Review

Plant-Based Diet and Supplements Reduced COVID-19 Severity and Mortality in Elderly Patients with Multiple Comorbidities (Part 2: Exploring the Underlying Mechanisms of Successful Intervention)

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Plant-Based Diet and Supplements Reduced COVID-19 Severity and Mortality in Elderly Patients with Multiple Comorbidities (Part 2: Exploring the Underlying Mechanisms of Successful Intervention)

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Abstract: The potential advantages of plant-based interventions in decreasing the incidence and lessening the severity and mortality of COVID-19 are yet to be widely acknowledged. Nevertheless, recent investigations propose that these interventions could be effective. Our recent publication (part one) features an interventional study in which we incorporated plant-based foods and provided supplementation to 3470 elderly COVID-19 patients with multiple comorbidities. We pay close attention to the precise selection of food items, the application of appropriate processing methods, and the provision of nourishing meals to our patients. Our outcome was highly successful as we achieved a zero mortality rate, and none of our patients experienced worsening conditions or required hospitalization. This second paper presents our theoretical framework on the mechanisms through which plant-based and supplement interventions can mitigate disease severity and mortality. However, only very recently have experts validated our hypotheses. The measures and methods used to address the ongoing SARS-CoV-2 pandemic through plant-based interventions and supplements are effective and may help prevent or manage future pandemics.

Keywords: plant-based; COVID-19; inflammation; supplements

1. Introduction

Several studies have demonstrated that a plant-based diet can effectively treat chronic inflammatory diseases, such as obesity, atherosclerosis, hypertension, hyperlipidemia, and hypercholesterolemia. Dietary interventions not only manage these diseases but can potentially reverse them [1–3]. By reducing the consumption of foods that promote inflammation and contribute to chronic inflammatory diseases, one can further enhance the positive impact of a healthy diet. In our cardiology practice, we have observed remarkable results in patients suffering from chronic inflammation-related illnesses. These patients achieved remission with limited medication. Patients with hyperlipidemia could also meet their lipid targets according to International guidelines. We also noticed improved kidney function and successful management of sugar levels for patients with type 2 diabetes or glucose intolerance without excessive medication or the need for insulin. Furthermore,

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we witnessed a regression of coronary obstruction in numerous cardiac patients, and there was a low occurrence of in-stent restenosis (ISR).

We hypothesized that a plant-based diet could reduce the incidence and severity of COVID-19 and potentially save lives. Our clinical trial was conducted between April 2020 and July 2023, enrolling 3,470 mostly elderly COVID-19 patients with multiple comorbidities. At the time of our investigation, there were no studies or recommendations indicating the advantages of a plant-based diet in managing the virus. However, subsequent observational studies revealed the potential role of plant-based diets in managing COVID-19. Undertaking interventional research on COVID-19 patients when no medications or vaccines were yet available was a high-risk endeavor. The driving force behind our initiative is our extensive expertise in plant-based diets and supplementation, coupled with our positive experiences, and our ultimate objective is to save as many lives as possible.

We propose that plant-based diets could enhance nitric oxide availability, alter the microbiota, improve endothelial function, reduce inflammation, combat oxidative stress, boost mitochondrial function, extend telomeres, and promote caloric restriction to combat COVID-19. These mechanisms may decrease the incidence, severity, and mortality rate of COVID-19 patients. Severe inflammation and blood clotting are major factors contributing to the high mortality rate of SARS-CoV-2 patients [4,5], and plant-based diets can help prevent these complications.

Our studies concentrate on employing plant-based foods, specifically their precise quantities, quality control, and preparation techniques, in addition to supplementation, to maximize the anti-inflammatory and antioxidant effects, lessen oxidative stress, and improve nitric oxide availability and endothelial repair. We employed supplements with established roles in chronic inflammatory diseases [6,7]. The significance of supplements, including nutraceuticals, in relation to COVID-19 has been recognized only recently [8,9,82–134]. We hypothesize that by combining our dietary intervention with strategic supplementation, we can reduce the severity and fatality rates of COVID-19 to the greatest extent possible.

2. Mechanism of Plant-Based in Reducing Incidence, Severity, and Mortality of COVID-19

2.1. Mechanism of Nitric Oxide in Fighting COVID-19

Nitric oxide (NO) is a naturally occurring molecule found in various cell types and organ systems that plays a crucial role in the cardiovascular system. Its functions include regulating basal vascular tone, preventing platelet activation, and limiting leukocyte adhesion to the endothelium. Furthermore, it significantly contributes to regulating myocardial contractility [10]. Unfortunately, conditions such as obesity, hypertension, hypercholesterolemia, and type 2 diabetes, which are commonly linked to risk factors for atherosclerosis, can lead to a decrease in NO release into the arterial wall due to impaired synthesis or excessive oxidative degradation [11]. Studies on experimental models and humans indicate that natural NO production reduces with age, which may be relevant to the number of diseases that affect the aging population [12]. It is believed that the elderly's NO deficiency may contribute to the severity and mortality of COVID-19 and the development of comorbidities [13]. On the other hand, children and young adults (below 19 years old) have low COVID-19 mortality rates, which may be due to their high NO content [14]. To measure our study population's NO, we used a salivary strip that has a 96% accuracy rate [15]. We can improve our patients' NO readings by modifying their diet and lifestyle [16]. Figure 1 illustrates the conversion of nitrate-rich foods to nitric oxide [17].

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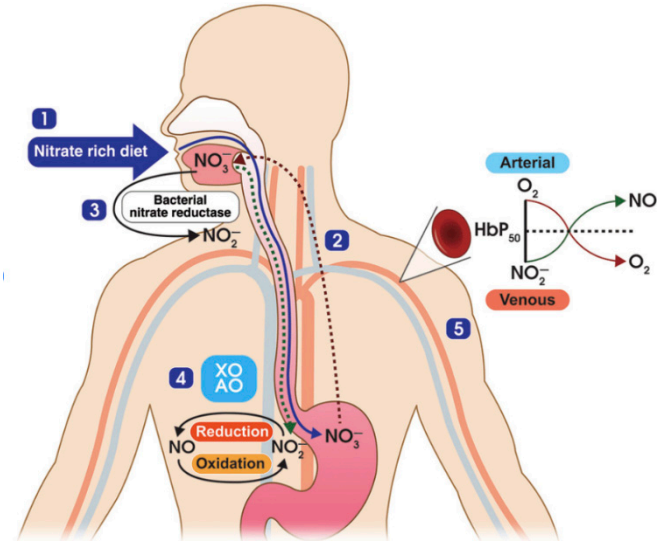

Figure 1. A schematic diagram of nitrate, nitrite, and nitric oxide (NO) pathway from exogenous (dietary) sources: dietary nitrate taken (1) is absorbed systemically (2) and is concentrated 10-fold in the salivary gland and enters the enterosalivary circulatory system where it is converted to nitrite by bacterial nitrite reductases on the dorsum of the tongue (3). When nitrite reaches the lumen of the stomach, acidic gastric juice converts nitrite to nitrosating species that can further react with ascorbic acid in gastric juice to yield NO (4). It can also reenter the circulation as nitrite and be reduced to NO by xanthine oxidase (XO) and aldehyde oxidase (AO) (4). Nitrite in the arterial circulation may also be reduced to nitric oxide due to hemoglobin deoxygenation causing vasodilation [17]. (Picture copied from Rajendran S, Shen X, Glawe JD, et al. Nitric Oxide and Hydrogen Sulfide Regulation of Ischemic Vascular Growth and Remodeling. Chapter in Comprehensive Physiology. 2019. **https://www.researchgate.net/publication/333740265).**

It has been observed that SARS-CoV-2 has the potential to reduce the availability of nitric oxide (NO) in the endothelium [18], as shown in Figure 2.

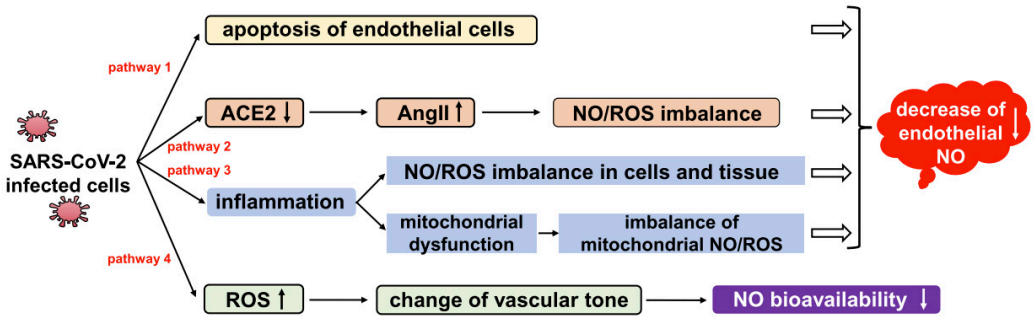

Figure 2. SARS-Cov-2 infected cells can decrease Nitric Oxide (NO) [18] (Picture copied from Fang W, Jiang J, Su L, et al. The role of NO in COVID-19 and potential therapeutic strategies. Free Radical Biology and Medicine. 2021; 163:153-162.).

It is suggested that the virus could affect the cardiovascular system, resulting in conditions like acute coronary syndrome, pulmonary embolism, and heightened COVID-19 mortality. It is worth mentioning that NO plays a vital role in the lungs, serving as a vasodilator, anticoagulant, anti-inflammatory, and antiviral agent [18], as demonstrated in Figure 3.

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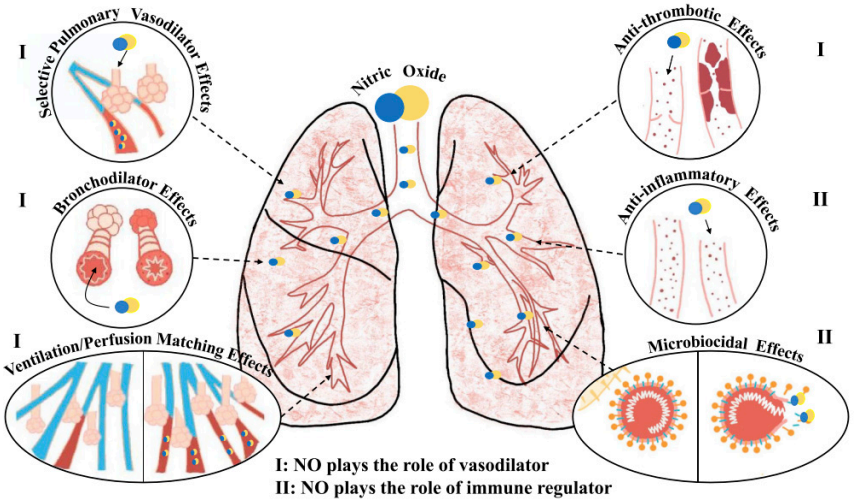

Figure 3. Six pathways of NO to function in the Lungs. (I) NO is a vasodilator, including selective pulmonary vasodilator effects, bronchodilator effects, increased blood flow to the alveoli, and anti-thrombotic effects. (II) NO is an immune regulator, including anti-inflammatory and microbiocidal effects [18] (Picture copied from Fang W, Jiang J, Su L, et al. The role of NO in COVID-19 and potential therapeutic strategies. Free Radical Biology and Medicine. 2021; 163:153-162.).

Research has indicated that NO can provide therapeutic advantages, including reducing pulmonary hypertension and increasing blood flow in ventilated lung units [13]. Furthermore, a higher baseline level of NO has been linked to fewer cold symptoms, indicating that it may enhance mucosal immunocompetence and aid in preventing airway infections [19]. Recent studies have also found that inhaled nitric oxide (iNO) may be beneficial in treating COVID-19 patients by improving arterial oxygenation. Given the high risk of refractory hypoxemia in these patients, clinical guidelines need to consider the potential advantages of iNO in managing ARDS, particularly for critically ill individuals [20].

To increase NO levels in vital organs such as the lungs, heart, and brain of COVID-19 patients, we recommend incorporating dietary nitrates from sources such as green leafy vegetables, beets, cabbage, pomegranate, watermelon, garlic, lemongrass, ginger, and turmeric into their daily diet [21]. Our study suggests that improving NO may lower severity and mortality rates in COVID-19 patients, as previously explained.

2.2. The Connection between Microbiota and COVID-19

The human body contains an estimated 38 trillion microorganisms, with the gut being the most densely and diversely populated organ. It's worth noting that the gut microbiota plays a crucial role in maintaining immune homeostasis. Specifically, the mucosal immune system, including the gut-associated lymphoid tissue (GALT) and bronchial-associated lymphoid tissue, acts as the primary line of defense against infections. The appendix, Peyer's patches, and isolated lymphoid follicles of the intestinal mucosa comprise the GALT. The interaction between immune cells of the GALT and gut microbiota is necessary to regulate the immune system. Considering that the majority (70-80%) of immune cells exist in the gut, it's essential to maintain a healthy gut microbiota system [22]. While the gut microbiota is well-studied, the microbial community of the lungs is not as well-understood.

Numerous studies have established a crucial link between the gut and lung systems, known as the "gut-lung axis." An abundance of evidence supports the connection between gut microbiota and lung immunity, with gut microbiota dysfunction being associated with impaired alveolar macrophage function and reduced bacteria-killing capacity. Furthermore, research has demonstrated that the disruption of gut microbiota caused by antibiotics can result in the survival and growth of pathogenic microorganisms in the lungs. The gut-lung axis is bidirectional, as microbial components

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can impact the lungs through the bloodstream, and lung inflammation can affect the gut microbiota. A study found that after exposure to the influenza virus, CD4 T cells from the lungs migrated to the intestine, causing dysbiosis of the gut microbiota and leading to abnormal Th17 response, intestine damage, and gastroenteritis [23]. Research has shown a correlation between chronic inflammatory diseases and the composition of gut microbiota [24].

Various simple therapeutic techniques have been proposed to modify microbiota and combat chronic illnesses. This includes changes to one's diet, as well as the use of prebiotics and probiotics. These modifications have the potential to mitigate the severity of COVID-19 through a multitude of mechanisms while also impacting the course of chronic illnesses like hypertension, diabetes, obesity, and coronary heart disease. By addressing these comorbidities, there is a lower risk of developing severe COVID-19 and facing mortality rates.

Disrupting beneficial microorganisms in the gut microbiota, leading to gut dysbiosis, can increase the risk of respiratory illnesses, sepsis, and ARDS. The intestinal barrier serves as a shield against harmful microbes and their byproducts from entering the bloodstream. However, when gut dysbiosis occurs, the gut barrier may become more permeable, resulting in a leaky gut. Studies have linked this condition to decreased short-chain fatty acids (SCFAs) such as butyric acid and acetic acid, produced by gut bacteria. This increase in gut permeability allows microbiota-derived lipopolysaccharides (LPS) and inflammatory components to translocate into the bloodstream, resulting in immune activation and inflammation. Toll-like receptor 4 (TLR4) plays a significant role in immune activation, and its activation by LPS can exacerbate a range of clinical conditions. Research has indicated that TLR4 activation by LPS can worsen mortality rates in cases of influenza infections [25].

SCFAs are essential for regulating immune and inflammatory responses. By promoting mucin production and maintaining an acidic pH in the gut environment, harmful microbes are discouraged from growing. Furthermore, SCFAs are vital for maintaining the integrity of the gut epithelium and preventing leakage or translocation. They also act as powerful histone deacetylase (HDAC) inhibitors, effectively reducing inflammatory responses by boosting the numbers and functions of T helper cells, regulatory T cells, and Th17 effector cells. SCFAs possess various anti-inflammatory properties by activating G protein-coupled receptors (GPCRs) like GPR43 and inhibiting the NF-kB pathway. Recent research has found that small amounts of SCFAs are present in the lungs, indicating a potential connection between the gut and respiratory system (gut-lung axis) [26]. These studies have also shown that SCFAs assist in creating macrophage and dendritic cell progenitors in the bone marrow. Additionally, SCFAs protect against airway inflammation and respiratory tract infections by enhancing the function of T cells [27].

Research suggests that cytokine storms may contribute to the varied symptoms of COVID-19. This could also explain why younger people may experience less severe symptoms, as their immune systems may not be as involved in the inflammatory response [28]. Studies have shown an age-related imbalance in gut microbiota, including decreased beneficial strains like Bifidobacteria and Lactobacillus and bacteria that produce SCFAs, which help maintain intestinal barrier integrity. Furthermore, evidence supports the idea that gut dysbiosis plays a significant role in chronic aging-related diseases. The severity and mortality rates of COVID-19 in elderly patients over 65 with pre-existing conditions such as diabetes, obesity, hypertension, and cardiovascular disorders are high [29].

Studies have shown that immunological aging is associated with "inflammaging," a subclinical inflammatory state that relies heavily on Th1 immune responses. Children, on the other hand, exhibit more Th2 response, which leads to less production of pro-inflammatory molecules. Recent research has extensively studied the gut microbiota and found links to various health conditions such as respiratory infections, inflammatory bowel disease, cardiovascular disease, type-2 diabetes, depression, and hypertension [30]. The high mortality rates in elderly individuals and those with underlying medical conditions who contract COVID-19 could potentially indicate a correlation between gut microbiota disturbances and disease severity and clinical outcomes [31]. Multiple studies have suggested increased cytokine and chemokine production, leading to viral

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hyperinflammation or a "cytokine storm," is mainly responsible for COVID-19 mortality [32], as illustrated in Figure 4.

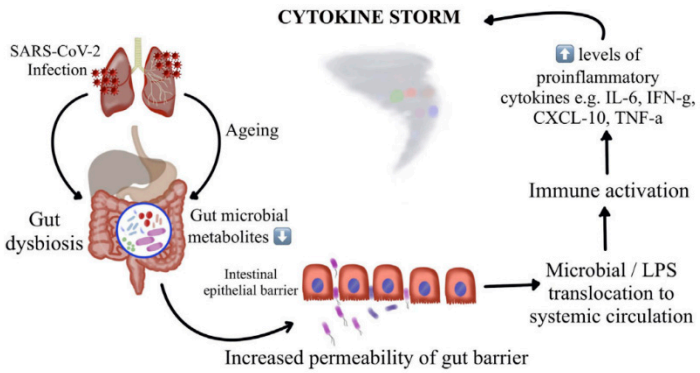

Figure 4. Schematic representation of the proposed hypothesis of gut microbiota perturbation leading to severe COVID-19 by cytokine storm [32] (Picture copied from Vignesh R, Swathirajan CR, Tun Z-H, et al. Could Perturbation of Gut Microbiota Possibly Exacerbate the Severity of COVID-19 via Cytokine Storm? Frontiers in Immunology. 2021; 11:607734).

Maintaining a balanced and optimal immune response is crucial in preventing potentially life-threatening inflammatory reactions, and a healthy gut microbiota plays a significant role in achieving this. The immune response can have varying clinical outcomes and consequences, depending on whether it is under-reactive or over-reactive, emphasizing the importance of balance.

Research has shown that dietary carnitine, primarily found in animal protein, can negatively impact human vascular health. When gut flora converts carnitine into trimethylamine (TMA), it is then transformed into trimethylamine N-oxide (TMAO) in the liver. Elevated levels of TMAO in the bloodstream have been linked to an increased risk of major adverse cardiovascular events, including myocardial infarction, congestive heart failure, stroke, and mortality. Additionally, studies have found a correlation between serum TMAO levels and inflammation and thrombosis, often observed in COVID-19 patients. If the gut microbiome is in a state of dysbiosis and produces TMAO, it can upregulate various molecular mechanisms, such as the nuclear factor kappa (NF-kB) molecular pathway, and promote the expression of scavenger receptors (SRs) on the surface of macrophages, leading to inflammation. High levels of TMAO have been shown to induce the expression of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin 1ß(IL-1ß) while reducing the expression of anti-inflammatory cytokines such as interleukin-10 (IL-10). Moreover, gut-derived TMAO has been found to enhance platelet aggregation and adhesion to collagen, thereby increasing the risk of thrombosis. It was hypothesized that high levels of TMAO in the body can lead to increased severity of COVID-19 [33].

Studies have indicated that those who adhere to a vegan or vegetarian diet tend to exhibit decreased levels of TMAO in their system. TMAO is a compound associated with a heightened likelihood of inflammation. Conversely, the consumption of specific foods such as red meat (including beef, pork, lamb, veal, processed meat, and ham), egg yolks, fish, and full-fat dairy products (such as whole milk, yogurt, cream, cheese, and butter) may result in elevated TMAO levels in the body.

The microorganisms that reside in our gastrointestinal (GI) tract, from the mouth to the anus, are an essential part of our overall health. The gut plays a fundamental role in maintaining our well-being, connecting various organs in our body through the gut-organ axis. Moreover, the gut-brain axis (GBA) influences our mood and behavior significantly. The gut microbiome-immune system-brain axis operates bidirectionally and can impact the progression of COVID-19, particularly when stress is involved. The communication between the gut and brain is facilitated by several systems, including the enteric nervous system (ENS), the autonomic nervous system (ANS), neuroendocrine

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signaling systems, and the immune system, which can all affect the gut microbiota. Therefore, healthy gut microbiota can help reduce stress levels during the pandemic [34].

In light of the COVID-19 pandemic, it's crucial to maintain a healthy mood and behavior to prevent cytokine storms. Several risk factors for cardiovascular disease can lead to dysbiosis, weakening the gut barrier and causing inflammation. This can increase the severity of COVID-19 symptoms in affected patients, as recent research has shown. Furthermore, studies have revealed a close relationship between gut microbiota, dietary lipid intake, and atherosclerosis development, involving metabolic and inflammatory factors. A novel pathway has been identified that connects these components, with the production of TMAO being linked to reduced bile acid synthesis and inhibited reverse cholesterol transport, ultimately contributing to the development of atherosclerosis. Heart failure has also been associated with microbial dysbiosis and abnormal metabolite production [35], which can exacerbate the prognosis of COVID-19 patients who already suffer from both atherosclerosis and heart failure (gut-heart axis).

Numerous health benefits have been associated with healthy microbial metabolites, such as anti-inflammatory, immunomodulatory, systemic-anti-obesogenic, antihypertensive, hypocholesterolemia, antiproliferative, and antioxidant effects. Recent research has shown that the gut microbiota can adapt rapidly following a change in diet, whether plant-based or animal-based, with noticeable changes appearing within three days [36]. This information suggests that even those with unhealthy eating habits can improve their microbiota through dietary changes, which is especially relevant for new COVID-19 patients in acute settings. A shift in gut microbiota composition occurs when transitioning from a plant-based diet to an animal-based one, with increased bile acid-metabolizing species. However, a plant-based diet effectively combats inflammation, as it is associated with reduced markers of chronic inflammation, such as CRP, IL-6, and Fibrinogen. These markers are significant concerning COVID-19 and its inflammatory effects [37]. Studies have also found that plant-based diets, such as Mediterranean, vegetarian, and vegan, can effectively decrease TMAO levels, while animal-based diets have the opposite effect. Interestingly, individuals who primarily follow a plant-based diet do not experience an increase in TMAO levels when they occasionally consume animal-based foods [38]. This is postulated due to the microbiota environment established over time.

Many experts suggest that the current COVID-19 pandemic presents a rare chance to assess how nutritional interventions may help fight infectious diseases. With this in mind, conducting tests during the pandemic can yield valuable information [39]. Our studies have revealed a significant link between consuming a diet that includes fresh, nutrient-rich foods like fruits, vegetables, legumes, whole grains, and healthy fats (such as seeds, avocado, and a moderate amount of oily fish) and limiting one's intake of sugary products, high-calorie empty nutrients, and high-salt foods, leading to a decrease in COVID-19 severity and mortality.

2.3. The Role of Inflammation and Endothelial Dysfunction in COVID-19

The role of chronic inflammation in developing vascular lesions cannot be overstated. This process causes endothelial dysfunction, triggering several other processes that contribute to the worsening of atherosclerosis. These processes include platelet aggregation, leucocyte adhesion, cytokine production, and increased endothelial permeability [40]. Unfortunately, atherosclerosis is often associated with acute coronary events, and COVID-19 can exacerbate this situation by inducing a severe inflammatory state that may trigger similar events. It's important to note that coronary artery disease resulting from atherosclerosis, as well as heart failure, hypertension, and atrial fibrillation, are all considered comorbidities for COVID-19, as they are also caused by chronic inflammation [41]. Patients with heart conditions who contract COVID-19 are at an increased risk of developing acute coronary syndrome, acute heart failure, and arrhythmia, which can lead to higher mortality rates.

Eating unhealthy foods such as sugary drinks, processed meats, saturated fat, trans-fat, cholesterol, snacks, cakes, pastries, sweets, high-fat dairy products, added salt and sugar, red meats, poultry, and eggs can contribute to chronic inflammation [42]. COVID-19 is classified as an acute inflammatory disease, and it can increase inflammatory markers such as LDH, ferritin, procalcitonin,

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D-Dimer, and acute phase response proteins. This virus can also trigger a cytokine storm, a severe inflammatory reaction that can be fatal [43]. Patients with chronic inflammation, regardless of comorbidities, are at risk for severe inflammation from COVID-19. In that case, their body will have to work extra hard to combat the inflammation and its complications. As a result, their chances of experiencing a cytokine storm and facing a higher mortality risk are understandably higher [44,45]. Conversely, eating foods with an excellent dietary inflammatory index (DII) is recommended to combat the inflammatory response in our COVID-19 patients, as outlined in Table 1

Table 1. Inflammatory and anti-inflammatory foods list.

Foods with poor DII	Foods with excellent DII
Red meat (steak and hamburgers) Animal products (fish, poultries, eggs, dairy products; milk, cheese, and butter) Processed meat (bologna, bacon, sausage and lunchmeat) Commercial baked goods (snack cakes, pies, cookies and brownies) White flour (bread and pasta), white rice Deep-fried items (French fries, fried chicken, and donuts) Sugary foods (soda, canned tea drinks, and sports drinks) Trans-fats (margarine, microwave popcorn, refrigerated biscuits, dough, and nondairy coffee creamers) Saturated fats (especially animal fats) Cholesterol (red meats, processed meats, eggs, fried foods and dairy products)	Plant-based proteins (beans, lentils, chickpeas, edamame, hemp seeds, tofu, tempeh, and nuts) Whole grains (oatmeal, buckwheat, quinoa, brown rice) Starchy vegetables (sweet potatoes and squash) Seeds (flaxseeds and chia seeds) Green leafy vegetables (bok choy, collard greens, kale, mustard greens, romaine lettuce, spinach, and arugula) Colorful vegetables (carrots, pumpkin, yellow/ green peppers and cauliflower) Fruits (berries, apples, grapes, oranges, peaches, figs, bananas, and kiwi) Spices and herbs (turmeric, ginger, cumin, peppermint, cinnamon, chili, parsley, bay leaf, and basil)

Fruits and vegetables are rich in polyphenols, which can inhibit the binding of SARS-CoV-2 spike protein to the ACE2 receptor, preventing viral entry into host cells and inhibiting viral RNA replication and protein processing [46]. Consuming red meat, refined sugar, saturated and trans fats, and high cholesterol, all of which promote inflammation, can make it easier for the COVID-19 virus to bind to host cells [47].

Adopting a healthy lifestyle for an extended period can significantly improve chronic disease conditions. Therefore, an individual with multiple comorbidities who embraces a healthy diet and lifestyle may observe a normalization of most chronic inflammatory markers, which can decrease the risk of chronic disease as a COVID-19 risk factor. Is plant-based intervention a viable option for individuals with chronic comorbidities who have contracted COVID-19 in the acute setting? While research has indicated that plant-based intervention can effectively reduce acute arthritic pain [48,49], our experience with COVID-19 patients has also demonstrated its efficacy. Even though inflammatory markers may not improve, patients reported symptom relief. Our study also supports this hypothesis.

2.4. Oxidative Stress Plays a Crucial Role in COVID-19 Infection

The coronavirus causes an imbalance in the body by increasing the production of reactive oxygen species (ROS) while reducing the body's ability to fight them off with antioxidants. This leads

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to an increase in redox stress, which in turn decreases the body's ability to fight off the virus and increases inflammation and cell damage. Ultimately, this can damage tissues and organs in the body. A diagram illustrating this process can be found in Figure 5.

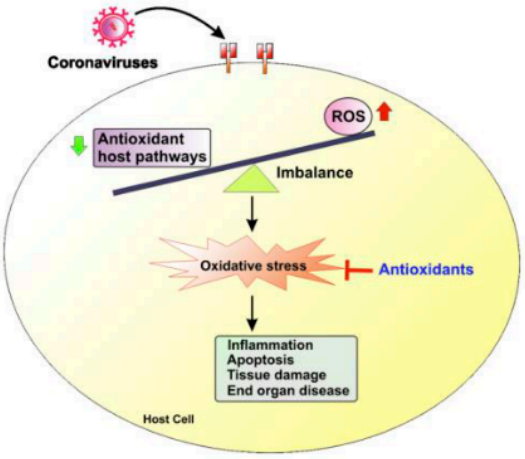

Figure 5. Redox imbalance in coronavirus infections. Coronavirus infection triggers an imbalance between Increased production of reactive oxygen species (ROS) and reduced antioxidant host responses that lead to increase redox stress in the host cell. Increased redox stress induces inflammation, apoptosis, tissue damage, and end-organ disease [50] (Picture copied from Gain C, Song S, Angtuaco T, et al. The role of oxidative stress in the pathogenesis of infections with coronavirus. Frontiers in Microbiology. 2023. DOI 10.3389/fmicb.2022.1111930)

Reactive oxygen species (ROS) are naturally occurring byproducts of metabolic processes in different organelles, including plasma and nuclear membranes, peroxisomes, endoplasmic reticulum (ER), and mitochondria. These ROS play a critical role in various cellular processes, such as energy production by mitochondria, host defense, cellular signaling, and gene expression regulation. Notably, mitochondria are the primary source of ROS (mito-ROS) during energy production. During viral infections, ROS levels can increase, and while they may have harmful effects on cells and tissues, they are also essential for antiviral immune function [50].

Too many reactive oxygen species (ROS) in the body can harm essential parts of cells like proteins, lipids, and DNA. ROS can also affect immune functions, cause inflammation, and damage organs and tissues. Multiple studies have found that oxidative stress plays a role in respiratory viral infections like influenza and RSV. In severe cases of COVID-19, increased oxidative stress can lead to inflammation, damage to endothelial cells, and blood clots, which can damage multiple organs. Moreover, SARS-CoV-2 can cause oxidative stress, interfering with inflammatory pathways and potentially cause long-term tissue harm [51,52].

Research suggests the elderly population is more susceptible to oxidative stress. There is a reciprocal link between chronic inflammation and reactive oxygen species (ROS), in which chronic inflammation leads to the buildup of ROS, and ROS also contributes to chronic inflammation [53]. Consequently, older individuals who have chronic inflammatory conditions or other medical conditions are at greater risk of experiencing severe illness in the event of contracting SARS-CoV-2 infections [54].

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Research has shown that consuming meat products, refined sugars, and fats can lead to an increase in reactive oxygen species levels, resulting in inflammation. However, studies indicate that incorporating a plant-based diet can potentially reduce oxidative stress and inflammation levels, which play a significant role in COVID-19 infection [55–58]. It may be prudent to explore dietary changes for COVID-19 patients as the current standard American diet or similar diets can increase oxidative stress and inflammation. Adopting a plant-based diet can not only help manage chronic inflammatory conditions but also enhance the likelihood of surviving the COVID-19 pandemic.

2.5. The Link between Mitochondria Health and COVID-19 Severity and Mortality

As we grow older, the powerhouses of our cells, known as mitochondria, undergo changes that cause a decline in their function. This decline is caused by the accumulation of mutations and oxidative damage induced by reactive oxygen species (ROS). As a result, the volume, integrity, and functionality of mitochondrial DNA (mtDNA) decrease. Moreover, the mitochondria of older adults are characterized by significant increases in ROS generation and diminished antioxidant defense, which lead to impaired function. This includes lowered oxidative capacity, reduced oxidative phosphorylation, and decreased ATP production. Additionally, mitochondrial biogenesis declines with age due to alterations in mitochondrial dynamics (fission and fusion) and inhibition of mitophagy, an autophagy process that removes dysfunctional mitochondria.

Acute and chronic inflammatory diseases are characterized by an excessive generation of reactive oxygen species (ROS), which cause damage to mitochondrial proteins, lipids, and mtDNA. This, in turn, negatively affects normal mitochondrial function and dynamics. When various mitochondrial products act as damage-associated molecular patterns (DAMPs) and are released into the cytosol or extracellular environment, they can cause inflammation. Protective measures are in place to prevent mitochondria from triggering harmful inflammatory responses, such as disposing of damaged mitochondria through autophagy. However, if these mechanisms are overwhelmed or not functioning correctly, inflammatory reactions instigated by mitochondria can become problematic and contribute to developing disorders associated with autoimmunity. Furthermore, inefficient inflammatory pathways can exacerbate infectious diseases and impede healing.

Atherosclerosis occurs due to the dysfunction of endothelial cells and the infiltration of lipids. Mitochondrial dysfunction can negatively impact various cells within the arterial wall, including macrophages, smooth muscle cells, lymphocytes, and endothelial cells, leading to heightened ROS levels. This can cause chronic inflammation, oxidative stress, and intracellular lipid deposition. Moreover, mitochondrial dysfunction is also a significant factor in other chronic inflammatory conditions, such as hypertension, obesity, and asthma [59,60].

As we learn more about COVID-19, it becomes increasingly clear that certain factors may contribute to its severity and mortality. These include age, age-related conditions, and underlying diseases such as CVD, obesity, hypertension, and metabolic syndrome (including type 2 diabetes). Interestingly, there may also be a potential role for mitochondria in disease development. The immune system is closely connected to mitochondria and its mtDAMPs, and recent research has focused on the possible involvement of mitochondria in SARS-CoV-2 infection. It has been suggested that the virus's hijacking of mitochondria could significantly affect COVID-19 pathogenesis [61], potentially leading to severe inflammation and damage to multiple organs. A new study in the journal Nature sheds light on why some people with COVID-19 develop these severe symptoms, revealing that the virus may be able to infect and cause fatalities in vital immune cells within the bloodstream and lungs. As we continue to investigate this virus, it will be crucial to explore whether mitochondrial dysfunction plays a role in destroying these immune cells [62].

Studies have proposed that people living in "blue zones" lead long and healthy lives by adhering to healthy habits such as exercising regularly, eating a balanced diet, mainly being plant-based, abstaining from harmful substances, managing stress effectively, having strong social support, and getting enough rest. These lifestyle choices contribute to maintaining healthy mitochondria. Mitochondrial function can be improved by consuming plant-based foods, specific natural products, caloric restriction, intermittent fasting, and exercise [63–65]. Our elderly patients have been living a

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Blue Zone lifestyle for many years, leading us to hypothesize that this has resulted in less severe symptoms and zero mortality due to their healthy mitochondria.

2.6. Potential Benefits of Telomere Manipulation in COVID-19 Treatment

According to the Centers for Disease Control and Prevention (CDC), age is the most significant factor in determining poor outcomes and severe illness in individuals with COVID-19. Data from the National Vital Statistics System (NVSS) at the CDC reveals that people aged 50-64 with COVID-19 are 25 times more likely to die than those under 30 years old. For individuals aged 65-74, the risk of death increases to 60 times, while for those over 85, it jumps to 340 times. This data includes all deaths in the United States from February 2020 to July 1, 2022, regardless of vaccination status [66,67].

Short telomeres have been associated with a higher risk of all-cause mortality and disease-specific mortality in the general population [68]. Studies suggest that COVID-19 severity in older individuals may be influenced by the same molecular pathways that cause aging. One of these pathways involves the gradual shortening of telomeres, which are protective structures at the ends of chromosomes. When telomeres become excessively short, they can hinder tissue regeneration and disrupt tissue homeostasis, leading to disease. Since the SARS-CoV-2 virus infects various cell types, it triggers cell turnover and regeneration to maintain homeostasis. Research has shown that people with shorter telomeres are at a higher risk of experiencing severe COVID-19 symptoms. Specifically, individuals with lower percentiles of telomere length and higher percentiles of short telomeres are at an increased risk of developing severe COVID-19 pathologies [69–71]. Both myeloid cells, which contribute to innate immunity, and lymphoid cells, which dominate adaptive immunity, play a crucial role in defending against SARS-CoV-2. When the virus enters the body, the production of myeloid cells is rapidly activated to resist the infection. However, the lymphoid cells responsible for producing T and B cells specifically designed to clear the virus are at risk of a shortfall. This is because T-cell production depends on the length of telomeres, which shorten with age. Thus, older people are at a higher risk of a T-cell shortfall when contracting SARS-CoV-2 than younger people. A poorly calibrated adaptive immune response, caused by a shortfall compounded by a T-cell deficit, might contribute to the severity of COVID-19 in people with inherently short T-cell telomeres. Additionally, the immune systems of these individuals might generate an inadequate T-cell response to anti-SARS-CoV-2 vaccination [73]. Furthermore, shortened telomeres can upregulate ACE2 (Angiotensin Converting Enzyme 2), which is the receptor for SARS-CoV-2. This means that telomere shortening in elderly individuals may increase their susceptibility to SARS-CoV-2 infection [74].

Chronic inflammation can cause shortening of telomeres and genes related to telomeres, and telomerase can also control the release of inflammatory cytokines. There is a two-way relationship between inflammation and telomere shortening. Inflammatory stimuli are several causes that can speed up telomere wear, and a pro-inflammatory state can lead to telomere dysfunction. Telomere attrition, in turn, can cause low-grade inflammation. [75].

Telomere shortening can be accelerated by oxidative stress and inflammation. However, consuming edible plants can be beneficial as they are rich in compounds with antioxidant and anti-inflammatory properties. These compounds can help counteract the process of telomere shortening. Observational studies have indicated that adopting a plant-rich diet, consuming seeds and their derivatives, and incorporating carotenoids into one's diet can promote telomere lengthening. This can lead to improved overall health and longevity. [76,77].

Elizabeth Blackburn, a Nobel Prize winner, discovered that switching to a vegan diet can cause changes in over 500 genes in just three months. This diet can activate genes that help prevent diseases and deactivate genes that cause chronic inflammatory diseases [78].

There are various ways to strengthen our telomeres, including exercising regularly, avoiding smoking, and consuming a diet rich in plant-based foods that protect telomeres. Dean Ornish and Elizabeth Blackburn conducted a study demonstrating how a plant-based diet can increase telomerase activity, the enzyme responsible for maintaining long telomeres. The ability to lengthen telomeres is crucial for longevity. While we cannot reverse chronological age, we can reverse biological age, which can help us reverse chronic illnesses in our patients. Additionally, if we can

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make our patients' biological age younger by one or two decades, their risk of developing severe COVID-19 will automatically decrease. We hypothesized that our elderly COVID-19 patients in the study had milder symptoms and no mortality linked to their telomere superiority.

2.7. Caloric Restriction Is Emerging as an Essential Factor in the Fight against Inflammation

Reducing caloric intake, commonly known as Caloric Restriction or CR, has been shown to have consistent anti-aging effects across various organisms. This practice has also been found to protect against age-related diseases, including chronic inflammatory disorders such as cardiovascular disease, diabetes, hypertension, hypercholesterolemia, and cancer. Calorie restriction can improve the body's balance by reducing oxidative stress and inflammation while boosting the production and activity of antioxidant enzymes and anti-inflammatory mediators. Studies have also revealed that CR can improve overall health and well-being, optimize energy metabolism, enhance cellular protection, improve insulin sensitivity and glucose regulation, induce functional changes in the neuroendocrine systems, reduce oxidative damage and inflammation, and even shape the gut microbiota [79].

The Mammalian Target of Rapamycin (mTOR) is a signaling system used by some viruses, including coronaviruses and other RNA and DNA viruses, to replicate and persist in host cells. Caloric restriction (CR) has been found to inhibit the mTOR pathway similar to the effect of Rapamycin in some animal models. This is significant because mTOR inhibition and promotion of autophagy can potentially be the link between the direct benefits of CR in COVID-19. CR could help fight the virus by interrupting the viral cycle (protein synthesis) [80].

Unhealthy habits like consuming excessive calories and leading a sedentary lifestyle are significant determinants of health issues and inflammatory diseases in our modern society. Both the quality of food consumed and overconsumption of food can pose problems. Understandably, COVID-19 patients who consume excessive calories and poor nutrients will find it challenging to fight inflammation, especially if their bodies are already inflamed [81]. We hypothesized that the whole food plant-based diet with an emphasis on caloric restriction may have contributed to the mild illness and zero mortality observed in our COVID-19 patients in our studies.

3. Supplements Their Significant Role in Managing COVID-19

3.1. Vitamin C

Extensive research on the anti-infective properties of vitamin C and its proven safety has led many experts to propose its potential as a treatment for COVID-19. Studies have shown that vitamin C can reduce the severity and duration of colds [82]. Numerous studies have suggested the potential benefits of vitamin C in supporting cellular health and defense against SARS-CoV-2 infection. This is believed to be due to the anti-inflammatory and anti-oxidative stress properties of vitamin C [83]. In severe COVID-19 cases, cytokine storms are observed, and a high dose of vitamin C may help fight oxidative stress, as seen in sepsis. In a study of ICU patients, a high dose of intravenous vitamin C shortened the time patients spent in the high-level care setting. Combined with corticosteroids and thiamin, it reduces mortality [84].

Vitamin C has been shown to have positive effects in treating patients who require mechanical ventilation due to acute inflammatory lung injury caused by oxidative stress. Compelling evidence suggests that high-dose intravenous vitamin C can effectively treat COVID-19 patients in China. Those who received intravenous bolus vitamin C experienced improved oxygenation, and all treated patients were ultimately discharged home [82].

Based on a recent meta-analysis of randomized controlled trials, vitamin C may provide a survival benefit for patients with severe COVID-19 [85,86]. However, larger-scale randomized trials must confirm its effectiveness in reducing mortality rates before recommending it in treatment guidelines.

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3.2. Vitamin D

T regulatory lymphocytes (Tregs) are essential in fighting against uncontrolled inflammation and viral infections. However, many COVID-19 patients have low Tregs levels. One way to increase Tregs levels is through vitamin D supplementation. Low vitamin D levels have been linked to increased inflammatory cytokines, significantly increasing the risk of pneumonia and upper respiratory tract viral infections. Additionally, there is an association between vitamin D deficiency and an increased likelihood of thrombotic episodes, commonly observed in COVID-19 patients [87–90]. During the COVID-19 pandemic, it was observed that many patients who developed severe disease or died were deficient in vitamin D [91,92].

A recent meta-analysis has suggested that vitamin D supplementation could positively impact the severity of SARS-CoV-2 illness, especially in patients with vitamin D deficiency [93].

3.3. Vitamin B_3, Precursor of NAD^+

There are three primary types of B_3 vitamins namely nicotinamide riboside (NR), nicotinamide (NAM), and nicotinic acid (NA). These vitamins are not only helpful in preventing pellagra, but they may also promote healthy aging and help prevent some of the physiological changes that occur with age-associated diseases, particularly NR [94]. It has been suggested that increasing NAD^+ levels might enhance the body's ability to fight off viruses and reduce inflammation. NR, NAM, and NA play essential roles as precursors of NAD^+ and contribute to the generation of NAD^+ through different metabolic pathways.

Recent studies indicate that these B_3 vitamins do not support healthy NAD^+ levels equally. The easiest way to increase NAD^+ concentrations is to provide additional precursors that can be converted into NAD^+. NMN, derived from NAM, is the molecule most structurally similar to NAD^+. It requires only one enzymatic step to be converted into NAD^+ and is currently the most effective method to raise NAD^+ levels [95,96]. Research on NAD^+ in vascular aging and disease, including hypertension, atherosclerosis, and coronary artery disease, has been promising. NAD^+ has been shown to reduce chronic inflammation, reactivate autophagy, and assist mitochondrial biogenesis. These findings suggest that supplementing with precursor NAD+ may be a useful therapeutic approach for treating these conditions [97], as we have done for our elderly patients long before the pandemic. Further research is required before recommending the use of precursor NAD+ to reduce the severity and mortality of COVID-19 patients.

3.4. Zinc

A recent randomized double-blind controlled trial found that oral zinc (Zn) supplementation can reduce the 30-day death rate and ICU admission rate and shorten the duration of symptoms [98]. Zinc is a trace element crucial in stimulating innate and acquired immunity. A recent meta-analysis has found that zinc supplementation is linked with reduced COVID-19 in-hospital mortality. Due to the scientific evidence and zinc's role in the human body, it should be considered an adjunct therapy for COVID-19 patients [99].

3.5. Copper

Both copper (Cu) and zinc play a crucial role in the production of an essential antioxidant enzyme known as superoxide dismutase (SOD). This enzyme aids in combating free radicals and decreasing oxidative stress. Maintaining the appropriate ratio between the two is essential to ensure the optimal functioning of this enzyme. It is important to know that zinc can lead to copper deficiency. Therefore, seeking guidance from a qualified healthcare professional is crucial to prevent adverse effects [100]. Cu plays a critical role in the functions of essential immune cells such as T helper cells, B cells, neutrophils, natural killer (NK) cells, and macrophages. These blood cells kill infectious microbes, produce specific antibodies against pathogens, and mediate cell-mediated immunity. In humans with Cu deficiency, there is an increased susceptibility to infections due to these blood cells' decreased number and function.

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Additionally, Cu can kill viral infections, including bronchitis, poliovirus, human immunodeficiency virus type 1 (HIV-1), and other enveloped or non-enveloped, single- or double-stranded DNA and RNA viruses. Moreover, Cu has a potent contact-killing capacity against several viruses, including SARS-CoV-2 [101].

3.6. Selenium

Several studies have suggested that lacking selenium may negatively affect viral disorders. Regarding COVID-19, research has yielded mixed results regarding the correlation between selenium deficiency and disease severity [102]. However, it has been reported that a shortage of selenium is linked to a higher risk of chronic diseases with inflammatory pathogenesis [103]. In viral disorders, supplementing with selenium has shown promising outcomes [104]. This could be due to selenium's anti-inflammatory, immune-boosting, and antithrombotic effects [105].

3.7. Coenzyme Q_{10} (CoQ10)

CoQ10 benefits cardiovascular health as it can help reduce total cholesterol, improve endothelial function, and fight inflammation and oxidative stress. This also makes it a suitable option for treating COVID-19 [106–110]. A recent meta-analysis found that CoQ10 supplements taken for 10 weeks or less at doses above 200 mg/day may lower malondialdehyde (MDA), TNF-α, and IL-6 levels. These are all involved in COVID-19 inflammation [111].

During the resurgence of the COVID-19 pandemic in China in 2023, there has been a growing demand for Ubiquinol - the active form of CoQ10. Supplementing with Ubiquinol has been found to significantly increase the concentration of CoQ10 in blood platelets, whole blood, and plasma, accelerating the regeneration of mitochondrial function. Recent research has shown that patients who have recovered from COVID-19 have reduced levels of platelet mitochondrial function and endogenous CoQ10. Mitochondria are the energy powerhouses of our cells and are vital for cellular metabolism and immune responses. Further research has suggested that mitochondria may play a role in antiviral defense [112]. We used CoQ10 on our cardiology patients, which we believe may also benefit from COVID-19 infection.

3.8. Astaxanthin

Twelve controlled trials involving 380 participants have shown that astaxanthin significantly reduces oxidative stress biomarkers, such as blood MDA levels. This effect is particularly notable in patients with type 2 diabetes mellitus, where astaxanthin has been found to improve superoxide dismutase activity and reduce serum isoprostane, especially in those who are overweight [113].

Natural astaxanthin can potentially alleviate cytokine release syndrome by regulating inflammatory cytokines. It achieves this by inhibiting the activities of key players such as NF-kB, NLRP3, and JAK/STAT-3 while regulating the expression of pro-inflammatory factors such as TNF-α, IL-1ß, IL-6, and IL-8. Additionally, natural astaxanthin has been shown to prevent oxidative damage. Given these benefits, it is reasonable to consider natural astaxanthin a potential therapeutic agent against inflammatory cytokine storm [114,115].

3.9. Quercetin

A recent systematic review and meta-analysis has indicated that quercetin may reduce the likelihood of admission to an intensive care unit, lower hospitalization rates, and potentially even decrease mortality in COVID-19 patients [116,117]. Quercetin is a commonly known antioxidant that has been found to possess anti-inflammatory and antiviral properties. According to studies, quercetin has been found to interfere with 85% of SARS-CoV-2 viral proteins in human cells [118]. A recent study highlighted quercetin's ability to block the SARS-CoV-2 viral S-protein receptor ACE2, thereby interfering with viral replication [119]. Proteases are enzymes that play a crucial role in virus replication.

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The flavonoid quercetin, found in plants, has been found to block the active site of 6LU7, the major protease in SARS-CoV-2, inhibiting virus replication [120,121]. Quercetin exhibits potent iron-chelating properties, in addition to its anti-inflammatory and antioxidant effects. Due to these properties, it can be a valuable therapeutic option for treating COVID-19 [122].

3.10. Curcumin

Curcumin is a natural polyphenolic compound with various benefits, such as antiviral, anti-inflammatory [123], anticoagulant, antiplatelet, and cytoprotective properties. It has been proven to help reduce the progression of several inflammatory diseases [124,125]. The mentioned effects have made curcumin a potential treatment option for COVID-19 patients. The pathophysiology of COVID-19 involves life-threatening inflammatory reactions, cytokine storms, and coagulopathy. Curcumin can be advantageous due to its anti-inflammatory effects by inhibiting inflammasome formation. Curcumin has been found to have antiviral effects by binding to the primary protease (Mpro) enzyme of SARS-CoV-2, which is necessary for viral replication. Additionally, curcumin can effectively block viral attachment and entry into host cells [126]. The spike protein and ACE2 receptor are both inhibited by curcumin in preventing virus-receptor interaction, according to modeling studies [127]. In a randomized trial, it was suggested that curcumin could speed up the recovery of acute inflammatory immune response [128].

The mRNA expression of interleukin-1ß and interleukin-6 was significantly reduced in COVID-19 patients after receiving nano-curcumin [129]. Moreover, further trials showed a significant reduction in the number of Th17 cells, gene expression, and serum levels of Th17-mediated cytokines upon administering nano-curcumin [130]. Recent systematic reviews and meta-analyses of randomized trials concluded that oral administration of curcumin as adjuvant therapy in COVID-19 patients could significantly reduce their mortality risk [131,132].

3.11. Taurine

Various studies suggest taurine can act as an antiviral, antioxidant, and anti-inflammatory substance. It can also help regulate vascular function. Taurine's potential effects are wide-ranging, from stopping viral invasion through the AT1R-mediated SARS-CoV-2/ACE2 endocytosis pathway to reducing inflammation and vascular injury by affecting both inflammatory and coagulation pathways. Like other infections, COVID-19 decreases taurine levels, which limits its protective properties under normal circumstances. It is hypothesized that early taurine administration during COVID-19 onset can halt cytokine storms, reducing morbidity and mortality. Overall, taurine seems to be a promising supplementary therapeutic option in COVID-19 [133,134], although clinical trials are necessary to confirm its effectiveness against this disease.

4. Conclusions

The use of plant-based diets has been associated with a reduction in COVID-19 incidence, severity, and mortality rates over time, as demonstrated by various studies [135–142]. Experts in the field, including Rayman M, Stewart G, Mellor D, and McCoway K, strongly reacted to a recent study published in BMJ Nutrition, Prevention & Health by Acosta-Navarro et al. [135] in early 2024. The study focused on the relationship between different types of diets and COVID-19 infection. The experts specifically highlighted the deficiency of essential nutrients, such as vitamins B12 and D, as well as minerals like iodine, iron, zinc, selenium, and calcium, in plant-based interventions. The experts also drew attention to the ambiguous definition of plant-based diets in the study, which included factors such as the quality, quantity, and food preparation methods, as well as the loose definition of plant-based diets encompassing ovo- and pesco-vegetarians. Since this study was purely observational in nature, further research with a clear definition of plant-based diets and appropriate supplementation may provide valuable insights and shed additional light on the subject, as per the expert commentary. In the context of our study, we have given considerable importance to the expert opinions regarding the inclusion of micronutrient supplements, including vitamin C, vitamin D,

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vitamin B3/NAD+, zinc, copper, selenium, and natural anti-inflammatory products such as astaxanthin, curcumin, quercetin, as well as CoQ10, taurine and multivitamins in COVID-19 management. To the best of our knowledge, as of the writing of this paper, no previous plant-based studies on COVID-19 have included the use of supplements. Our research led us to propose the hypothesis that dietary supplements could bolster the anti-inflammatory, immune regulatory, and anti-viral characteristics of a plant-based diet. However, it was only in recent years, following the outbreak of the COVID-19 pandemic, that experts have highlighted the importance of using supplements in managing the virus [82–134]. One key distinction between our research and others is that we accounted for variations in food quality, quantity, and preparation methods. Additionally, we closely monitored our participants' dietary intake throughout their illness. These factors that distinguish our study from others in the field are of paramount importance. It is crucial to evaluate the disparities between our research outcomes and those of other studies [135–142] when considering these elements, particularly the lack of disease progression, hospitalization, and mortality among our participants. Our study stands out due to these unique characteristics, which merit special attention.

Our research and theories have not only saved the lives of COVID-19 patients but have also improved and reversed their chronic diseases, thereby enhancing their quality of life and extending their lifespan. Furthermore, our findings may offer protection against future pandemics, as the World Health Organization (WHO) has predicted.

Reviewing the historical record from the start of the 20th century, it is evident that a diet emphasizing plant-based foods and adopting a healthier lifestyle has safeguarded numerous individuals from various pandemics [143,144]. Furthermore, our extensive knowledge of supplementation will enrich our understanding of how to combat COVID-19 and may also motivate us to prepare for future pandemics.

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