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Opinions on the current pandemic of COVID-19: Use functional food to boost our immune functions

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Abstract

The pandemic of novel coronavirus caused COVID-19 had resulted in a high number of hospitalizations and deaths and caused a devastating toll on human and society health. The symptoms of the infected patients vary significantly, from life-threatening to mild or even asymptomatic. This clinical observation led to hypothesize on the critical role of host innate immunity in the disease development and progression. As the first defense barrier against microorganisms, the innate immune reaction determines not only the viral infection rate but also immune-mediated response. Therefore, promote healthy behaviors to enhance innate immunity with functional food and nutritional agents may be a rational strategy for minimizing damages caused by viruses to global health.

Keywords:

SARS-CoV-2, viral infection, innate immunity, nutrition, Zinc, COVID-19

1. COVID-19 pandemic and anti-viral challenges

Humans are continually exposed to multiple endogenous and exogenous viruses. There are estimates that a single human being can generate up to 10^{12} new viral particles per day (Virgin, Wherry et al. 2009). New viruses are discovered continuously; however, only a small subset of the viral population can cause severe diseases. The likelihood of viral infection is significantly increased if the host has compromised immune protection, which results in imbalances between the host proinflammatory responses and anti-viral activities (Sumbria, Berber et al. 2019).

The global pandemic of coronavirus COVID-19 has swept the world. The virus causes pneumonia of varying severity and vasculitis that has resulted in a high number of hospitalizations and deaths (Case Rate Fatality estimated at 2.1-4.9%) (Wu, Leung et al. 2020). As the global case numbers keep soaring, health experts are scrambling to find a cure.

Vaccines have been proposed as a solution to this disease. Vaccines work by preparing the body to fight disease without exposing it to disease symptoms. It stimulates the adaptive immune system by exposing the body with inactivated or weakened antigens. The immune system can recognize the antigens as a foreign enemy, produce antibodies in response, and store the information for the future. If the bacteria or virus reappear, the immune system will recognize the antigens immediately and quickly mount a rapid defense by producing massive amounts of antibodies before the pathogen can spread and cause disease (Siegrist 2008).

The COVID-19 belongs to the coronavirus family, which includes Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) that had similar symptoms resulting in respiratory illness (Channappanavar and Perlman 2017). While these viruses are not identical, many similarities in the genome may jumpstart in developing a vaccine.

Time is an essential factor in the development of vaccines against emerging viruses, especially those with pandemic potential. The development of vaccines is an expensive, time consuming, and complex process that includes identifying antigens, testing in animal models, and evaluating in humans for safety and efficacy. Despite decades of efforts, there are still no vaccines against

viruses that kill millions of people every year, including HIV (Cohen 2020) and respiratory syncytial virus (RSV) (Besteman and Bont 2019). In a recent review of 22 studies and evidence from four systematic reviews (Demicheli, Jefferson et al. 2018), the efficacy of the inactivated influenza vaccination is only between 16–59% in healthy adults depending on whether the results are clinically derived or empirically derived. There was no evidence on the impact of the influenza vaccine on overall mortality (Samuel and Miller 2019). There are currently no vaccines approved to prevent other viral infections after years of development work and clinical trials (Castilow, Olson et al. 2007, Anderson, Dormitzer et al. 2013).

On the other hand, most synthetic anti-viral drugs are expensive, toxic, and ineffective to stop diseases. As of the time of writing this manuscript, there are no clinically effective anti-viral drugs against coronaviruses, like SARS-CoV and MERS-CoV (de Wit, van Doremalen et al. 2016). Anti-viral medications like Remdesivir can stop the virus from replicating, halting the disease state from in vitro and in animal models (Wang, Cao et al. 2020). Even though the FDA had conditionally approved its use in selective situations, the therapeutic potential of Remdesivir is still controversial and warrants further investigation (Cao, Deng et al. 2020, Grein, Ohmagari et al. 2020, Wang, Zhang et al. 2020). There are currently four FDA-approved influenza drugs recommended by CDC, but they all carry side effects and are only used in select situations to reduce the duration of illness (Shaw 2017). Additionally, pathological viruses are constantly changing, and can sometimes mutate into different strains or sequences that could make anti-viral drugs work less effectively or not at all against these viruses. A different approach is urgently needed to combat these viruses.

The curve of COVID -19 urgently needs to be flattened. Identify alternative preventive and therapeutic strategies to contain the viral infection, especially in a scenario where the virus may become endemic and recurrent seasonal.

2. Clinical features of COVID-19 immune responses

The fact that many people infected with SARS-CoV-2 show only mild or even no symptoms in contrast to the viral-induced damage to more vulnerable populations, including the elderly and patients with chronic conditions. It suggests that the host immune system could be the key to defeat this virus.

The human body is equipped with a complicated and effective immune defense to protect the body against infection and disease. This complex network consists of cells, tissues, and organs that specializes in defending against foreign substances and pathogenic microorganisms, including bacteria, viruses, and fungi. Humans have two kinds of immune systems—innate and adaptive immune systems. The innate immunity involves an immediate, nonspecific defense mechanism that activates almost immediately in response to foreign invaders. It includes barriers, a variety of cells, and molecules to form the first line of the defense, such as airway mucus, anti-microbial soluble proteins (e.g., complement, lysozyme), cells secreting inflammatory mediators (basophils, mast cells, and eosinophils), natural killer (NK) cells, and phagocytic cells (macrophages, neutrophils, dendritic cells). They work together to prevent and control infection. The adaptive immune response, which includes both B cell-based humoral immunity and T cell-based cellular immunity, reacts much more specifically and powerfully to invading pathogens. The development of acquired immunity is a time-dependent, exposure-driven process. T and B lymphocytes 'learn' about the local infectious disease ecology through exposure.

In COVID-19 patients, two clinical features seem to correlate with disease severity and death, overly active of some innate immune cells, and suppressive of lymphocytes for adaptive immunity.

In particular, the number of both inflammatory macrophages and activated neutrophils is found to increase in the lung (Xu, Shi et al. 2020). A significantly higher proportion of activated mast cells, neutrophils, and a higher neutrophil-lymphocyte ratio (NLR) were also observed (McKechnie and Blish 2020). On the other hand, a marked decrease in the circulating T cell (both $CD4^+$, $CD8^+$), B cells (Qin, Zhou et al. 2020) in the COVID-19 patients. In addition, most of the patients with severe COVID-19 displayed significantly increased serum levels of proinflammatory cytokines (e.g. IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP-10, MCP-1, CCL3, and TNFα) (Mehta, McAuley et al. 2020), and inflammation markers C-reactive protein (Hs-CRP) and procalcitonin serum levels. The server COVID-19 patients usually have sudden deterioration around 8-9 days after onset, suggesting that the coronaviruses could hijack innate immune surveillance at the early infectious stage. At later stages, the hyper-inflammatory reaction could be initiated by innate immune cells to create fatally cytokine storms (Siddiqi and Mehra 2020). The COVID-19 clinical feature fits characteristics of the "primary cytokine" storm

induced by innate immune cells such as alveolar macrophages, epithelial cells, and endothelial cells, rather than those observed in "secondary cytokine" storm induced by activated T cells in the late stage of viral infection (Xi-zhi and Thomas 2017). These precious COVID-19 patients derived data suggest deleterious innate immune function may be the Achille tendon of COVID-19.

Modulate innate immunity may hold the key to defeat COVID-19

The pathogenesis of COVID-19 is complicated and multifactorial, involving both viral and host factors. However, it is well-established nutritional deficiency can impair immune functions and responsible for the increased susceptibility to pathogen infection and disease progression. Deficiencies in certain nutrients may overly activate tissue-resident innate immune cells, impair phagocytic function, and released a wrong set of signals to activate inflammation cascade or recruit wrong types of immune cells at the infection site. Malnutrition at cellular level adversely affects several aspects of adaptive immunity, including cytokine production as well as antibody- and cell-mediated immunities (Erickson, Medina et al. 2000, Lesourd 2004).

Even though many inflammation-associated diseases result from dysregulation of innate immunity, few pharmaceutical drugs have been developed based on innate immune research. Many nutritional food components, minerals, and herbal medicines have demonstrated their ability to maintain, improve, and modulate the innate immune functions. Therefore, to control the viral infection and their pathological consequences, the application of nutrients and botanicals to regulate multiple players at different phases of the disease should be considered. Their actions may include the prevention of viral attachment and entry, inhibition of viral replication, boosting viral clearance, balancing the hemostasis of immunity, controlling the inflammation, and resolving the repair and remodeling process.

Viral-associated molecules (immunostimulants) triggers two types of innate immune responses, inflammation, and phagocytosis. The inflammatory response involves acute phase proteins and the recruitment of phagocytic cells to the injury or infection sites to defend against a wide range of pathogens (Ulevitch 2004). These cells express surface receptors that identify unique recognition patterns on the microorganism surfaces. For example, scavenger receptors, Toll-like receptors, and Nod-like receptors are major representatives within the host receptors groups (Kollmann, Levy et al. 2012). Through receptor-ligand binding, signal transduction initiates a

complex cascade of cellular reactions, which leads to the production of one or more of a wide array of effector molecules. Important innate effector molecules are oxygen and nitrogen species, antimicrobial peptides, lectins, fibrinogen-related peptides, leucine rich repeats, pentraxins, and complement-related proteins (Bals and Hiemstra 2004). Recently, more cells have been identified to possess innate immune functions, such as airway epithelial cells (Bals and Hiemstra 2004, Hiemstra, McCray et al. 2015) and stromal cells (Owens 2015). For example, airway epithelial cells contribute to innate deference by different mechanisms including the barrier function, mucociliary clearance, as well as the production of antimicrobial peptides, reactive oxygen species (ROS) and nitrogen species (RNS) and range of cytokines (Hiemstra, McCray et al. 2015).

Tissue-resident mast cells are present in the submucosa of the nose, airway, and lungs, playing a pivotal role in the inflammatory response (Gonzalez-de-Olano and Alvarez-Twose 2018). The pathogens, including viruses, interact with MCs to produce both positive and negative reactions in the host. MCs activation and degranulation could occur through RNA virus-induced Toll-like receptor-3 (TLR3) to produce interferon (IFN) α and β and IL-8 and to recruit NK cells (Kritas, Ronconi et al. 2020). In this sense, MCs may play a significant anti-viral role in COVID-19 pneumonia. However, in another scenario, the virus could stimulate mucosa MCs to release inflammatory cytokines and mediators, such as TNF-α, IL-1, IL-6, IL-33, IL-18 and proteases, histamine, prostaglandin D2, leukotriene C4, resulting in lung inflammation and bronchoconstriction (Kritas, Ronconi et al. 2020). Therefore, stabilize MC membrane and reduce mast cell activation may be a target. Along the same line, it is worth noting that recent cell culture-based studies indicate some naturally occurring flavonoids, such as quercetin (Weng, Zhang et al. 2012), luteolin, and tetramethoxyluteolin (Weng, Patel et al. 2015), have significant MCs-stabilizing activities.

In the lung, macrophages are the most abundant immune cells essential for host innate immune defense, surfactant homeostasis, and lung development and repair (Locati, Mantovani et al. 2013). Macrophages interact with other cells, such as epithelial cells, dendritic cells and T cells to perform immunosurveillance functions via phagocytosis, secretion of viricidal factors, nitric oxide, tumor necrosis factor (TNF), and interferons (O'reilly, Hickman-Davis et al. 2002). Besides traditional immune cells, airway epithelial cells also exert innate immune functions by producing hydrogen peroxide (H_2O_2) through an "oxidative extracellular microbicidal system",

consisting of the endogenous airway oxidase (DUOX), and lactoperoxidase (LPO) (Rada and Leto 2008). Many micronutrients such as zinc, selenium, copper, and iodine modulate the DUOX system to promote oxidative killing power against viruses. In addition, several polyphenols activate mononuclear cells and increase their phagocytic response through influencing MAPK and nuclear factor κB (NF-κB) signaling pathways (Chen, Yu et al. 2000).

Viruses cause infections that are often associated with redox modification's characteristic of oxidative stress. Inflammatory cell infiltration causes damage in the lung through excessive secretion of proteases and reactive oxygen species (Nathan and Cunningham-Bussel 2013). Viral infection and replication in airway epithelial cells could cause high levels of virus-linked pyroptosis. The debris and oxidants are highly inflammatory to induce aberrant inflammatory responses through the vicious cycle. Redox changes to an oxidized state also play a critical role in the activation of numerous cell pathways that are hijacked by viruses to assure their replication and suppress the patient's immune defense. Many antioxidative nutritional supplements, such as vitamin C, glutathione, NAC, organic sulfur compounds, and botanicals, can dampen the inflammatory responses.

3. Nutrients, medicinal phytochemicals, and functional foods have been shown to have beneficial effects on immune function

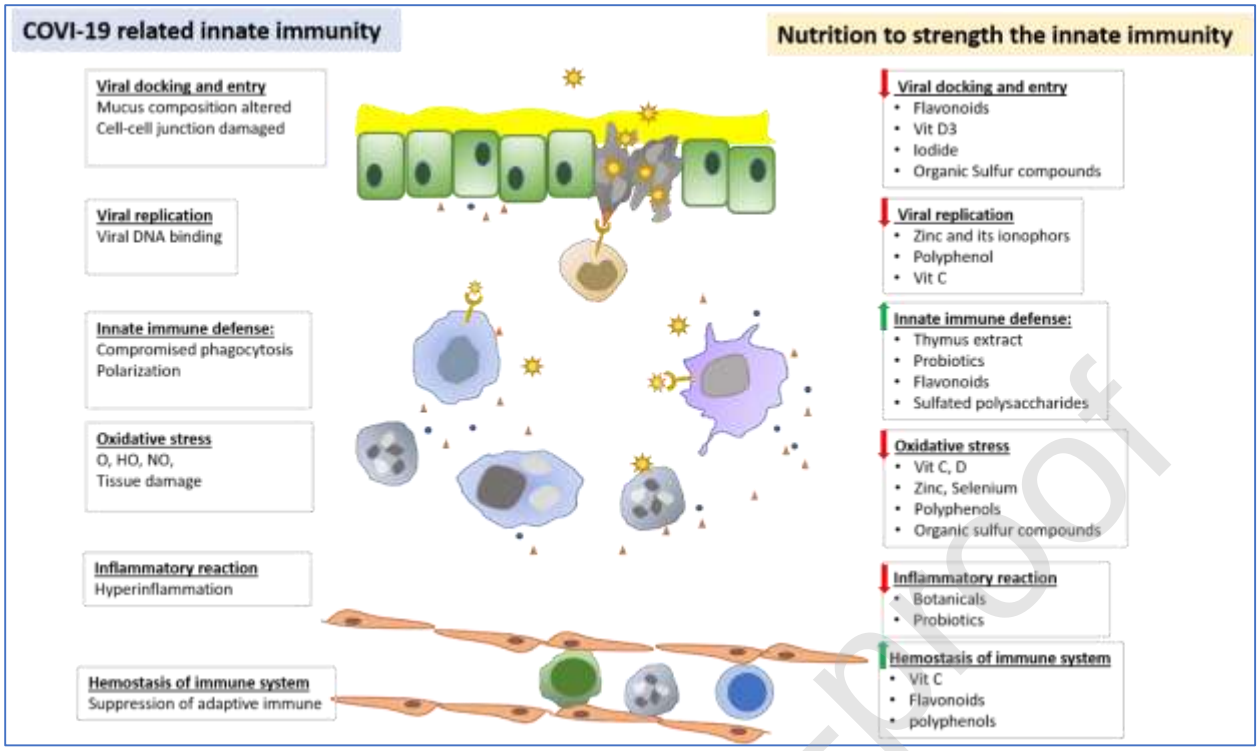

Fig 1. Nutrients and botanicals regulate innate immune functions in defecting viral infection

Vitamin C The health benefits of vitamin C has been well established. It is considered an essential nutrient that cannot be synthesized by humans, having multiple effects related to its ability to donate electrons (Carr and Maggini 2017). Vitamin C is important for things like wound healing, tissue repair, is required for certain enzymes to work, and has immune-modulating effects. Vitamin C is a potent antioxidant, protecting important biomarkers from free radicals and exposure to toxins and pollutants (Carr and Frei 1999). Additionally, it also boosts the generation of metabolic energy by acting as a cofactor in carnitine biosynthesis, a molecule responsible for the transport of fatty acids into the mitochondria (Du, Cullen et al. 2012). It is also used as a common adjuvant for the treatment of the common cold, with meta-analysis showing its effectiveness in decreasing the severity, duration (Douglas, Hemila et al. 2007), and incidence of the common cold (Johnston, Barkyoumb et al. 2014).

Vitamin D (VitD) is one of the oldest evolutionary hormones. In addition to the regulation of minerals metabolism, it has been recognized to play a role in the regulation of inflammation and protection from viral infection (Kulie, Groff et al. 2009, Beard, Bearden et al. 2011). Studies have confirmed that low VitD levels correlate with the incidence and risk of several viral

infections and flu (Laaksi, Ruohola et al. 2007, McNally, Leis et al. 2009). Vit D3 receptor located on all immune cells. It is known VitD regulates monocyte and macrophage activation that is important for not only kill the virus but also clean up the debris that collects in the lung air sac during infection. VitD enhances regulatory T cell function, and VitD also inhibits proinflammatory cytokine expression, which could be potentially relevant in infection and could counteract the cytokine storm. However, VitD deficiency is a global health problem. It occurs in 20%–60% in Europe and up to 80% in Middle East countries. Severe deficiency is found in >10% of Europeans (Lips, Cashman et al. 2019). VitD deficiency showed a significant relationship to the development of asthma attacks (Arikoglu, Kuyucu et al. 2015); it is a risk factor for infection, sepsis, and mortality in ICU patients (de Haan, Groeneveld et al. 2014). Recent studies found there is a significant association between low serum concentrations of zinc and VitD (Shams, Afshari et al. 2016) (Ziaei, Norrozi et al. 2007). VitD produced in the skin during exposure to the sun, and humans have the lowest levels of VitD in winter and spring (Coussens 2017). Available evidence from systematic review suggests that high dose vitamin D may prevent asthma exacerbation (Pojsupap, Iliriani et al. 2015). Therefore, Vitamin D supplementation may be required for many individuals, especially in winter to prevent and alleviate symptoms from COVID-19

Zinc is an essential nutrient that people need to stay healthy. Zinc is found throughout the body, in the cells, and is a factor for enzymes to work. It necessary for the immune system to function normally. In fact, when zinc is deficient, one of the significant clinical symptoms is depressed immunity, which leads to increased infections and frequency of disease (Anderson, Dormitzer et al. 2013). Studies have shown that this micronutrient is crucial for maintaining homeostasis of both innate and adaptive immune systems, and its deficiency is correlated with compromised immune cell development and functions. The use of zinc has been proven effective against infectious diseases in the human population. Double-blinded placebo-controlled trials have shown that daily zinc supplementation can reduce the incidence and duration of chronic diarrhea by 25-30% (Yazar, Güven et al. 2016), lower rates of acute respiratory infection up to 45 % (Rerksuppaphol and Rerksuppaphol 2019), and can even decrease the duration of the common cold (Singh and Das 2013).

Iodine is recognized as a necessary nutrient for proper immune function by the Institute of Medicine and as well as the United Nations Nutritional Policy Board (Hetzel 1988, Trumbo,

Yates et al. 2001). There have been many historical reports of immune deficiencies among populations of iodine-deficient people (Black 2003). This is because leukocyte myeloperoxidase enzyme uses iodine in cell-mediated immunity and is an essential component of many immune cells (Klebanoff, Kettle et al. 2013). Additionally, iodides also have many other biologic effects, including regulating inflammation, improves phagocytosis of bacteria by immune cells, and boosting the innate immune system (Bilal, Dambaeva et al. 2017). Because iodine molecules tend to sublimate, instability is its biggest drawback. Lack of iodine is widespread in modern dietary and lifestyle. High dietary perchlorate, glucosinolate, thiocyanate, calcium nitrate, cobalt and rubidium interfere with iodine metabolism and may increase iodine requirements (Friedman 2013, Rogan, Paulson et al. 2014). Household hygiene products such as chlorine containing beach and fluoride in water and toothpaste further depletes iodine in our body.

Andrographis paniculata is a medicinal plant whose underground stem and leaf are used to make medicine. Andrographis has a history of use in both Ayurvedic and traditional Chinese and Vietnamese medicine for thousands of years to prevent and treat the common cold and flu (influenza). It contains several bitter components that seem to have both immune-stimulating, anti-viral, antibacterial, and anti-inflammatory activities. Randomized double-blind studies have found evidence that Andrographis may reduce the severity of symptoms in individuals suffering from the common cold. (CHANTRAKUL, PUNKRUT et al. 1991, Hancke, Burgos et al. 1995, Melchior, Palm et al. 1997, Caceres, Hancke et al. 1999). Several well-designed clinical studies have shown the robust clinical efficacy of the herb for viral infections, showing statistically significant efficacy of Andrographis compared to control (Saxena, Singh et al. 2010, Jayakumar, Hsieh et al. 2013).

Echinacea purpurea is an immune stimulant and is effective in the prevention and treatment of colds and influenza. Research suggests that Echinacea stimulates the immune system by activating immune cells such as lymphocytes and macrophages (See, Broumand et al. 1997). Additionally, Echinacea appears to increase the production of interferon, a group of signal proteins released in response to viruses, speeding up the immune response of viral infections (Luettig, Steinmüller et al. 1989). Several double-blind, clinical studies have confirmed Echinacea's effectiveness in treating colds and flu (Melchart, Linde et al. 1994, Dorn, Knick et al. 1997, Brown 1998, Melchart, Walther et al. 1998, Grimm and Müller 1999, Percival 2000).

Garlic has been used for centuries as both a food ingredient and a medicine. Eating garlic provides a wide variety of health benefits including enhanced immune function (Kyo, Uda et al. 2001, Majewski 2014, Varshney and Budoff 2016). Garlic contains powerful anti-viral phytochemicals such as ajoene and allicin that help the immune system to fight pathogens. These compounds boost the disease-fighting response of white blood cells in the body when they encounter viruses, including ones that cause the common cold or flu (Nantz, Rowe et al. 2012, Arreola, Quintero-Fabián et al. 2015). Other studies have shown that the ingestion of garlic reduces the risk of viral infection in the first place, shortens the disease duration, and relieves the severity of symptoms (Josling 2001, Nantz, Rowe et al. 2012).

Astragalus radix (Hwang-Qi) is most commonly used in traditional Chinese medicine and holistic medicine. It contains many functional components to strengthen the host defense system described as tonic medicine in "Chinese pharmacopeia" (Grover, Yadav et al. 2002). There are preclinical studies that have suggested some immune-stimulating effects, including stimulating murine macrophages to produce more interleukin-6 and tumor necrosis factor, two cytokines involved in the inflammatory process, and in the *in vitro* antitumor activity (Yoshida, Wang et al. 1997). Chemical components of Astragalus include polysaccharides mannose, D-glucose, D-galactose, xylose, and L-arabinose, which are used as immunomodulating agents in mixed herbal decoctions to treat common colds, diarrhea, fatigue, and anorexia (Yin, Chen et al. 2010, Li, Zhong et al. 2011).

Probiotics influence many functions in the body, including promoting a healthy gut, enhancing the immune system, and reducing the risk of infection in children and adults. The last decade has shown the close connection between gut health and immune function. Microbiomes or colonies of bacteria that live in the gut, directly communicate with the cells of the immune system (Ashraf and Shah 2014). The body has a symbiotic relationship with the gut microbiome since these bacteria are responsible for supporting the production of stomach acid and saliva, which can boost the first line of immune defense. When the microbiome is happy and healthy, the immune system responds quickly and effectively to viral infection (Caricilli, Castoldi et al. 2014, King, Glanville et al. 2014, Lei, Nair et al. 2015, Ozen, Kocabas Sandal et al. 2015). In addition to immune health, researchers have found evidence that supplementation of probiotics affecting body weight, energy level, and brain function (Cerdó, García-Santos et al. 2019, Jäger, Mohr et al. 2019). Gou et al.{Gou, 2020 #477}recently reported that the disruption of gut microbiome

features by the host and environmental factors might predispose healthy individuals to the abnormal inflammatory response observed in COVID-19.

Thymus extracts are usually derived from thymus glands of young calves. The thymus is responsible for the production of T lymphocytes, immune cells critical for body function. Two double-blind placebo-controlled trials enrolled children with frequent respiratory infections, such as colds, and found that treatment with thymus extract reduced the rate of infection (Fiocchi, Borella et al. 1986, Longo, Lepore et al. 1988). In another double-blind study revealed thymus extract, when given orally to children with recurrent in respiratory infections (RRI), was able to reduce the number of RRIs when compared to placebo controls or to previous year infections in the same child. Continued use prevented relapses of infections and produced an increase in phagocytic responses of alveolar macrophages and serum immunoglobulins (Kouttab, Prada et al. 1989). Another placebo-controlled trial compared calf thymus extract to pharmaceutical immunomodulator levamisole to treat children suffering from chronic bronchitis. Both treatment groups (thymus extract and levamisole) showed statistically significant decreases in the number, severity, and duration of episodes, requiring less antibiotic therapy, and greater normalization of the number and function of T lymphocytes (Wilson 1999).

Immune psychology plays a significant role in the prevention and disease courses**.** Stress is a significant contributing factor in immune function. A meta-analysis of 300 empirical studies found that certain types of stress (both psychological and physical) altered different aspects of the immune system. Brief stressors tend to suppress cellular immunity, lowing defense against viruses while preserving humoral immunity. Chronic stressors tend to contain both types of immunity. Research has shown that people in stressful situations have measurably slower wound healing, a higher incidence of infection, or worse prognosis for infection (Segerstrom and Miller 2004, Gouin and Kiecolt-Glaser 2011).

Conclusion

The quality and magnitude of immune defense dictate how viruses interact with hosts in causing symptoms, severity, duration, infectivity, and outcomes of the disease. Human has multiple defense mechanisms that can protect the body against viruses, bacteria, and fungus infection. Exploring the application of non-toxic pharmaceutical drugs, nutritional agents, and maintaining proper psychosocial environmental may prove key in enhancing the early innate immune and

later specific adaptive immune (humoral and cell-mediated) responses. These approaches might prove to be effective and economical strategies to prevent the spread and improve the treatment efficacy against the COVID-19 pandemic.

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