





**FIGURE.** Dietary factors and potential intervention strategies for COVID-19.

management of COVID-19. But at present, we must await such results.

## IMMUNE NUTRITION

A healthy immune response depends on adequate diet and nutrition. For example, sufficient protein intake supports optimal antibody production, vitamin D activates antibody-secreting cells, and vitamin A stimulates T-cell proliferation. A wealth of clinical data show that vitamins (ie, A, B<sub>6</sub>, B<sub>12</sub>, C, D, E, and folate), trace elements (ie, zinc, iron, selenium, magnesium, and copper), and omega-3 fatty acids (ie, eicosapentaenoic acid and docosahexaenoic acid) play a complementary role to enhance immune function. Micronutrients are vital for immunomodulation, and their deficiency could increase susceptibility to viral infections. Individuals at high risk for specific nutrient deficiencies are likely to benefit from dietary supplements if they are truly deficient; if they are not deficient (as assessed with selected biomarkers), then there may be little benefit by providing more of the nutrient or purported bioactive. In summary, individual dietary and nutritional status could be critical for determining the clinical outcomes of COVID-19.

### Modulators of Immunity and Hyperinflammation (“Cytokine Storm”)

The development of SARS-CoV-2-evoked pneumonia with hyperinflammatory responses in the lung is collectively known as the “cytokine storm.” A clinical analysis of COVID-19 patients (n = 150) revealed a link between fatality and elevated ferritin levels and interleukin (IL)-6, suggesting that the high case fatality rate (CFR) in patients was related to virus-induced hyperinflammation.<sup>2</sup> The

cytokine profile of severe COVID-19 cases also showed an increase in tumor necrosis factor α, IL-2, IL-7, interferon (IFN)-γ inducible protein 10, Granulocyte Colony Stimulating Factor, macrophage inflammatory protein 1-α, and monocyte chemoattractant protein 1.<sup>3</sup>

No effective drugs are currently available to suppress the cytokine storm, although several have been proposed. These proposed drugs include 4-phenylbutyric acid (a drug often used to treat urea-cycle disorders) and tocilizumab (a monoclonal antibody known to block IL-6 in rheumatoid arthritis).

From a nutritional intervention perspective, the low toxicity, antioxidant, anti-inflammatory, and antiviral activities of some minerals and natural bioactives may be considered. If they are administered before the onset of cytokine storm, these substances may improve the symptoms and outcomes of COVID-19. Thus, it may be most important to maintain a potent immune system through more healthful dietary patterns.

*Zinc (Zn<sup>2+</sup>)* down-regulates inflammation via inhibition of the nuclear factor kappa B signaling pathway and modulates T-cell activity to limit the cytokine storm.<sup>4</sup> In a human clinical study, COVID-19 patients (n = 411) taking zinc sulfate (220 mg) with hydroxychloroquine and azithromycin showed an increased frequency of patient discharges from hospital and decreased need for ventilation and intensive care unit (ICU) admission with low CFR.<sup>5</sup> This combination dietary supplement and drug intervention is used as a prophylactic protocol in a prospectively followed cohort (NCT04326725; active, not recruiting) and a human RCT (NCT04377646; not recruiting).

*Vitamin C (ascorbic acid)* improves immune function by down-regulating inflammatory mediators such as IL-6 and endothelin-1, which may reduce the duration of

COVID-19 symptoms, facilitate rapid recovery, and shorten the length of mechanical ventilation and ICU stay when consumed at 2 g/d (intravenous) for 96 hours.<sup>6</sup> A combination of vitamin C (3 g q6 for 7 days) and quercetin (250–500 mg bid) showed antiviral synergism and protection of high-risk COVID-19 patients.<sup>7</sup> Using a bioinformatics system, a combination of vitamin C and glycyrrhizic acid demonstrated antiviral activity based on 17 targeted outcomes and thus may be beneficial to test in COVID-19 patients.<sup>8</sup> No human studies on this cocktail are available at present.

*β-Glucan* (in branched form) seems to modulate immune responses against several viral infections. It activates macrophages, dendritic cells, natural killer cells, and neutrophils, resulting in an effective T- and B-cell response against SARS-CoV-2. These effects could decrease the duration and severity of COVID-19 symptoms.<sup>9</sup> In a 2-week mouse study, *β*-glucans from maitake fruit body extract and whole mycelial mushroom powders of Shiitake, Reishi, Agaricus, and Chaga increased the production of IL-1 $\beta$ , tumor necrosis factor  $\alpha$ , and IFN- $\gamma$  in peripheral blood and potentiated the antibody response to influenza infection.<sup>10</sup> *β*-Glucan extracts from the edible mushroom *Lentinus edodes* reduced proinflammatory cytokines and oxidative stress. These extracts elicited immunomodulatory and pulmonary cytoprotective effects with prophylactic implications in COVID-19 patients, especially in down-regulating the cytokine storm.<sup>11</sup> The oral doses of 500 mg *β*-glucan have been suggested for an effective antiviral intervention. Clearly, more research is needed to confirm the potential clinical value among COVID-19 patients.

*Curcumin*, the primary yellow-orange curcuminoid derived from turmeric, has a long history of potential benefits as a plant-based bioactive.<sup>12</sup> Pharmacokinetic studies with rodent models and among humans indicate a poor absorption of this curcuminoid.<sup>13</sup> For example, the oral administration of curcumin at 2 g/kg body weight to healthy humans resulted in virtually undetectable serum levels (0.006  $\pm$  0.005  $\mu$ g/mL at 1 hour). Regardless, numerous *in vitro* and *in vivo* studies suggest that curcumin, and perhaps its metabolites, may function as proinflammatory and anti-inflammatory mediators, such as IL-6, IL-8, IL-10, and cyclooxygenase-2, and promote the apoptosis of neutrophils and scavenge the reactive oxygen species (ROS) that may exacerbate the inflammatory response.<sup>14</sup> Curcumin may be beneficial against pneumonia and acute respiratory distress syndrome resulting from COVID-19 infection as suggested by several *in vitro* studies and rodent models.<sup>15</sup> As with other interventions, research is needed to confirm these findings among humans.

Several flavonoids demonstrate potent anti-inflammatory effects against CoVs. For example, emodin, a unique anthraquinone found in aloe, rhubarb and buckthorn, appears to ameliorate the asthmatic airway inflammation by inhibition of activated macrophages in a murine model

when administered intraperitoneally at 20 mg/kg body weight per day.<sup>16</sup> Another plant-derived flavonoid, scutellarein, exerts anti-inflammatory activity by down-regulation of cyclooxygenase-2 and inducible nitric oxide synthase via inhibition of the NF- $\kappa$ B pathway.<sup>17</sup> Certain carotenoids and polyphenols interact with transcription factors such as NF- $\kappa$ B and nuclear factor erythroid 2-related factor 2, to elicit anti-inflammatory and antioxidant effects.<sup>18</sup>

## REDOX NUTRITION

The severity of COVID-19 is associated with clinical onset of hypoxia triggered by imbalance in the redox state, inflammation, and the ensuing cytokine storm. An imbalance in redox increases oxidative stress and triggers a cascade of events that may increase COVID-19 susceptibility among high-risk individuals. The purpose of what might be termed “redox nutrition” is to restore mitochondrial function and establish cellular redox homeostasis. An evidence-based cocktail of redox nutrition-based anti-SARS-CoV-2 supplements may provide (a) promotion of mitophagy to remove dysfunctional mitochondria damaged by ROS and reduce immune evasion of viral pathogens; (b) bioavailability of transition metals to catalyze oxidation and create a reduced environment to maintain intracellular pH; (c) essential micronutrients and bioactive compounds with potent antioxidant activity; (d) functional nutrients with anti-inflammatory and vasodilatory activity; and (e) immunomodulatory molecules to resolve hypoxia and associated dysfunctions.<sup>19</sup>

### Nutritional Regulation of Oxidative Stress

Oxidative stress is an imbalance between the production of ROS and their elimination by protective mechanisms in the body. Oxidative stress activates a variety of transcription factors involved in inflammatory pathways. Oxidative stress during viral infection is associated with the induction of hyperinflammation (cytokine storm), the underlying cause for severe clinical symptoms and fatality outcomes in COVID-19 patients. The roles of certain natural antioxidants to ameliorate oxidative stress and reduce pathological complications associated with COVID-19 are highlighted.

*Selenium (Se)* is an essential cofactor for several redox enzymes and, in concert with vitamin E, reduces the formation of ROS. Selenium inadequacy has been implicated in the pathogenicity of several viruses. Selenium status, based on hair analysis, showed an association ( $R^2 = 0.74$ ) between the cure rate of COVID-19-infected patients in the Wuhan, China, outbreak, but this association varied among cities outside Hubei Province.<sup>20</sup> Selenium and selenoproteins, such as glutathione peroxidase and thioredoxin reductase could modulate the interlinked redox homeostasis, stress and inflammatory responses, as well as impact viral replication.<sup>21</sup> Some suggest that for optimal function of these enzymes, a daily intake of at least 100  $\mu$ g Se/d is needed.<sup>22</sup>

The recommended daily intake for selenium in the United States is 55 µg. However, research is still needed to establish whether such levels of Se are, in fact, safe and efficacious.

*Astaxanthin* is a lipid-soluble carotenoid in the class of terpenes and occurs naturally in some algae, yeast, salmon, and shrimp. Some studies suggest that astaxanthin exhibits potent free radical scavenging activity. It decreases the membrane fluidity and increases the activation of nuclear factor erythroid 2-related factor 2/heme oxygenase-1 pathway and elevates redox enzymes, that is, catalase, superoxide dismutase, peroxidase, thiobarbituric acid reactive substances, and NAD(P)H quinone oxidoreductase-1 glutathione-S-transferase-α1.<sup>23</sup> Astaxanthin is also a potent inhibitor of superoxide and nitrogen dioxide radicals, cytosolic calcium, ROS, myeloperoxidase (MPO), and other oxidative mediators. Some international regulatory agencies suggest or have approved that the effective dosage for antiviral activity of astaxanthin is between 2 mg/d (acceptable daily intake in Europe) and 24 mg/d.<sup>24</sup> Within the United States, the Food and Drug Administration provided “no objection” letters for nearly 20 New Dietary Ingredient Notifications for astaxanthin with daily doses between 2 and 24 mg. Whether these doses are efficacious remains to be determined.

### **Metallo-Proteins and Redox Homeostasis**

Redox biochemistry is likely a key factor in metabolic disorders associated with COVID-19. Impaired redox state and the ensuing oxidative stress have been linked to increased susceptibility of individuals to SARS-CoV-2. For example, inadequate or depleted glutathione, a peptide from glutamate, glycine, and cysteine that is synthesized in the cytosol of all human cells, has been linked to severe symptoms and CFR among COVID-19 patients.<sup>25</sup> Three metallo-proteins, lactoferrin (LF), ceruloplasmin, and MPO, constitute the innate molecular machinery to regulate oxidative stress and redox homeostasis.

*Lactoferrin (LF)*, the iron-binding mammalian milk protein, is a potent regulator of cellular redox and may play a significant role in the clinical management of COVID-19.<sup>26</sup> Binding of LF to Fe<sup>3+</sup> ions could block iron-mediated catalysis and oxidative disturbances in cell membranes. Oxidative stress and its related metabolic syndromes are virulence factors in the pathogenesis of COVID-19. As an innate free radical scavenger, LF regulates oxidative stress and various proinflammatory cytokines. Thus, LF could contribute to the suppression of COVID-19 infection and inflammation, either acting as natural barrier for both respiratory and intestinal mucosa or reverting the iron disorders related to viral colonization.<sup>27</sup> Lactoferrin may also induce the expression of antiviral cytokine mRNA, such as IFN-α and IFN-β, that could inhibit viral replication in infected cells. These inhibitory effects are achieved through competitive binding of LF to host cell receptors (ie,

Heparan Sulfate Proteoglycans, ACE2, sialic acids, etc), and/or directly to SARS-CoV-2 capsid (ie, S, E, M, N proteins). The antiviral effects of LF are widely studied and several human RCTs have shed light on the possible mechanisms of action, therapeutic efficacy, and safety of this multifunctional milk protein.<sup>28</sup>

*Ceruloplasmin*, a glycoprotein initially synthesized in the liver, is not involved with copper metabolism per se. It has considerable ferroxidase activity and is critical in maintaining iron homeostasis.<sup>29</sup> Interestingly, nearly 40 years ago, several in vitro studies indicated the presence of ceruloplasmin in culture medium inhibited replication of H0N1 and H1N1 viruses.<sup>30,31</sup> However, these findings have not been used to study COVID-19.

*Myeloperoxidase* is expressed primarily in neutrophils, and to a lesser degree in monocytes. The expression of this enzyme may increase health risks and provide benefits, depending on the inflammatory disease state of the host.<sup>32</sup> Although MPO has been implicated in an array of inflammatory conditions in rodent models and humans, such as rheumatoid arthritis, metabolic syndrome, and pulmonary inflammation, its potential role to induce proinflammatory cytokines among COVID-19 patients has not been characterized. Importantly, its contributions to the establishment of neutrophil extracellular traps that may trigger immunothrombosis and, in part, may explain the prothrombotic clinical presentations in COVID-19 acute respiratory distress syndrome remain unclear.<sup>33</sup> Thus, great care is needed in use of this bioactive.

### **NUTRIENT-RELATED DISRUPTION OF VIRAL ENTRY AND REPLICATION**

Inhibition of viral docking to host cell surface receptors, membrane fusion, cellular entry, and viral replication seem to be potent intervention strategies to combat COVID-19. The Spike (S)-protein, a class I fusion molecule on the viral surface, is essential for COVID-19 infection. Spike-protein binds to the human angiotensin-converting enzyme 2 (ACE2) receptors for entry into the host cell. After the cellular entry, the viral genomic RNA interacts with the host ribosome and translates into 2 proteases, 3CLpro and PLpro, for processing the assembly of new viral particles. For replication of the RNA genome, the virus encodes RdRp, a replicase enzyme. These 4 proteins are critical for the virulence of SARS-CoV-2. Intervention strategies to target Spike, RdRp, 3CLpro, and PLpro for the effective clinical management of COVID-19 are in active development in several laboratories worldwide.<sup>34</sup>

### **Phytochemical ACE2 Receptor Blockers**

Several phytochemicals interfere with viral docking to host cells and block the entry of SARS-CoV-2. Based on docking experiments, curcumin (from turmeric), nimbin (neem), withaferin A (from plants in the Solanaceae family), piperine

(from black and white pepper), mangiferin (from a small fern, *Asplenium montanum*, and its hybrid descendants), thebaine (also known as paramorphine, primarily from Iranian opium/Persian poppy), berberine (from barberry, tree turmeric, Oregon grape, and goldenseal), and andrographolide (from various plants of the genus *Andrographis*) have been identified as potential disruptors of CoV S-protein interaction with human ACE2 receptor. Other natural compounds such as resveratrol (from red grapes and blueberries), quercetin (widely distributed among edible plants), luteolin (from parsley, celery, lemons and other citrus fruits, and melons), naringenin (from grapefruit and orange peel), zingiberene (primarily from ginger), and gallic acid (from carob, strawberries, grapes, bananas and other fruits) demonstrate binding affinity only toward the human ACE2 receptor; therefore, they may be useful for ACE2-mediated attachment inhibition of SARS-CoV-2.<sup>35</sup> It is important to point out that cellular studies are a long way from proof of efficacy and that more clinical research is required to determine if plant-based ACE2 receptor blockers have risk reduction effects.

*Resveratrol* intake up-regulates ACE2 and interferes with CoV binding to host cell surface receptor. Conversely, a high intake of dietary fat (~50%-60% of total energy intake in a mouse model) could elicit a detrimental effect by ACE2 down-regulation.<sup>36</sup> Several other rodent model studies with varied dietary fat, carbohydrate, and protein content indicated either an absence of or improved effect on ACE2 expression.<sup>37,38</sup> In the same model, it seems that resveratrol may be a potent disruptor of viral S-protein and human ACE2-receptor complex. A high-affinity interaction of resveratrol with host receptor-virus complex was documented in molecular dynamic simulation experiments.<sup>39</sup> Again, the potential value of this lead depends on more research in humans.

*Quercetin*: Molecular dynamics simulation studies have indicated that quercetin binds and perturbs the hACE2-S-protein complex (human angiotensin-converting enzyme 2 and spike glycoprotein complex). In silico studies have further supported that quercetin may be an effective disruptor of hACE2-S-protein complex.<sup>40</sup> The COVID-19 main protease (M<sup>Pro</sup>) enzyme plays a functional role in viral replication and transcription. Quercetin derivatives, such as quercetin-3-D-xyloside and quercetin 3-O- $\alpha$ -L-arabinopyranoside, seem to be potent inhibitors of COVID-19 M<sup>Pro</sup> enzyme activity.<sup>41</sup> Thus, these derivatives deserve more clinical study.

## Inhibitors of Viral Replication

Antiviral drugs, including chloroquine/hydroxychloroquine, remdesivir, and lopinavir/ritonavir, are effective inhibitors of SARS-CoV-2 in vitro. Because of the high-dose requirement and narrow therapeutic index of these drugs, patients often experience severe side effects. Currently, there is no approved therapy for COVID-19; therefore, the World Health Organization endorses these for supportive care

only. However, frontline clinicians and researchers are exploring several virus-based and host-based interventions.

*Vitamin D* may reduce the risk of COVID-19 infections by several mechanisms, including (a) induction of cathelicidins, which are antimicrobial peptides that serve a critical role in mammalian innate immune defense against invasive bacterial infection, and defensins, which are host peptides for the defense against bacteria, to lower viral replication rates; (b) down-regulation of proinflammatory cytokines that damage lung epithelia and cause pneumonia; and (c) up-regulation of anti-inflammatory cytokines.<sup>42</sup> Vitamin D is suggested to play a role in COVID-19 pathobiology, where ecological studies indicated that the rate of infection was higher in countries at higher latitudes and/or with lower vitamin D status.<sup>43</sup> A clinical study on COVID-19 inpatients (n = 134) found that a smaller number of patients in the ICU had 25-OH-D greater than 50 nmol/L (19%) compared with those in conventional medical wards (39.1%).<sup>44</sup> An association between vitamin D deficiency and hospital admission, disease severity, and mortality among patients from primary care and specialized clinics (n = 691) has been reported.<sup>45</sup> However, several other reports on this topic indicated no association between vitamin D status and risk of COVID-19 infection.<sup>46,47</sup> To reduce the risk of COVID-19 infection, some suggest 10 000 IU/d of vitamin D<sub>3</sub> for a few weeks to rapidly raise 25(OH)D levels, followed by 5000 IU/d. The goal is to raise 25(OH)D levels greater than 40 to 60 ng/mL (100–150 nmol/L). For treatment of COVID-19 patients, higher vitamin D<sub>3</sub> doses might be beneficial to help rapid recovery, a topic currently under debate in the UK parliament.<sup>42</sup>

## CONCLUSIONS

Nutrition is a biochemical process that involves metabolism, energy balance, cellular stress, and the gut biome, with cumulative health outcomes in the human population. Diet is well established as a major contributor in the clinical management of several metabolic disorders; accordingly, COVID-19 virulence is compounded with comorbidities such as type 2 diabetes, obesity, and cardiovascular disease. It is important to understand the interaction of dietary patterns and chronic noncommunicable illness in populations with low viral spread rates and reduced CFRs for COVID-19. The global experience with the COVID-19 outbreaks emphasizes the importance of rapid diagnosis of malnutrition and immediate implementation of caloric/protein-balanced nutrition care. These activities are critical to achieve success with nutritional interventions as well as lower mortality rates. Patients with mild symptoms of COVID-19, especially in advanced age with comorbidities, require an effective nutritional protocol. The prospects for the development and evaluation of nutritional supplements specifically selected and ultimately combined may prove

to be a valuable adjunct to those in the management of viral disease. However, at present, the critical evidence from human investigation remains deficient.

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