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COVID-19: repositioning nutrition research for the next pandemic

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At the time of this writing, the COVID-19 pandemic will have infected more than 17 million people and taken the lives of nearly 700,000 individuals world-wide [1]. While containment and treatment strategies have focused primarily on social distancing, therapeutics, and vaccines, the pandemic has also revealed serious underlying vulnerabilities in individuals infected by the coronavirus, SARS-CoV-2. The vulnerable aspects include advanced age, obesity [and its comorbidities, diabetes and chronic heart diseases], systemic coagulopathy or thrombosis [2], acute respiratory failure (e.g., hypoxia), inflammation, immunodeficiency, and neuropathologies [3,4]. The evidence for vulnerable people is supported by early reports on the COVID-19 pandemic in the United States that revealed ethnic, racial, and socio-economic disparities that resulted in some sectors of the population being disproportionally affected by COVID-19. Some of the sectors showing disproportionate rates of infection and death included men, American Indians, Alaska Natives, Blacks, Latinos, older adults, recent immigrants, and individuals with low income [5,6]. What is largely missed by the public, researchers, and healthcare providers is how nutrition and food intersect with this multiplicity of COVID-19 symptoms and disparities, in different ways and to different degrees.

It is well documented that nutrition, food, herbals, nutrients, and supplements, including various combinations and compositions, support metabolism and physiology required for health [7,8]. Table 1 shows the nutrients and herbals that complement the immune system and control inflammation to promote cell-associated antibody production and cell-mediated immunity [9]. A balanced diet, with the myriad of nutrients vital to health, supports normal B and T cell functions for optimal disease-reducing immunity [10]. In the case of COVID-19, the goal of nutrition is to reduce infection and disease progression while improving recovery during the course of the disease (Table 1). Therefore, it is critical that the medical community and supporting healthcare professionals understand the role of nutrition for maintaining health and reducing disease risk. In light of improving nutrition to avert or control COVID-19 infections, healthcare providers must support proper nutrition, and specifically, the nutrition necessary to protect those in high risk groups such as the elderly. Many elderly individuals suffer from poor nutrition because of marginal intakes of critical vitamins, minerals, and essential amino acids necessary for a robust immune system. This situation is further exacerbated by the declining gastrointestinal uptake of micronutrients and macronutrients that occurs with advanced age [11].

A recent review describes the role of nutrition in viral infections [12]. The fat-soluble vitamins A, D, E, and specific minerals play a significant role in the physiology of the immune system [10,12]. Vitamin A improves responses to vaccines and augments both cellular and humoral immunity. The function of vitamin D is important for aging and protection against viral infection. Vitamin D supports innate immune responses to influenza A-B, parainfluenza 1–2, and low vitamin D status is associated with an increased risk of both upper and lower respiratory tract infections [12]. Thus, vitamin D status appears to play a role in antiviral immunity and depending on vitamin D status, immunity could be compromised, especially in the elderly. Vitamin E deficiency is known to impair both humoral and cellular immunity [9]. Additionally, the fat-soluble vitamins serve a role in tissue growth. Vitamin C can also support antiviral immune protection in rodents and general functions in antioxidants pathways as well as co-factors for physiology of immune tissues [12].

Trace elements that support immune functions include Zn, Cu, and Mg. Marginal Zn status is associated with increased susceptibility of infections including viral [9], and Se has pleiotropic effects ranging from antioxidant to anti-inflammatory properties. Cu supports differentiation of immune cells, while Mg influences the synthesis of immunoglobulins such as immunoglobulin M. Immunoglobulin is a target of antibody testing for COVID 19 exposure [12].

In addition to the important roles vitamins and minerals play in immune function, the essential fatty

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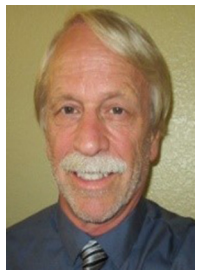
Table 1 – Examples of nutrients and phytochemicals with potential preventative or therapeutic impact on risk factors associated with acute COVID-19

Nutrient, phytochemical	Risk factor	Associated pathway/ select biomarker[s]	References
***n*-3 PUFA**	Inflammation and immune dysregulation	ECS, NF-kB, TNF-α, MCP-1	[9,13,24-33]
EPA	Cardiovascular disease	PI3K/Akt, MAPK/ERK	[28,34,35]
DHA	Obesity	ECS, PI3K/Akt, MAPK/ERK, AMPK	[13,24,27,36-48]
	Diabetes	ECS, PI3K/Akt, MAPK/ERK, GLUT4	[13,24,26,27,34,44,45]
	Respiratory inflammation/disease	TLR-4, GPR120, 7nAChR	[25,46-50]
	Neurodegeneration/ neuroinflammation	ECS, COX-2, 15-LOX	[13,51-52]
Phytochemicals	Inflammation and immune dysregulation	NOX, NF-kB, Erk, Akt, TNF-α	[53-64]
[–]Epicatechin	Cardiovascular disease	TGF-β1/smad3, NOX, eNOS	[53,54,65,66]
Resveratrol	Diabetes	NOX, NF-kB, JNK1/2	[60,61]
Curcumin	Respiratory inflammation/disease	PI3K/AKT/HIF-1α, MAPK/ERK/HIF-1α,	[55,61-64,67]
EGCG	Neurodegeneration/ neuroinflammation	TLR-4/NF-kB, PI3K/Akt	[52,56,61,68-69]
Vitamins	Impaired immune system, inflammation	Cell proliferation & maturation, IL-6, TNF-α, NF-kB, COX-1	[9-10,70-71]
Vitamin A	Respiratory inflammation/disease	Improves responses to vaccines, cellular and humoral immune responses	[12]
Vitamin D	Respiratory tract infections, compromised antiviral immunity	VDR, hCap-18/LL-37	[10,12,70,72-75]
Vitamin E	Deficiency impairs immune responses	Antioxidant functions, control free radicals	[10,12]
Vitamin C	Poor immune tissue development	Supportive antioxidant role, potential for antiviral immune protection	[12]
B-12 / Folate	Neurodegeneration/ neuroinflammation	TNF-α, IL-6, Hcy	[76-79]

ECS, endocannabinoid system; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; EGCG, epigallocatechin gallate.



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acids also have modulating effects on immunity and inflammatory processes [10]. The essential fatty acids and related long chain polyunsaturated fatty acids (PUFA) serve as substrate for oxylipins (OxL) and endocannabinoids (eCB) produced by immunocompetent cells supporting immune functions and modulating inflammation [13]. A balanced diet must include adequate essential fatty acids and both n-6 and n-3 PUFA for OxL and eCB that modulate the immune system and control inflammation. Unfortunately, by the time an individual is in the depths of the COVID-19 infection, the benefits of nutrition-based interventions can do little to mitigate or reverse the course of the disease. However, proper nutrition and nutrition support can help by improving immune responses and aid inflammatory processes.

The COVID-19 pandemic provides nutrition researchers and educators new opportunities to inform the public, particularly those in high-risk groups, about the potential life-saving benefits of good nutrition and healthy eating habits [3,14]. While it may be too late for some, there is still time for others to begin preparing their bodies and physiologies for the next infectious pandemic. In this case, providing good nutrition, adequate protein and calories, and likely vitamin and mineral supplements to the aged community can only help their immune system and general health.

As virologists, epidemiologists, and physicians mount a full-court press against the COVID-19 pandemic, one might ask what role can nutrition scientists play in these interdisciplinary efforts? The answer is that nutrition research has much to contribute to the anti-COVID-19 campaign, even if the connection is nonobvious, complex, and challenging to comprehend by the general public and policymakers. What most individuals are familiar with are excellent dietary recommendations, such as those found in the 2015–2020 Dietary Guidelines for Americans, 8th edition [15]. While these recommendations help Americans eat healthier, with the benefits of improved adaptive immune systems and metabolic responses, the rationale to follow a sound diet will also help promote resistance to COVID-19 – like infections. With knowledge of nutrients, food, and herbals that support the immune system, health professionals can advance the exciting developments in nutrition research that could take nutritional intervention to the next level and into the intensive care unit.

The intellectual space between starvation/death and health/wellness is wide and punctuated with many historic landmarks and breakthroughs from the food and nutrition sciences [16]. Over the past two decades, however, the “omics” revolution and big data analytics have created new opportunities to shrink the distance between diet-derived bioactive compounds (*e.g.*,

vitamins, minerals, non-nutritive signaling molecules, herbals) and pharmaceuticals. Historically, compounds like opium, menthol, and salicylic acid help address many of humankind's ailments. Today, we have examples like oseltamivir (Tamiflu), a medicinal compound from the Chinese star anise, a well-known spice and food flavoring. As an inhibitor of neuraminidase, a desialylating enzyme, oseltamivir prevents the release of newly formed influenza viruses from the surface of the host cell, thus preventing their spread to other host cells [17].

Today, the scientific literature contains many examples of diet-derived signaling molecules capable of controlling disease processes *in vitro* and *in vivo*. A recent study showed that a novel caffeic acid derivative is capable of suppressing the growth of colorectal cells in culture and in xenograft mouse models [18]. This was achieved by inhibiting cell-cycle regulators and corresponding blockage of the Akt and STAT3 signaling cascades. While not directly related to the COVID-19 infection, this study highlights the convergence of nutrition research, biomedical research, and molecular signaling dynamics to address other life-threatening conditions like cancer. Similar approaches are currently being used to understand and address those comorbidities related to COVID-19. As shown in Table 1, there are several nutrients and diet-derived compounds that are important for the immune system or are under evaluation for their potential preventive and/or therapeutic properties.

The current COVID-19 pandemic has been a game-changer for nutrition science, which has predominantly focused its attention on human development, maintenance, and noncommunicable disease [10]. For the first time in the history of modern nutrition, the spotlight is aimed at the link between nutrient overconsumption and a communicable disease. Understanding how this occurs is not simple and requires nutrition researchers to look beyond vitamin-mineral deficiencies and energy balance. Today, we must examine the intersectionality of nutrition and health as a complex system [19,20]. In this system, thousands of interconnected and interdependent components of the cell are poised at the edge of a "decision space" ready to tip into the modalities of health or disease, depending upon the quality and quantity of nutritional inputs. This is to say that while scrutinizing one's favorite polyphenol, enzyme, or regulatory protein is still required, it is not sufficient to blunt the disease process with today's nutritional interventions. More combinatorial, computational, and team science approaches are required.

Recently, MIT researchers predicted a new chemical entity (Halicin) that when synthesized, proved to have broad-spectrum, antibiotic properties. This amazing feat was accomplished using chemical datasets comprised of 107 million chemical entities [21]. While Halicin is not a nutrient, the use of deep learning, training algorithms, and artificial intelligence could prove useful to nutrition scientists seeking novel nutritional/therapeutic compounds based on diet-derived phytochemicals and proteins. Consortia such as the Food Biomarker Alliance [22, 23] are building large datasets of diet-derived compounds that could be used as scaffolds from which to predict new compounds. Whether such in silico designed nutrition/therapeutic compounds would be delivered as supplemental nutrition or as a medical food remains to be seen. The key message for nutrition science is that new breakthroughs in data science, cell signaling, and nutrimetabolomics [23] should make it possible to reposition itself for the next pandemic. By incorporating these interdisciplinary tools and approaches, nutrition research can move closer to the frontlines in the battle against viral infections like COVID-19, or worse.

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