily dietary allowances. [34] The action and daily treatment dosage are depicted in Table 3.

FUTURE ASPECTS

Nutraceutical compounds are able to decrease the duration and also to alleviate the severity of the infection by suppressing the inflammation storm caused by

Table 3: List of Micronutrients with their Daily Treatment Dosage for Adults and Mechanism of Action [34]

Micronutrients	Dosage	Mechanism of Action
Vitamin A	500–2200 µg/day	• Regulates number and function of NK cells; Downregulates IFN-γ production; • Helps to regulate the production of IL-2 and the proinflammatory TNF-α, which activates the microbial action of macrophages; • Maintains normal antibody-mediated Th2 response by suppressing IL-12,TNF-α and IFN- γ production of Th1 cells; maintaining functioning of B cells, necessary for generation of antibody responses to antigen.
Vitamin B6	1.6–3.5 mg/day for males 1.3–2.1 mg/day for females	• Essential in synthesis and metabolism of amino acids, which are the building blocks of cytokines and antibodies; • Lymphocyte proliferation, differentiation, maturation and activity; maintains Th1 immune response;
Vitamin B12	1.9–9.3 µg/day for males 1.0–8.8 µg/day for females	• Increases numbers of cells with a role in cell-mediated immunity (facilitates production of T cells such as cytotoxic T cells, helps to regulate ratio between T helper cells and cytotoxic T cells) • Important for antibody production and metabolism, via folate mechanism
Vitamin C	64–153 mg/day	• Plays roles in production, differentiation and proliferation of T cells; resulting in increased generation of antibodies and increased phagocytosis; • Antioxidant properties protect leukocytes and lymphocytes from oxidative stress
Vitamin D	1.6–10.9 mg/day for males 1.2–10.1 mg/day for females	• Calcitriol helps to restore the immune function of macrophages and promote antigen processing; • Inhibitory effects mainly in adaptive immunity (e.g. Th1-cell activity) and stimulatory effects in innate immunity(induction of antimicrobial peptide, reduce cytokine storm)
Vitamin E	3.3–17.7 mg/day for males 4.2–16.1 mg/day for females	• Enhances lymphocyte proliferation and T-cell-mediated functions; • Important fat-soluble antioxidant that hinders the chain reaction induced by free radicals (chain-breaking effect) and enhances IL-2 production
Folate	203–494 µg/day for males 131–392 µg/day for males	• Can increase innate immunity in older people ; Alters age-associated decrease in NK-cell activity; Supports Th1 response; • Essential for antibody response to antigens (especially IgG)
Iron	10.6–26.9 mg/day for males 8.2–22.2 mg/day for females	• Regulates the cytokine production and action; • Important in differentiation and proliferation of T cells; helps to regulate the ratio between T helper cells and cytotoxic T cells
Copper	1100–2300 µg/day for males 1000–2200 µg/day for females	• Accumulates at sites of inflammation; • Part of copper/zinc-superoxide dismutase a key enzyme in defence against ROS; • Free-radical scavenger; changes in copper homeostasis a crucial component of respiratory burst; • Increase the ability of neutrophils to engulf pathogens; • Critical for IL-2 production and response; maintains intracellular antioxidant balance, suggesting important role in inflammatory response
Magnessium	256–465 mg/day for males 192–372 mg/day for females	• Protect DNA against oxidative damage; high concentrations reduce superoxide anion production; Cofactor in antibody synthesis, role in antibody-dependent cytolysis and IgM lymphocyte binding; • Important in the process of antigen binding to macrophage RNA.

inflammation mediators such as cytokines. Major constituents of nutraceuticals such as luteolin, apigenin, quercetin and chlorogenic acid have reported to possess antiviral activity against coronavirus and influenza. They have multiple binding sites but not specific activity against one protein. These constituents are widely present in several plants. It is crucial to explore the potential of these nutraceuticals. There are many studies carried out on luteolin, apigenin, quercetin, chlorogenic acid and other catechols/ phenolic compounds. It should be noted that there is some thought that these compounds may integrate into Pan-Assay Interference Compounds (AINS). More studies should be carried out which can emphasize the preventive action of nutraceuticals and use of these compounds as an adjunct to the standard treatment.

CONCLUSION

Respiratory viral infections (e.g. Influenza and Coronaviruses) bring about mild to severe respiratory conditions in patients. COVID-19 caused by SARS-CoV-2, the novel virus, has become a “global pandemic”. The risk is greater among the people with compromised immune system e.g. people with co-morbidities like hypertension, diabetes mellitus and COPD. With few potential drugs undergoing clinical trials, their limited supply, lack of time and unavailability of vaccine and cure, it is important to

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discuss preventive strategies. People with a stronger immunity system don't fall prey to these diseases. Thereby, immunity should be strengthened in times of seasonal flu and viral pandemics. Every year respiratory viral infections affect the medical and public health infrastructure globally. The mortality and morbidity of COVID-19 among the weaker and less immune groups of patients shed light on the importance of innate immunity. Nutraceuticals or commonly called functional foods coming from natural sources have been used for multiple diseases for centuries. Ferulic acid, Zinc, Vitamin C, spirulina, glutathione and glycyrrhizin possessing antioxidant, anti-inflammatory and immunomodulatory mechanisms can potentiate the anti-viral effect. These nutraceuticals have found to be beneficial in fighting against many respiratory viruses. The combination therapy of nutraceuticals with pre-existing drugs can successfully combat respiratory viruses.

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