Journal of Medicinal Chemistry

pubs.acs.org/jmc

Perspective

Antioxidant, Anti-inflammatory, and Immunomodulatory Roles of Nonvitamin Antioxidants in Anti-SARS-CoV-2 Therapy

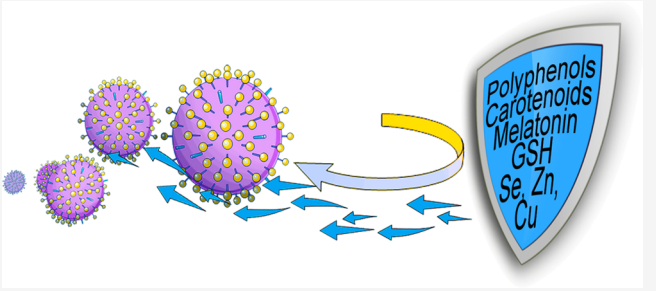
Aurelia Magdalena Pisoschi,* Florin Iordache, Loredana Stanca, Iuliana Gajaila, Oana Margarita Ghimpeteanu, Ovidiu Ionut Geicu, Liviu Bilteanu, and Andreea Iren Serban

Cite This: https://doi.org/10.1021/acs.jmedchem.2c01134

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Viral pathologies encompass activation of pro-oxidative pathways and inflammatory burst. Alleviating over-production of reactive oxygen species and cytokine storm in COVID-19 is essential to counteract the immunogenic damage in endothelium and alveolar membranes. Antioxidants alleviate oxidative stress, cytokine storm, hyperinflammation, and diminish the risk of organ failure. Direct antiviral roles imply: impact on viral spike protein, interference with the ACE2 receptor, inhibition of dipeptidyl peptidase 4, transmembrane protease serine 2 or furin, and impact on of helicase, papain-like protease, 3-chyomotrypsin like protease, and RNA-dependent RNA polymerase. Prooxidative environment favors conformational changes in the receptor binding domain, promoting the affinity of the spike protein for the host receptor. Viral pathologies imply a vicious cycle, oxidative stress promoting inflammatory responses, and vice versa. The same was noticed with respect to the relationship antioxidant impairment-viral replication. Timing, dosage, pro-oxidative activities, mutual influences, and interference with other antioxidants should be carefully regarded. Deficiency is linked to illness severity.



INTRODUCTION: GENERAL ASPECTS

Increased oxidative stress, activation of pro-oxidative pathways, and inflammatory burst are often encountered in COVID-19 severity, mainly when this pathology is associated with chronic diseases encompassing lowered antioxidant defense. These aspects sustain the importance of antioxidant intervention in preventing and alleviating both oxidative stress and activation of inflammatory cytokines.[1−3]

SARS-CoV-2 is a positive-stranded RNA virus, and its genome encodes approximately 26 proteins responsibile for virus survival and multiplication in the host. This pathology involves lowering of the host immune response, oxidative stress, and increased inflammation denoted as cytokine storm, responsible for lung impairment, fibrosis, and pneumonia.[4]

The relationship between reactive oxygenated species and the immune response has been extensively documented. Under physiological conditions, mitochondrial reactive oxygen species (ROS) are responsible for the regulation of immune signaling pathways. Increased mitochondrial ROS generation takes place in plasmacytoid dendritic cells. Type I interferon generation in these cells synchronize antiviral immune response and is important for the clearance of several acute viral infections. The involvement of mitochondrial reactive oxygen species in the antiviral signaling pathways is due to receptors present in distinct cell compartments: endosomal toll-like receptors located in plasmacytoid dendritic cells mediate the onset of type I interferon production, while the late phase can be promoted by cytosolic retinoic acid-inducible gene I activation.[5] It is important to stress upon the dual function of mitochondrial ROS, to promote cell adaptation but also cell damage. Under conditions of antioxidant−oxidant imbalance and decrease of the cell's redox buffering capacity, the impairment in key biomolecules can lead to diabetes, cancer, neurodegeneration, and inflammatory response.[6,7]

In viral infections such as COVID-19, antioxidant intervention consists in blocking the reactive oxygen species that are produced by activated immune cells.[8] Particularly in respiratory viral infections, the inhibition of NRF2 (nuclear factor-erythroid factor 2-related factor 2)-mediated pathways, and the triggering of NF-κB signaling are sources of both oxidative damage and inflammatory response.[9−11]

The cytokine storm is a severe immune condition implying swift proliferation and overactivation of T cells, natural killer cells, macrophages, and enhanced production of inflammatory cytokines and chemical mediators by immune cells.[12−14]

Received: July 14, 2022

SARS-CoV-2 pathology is associated with high plasma levels of TNF-α, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-gamma induced protein 10 (IP-10), monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha and interferon alpha.[15−17] Higher levels of IL-1, IL-6, IL-12, IFN-γ, TGF-β, and chemokines (CCL2, CXCL10, CXCL9, and IL-8) were noticed in severe pathology compared to uncomplicated disease.[17,18] Such hyperactivation of pro-inflammatory factors results in epithelial and endothelial cell apoptosis in lungs, which impairs the microvascular and alveolar epithelial cell barrier, leading to vascular permeability, alveolar edema, and hypoxia. Reactive oxygen species, pro-inflammatory cytokines (IL-6, IL-8, IL-1β, granulocyte macrophage-colony stimulating factor), and chemokines (CCL2, CCL-5, IP-10, and CCL3) are responsible for lung fibrosis, severe acute respiratory syndrome, potentially associated with fatality risk.[14,19]

The cytokine release syndrome is associated with the occurrence of clinical symptoms. Chills, fever, and fatigue are caused by IFN-γ; flu-like symptoms (as previously described) are caused by TNF-α, to which vascular permeability, cardiomyopathy, pulmonar injury, and acute-phase protein synthesis can also be associated.[20] IL-6 also leads to vascular permeability, coagulation pathways activation, and diffuse intravascular coagulation. It is a promoter of myocardial dysfunction, resulting in cardiomyopathy, being associated with particular severe symptoms of cytokine release syndrome.[14,21−23] The activation of other critical components of the inborn immune system, linked to the oxidative burst, has been associated with illness severity and organ dysfuynction. The presence of reactive oxygenated species in the cytosol promotes the activation of the NLRP3 inflammasome.[24] The latter is part of a complex that also includes caspase-1 and the bipartite adaptor protein (apoptosis-associated speck-like protein) that incorporates a caspase-recruitment domain.[25] The NLRP3 inflammasome is the source of caspase-1 activation and IL-1β release in inflammatory processes. The increase in IL-1β induces increased levels of IL-6 and TNF-α in activated macrophages. The outcome is neutrophil boost in the lung (fibrosis) and cytokine storm in elderly patients.[11,26] So, hampering cytokine storm in COVID-19 essential to counteract the immunogenic impairment in endothelium and alveolar membranes.[8]

As it will be detailed in the sections of this review, viral pathologies imply a vicious cycle-like mechanism, oxidative stress promoting inflammatory responses by activating transcription factors linked to inflammation. On the other hand, cytokine storm itself triggers oxidative stress via inflammatory mediators.[8] In COVID-19, the increased antioxidant utilization to couteract free radical damage results in decreased antioxidant profile. The plasma levels of vitamins C, A, and E, as well as the activities of glutathione, glutathione peroxidase, superoxide dismutase, and catalase were much lower in COVID-19 patients when compared to controls. The same trend was noticed in the case of minerals like selenium, zinc, magnesium, and copper, while for chromium, no significant difference has been observed. With respect to oxidative stress markers, 8-isoprostaglandin F2 alpha was significantly more elevated, while malondialdehyde level was smaller in COVID-19 subjects when compared to controls. Other comorbidities such as hypertension, diabetes, or malaria result in an increased risk of exposure to oxidative stress.[17] The role and intervention of natural compounds, including those present in nutraceuticals, in COVID-19, encompass antioxidant, anti-inflammatory, immunomodulatory, and antiviral potential.

As the general mechanisms of action of antioxidative compounds has been largely described in previous reviews, as well as of the role of vitamins in COVID-19, we will focus on the role of nonvitamin antioxidants in couteracting oxidative stress and inflammation in this viral infection.[27−29] Alongside diminution of oxidative stress and associated inflammation, antioxidants can impact pathways that are crucial for virus survival and replication. Mechanisms of action will be reviewed in each particular case: impact on viral spike protein affecting binding to receptor and membrane fusion, direct interference with the activity of the angiotensin-converting enzyme II (ACE2) receptor that the virus uses to entry the host cell, inhibition of DPP-4 (dipeptidyl peptidase 4, that was identified as coreceptor for viral entry), TMPRSS2 (transmembrane protease serine 2) or furin that also enable virus access in the host cell by promoting spike protein cleavage, inhibition of helicase, impact on PLpro (papain-like protease), 3CLpro (3-chyomotrypsin like protease), or RdRp (RNA-dependent RNA polymerase) that promote viral replication.

GLUTATHIONE AND ITS PRECURSORS

Glutathione. Glutathione is an antioxidant tripeptide constituted of glutamic acid, cysteine, and glycine (Figure 1).

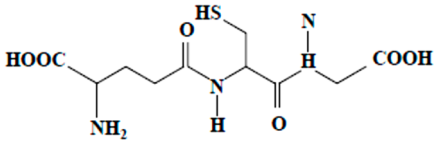


Figure 1. Glutathione, key contributor to the endogenous antioxidant profile.

It is part of the endogenous defense against ROS. Glutathione can be found in both reduced (thiol, GSH) and oxidized (disulfide, GSSG) state. In healthy cells and tissues, an amount greater than 90% of the total glutathione level is present in its reduced form, the rest being found in the oxidized form. An increased disulfide/thiol ratio points toward oxidative stress occurrence. Through the global cell redox homeostasis, noxious reactive oxygenated or nitrogenated species and oxidized glutathione are maintained at small levels, whereas reduced glutathione is kept at a high level.[30]

In the glutathione redox cycle, regeneration of glutathione (thiol form) from its oxidized form (disulfide) is catalyzed by glutathione reductase. This redox process takes place with the contribution of NADPH, generated from glucose oxidation in the pentose phosphate pathway.[31] Glutathione can preserve exogenous antioxidants to their reduced state: it can replenish the vitamin C profile by regenerating ascorbic acid from ascorbyl radical or dehydroascorbate.[32,33] Also, vitamin E can be regenerated from the corresponding chromanoyl radical by glutathione intervention.[32,33] It has been reported that the glutathione−ascorbate redox cycle is a contributor to the cells' detoxification from hydrogen peroxide.[34]

The anti-inflammatory and immunomodulatory roles of glutathione represent a focus of research: it has been reported that high intracellular glutathione levels lower pro-inflammatory cytokine (IL-1, IL-17, TGF-β) generation and trigger the

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

expression of enzymes responsible for glutathione synthesis in vitro. The level of the pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 was lowered when the whole blood cultures were treated with *N*-acetylcysteine, a glutathione precursor.[30] The confirmed antioxidant abilities are complemented by the anti-inflammatory and immunomodulatory potential: lowering the level of reactive oxygenated species generation by glutathione is linked to the inhibitory effect on NF-kB activation, leading to limitation of the cytokine storm.[31]

The relationship between glutathione and other key biocompounds has been investigated. Glutamate-cysteine ligase activation by vitamin D and subsequent increase in reduced glutathione amount, diminution of oxidative stress, and proinflammatory cytokines level are other factors preventing cytokine storm.[35−38] Diminished levels of glutathione, defective vitamin D responsive genes, and vitamin D inadequacy have been noticed in obesity and diabetes, intensifying COVID severity.[39−41] Improved glutathione status in a vitamin D deficient mouse model, after cosupplementation with vitamin D and L-cysteine (as glutathione precursor), was linked to a much greater increase in circulating 25(OH)D amount, as well as with a lowering of the oxidative stress, TNF-α and insulin resistance levels, compared with supplementation with vitamin D only.[39] Vitamin D and L-cysteine, in cosupplementation, improved the levels of glutathione and vitamin D regulatory genes at the cellular and tissue level, reducing inflammation biomarkers in the blood, compared with vitamin D only, as reported in animal studies.[38]

A novel experimental study proved that glutathione deficiency and the accompanying increased oxidative stress epigenetically modifies vitamin D regulatory genes.[42] This suppressed gene expression correlated to glutathione deficiency impairs vitamin D biosynthesis, finally resulting in secondary vitamin D deficiency. Restoring glutathione levels by L-cysteine administration can positively alter the level of methyltransferases and increase the expression of genes linked to vitamin D metabolism. The role of glutathione in the control of endogenous vitamin D level is important, and its presence in treatment can attenuate vitamin D deficiency. So, it was suggested that glutathione deficiency represents a major cause underlying impaired vitamin D biosynthesis and can be responsible for illness severity and death in COVID-19 patients.[43]

The relationship between vitamin D and glutathione has received much attention in anti-SARS-CoV-2 therapy; due to the relevance of their relationship, both deficiencies being interconnected and strongly impairing immunity.[38,39,43] Similarly to glutathione, vitamin D contributes to lowering oxidative stress by triggering antioxidant pathways and by inhibiting pro-oxidant pathways, and its deficiency is directly related to oxidative stress. Vitamin D is involved in maintaining the cellular redox status, triggers the expression of antioxidant enzymes and low molecular thiol antioxidants, and modulates both innate and adaptive immune responses.[44−46]

At physiological concentrations, vitamin D is involved in the modulation of ROS-scavenging enzymes responsible for preserving the redox homeostasis in the cellular environment, such as superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, and glucose 6-phosphate dehydrogenase.[46]

Besides triggering antioxidant signaling pathways, vitamin D also modulates the activity of Klotho, a regulator of phosphate homeostasis,[47] involved in the control of oxidative stress and endowed with antiaging properties.[48] Vitamin D is also an activator of nuclear factor-erythroid factor 2-related factor 2, a pivotal component in the control of oxidative stress;[49] it contributes to the induction of the expression of several antioxidant response elements and exploits antioxidant response element-related signaling pathways to achieve depletion of reactive oxygen species.[50,51] Vitamin D receptor binding to retinoid X receptor and to vitamin D response element leads to the activation of Nrf2,[48] a transcription factor also impacted by glutathione. Keap1 (Kelch-like ECH associated protein 1), an essential modulator of the Nrf2 transcription factor, is also activated by vitamin D.[46]

Vitamin D impact on the renin−angiotensin−aldosterone system was also investigated, as it is also essentially linked to both oxidative and cytokine bursts. The presence of vitamin D hampers the transcription of renin gene, impeding the accumulation of angiotensin II, an activator of NAD(P)H oxidase, involved in ROS accumulation.[52] Vitamin D is involved in inflammatory response pathways, acting as modulator of T and B cells, main components of the adaptive immune response.[53] Vitamin D upregulates Th2 and T regulatory lymphocytes but inhibits Th1 lymphocytes, modulating inhibitory and inflammatory cytokines.[54] Vitamin D can lower the production of cytokines responsible for enhanced inflammation-cytokine storm (IL-1, IL-2, IL-6, IFN-γ, and TNF-α) and can enhance the release of anti-inflammatory cytokines: IL-10, IL-4, IL-5, and TGF-β.[46,55]

Another key feature of vitamin D is its impact on thioredoxin, consisting in the ability to promote the expression of a thioredoxin inhibitor−thioredoxin interacting protein.[56] This results in a diminished ability of thioredoxin to promote angiogenesis, thereby curtailing the extent of SARS-CoV-2-induced pulmonary inflammation.[46]

Combined supplementation, vitamin D and L-cysteine, has the potential to correct not only vitamin D status but also to increase glutathione level and, subsequently, antioxidant capacity. So, boosting the intracellular glutathione redox status and 25(OH)D level may constitute a novel therapeutic alternative for overcoming impaired immunity and inflammation in COVID-19 subjects.[38]

By employing web-based predictive strategies that are relative to molecular interactions and focused on protease cleavage sites, it has been proved that the viral main protease targets glutamate−cysteine ligase involved in the rate-limiting step of glutathione synthesis, glutathione peroxidase (GPX1), and other selenoproteins like selenoprotein F (SELENOF) or thioredoxin reductase 1.[57] These observations showed consistency with the viral ability to interfere with DNA synthesis and to promote RNA synthesis via increase in the ribonucleotide profile by that enhancing multiplication. Moreover, these findings are confirmatory for the correlation between oxidative stress, associated inflammatory response, and the impairment in glutathione precursors and dietary selenium.[43,57] Endogenous glutathione impairment can enhance the oxidative damage of the lungs induced by SARS-CoV-2, leading to acute respiratory distress syndrome, organ failure, and even death. With respect to the antiviral activity of glutathione, individuals with low glutathione levels seem to present a greater susceptibility for uncontrolled replication of the virus and, therefore, increased viral load.[43] The worsening of clinical manifestations in COVID-19 patients was correlated to the negatively affected redox homeostasis, assigned to low level of reduced glutathione and high ROS generation.[43]

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

COVID-19 subjects with moderate to severe symptoms presented more elevated reactive oxygenated species levels and smaller glutathione levels than those with mild symptoms. Lowered glutathione in the alveolar fluid led to amplified lung cell injury by oxidative stress, enhanced inflammation, and acute respiratory distress syndrome, and it was asserted that this could be amended by *N*-acetylcysteine administration.[43] These reports suggest that the virus cannot effectively replicate at higher cellular glutathione amounts, so lower viral loads are noticed with milder clinical symptoms.[43] It was concluded that protection of host immune cells by glutathione is due to its antioxidant potential and immunomodulatory activity. The preventive activity is evidenced against both increased viral loads and liberation of inflammatory cells into the lung-cytokine storm.[43]

Various mechanisms underlying the immunomodulatory and antiviral action of glutathione have been advanced. In antigen presenting cells, decreased glutathione levels impair the discrimination of T cells into Th1 or Th2 phenotypes. Impaired levels of glutathione in antigen-presenting cells impede the ability of macrophages to process antigens and secrete IL-12, leading to a polarization of Th2 response. Conversely, increased glutathione levels (thiol form) favor the Th1 response. Tuning the intracellular GSH/GSSG balance enables modulation of the amounts of IL-12 secreted by macrophages. So, glutathione and its precursors can function as immunomodulators to boost the Th1-related immune response via IL-12 secretion. Moreover, such immunomodulatory compounds can directly impact the replication and survival of viruses and bacteria.[58]

The variations in the antioxidant activities of glutathione S-transferases, known for their ability to catalyze the reaction of the reduced glutathione with xenobiotic substrates, were linked to the susceptibility to develop clinical signs. Individuals presenting variant GSTP1-Val allele had lower chances, but those carrying variant GSTM3-CC genotype were more susceptible toward COVID-19. Moreover, combined GSTP1 (rs1138272 and rs1695) and GSTM3 genotype resulted in a risk concerning both COVID-19 occurrence and severity. Further investigations are nonetheless required to thorougly elucidate the implications of glutathione S-transferases in SARS-CoV-2 infection.[59]

So, glutathione impairment interferes with the capacity to sustain the immune responses. Conversely, adequate glutathione amounts can contribute to hampering virus multiplication, and the resulted lowered viral loads can lead to disease (symptom) alleviation. Adequate glutathione levels are required mainly in subjects with severe inflammatory response, to fight oxidative stress and prevent end-organ decay. This observation is consistent with the reported increased fatality in subjects with glutathione depletion.[60] The suboptimal cell's functioning promoted by glutathione deficiency contributes to disease progress.[61] Glutathione deficiency amplifies viral load, but also endogenous glutathione impairment has been identified as possible repercussion of progression of COVID-19 patients from mild to severe illness. Nevertheless, its short half-life and lack of permeability to many biological membranes make direct glutathione supplementation difficult.

***N*-Acetylcysteine.** The use of glutathione precursor *N*-acetylcysteine can improve its intracellular levels. Acetylcysteine (Figure 2) has mucolytic properties and acts as a thiol reducing agent, depleting the disulfide bonds (S−S) to thiol groups (−SH). It represents the supplement form of cysteine,

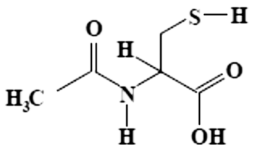


Figure 2. *N*-Acetylcysteine, another thiol-containing antioxidant.

the amino acid present in the structure of glutathione tripeptide, contributing to the improvement of the intracellular −SH content and, consequently antioxidant pool.[62]

A series of studies were directed toward the antioxidant, antiinflammatory, and immunomodulatory features of *N*-acetylcysteine, as a precursor of glutathione, endowed with the potential to replenish the antioxidant pool. It triggers protein and mRNA expression of manganese superoxide dismutase, but it does not exert the same effect on the mRNA expression of other antioxidative enzymes such as glutathione peroxidase 1, copper zinc superoxide dismutase, and extracellular superoxide dismutase.[63] *N*-Acetylcysteine administration can reverse glutathione deficiency induced by glucose 6-phosphate dehydrogenase impairment that facilitates coronavirus infection and predisposes to hemolysis upon coronavirus infection in cases of pro-oxidant therapy administration.[64] *N*-Acetylcysteine inhibits the pro-inflammatory pathways linked to oxidative stress, as well as mTOR (mammalian target of rapamycin)-dependent cytokine storm that results from the immune response overactivation.[64] *N*-Acetylcysteine diminishes IL-1β, IL-6, IL-8, IL-10, IL-17, and IBF-alpha in sepsis and alleviates cytokine storm that produces organ failure.[61] It inhibits the NF-κB activation mediated by oxidative stress, as well as the biochemical pathways upregulating pro-inflammatory genes.[65] IL-6, a cytokine impacted by *N*-acetylcysteine is mainly responsible for inflammation and mitochondrial oxidative stress at complex I of the electron transport chain. The resulted activation of mTORC1, one of the multiprotein complexes constituting mTOR, enhances inflammatory response.[64]

The benefits associated with glycine/*N*-acetylcysteine supplementation consist in restoring the antioxidant pool by correction of glutathione deficiency, resulting in lowered oxidative stress and inflammation and counteracting mitochondrial and endothelial dysfunction.[66] *N*-Acetylcysteine ability to lower oxidative stress markers and inflammatory factors such as TNF-α can lead to protective effect toward lung tissue.[63] At doses higher than 1.200 g, this thiol antioxidant hampers the generation of pro-inflammatory cytokines, such as IL-9 and TNF-α, and also exhibits vasodilating properties by raising cyclic guanosine monophosphate levels and favoring the regeneration of endothelial-derived relaxing factor.[62]

Anti-inflammatory and antioxidative actions were noticed in an ex vivo model of chronic obstructive pulmonary disease aggravation: *N*-acetylcysteine administration lowered pro-oxidative markers (malondialdehyde, hydrogen peroxide, peroxidase activity, nitric oxide) at doses higher than 1 μM, as well as the release of IL-1β, IL-8, and TNF-α, induced by lipopolysaccharide incubation, at doses higher than 300 μM.[67] The reduction of the intracellular hydrogen peroxide concentration, and the replenishment of the intracellular thiol profile by *N*-acetylcysteine were assigned to the inhibition of NF-κB translocation to the cell's nucleus and to the phosphorylation of p38 mitogen-activated protein kinase.[68]

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

It has been reported that spike protein binding to ACE2 results in lowered expression of the latter, producing angiotensin II accumulation.[65] Angiotensin II (a vasoconstrictor that increases blood pressure) enhances reactive oxygen species generation via activation of NADPH oxidase and peroxynitrite anion production. On the contrary, the angiotensin 1−7 peptide resulted from ACE2 activity and downregulates pro-oxidative pathways, alleviating the cellular impairment caused by oxidative stress.[31] The attachment of spike protein to ACE2 negatively impacts angiotensin II degradation and the occurrence of angiotensin 1−7 (a heptapeptide that functions as vasodilator), resulting in lung injury; angiotensin II type-1 receptor overactivation generates increased pulmonary vascularity, adding to illness severity.[69]

In the complex context of this viral pathology, the reductive abilities of *N*-acetylcysteine are beneficial, as the binding affinity of SARS-CoV/CoV-2 spike protein to the receptor proved much lower when the disulfide bonds of both ACE2 and SARS-CoV/CoV-2 spike protein are reduced to thiol groups by *N*-acetylcysteine contribution.[70] These reports proved consistency with the results of a molecular dynamics study predicting that *N*-acetylcysteine can reduce disulfide bonds on both spike protein and ACE2 receptor. This reduction of disulfides to sulfhydryl groups thoroughly hinders the binding of SARS-CoV/CoV-2 spike protein to ACE2 receptor via the receptor binding domain, confirming the importance of investigating the link between oxidative stress, reductive abilities, and molecular recognition in this viral infection.[71] Moreover, both animal and clinical studies reported that supplementation with *N*-acetylcysteine, alters the function of the renin/angiotensin system in vivo, activity mediated via inhibition of angiotensin-converting enzyme activity.[72] In COVID-19, *N*-acetylcysteine can hinder overproduction of angiotensin II as it hampers ACE2 binding by *S protein*, so angiotensin II can be converted to angiotensin 1−7. In the absence of the thiol antioxidant, angiotensin II can accumulate. By interfering with the angiotensin-converting enzyme, *N*-acetylcysteine can impart protective effect from the detrimental potential of angiotensin II, thus impacting an activity that supports SARS-CoV-2 infection. This leads to a decrease of lung impairment and illness severity.[69] Apart from impacting spike protein, *N*-acetylcysteine has the potential to interfere with SARS-CoV-2 E (envelope) protein structure and activity. *N*-Acetylcysteine hinders the ability of cysteine-containing motifs belonging to spike protein and E protein to interact through disulfide bridges, decreasing SARS-CoV-2 infective ability.[69,73]

As low molecular thiol antioxidants used in antiviral therapy like *N*-acetylcysteine target disulfide bridges in the structure of the receptor binding domain of both S protein and ACE2 host receptor, a key aspect worthy of investigation is the impact of reduction (antioxidant influence) on the affinity of the receptor binding domain of CoV-2 spike protein for the corresponding host receptor.[74] The relationship between oxidative stress and COVID-19 was investigated at the molecular level by performing a detailed analysis of the interactions established at the protein−protein binding interface. By applying molecular dynamics simulations for 200 ns, the interaction region characterizing the receptor binding domain−ACE2 complex was studied for various oxidized (−S−S− containing) and reduced (−SH containing) states of the receptor binding domain and ACE2. Under normal, nonpathological conditions, ACE2 is responsible for oxidative stress containment, mainly angiotensin-II-related oxidative stress. The binding of the viral spike protein interferes with the role of ACE2 in lowering oxidative stress. It gives rise to a vicious cycle, where oxidative stress enhances infectivity and vice versa.[74]

It was proved that already existing oxidative stress leads to the development of a docking-ready conformation in the viral spike protein, enabling enhanced binding affinity to human ACE2. The molecular docking-based investigations revealed that the bending motion at the protein−protein interface becomes highly altered when disulfide linkages are reduced to thiols, whereas in the native complex, the disulfide bonds maintain the structural complementarity between the protein and the associated compounds, leading to the preservation of the inner conformational dynamics.[74]

Also, it has been revealed that subsequent to receptor binding domain attachment, the disulfide-to-thiol conversion in its structure exerts only a restricted influence on the affinity of the spike protein for the host cell receptor. The formation of disulfide bonds, essentially occurring during oxidative stress, induces in the receptor binding domain a conformation prone to binding to the ACE2 receptor.[74] The minutious conformational analysis of the two proteins' interaction revealed that the concave surface of the viral spike protein binds to two long helix regions (corresponding to residues 19−53 and 55−84) of ACE2, which present a hinge-like behavior. The study of the interaction zones (viral receptor binding domain-bound ACE2), showed that the interactions involving the central ACE2 zone (being represented by a large α-helix comprising residues 19−53) proved the most robust, enabling preservation of the hinge motion noticed in the course of the simulated dynamics. As noticed by the collective motion analysis, the long helix behaves like an axle on which the concave surface of SARS-CoV-2 spike protein can dock.[74]

Nevertheless, if disulfide to thiol reduction takes place before spike protein binding to a host receptor, a significant conformational alteration occurs in the receptor binding domain of the spike protein that thoroughly impacts this binding. These significant conformational alterations mainly involve the binding motif: particularly the loop corresponding to residues 470−505 is subject to an important conformational change, leading to the loss of the concave surface, fundamental for receptor binding domain affinity for ACE2.[74]

It was proved that the interaction of the two proteins is mostly impaired when all of the seven disulfides linkages are reduced to thiols. Essentially, upon reduction of disulfide bridges to thiols, the Gibbs free energy associated with the binding is affected by the loss of the interactions present at the protein−protein interface.[74]

COVID-19 is associated with oxidative stress and endogenous antioxidant impairment. The imbalance between an enhanced reactive oxidative species generation and a deficient antioxidant profile linked to low reduced glutathione level is related to disease severity and longer hospitalization periods. This impairment impacts the capacity to detoxify the cellular environment, to fold proteins, to replenish the endogenous antioxidant pool, and to ensure an immune response and regulate apoptotic mechanisms. Nebulization with glutathione and *N*-acetylcysteine as adjunctive therapy could show benefits at the onset of the disease under conditions of accurate diagnosis. Nevertheless, more confirmatory studies are necessary.[61] Oral and intravenous glutathione, as well as precursors like *N*-acetylcysteine and alpha lipoic acid, constitute therapeutical alternatives to block

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

NF-kB, hamper cytokine storm, and alleviate respiratory symptoms in COVID-19 pneumonia.[75]

It has been reported that reduced glutathione amounts diminish in COVID-19, given an impaired translocation of Nrf2,[76,77] a factor involved in the preservation of glutathione level. It has been found that Nrf2 activation and NF-κB inhibition represent the result of ACE2 activation and are correlated to antioxidative response.[78] Glutathione precursors like lipoic acid and *N*-acetylcysteine represent phase II-inductors that by activation of Nrf2 trigger the expression of antioxidant enzymes, such as heme oxygenase-1 that antagonizes NADPH oxidase and contributes to the antioxidant pool by restoring intracellular bilirubin from biliverdin. Nutraceuticals containing lipoic acid, *N*-acetylcysteine, and other phase II-inductors like ferulic acid, berberine, melatonin, broccoli sprout powder, biotin at high-dose, taurine, and soy isoflavones, can downregulate TGF-β signaling and lower the risk, or alleviate severity, in pro-fibrotic pathologies.[79]

Alpha Lipoic Acid. Alpha lipoic acid contributes to maintaining endogenous elevated glutathione amounts (thiol form) when compared to the oxidized form. Alpha lipoic acid (Figure 3) has anti-inflammatory potential, lowering the proinflammatory cytokine release and exerting a protective effect against COVID-19 severity.[77]

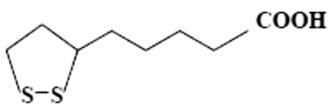


Figure 3. Alpha lipoic acid, an endogenous antioxidant presenting a dithiolane ring.

Alpha lipoic acid promotes the activity of the enzymes involved in reduced glutathione synthesis such as glutamate−cysteine ligase, and functions as a cofactor of mitochondrial antioxidant enzymes.[77,80] It was asserted that alpha lipoic acid is able to lower oxidative damage by functioning as a cofactor of mitochondrial α-ketoglutarate dehydrogenase, essential for maintaining redox status, being involved in the modulation of cytochrome *c* synthesis and cell death.[80] Alpha lipoic acid restores endothelial nitric oxide synthase activity by this promoting endothelial function. By sustaining mitochondrial function, it is involved in the cells' and tissues' homeostasis in critical conditions. The replenishment of reduced glutathione level via increase in cysteine uptake indirectly contributes to strengthening the immunity.[76,77,81]

Studies dealing with alpha lipoic acid supplementation in COVID-19 reported a diminished SOFA score and a 2-fold increased mortality in the control group by comparison to the lipoic acid supplementation group.[82] These influences can be ascribed to alpha lipoic acid's strong antioxidant features and immunomodulatory role, encompassing control on T cell activation and alleviation of cytokine storm.[83] With respect to the direct antiviral potential, it is thought that the virus access in the cell can be impaired by incorporation of alpha lipoic acid in therapy: as the affinity of the virus for the ACE2 receptor is enhanced by the oxidation of the cysteine moieties present in the receptor binding domain of S protein and in the peptidase domain of ACE2, the disruptions in the redox homeostasis can favor the infective ability of the virus. So, as in the case of *N*-acetylcysteine, the reductive potential brought by alpha lipoic acid can be exploited to hamper virus access in the cell.[77,84]

Like glutathione, alpha lipoic acid exerts antiviral potential by lowering NF-kB activation and oxidative damage. Alpha lipoic acid controls overexpression of ADAM17 that induces oxidative stress. Moreover, this metalloprotease leads to ACE2 shedding, the proteolytic ACE2 dissociation that leads to the loss of membrane-bound form and release of the soluble form, catalytically active.[85] The contribution of soluble ACE2 produced after shedding to the pathological picture is still controversial. Recently, it has been confirmed that soluble ACE2 can also act as receptor, enabling viral access in the cell and then spread in the infective area. Soluble ACE2 at high concentrations was particularly correlated to the disease: the amounts of soluble ACE2 in serum and bronchoalveolar lavage fluid showed positive correlation with disease severity. Nevertheless, clinical-grade recombinant human ACE2, a soluble, exogenous form of ACE2 can bind to SARS-COV-2 and is likely to inhibit viral infection, as shown by studies performed on engineered human tissues. Modulation of soluble ACE2 generation and supplementation with recombinant human ACE2 represent novel therapeutic alternatives that still require further investigation.[86] Lipoic acid can also exert a beneficial role by impacting TNF-α (that requires ADAM17 contribution to be proteolytically released from the surface of the cell, in order to activate cell signaling) and EGFR (epidermal growth factor receptor).[85] It has been reported that SARS-CoV lung fibrosis is caused by an overactivated host response to pulmonary injury mediated by EGFR signaling.[87]

As the viral access in the cell was related to acidic pH, it was suggested that alpha lipoic acid promotes host's defense by an increase of the cell's pH via activation of ATP dependent K^+ channels and increase in potassium ion levels. It also hampers cell damage by lowering lactate release in COVID-19 patients. In combination with insulin, it exhibits a synergistic effect, showing benefits in COVID-19 patients with diabetes.[88]

SELENIUM

Selenium is part of the endogenous antioxidant pool, being required for both inborn and acquired immunity.[89] Glutathione peroxidases and thioredoxin reductases, the most important selenoproteins endowed with antioxidant potential, are present in the cytoplasm, in organelles and in the extracellular matrix, exerting a pivotal role in the endothelial cell function.[90,91] A series of studies describe the mechanism underlying the antioxidant and immunoregulatory effect exerted by selenium compounds. It has been asserted that selenium boosts immunity through its role as cofactor of enzymes that are responsible for critical post-translational protein modification.[92] Selenium exerts antioxidant role, counteracting the increase in reactive oxygenated species level in inflammatory processes and modulating immune function. Deficiency results in lowered T cells count and natural killer cell activity,[93] enhancement of virus replication rate, and genome mutation, mainly in the case of RNA viruses.[94] Higher mortality rate linked to COVID-19 pathology was noticed in selenium deficient areas,[95,96] including some parts of China, New Zealand, and Europe and affecting 500 million to 1 billion people on a global scale.[97]

Selenoproteins trigger immune-cell function by up-regulating the IL-2 receptor, optimizing the ability of T and B lymphocytes to respond to IL-2.[98] These antioxidant enzymes use arachidonic acid as aprecursor to synthesize lipid mediators endowed with anti-inflammatory potential, protecting cells from proinflammatory gene expression that is favored under

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

oxidative stress conditions.[99−101] Glutathione peroxidase, containing a selenocysteine residue at its active site, is responsible for hydrogen peroxide depletion, protects integrity of the cellular membrane, hampers DNA injury, and can diminish mortality rate in sepsis.[89] It has been reported that selenium-containing enzymes, in combination with vitamin E, exert a protective effect on cells and tissues, hampering the generation of free radical species.[102] Moreover, selenium deficiency triggers expressions of oxidative stress and pro-inflammatory markers like cyclooxygenase-2, prostaglandin E synthase, TNF-α, and nuclear transfer factor B in the gastrointestinal tract.[103] Zeng et al. reported that pancreatic mRNA expressions of proinflammatory cytokines TNF-α and IL-1 were lowered as responses to selenium administration.[104] In patients with respiratory distress syndrome, selenium supplementation hampers oxidative decay, re-establishing antioxidant profile of the lungs,[91,105] lowers IL-1β and IL-6 levels,[105] induces suppression of pathogen-activated NF-κB, and, consequently, of pro-inflammatory cytokines.[106] Also, selenium supplementation results in improved selenoenzymes level (including that of glutathione peroxidase), catalase activities[107] and CD^+ T cell counts.[108]

Selenium supplementation improves immune response in the elderly, increasing total T cells, namely $CD4^+$ T cells, boosting the number of natural killer cells, with subsequent increase in their cytotoxicity.[109] Also, it promotes the blood level of antibodies[30] and increases gamma-interferon, resulting in an earlier maximum T-cell proliferation and a boost in T-helper cells.[110,111] Dietary selenium contributes to proliferation and differentiation of CD4+ T cells in mice, following a mechanism based on free thiol profile increase following supplementation.[112]

An increase in IL-8, IL-10, and T-cell proliferation was noticed at selenium supplementation in a dose-dependent manner. Nevertheless, a lower granzyme B content of CD8 cells was noticed in a study focused on selenium influences on immunity acquired by influenza vaccine in elderly.[109] Alongside the anti-inflammatory role, antiviral influences of selenium supplementation have been detailed before SARS-CoV-2 pandemic.[113,114] Lung selenoproteins lower the extent of viral invasion and tissue impairment as they act as antioxidants and immunomodulators.[115,116] It has been reported that selenium deficiency accelerates mutation, replication, and hence virulence of RNA viruses. SARS-CoV, as single-stranded RNA viruses, mobilize cellular selenium to synthesize their own selenoproteins, impairing the host's glutathione peroxidase and thioredoxin reductase levels.[115,117] Infection of Vero E6 cells with SARS-CoV-2 markedly down-regulated the expression of a number of selenoproteins, at the same time triggering the expression of IL-6 inflammatory cytokine.[101,118] SARS-CoV-2 interferes with the host's selenoprotein system, and it is thought that a deficient status might occur during the acute phase of disease under conditions of enhanced viral replication. It has been suggested that redox-active selenium species resulted from high selenium intake are likely to lead to SARS-CoV-2 protease inhibition.[101,119]

Ebselen is an organoselenium compound endowed with antiviral potential, consisting in inhibition of main SARS-CoV-2 protease and acts as glutathione peroxidase and peroxiredoxin mimetic.[91,120] The ebselen-induced inhibition of SARS-CoV-2 protease relies on the selenosulfide formed from reaction between ebselen and protein thiols.[101,121] This inhibitory action of ebselen was assigned to its interaction with Cys145 and His41 residues present in the active site of main protease.[122,123] Sodium selenite, another selenium-containing compound endowed with antiviral potential, oxidizes −SH groups in the viral disulfide isomerase, imparting viral inaccessibility to healthy cells.[124] Sodium selenite at pharmacological doses can contribute to thioredoxin reductase and glutathione peroxidase biosynthesis, replenishing the thiol profile and, consequently improving antioxidant defense in human endothelial cells.[125,126] The ability to restore DNA synthesis in the cell has also been reported.[127,128] Selenite downregulates intracellular caspase-3 by altering a key cysteine residue located in the active site.[101,129]

Because of its significant role in boosting antioxidant status and inborn immunity, as well as in alleviating inflammation, it was inferred that selenium supplementing may be supportive in the fight against COVID-19.[4,114] In selenium deficiency, not all of the tissues present equally diminished selenium stores, but it is known that immune cells are among the first undergoing a swift decrease of selenium level related to an impaired selenoprotein synthesis.[91] In China, selenium levels vary between the smallest and the highest globally, as shown by hair selenium levels, and a more increased mortality rate was noticed in COVID-19 patients from low-selenium regions, as reported by Zhang et al.[95] Deficiency in selenium negatively affects the host immune system but also facilitates swift mutations of RNA virus benign variants to virulent ones.[130] Hence, selenium supplementation, aiming at achieving an appropriate level, mainly for COVID-19 patients in the intensive care unit, was considered. Selenium supplementation after sepsis in mechanically ventilated subjects could diminish the risk of ventilator-associated pneumonia and increased the activity of glutathione peroxidase in septic patients.[131] Parenteral selenium administration lowered both frequency of ventilator-associated pneumonia and disease severity in critically ill patients suffering from systemic inflammatory response syndrome.[132] Another clinical trial concerning critically ill patients showed that high selenium doses ameliorated antioxidant profile illustrated by plasma glutathione peroxidase (GPx3) level but had no positive effect on the incidence of post-treatment ventilator-associated pneumonia.[133]

It has been asserted that selenium role in COVID-19 also requires investigation in selenium deficient countries other than China.[119,134] The result of a meta-analysis reveals that high selenium doses as complementary therapy in critically ill adult patients might lower 28-day mortality. The long-term effect on mortality and the prevalence of respiratory or renal complications should require confirmation in further researches.[134]

Studies approaching selenium supplementation reported that a selenium overload could exert a prejudicial effect on the host's immune response to anti-influenza vaccines in the elderly.[93] Nevertheless, in other studies, no correlation could be identified between selenium status or supplement intake and humoral immune response to mRNA vaccine against SARS-CoV-2. In this case, one of the limitations was the lack of assessment of cell-mediated vaccination response.[135] Supranutritional selenium levels can modulate the Th1 to Th2 balance, favoring the Th1 phenotype.[136] The latter shows benefits in boosting the cell's immunity but is also linked to the presence of pro-inflammatory cytokines.[137] Nevertheless, Se supplementation also shifts macrophage activation from a pro-

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

inflammatory state toward an anti-inflammatory state, promoting cell development after injury.[138]

So, several key aspects should be regarded concerning selenium: selenoproteins are involved in endothelial homeostasis and maintain nonprothrombotic platelet activation status. Mainly when present in glutathione peroxidase, thioredoxin reductases, selenoprotein S, methionine sulfoxide reductase B1, and selenium are endowed with anti-inflammatory, immunomodulatory, and antiviral features. Selenium status influences the functions of leukocytes such as adherence, migration, phagocytosis, and cytokine synthesis. Supplementation improves selenoprotein profile, alleviates viral-induced oxidative stress, organ decay, and cytokine storm and hinders the mutation to virulent variants of SARS-CoV-2.[139] Perturbations induced by SARS-CoV-2 in selenium homeostasis can potentially lead to coagulopathy.[140]

The impact of selenium deficiency on the viral genome leads to an increase of SARS-CoV-2 virulence. The serum selenium levels of COVID-19 subjects were analyzed comparatively to that of healthy controls and was found to be significantly smaller.[141,142] So, diminished serum selenium levels may constitute a risk for infection,[141] and most reports relate them to an impact on COVID-19 severity and fatal outcomes.[143] Low selenium and impaired selenoprotein P amounts were related to illness severity, linked to increased oxidative stress.[144] Selenoenzymes (GPx-1, GPX, and selenoprotein P) become depleted in infected cells. Moreover, oxidative and nitrosative stress and antioxidant impairment promote multiplication of the virus and viral RNA mutation, resulting in severe tissue damage in the host.[94,145] SELENOP (selenoprotein P) activity was reported to decrease earlier than GPX3 activity in sepsis and septic shock.[146] Selenium status determined at ICU admission is thought to represent a predictor of survival in ICU.[147] So, as for other antioxidants like glutathione, a vicious cycle is observed in relation to the infectious disease: the virus hijacks the host's antioxidant (including selenoprotein) profile, and the deficiency promotes the infective potential. Avoiding severe selenium deficiency is advisible during COVID-19 pandemic.[135] Zinc and SELENOP status, considered in the reference ranges, are viewed as viable indicators in COVID-19 survival. It was asserted that individualized supplementation of these micronutrients involved in lowering the oxidative burst induced by the pathogen may be beneficial during convalescence.[139]

Cautious supplementation is the most appropriate, as there is a slight difference between proper and toxic amounts.[148] The daily recommended selenium intake is 1 μg/kg of body weight. In conformity to the D-A-CH reference, the recommendation is 70 μg of selenium per day for men and 60 μg per day for women.[141] Results reported in clinical studies and nonexperimental studies point that, at a broad range of exposure amounts, selenium may enhance the risk of type 2 diabetes. Selenium-containing chemical species, the overexpression of selenoproteins and the interference with glucose metabolism are topics of interest in diabetogenesis.[149]

More evidence on an adequate selenium status in COVID-19 subjects, with and without illness severity, should occur rapidly, as selenium supplementation is largely investigated with respect to its capacity to decrease disease impact.[91] The importance of validation at the individual scale and the necessity to avoid toxicity have been stressed upon. Using nanoselenium may result in good biocompatibility and lowered toxicity. Even though there are not sufficient experimental results, it is thought as a viable future therapeutical alternative against SARS-CoV-2.[150]

■ ZINC AND COPPER

Zinc, a transition metal, is the second most abundant trace metal in the human body after iron, and it exerts a series of significant functions in the cell: acts as membrane stabilizer, antioxidant, anti-inflammatory agent, is involved in signaling pathways, and triggers antiviral immunity.[151] It is estimated that Zn inadequacy and deficiency affect around 30% of the world's population, mainly the elderly; hence, it was inferred that zinc supplementation may exert a protective role against infection in elderly individuals.[152]

Zinc is part of the endogenous organism's antioxidant defense, being a cofactor of zinc copper superoxide dismutase, that depletes superoxide anion radical, so low Zn levels impair the antioxidant system and promote oxidative stress. Reactive oxygen species generation at low zinc levels were related to a diminished activity of Cu/Zn-specific superoxide dismutase, a key component of the first line antioxidant defense.[153,154] Zn inhibits nicotinamide adenine dinucleotide phosphate oxidase, a pro-oxidative enzyme and superoxide generator, and promotes metallothionein synthesis.[155] Metallothioneins, low molecular weight cysteine-rich proteins that can bind divalent metals such zinc or copper, determine the sequestration of the reactive oxygen species generated under stress conditions and can reduce hydroxyl radicals.[156−158] The release of the divalent zinc cation from its complex formed with metallothioneins or with cysteine residues of other proteins can lower reactive oxygenated species amounts, including those generated in viral infections. So, in this manner, zinc acquires indirect redox activity responsible for ensuring the endogenous antioxidant profile and anti-inflammatory activity.[159,160]

Zinc regulates antiviral and antibacterial immune response, controls the inflammatory response, inhibits SARS-CoV-2 RNA polymerase and NF-κB signaling, and tunes regulatory T-cell functions, which can alleviate cytokine burst.[161] Disturbances in zinc signaling can result in immunodeficiency by depression of both primary and secondary immune responses.[162] Zinc modulates oxidative stress and metal homeostasis by controlling responsive metal transcription factor 1 and boosts the expressions of both metallothioneins and zinc transporter-1 genes. Responsive metal transcription factor 1 triggers the expression of the selenoprotein 1 gene, which encodes an antioxidant protein with glutathione-binding and free-radical scavenging potential.[155,163]

Zn deficiency results in oxidative impairment to DNA, proteins, and fats.[164] Conversely, zinc supplementation can notably lower malonyldialdehyde and improve total antioxidant capacity and glutathione level, so zinc supplementation can prove useful in oxidative stress-related pathologies. No effect was noticed on nitrogen monoxide levels.[165] Moreover, zinc also acts as an inhibitor of free radical reactions induced by other transition metals like copper.[166] Another mechanism by which zinc acts as an antioxidant species is by triggering glutamate−cysteine ligase expression, the enzyme that promotes de novo glutathione synthesis.[155] Furthermore, oxidative stress is linked to an impairment in the synthesis of endogenous first line of defense antioxidants superoxide dismutase and glutathione peroxidase.[167]

Zinc is a key component of the immune response, involved in the recruitment of neutrophils, enhancing chemotactic activity and phagocytosis, promoting the number and activity

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

of CD4+ and CD8+ T cells, and triggering IL-2 and soluble IL-2 receptor expression.[168] A large spectrum of responses involving innate and adaptive immunity disturbances are noticed in zinc deficiency. Zinc deficiency can result in impaired polymorphonuclear cell chemotaxis and phagocytosis, enhanced production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, and altered modulation of natural killer cells' activity.[96] Zinc impairment negatively affects the development of B and T lymphocytes as well as the antibody synthesis (mainly in the case of immunoglobulin G) and diminishes eosinophil count.[169−171] The thymic atrophy noticed in zinc deficiency was identified as a source of T-cell lymphopenia and diminution of premature and immature B cells, with subsequent lowered antibody synthesis.[172] Zinc insufficiency results in lymphopenia and lowered T-lymphocyte mediated immunity because thymulin activity, important for the development and maturation of T cells for differentiation and enhancement of the activities of T and NK cells, depends on the presence of zinc in the molecule.[58] The immunodeficiency and severe lymphopenia observed at zinc impairment was also assigned to a reduction in B cells developing in the bone marrow. It was reported that zinc gluconate supplementation inhibits the NF-kB-dependent transcription of inflammatory genes, alleviates airway neutrophil infiltration, lowers TNF-α, IL-6, and IL-1β, and promotes a protective type-I interferon effect.[151,173] The inhibitory effect on NF-κB signaling, as well as the modulation of T-cell functions, can contribute to the hindrance of cytokine storm.[161]

Studies performed on rat models reveal that zinc deficiency enhances vascular cell adhesion molecule (VCAM)-1 expression, affecting lung tissue, a process that can be partly reversed by zinc supplements administration.[174] Zn impairment led to apoptosis in lung epithelial cells[175] and up-regulation of the Janus kinase (JAK)-STAT signaling in lungs during sepsis. The anti-inflammatory potential of zinc encompasses downregulation of pro-inflammatory pathways, among which is the IL-6-mediated triggering of STAT-3 in sepsis.[4,176,177] Zinc inhibits STAT-3 activation and the production of acute phase proteins such as pro-inflammatory amyloid A, that has IL-6 as key inductor.[176] Conversely, Zn-deficiency increases susceptibility to pathogens and illness severity and contibutes to anosmia and ageusia, confirmed symptoms in COVID-19.[178,179] Low zinc plasma levels in COVID-19 subjects were correlated to disease severity, as zinc deficiency negatively affects function and lymphocyte counts. An improved plasma zinc level can impede viral replication, viral protein synthesis, and lower oxidative burst, representing a therapeutic alternative against COVID-19.[180,181] The presence of zinc ionophores pyrithione or pyrrolidine-dithiocarbamate promotes the capacity of zinc divalent cations to inhibit RNA dependent RNA polymerase activity, so it contributes to hampering viral replication.[114,182−185]

The ability of zinc to inhibit the synthesis, replication, and transcription complex of coronaviruses, was proved by in vitro studies performed on Vero-E6 cells.[182,186] Lowering of recombinant human angiotensin converting enzyme-2 activity in rat lungs by exposure at zinc doses of 0.1 mM was also reported.[187]

Given its immunomodulatory, anti-inflammatory, and direct antiviral potential, zinc was included, alongside other therapeutic agents in the treatment against COVID-19,[130,185,188] as long-lasting hypozincemia was confirmed as risk factor for severe illness.[189,190] Clinical studies showed that oral zinc supplementation has the ability to lower the occurrence of acute respiratory infections by 35%. Zinc also reduces the period of flu-like symptoms by 2 days and increases recovery rate.[191] Doses recommended in different reported studies are comprised between 20 and 92 mg weekly.[4] According to the National Institutes of Health Treatment Guidelines against Covid-19, "the doses used in registered clinical trials for patients with COVID-19 vary between studies, with a maximum dose of zinc sulfate of 220 mg (50 mg of elemental zinc) twice daily".[192] A potential beneficial effect of zinc sulfate on the incidence of ventilator-associated pneumonia in ICU patients was reported.[193,194] In combination with melatonin and vitamin C, zinc reestablished the antioxidant profile affected by oxidative stress, could counteract DNA damage in lymphocytes, and restored immunological parameters. The antioxidant combination proved more efficient than the use of a single antioxidant and had the potential to alleviate the severity of the viral infection in human and animal subjects, constituting a potential prophylactic strategy in SARS-CoV-2.[195]

Nevertheless, up to now, not all of the data available on zinc supplementation show consistency with respect to benefits.[151] Zinc in combination with low-dose hydroxychloroquine markedly diminished the number of hospitalizations, as shown in a retrospective study encompassing 141 individuals.[196] On the contrary, in a novel randomized clinical trial including ambulatory COVID-19 patients, high-doses of zinc gluconate, alone or in combination with ascorbic acid, could not lead to a significant reduction in symptom persistence nor in the number of hospitalizations and deaths.[197]

The beneficial role of zinc supplementation in promoting the clinical efficacy of chloroquine/hydroxychloroquine against COVID-19 has been discussed, as chloroquine behaves as a zinc ionophore, mainly in lysosomes.[96] It was considered that the combination zinc−chloroquine (or hydroxychloroquine) could potentially lead to a more efficacious inhibition of RNA polymerase replication.[198] Nevertheless, the concerns with respect to chloroquine/hydroxychloroquine cardiotoxicity should be seriously taken into consideration.[199,200] Prolonged administration at high doses can result in copper deficiency, with serious effects like neurological complications.[165,201] Moreover, zinc supplementation might be accompanied by gastrointestinal problems and headaches.[202] Too low or excessive amounts can convert zinc into a pro-oxidant, with pro-inflammatory and pro-apoptotic effects. The copper deficiency induced by zinc excess may result in impaired expression of copper-dependent enzymes, such as superoxide dismutase and ceruloplasmin, components of the endogenous antioxidant defense system.[155,203,204]

Hence, zinc inclusion in therapy sustains the antiviral and antibacterial immune response and modulates the inflammatory response. Zn inhibits NF-κB signaling and modulates Treg cell functions through this hindering cytokine storm. In vitro inhibition of COVID-19 RNA polymerase has been reported that can boost the antiviral potential of zinc ionophores such as chloroquine. Also, zinc lowers ACE2 receptor activity and promotes interferon α production, boosting its antiviral potential.[205−207] The clinical benefits noticed in zinc supplementation were also ascribed to the promotion of gamma interferon production and to the ability to stimulate macrophages to release IL-12 that enables activation of natural killer cells and T cytotoxic cells. The anti-inflammatory role of

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

zinc also encompasses lowering of IκB kinase response.[208] In vitro studies proved that zinc impairment promotes production of IL-6 and IL-1β inflammatory cytokines and induces elevated expression of ICAM-1 (intercellular adhesion molecule 1), involved in extravasation of leukocytes. Also, it promotes the expression of Cluster of Differentiation 86, a protein expressed in dendritic cells involved in T cell activation, as well as of human leukocyte antigen-DR isotype, in human cultured monocytic cells.[209,210] It has been reported that diminished free seric zinc levels are linked to an increased fatality risk, so free zinc levels may constitute an indicator of COVID severity. Total seric zinc impairment assessment by total reflection X-ray fluorescence showed that free serum zinc amounts in COVID-19 subjects were significantly smaller than in control subjects. Moreover, patients overcoming this disease exhibited considerably higher free zinc amounts than nonsurvivors.[211]

Nevertheless, like for many supplements, Zn inclusion in anti SARS-CoV-2 therapy is controversial, as the clinical studies do not consistently converge toward a definite conclusion with respect to benefits. Moreover, the results of these studies can be biased by the occurrence of conflicts of interest.[207] Excessive intake of zinc, as in the case of other trace elements like selenium, can have toxic effects at amounts higher than the upper intake level, therefore inappropriate supplementation can lead to undesired consequences.[212] It has been suggested that even levels close to the recommended daily allowance (150 mg daily), can interfere with copper and iron utilization and can negatively impact HDL levels.[213] Moreover, it has been found that Zn^{2+} also participates as a cofactor, ensuring the activity of viral proteins. Zn^{2+} can be exploited as a second messenger in the cell and may result in apoptosis or an impairment in protein synthesis at high concentrations.[214] Also, zinc represents an important mineral element required for the development of fungi, including pathological strains (Mucorales), causing mucormycosis.[215−217]

Supplementation is mainly recommended as prophylaxis, as well as adjunctive treatment in combination with classical antiviral therapy. It is considered that Zn alone is not a medication per se against COVID-19 but can be incorporated in coadministration that is effective mainly at the onset of infection. Adequate vitamin and mineral levels, mainly zinc, as part of an appropriate antioxidant pool, exert an important role in prophylaxis and during treatment with antivirals, potentiating the activity of chloroquine, hydroxychloroquine, or ivermectin.[207] It has been reported that zinc levels are influenced by the presence of other antioxidant biocompounds, dietary compounds, or drugs. Zinc absorption is promoted by glutathione, citric acid, and in acidic medium and is lowered by folate, phytic acid, gallic acid, or tannins. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors increase zinc excretion, an aspect relevant for zinc inclusion in therapy.[218]

Copper exerts a significant role in the immune function, as it is involved in production and differentiation of immune cells. It promotes T-cell proliferation and natural killer cells' activation.[219,220] Copper is endowed with direct antimicrobial potential exerted through its toxicity and promotes development of neutrophils, monocytes, and macrophages.[221] Copper impairment leads to alterations in ceruloplasmin and erythrocyte superoxide dismutase activities, weakening the endogenous antioxidant pool.[222] Also, a low copper diet has been shown to result in diminished peripheral blood mononuclear cell proliferation.[223]

With respect to its role in viral pathologies, copper can interfere with RNA replication and protein synthesis, as proved by its behavior against influenza virus A/WSN/33 (H1N1).[224] So, copper can be efficacious in preventing respiratory viruses, including those related to SARS and MERS.[114,225] Copper ion is able to inhibit papain-like protease-2, a protein that SARS-CoV-1 uses to replicate, as proved in a cell-based study.[226,227] Copper-deficient humans present an elevated susceptibility to infections due to the associated diminished number and function of immune cells. Enhancement of plasma copper levels can trigger both the innate and adaptive immunity and boosts the ability to fight against SARS-CoV-2.[114,228] The potential of copper for incorporation as auxiliary therapy against COVID-19 can be exploited, encompassing supplementation and mineral deficiency correction.[96,114]

Extracellular superoxide dismutase (enzyme presenting both copper and zinc at its active site, vital for reactive oxygenated species depletion) gene/protein therapy might be efficacious in alleviating acute lung injury and acute respiratory distress syndrome in COVID-19 infection.[229] Serum copper amounts were found to be smaller in subjects with severe disease, and serum zinc amounts during parenteral nutrition were conversely associated with the hospital stay duration but not with fatal prognosis.[230] These benefits were assigned to the involvement of copper in supporting the function of cells essential for the immune response such as T helper cells, B cells, natural killer cells, and macrophages, in that sustaining host cells' immunity and the antibody synthesis. Adequate plasma copper amounts promote the inborn and adaptive immunity. In copper-deficient animals, copper supplementation boosts synthesis and activity of IL-2, which enhances proliferation of T helper cells and the cytotoxicity of NK cells.[225,231,232]

Humans presenting copper deficiency exhibit an elevated susceptibility to infections, given the diminished number and impaired function of immune cells. It was reported that copper supplementation in COVID-19 can promote immune response, mainly in the elderly, that may present pronounced copper deficiency. Moreover, copper impairment can result in neutrophil overactivation and build up in the liver, contributing to inflammation.[228]

Interferences of copper with other micronutrients, mainly zinc metabolism, were largely documented. In healthy individuals, copper and zinc are competitively metabolized via absorption from the jejunum due to the ability of metallothioneins to bind both elements. High zinc amounts (>150 mg daily) can lead to copper deficiency in healthy subjects.[228] Metallothioneins, whose expression is promoted by zinc supplementation, exhibit a high affinity for copper, leading to copper deficiency, that is likely to result in neutropenia, anemia, and even myelopathy.[233] It was suggested that sustained zinc supplementation exceeding the recommended daily allowance is likely to result in a risk of SARS-CoV-2 severe infection.[228] Nevertheless, novel studies report that the Cu:Zn ratio tends to increase during the acute phase of COVID-19, which can be explained by copper and zinc activation and redistribution, starting from the onset of the infection. This process involves the utilization of these metal elements from the liver deposits for activation of pro-inflammatory cytokines and synthesis of acute phase reactants induced by IL-1.[234,235]

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

With respect to increased Cu:Zn ratio, it has been proved that this can be linked to a severe disease status, and it has been considered as a predictor of diminished oxygen saturation.[236] High levels of copper can enhance oxidative stress by generating hydroxyl radicals in Fenton systems. The Fenton reaction is also promoted by an excess of iron, which is commonly encountered during infections. Ferritin concentrations become elevated to reduce excess Fe, which is consistent with the observed high percentage of patients in the acute phase, presenting ferritin levels superior to the upper value.[235] On the other hand, while too high amounts of copper can be noxious, sites characterized by copper impairment can determine a stress response from pathogens, so copper amounts must be kept optimally (RDA is equal to 900 μg daily).[228] It has been reported that copper inactivates viral genomes and irreversibly impacts the morphology of the virus, encompassing envelope breakdown and surface spike protein dispersion.[237]

Copper oxide nanoparticles and copper ions may inhibit viral access and replication and degrade mRNA and capsid proteins that ensure viral survival.[228] Given the structural similarity of corona viruses, it is thought that materials based on copper alloys can be efficacious against all coronavirus strains. Copper-based alloys and nanomaterials can constitute a preventative strategy against Covid-19.[237] The incorporation of copper-based nanoparticles in antimicrobial polymers can lead to the synthesis of novel biocidal materials (nanocomposites) with enhanced antiviral effect.[238]

MELATONIN

Melatonin. Melatonin is a neuroendocrine hormone responsible for the circadian rhythm, synthesized and released primarily by the pineal gland. As a small molecule endowed with amphiphilic character, structurally an indoleamine (Figure 4), it can cross biological membranes, enter cells with great facility, and interact with subcellular organelles.[239]

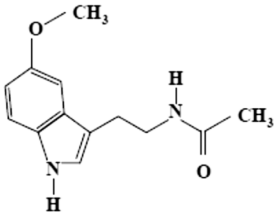


Figure 4. Melatonin, *N*-acetyl-5-methoxytryptamine.

The SARS-CoV-2 infection is prevalent, with more pronounced clinical outcomes in individuals suffering from diabetes and obesity, as well as in aged individuals. In these categories of population, the diminution in the endogenous antioxidants profile and enhanced oxidative stress are linked to a weakness of the immune system.[240] Impairment of the immune response, enhanced inflammation (high levels of proinflammatory markers), and cytokine overactivation (cytokine storm) are common in diabetic and obese subjects and can represent the source of severe clinical manifestations.[241] A correlation has been established between the large number of SARS-COV-2 cases and the small levels of blood melatonin in elderly people and those with chronic metabolic pathologies. The low levels of endogenous antioxidants, including antioxidant enzymes and melatonin, accompanied by a weak immune system, increases susceptibility to inflammation. The potential of melatonin to diminish viral infections in obese and diabetic subjects was assigned to its features: antioxidant potential leading to improved endogenous antioxidant profile and immunomodulatory and enhanced anti-inflammatory abilities, as confirmed by data published in the past 50 years. These characteristics prove melatonin is useful as a therapeutic alternative in SARS-COV-2 for patients with or without chronic metabolic diseases.[240] The antiviral action of melatonin has been previously reported against viruses other than COVID-19.[242,243] Results obtained on many experimental models involving inflammation and/or oxidative stress proved that both antioxidant and anti-inflammatory abilities of melatonin protect from lung impairment.[244]

The immunomodulatory roles of melatonin involve a dual aspect, with proinflammatory and anti-inflammatory actions. The proinflammatory features enable this antioxidant to fight pathogens, whereas the anti-inflammatory action is exerted in advanced inflammation such as sepsis, organ decay, and oxidative stress, but also in low-grade inflammation corroborated with neurodegeneration and aging. Melatonin can follow several mechanisms: alongside its capacity to lower proinflammatory cytokine production and trigger anti-inflammatory cytokine synthesis, melatonin has an antioxidant potential and can lower the expression of inducible nitric oxide synthases, inhibit neuronal nitric oxide synthases, attenuate cyclooxygenase-2, inhibit high-mobility group box-1 signaling and toll-like receptor-4 activation, prevent inflammasome NLRP3 activation, and hamper NF-κB activation.[240,245]

Melatonin attenuates the mitochondrial oxidative damage that occurs as a consequence of enhanced inflammation during sepsis; it scavenges reactive oxygenated species and hampers the release of mitochondrial DNA to the cytosol, blocking the activation of the NLRP3 inflammasome. The consequent inactivation of caspase-1 hampers procytokine maturation, including that of pro-IL-1β, suppressing the positive feedback of IL-1β on the corresponding membrane receptor and the subsequent NF-κB activation.[246,247] By these effects, melatonin counteracts the damages caused by an overactivated immune response in SARS-CoV-2.[246] The efficient immunomodulatory effect of melatonin has been proved by both in vitro and in vivo studies: melatonin is involved in maturation and proliferation stages of natural killer cells, T and B lymphocytes, monocytes, and granulocytes in bone marrow and other tissues.[248,249] With respect to the anti-inflammatory features, it has been proved that melatonin lowers lipopolysaccharide-stimulated expression of pro-inflammatory cytokines, chemokines, and acute-phase proteins, targeting IL-1β, IL-6, TNF-α, CCL2, CCL5, C-reactive protein, serum amyloid A, aptoglobin, ceruloplasmin, granulocyte-monocyte colony-stimulating factor, and α-1 antitrypsin. Moreover, melatonin administration can promote the expression of the negative acute phase protein fibrinogen and the anti-inflammatory cytokine IL-1Rα.[250] Melatonin is responsible for the management of pro-inflammatory cytokines, lowering inflammatory responses such as those related to IL-1β, TNF-α, and IL-6. It alleviates T cell proliferation and lowers both IL-6 and IL-10 expression.[251] Melatonin suppresses the generation of Toll-like receptor 9 (TLR9)-activated proinflammatory cytokines in macrophages. This activity, independent of melatonin receptors, takes place via inhibition of ERK (extracellular signal-regulated kinase) 1/2 and protein kinase B activation[252] and by downregulation of inducible nitric oxide synthase through NF-κB modulation.[253]

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

Hence, given its confirmed antioxidant and anti-inflammatory properties, melatonin contributes to overcoming cell injury and lung damage. In the absence of acetyl-coenzyme A (cofactor of arylalkylamine *N*-acetyltransferase, the rate limiting enzyme responsible for melatonin synthesis), melatonin is no longer available in mitochondria to scavenge reactive oxygen species and lower inflammatory responses. The main damage occurs in the respiratory tract that leads to the main signs of COVID-19 disease. Endogenous melatonin synthesis significantly lowers with age especially in fragile, elderly persons. So, the lowered melatonin profile, and subsequently antioxidant pool, is consistent with the more serious symptoms of COVID-19 in older individuals.[254] The promoted aerobic glycolysis, a characteristic of an enhanced proinflammatory state linked with a deficiency of locally produced melatonin, favors cytokine storm and the extended tissue damage occurring in COVID-19. Supplementation reverses aerobic glycolysis by suppressing both HIF1α (hypoxia-inducible factor 1α) and mTOR and at the same time promotes pyruvate dehydrogenase complex activity and acetylcoenzyme A synthesis, which finally leads to melatonin production.[255] It has been reported that a combination between mitochondria-produced melatonin and parenteral melatonin reduces the cytokine storm and its negative consequences, alleviating the severity of symptoms in COVID-19.[254]

Although melatonin is not a confirmed direct virucide, it has been stipulated that it possesses indirect antiviral actions due to its antioxidant, anti-inflammatory, and immune promoting attributes.[243,256] Melatonin triggers the expression of Nrf2 and antioxidant genes, promoting phase II protective genes, such as those corresponding to heme oxygenase-1 or glutathione-*S*-transferase.[257]

In novel in silico studies, it has been suggested that melatonin directly controls the activity of proteins associated with COVID-19 through modulation of calmodulin, calreticulin, and myeloperoxidase, or indirectly, via control on G-protein-coupled receptors (melatonin receptor 1A, encoded by MTNR1A gene, and melatonin receptor 1B, encoded by MTNR1B gene) signaling or on nuclear melatonin receptor (ROR alpha, ROR beta) signaling.[258−260] In vitro studies have proved that melatonin binds to calmodulin, a regulator of ACE2 expression, inhibiting it in a calcium ion-dependent pocket. As a result of this ability, melatonin was considered an indirect inhibitor of receptor−virus interaction during membrane fusion.[257,261] Inhibitory actions exerted on calmodulin and main protease could be exploited to further develop the antiviral potential of melatonin.[257,262] It has been asserted that the potential of melatonin and mercaptopurine to target ACE2, papain-like protease, or c-Jun signaling can be exploited in the development of combinatorial, synergistic therapy against SARS-CoV-2.[259] Nevertheless, the mechanistic details and levels at which melatonin lowers COVID-19 severity still need being elucidated, and further confirmations would be required by the results of clinical trials.[258] The reported data point out that melatonin could be effective as treatment against COVID-19. It was characterized as having a good safety profile, being inexpensive, nontoxic on a large dose range, and having an extended shelf life.[254]

POLYPHENOLS

Polyphenols represent the richest class of plant-sourced bioactive principles, being synthesized as secondary metabolites, imparting protection against oxidative damage, the action of UV radiation, or pathogen invasion. From the structural point of view, the term polyphenol denotes compounds presenting hydroxyl groups grafted on an aromatic structure possessing one or more phenolic rings, with the basic structure depicted below (Figure 5).

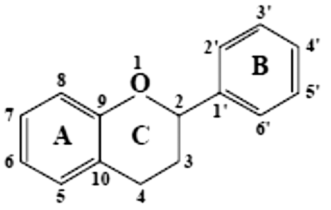


Figure 5. Representation of the flavinic skeleton

Relying on structural considerations, polyphenols can be classed into nonflavonoid and flavonoids. Nonflavonoids include phenolic acids (benzoic acid or cinnamic acid derivatives), polyphenolic amides, and other polyphenol compounds (including stilbene derivatives or lignans) Flavonoids include flavonols, flavan-3-ols (that mainly refer to catechins and protoanthocyanidins which are oligo- or polymeric forms of monomeric flavan-3-ols), flavones (that essentially differ from flavonols by the absence of a hydroxyl group at position 3), isoflavones, flavanones, and anthocyanins.[263,264] Complex structures such as tannins can derive from gallic acid (hydrolizable tannins), from phloroglucinol (phlorotannins), or from flavan-3-ol (condensed tannins). Polyphenols are well-known for their major pleiotropic activities, encompassing antioxidant, anti-inflammatory, and immunomodulative potential as well as antiviral activity.[265] Their health benefits have become the aim of numerous research.[266−269] The antiradical and antioxidant activity of phenolics were related to the number and position of hydroxyl groups on the aromatic ring. The presence of hydroxyl groups in the ortho position was identified as the main imparting the antioxidant and antiradical scavenging power. 3,4-Dihydroxycinnamic (caffeic) acid, 3,4-dihydroxybenzoic (protocatechuic) acid, and 2,3-dihydroxybenzoic (*o*-pyrocatechuic) acid are endowed with enhanced antioxidant and antiradical power. Nevertheless, it was reported as smaller than the one characterizing gallic acid.[270]

With respect to the mechanistic aspects underlying the antioxidant activity, a study dealing with five flavanones widely found in plants (ampelopsin, dihydro-orobol, eriodictyol, hesperetin, and taxifolin) showed that in water phase, they follow a consecutive proton loss (deprotonation suffered by all the hydroxyl groups), yielding polyanionic forms. The multiple proton loss reactions start with the hydroxyl group located at position 7. The second proton-loss reaction preferentially involve the −OH groups present on the B ring, given the better delocalization of the negative charge, by conjugation on the entire flavinic skeleton. Furthermore, the resulted polyanions trap three free radical species in three successive electron transfer reactions. In flavonoids, intramolecular hydrogen bonds are encountered in all geometries characterized by maximum stability. These can lower the antioxidant activity of −OH groups that act as hydrogen-bond donors (like those present in positions 3, 5, or 3′) but can promote the antioxidant activity of −OH groups that act as hydrogen-bond acceptors (like those present in position 4′).[271]

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

Polyphenols trigger the activities of endogenous antioxidative enzymes, interfere with immune cell modulation, with proinflammatory cytokine synthesis and gene expression, upregulating immune function.[7] Polyphenols are the major contributors to the antioxidant profile of the plant-sourced diet, lack toxicity, are involved in disease prevention and improve health status, nutrition representing one of the key factors influencing the antioxidant/oxidant balance and inflammation.[272] Antitumor and prebiotic properties were also linked to polyphenol intake. It has been shown that these phytocompounds can be involved in preventing and treating a series of chronic degenerative pathologies, including nutritional diseases, such as metabolic syndrome, type 2 diabetes mellitus, nonalcoholic fatty liver disease, insulin resistance, or atherosclerosis. Their pharmacological potential was also noticed in inflammatory lung diseases.[273,274] Moreover, polyphenols are endowed with inhibitory activity exhibited against viral components and actions.[264,275,276] Given the restricted bioavailability of most polyphenols, the systemic effects of these phytocompounds have been ascribed to the gene-mediated antioxidative, anti-inflammatory, and immunomodulatory attributes that were exploited to defend host cells and mitigate illness severity in COVID-19.[3,277] It has been found that the antioxidant and antiviral activities are exerted in the gastrointestinal system where polyphenols are present in high concentrations.[277] The intake of fruits and vegetables can support and maintain a positive health status by overcoming oxidative stress, inflammation, as well as the associated pathologies. Polyphenols inhibit the activity of particular enzymes involved in reactive oxygen species generation (NADPH oxidase, xanthine oxidase) and trigger endogenous enzymes with antioxidative potential such superoxide dismutase, catalase, and glutathione peroxidase. The immunomodulative potential is exerted through the ability to interfere with proinflammatory cytokine synthesis and with the expression of corresponding genes.[278,279]

Dietary polyphenols can impact dendritic cells, exert immunomodulatory activity on macrophages, increasing proliferation of B and T cells and suppressing Th1, Th2, Th17, and Th9 cells.[280] The counteraction of their diminished bioavailability and subsequent increase in their active concentration in the airways, as the main site of infection, can be obtained by employing inhalers or nebulizers.[265] The inhibition of several key mediators of the inflammatory response in macrophages by polyphenols has been reported. It has been shown that extra virgin olive oil and olive vegetation water enriched with polyphenols has the ability to lower the expression of both IL-6 and C-reactive protein. Catechins and quercetin modulate the synthesis of pro- and anti-inflammatory cytokines: they promote IL-10 synthesis while inhibiting TNF-α and IL-1β.[281] The incorporation of such compounds in the diet may hamper COVID-19-associated inflammation by counteracting the activation of TNF-α and pro-inflammatory interleukins like IL-1β, IL-6, and IL-8.[282] The intake of anthocyanins from red berry fruits contributes to low levels of IL-6, IL-12, and high-sensitivity C-reactive protein, so a diminished inflammation score in blood.[283,284] The anti-inflammatory potential of pomegranate fruit extract was assigned to its inhibitory effect toward inflammatory cytokines induced by PGE2 or nitric oxide.[284] Methanol extracts obtained from green and red Kohlrabi cultivars could inhibit lipopolysaccharide-induced NO generation in a dose-dependent mode. This effect was achieved by suppression of inducible nitric oxide synthase and cyclooxygenase-2.[285] More specific investigations pointed toward the relationship between the phenolic structure and the mediators linked to pro-inflammation. It was asserted that the main structural features influencing the nitric oxide inhibitory potential of flavonoids are the C2−C3 double bond; the heavy substituents can diminish or even annul the inhibitory effect (in this case, aglycones exert better effect than glycosides); the presence of hydroxyl groups in 7 or 4′ positions, but this characteristic should be associated with one of those mentioned before.[286,287]

In a double-blind, randomized, placebo-controlled clinical trial involving healthy adults, polyphenol-rich green tea extract could boost systemic immunity by promotion of gamma delta T cell function, hampering upper respiratory tract infection, and lowering flu-like symptoms.[288] The benefits of polyphenol intake in COVID-19 were ascribed to diverse mechanisms. Alongside the strengthening of the body's antioxidant and anti-inflammatory responses, direct antiviral potential has been investigated. Impacting viral proteins, hampering virus replication (inhibiton of RdRp) or blocking cell receptors are reported mechanisms by which phenolics prevent host cells' invasion by the virus.[265,289] Polyphenols behave as active inhibitors of proteases involved in viral replication, as they are prone to establish hydrogen bonds with proteins.[290] The same mechanism, advanced by molecular docking or in silico studies describing the impact on S protein, should be reconfirmed by results of preclinical and clinical studies.[265] Nevertheless, the viral S protein and the related host cell receptor ACE2 are considered as therapeutic targets. By the attachment to either S1 or S2 domain of the SARS-CoV-2 spike protein, it has been asserted that phenolic compounds are able to interfere with key steps of viral activity such as binding to ACE2 receptor or internalization by fusion.[291−294] Structurally, this glycoprotein vital for attachment of virus, fusion, and access in the host cell, is heterotrimeric, with three distinct polypeptide chains: A, B, and C.[294,295] The affinity of phenolics for chain A of SARS-CoV-2 spike protein has been reported.[296−299] For the virus to affect the host cell, the spike glycoprotein has to be dissociated in its subunits S1 and S2.[294,299] S1 subunit includes the receptor binding domain which enables direct attachment to the receptor peptidase domain of ACE2, and the S2 subunit is responsible for membrane fusion.[296,299−302] So, after cleavage of S1 domain, the fusion peptide region is exposed, and then the dissociated S2 domain fuses the viral and cellular membranes and releases the nucleocapsid of the virus into the host cell.[294]

Numerous studies were directed toward the screening of either the behavior of a series of phenolics in SARS-CoV-2 or of their individual activities: benzoic acid derivatives (gallic acid), stilbene derivatives (resveratrol), andother phenolic nonflavonoids with particular structure (curcumin, a diphenolic dienone, or ellagic acid, the dilactone of hexahydroxydiphenic acid). Flavanols such as catechin, esters formed by catechins and gallic acid (gallocatechin gallate or epigallocatechin gallate), theaflavins (formed from the condensation of flavan-3-ols and abundant in tea leaves), along with their gallic ester derivatives, flavones (quercetin, luteolin, baicalein, and kaempferol), flavanones (naringenin), and flavonoid glycosides (rutin, mearnsitrin, myricitrin, and hesperidin), are also approached. A series of studies have proved polyphenols' ability to interfere during different steps of coronavirus entry in the host cell and replication. In-depth investigations of the

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

antiviral potential describe impact on viral proteases (interactions established between phenyl rings of polyphenols and viral proteins), on the RNA strand, or the ability to control mitogen activated protein kinase signaling, interfering with the defense ability of the host cell.[295]

STUDIES DEALING WITH NONFLAVONOIDS

Resveratrol. The ability to promote ACE2 protein expression and its consequences was critically debated and investigated in case of resveratrol. Given this capacity, it might be thought that this polyphenol would be able to promote the occurrence of infection and associated symptoms, as it was first asserted that ACE2 protein expression represents a prerequisite for the virus entry in the host cell, the SARS spike protein needing attachment to ACE2 receptor. Some studies reported in the case of ACE2 knockout mice, which showed resistance to infection, proved consistency with these observations.[303,304] Nevertheless, research focused on the critical stages of the disease reported that ACE2 activity can impart protection against acute lung injury and ARDS, which proved to be more severe in mice with ACE2 receptor inactivation.[305] Following SARS-CoV-2 infection, ACE2 deficient animals were characterized by impaired vascular permeability, lung edema, and dysfunction and increase in neutrophil number, indicating acute inflammation. Administration of recombinant ACE2 protein, catalytically active, led to an alleviation of the previously mentioned adverse consequences.[306,307]

Supplementation with resveratrol can lower ACE-2 overexpression at the level of the adipose tissue. This impact, combined with a diminution in lepin, adipokine with proinflammatory activity, can help in lowering the negative viral impact and illness severity by resveratrol intervention.[308,309] Moreover, resveratrol has the potential to act as antagonizer of IL-6, IL-1β, TNF-α, and NF-κB signaling pathways as well as to lower both cyclooxygenase-1 and cyclooxygenase-2 expression.[310,311] Given its abilities in modulating the renin−angiotensin system and ACE2 expression, as well as in alleviating a cytokine storm, resveratrol can be employed in anti-COVID-19 therapy by inclusion in combination with zinc in nanoformulation-based drug delivery systems. Pterostilbene (a resveratrol analogue) −zinc combinations can also be administered in the absence of a nanocarrier. The ability to block viral replication was proved in vitro for both stilbene derivatives.[310]

Apart from spike protein, polyphenol intake can impair the activity of other SARS-CoV-2 protein compounds (enzymes), which are required for virus duplication and infective potential.[312] The viral genome exploits the host ribosomes and is translated into a polypeptide chain, eventually dissociated by papain like proteases and 3-chyomotrypsin like protease, encoded by the viral genome, to form nonstructural proteins involved in viral replication.[313] Resveratrol and polydatin isolated from *Polygonum cuspidatum* can act as specific inhibitors of 3-chymotrypsin-like protease and papain-like protease, as proved by in vitro studies.[314] In the case of flavonoids, it was asserted that the hydroxyl group of at 7-position, confirmed as having the best reactivity in polar solvents,[271] is the one allowing binding to 3-chymotrypsin-like protease and papain-like protease, important targets in stopping virus replication.[312]

Hydroxytyrosol (3,4-dihydroxyphenylethanol), a benzenediol derivative endowed with antioxidant properties, found in the leaves and fruits of *Olea europaea* and metabolite of oleuropein, possesses antiviral activity exerted against enveloped viruses (influenza A). Hydroxytyrosol and oleuropein (a glycosylated seco-iridoid) and can inhibit the fusion of viruses with cell membranes.[315] Docking studies reported that hydroxytyrosol and α-cyclodextrin, present alone or in combination, impact the viral spike glycoprotein and its receptor ACE2, in that they are potential endocytosis inhibitors. Nevertheless, further studies are necessary to confirm the antiviral potential.[316]

STUDIES DEALING WITH NONFLAVONOIDS AND FLAVONOIDS

Curcumin (a diarylheptanoid that gives the yellow color of turmeric), brazilin (isoflavonoid, organic heterotetracyclic compound, a member of catechols and a tertiary alcohol), and theaflavin-3,3′-digallate were investigated for their ability to impact key mechanisms that are critical for virus entry in the cell and internalization. Theaflavin-3,3′-digallate (at 25 μg/mL concentration) and curcumin (above 10 μg/mL concentration), but not brazilin, can exert inhibition on ACE2 receptor activity, lowering its activity in both cell-free and cell-based assays. Nevertheless, none of these compounds could downregulate the expression of ACE2 receptor at the protein level in A549 cells. Brazilin and theaflavin-3,3′-digallate, and to a larger extent, curcumin, lower the activity of transmembrane serine protease 2 in cell-free and cell-based assays. An analogous pattern was noticed with cathepsin L that promotes shedding of ACE2 ectodomain and access of SARS-CoV-2 into the host cell. Theaflavin-3,3′-digallate proved a smaller ability to diminish cathepsin L expression at the protein level. Nevertheless, because a pseudovirus and A549 cells that naturally express diminished levels of ACE2 were employed in this research, further validation using primary alveolar type II epithelial cells and SARS-CoV-2 virus is required.[317]

Curcumin significantly impacts SARS-CoV-2 nucleocapsid protein and nsp10 protein, as these are essential for the detection and processing of viral RNA. This efficient binding affinity to nucleocapsid and nsp10 proved close to that of remdesivir, ivermectin, and azithromycin. Although the affinity of curcumin for proteases or spike protein is not similar to the affinity for nsp10 and nucleocapsid, it has still been noticed that the inhibition constants recommend this phytocompound as a therapeutical alternative against SARS-CoV-2. So, curcumin can be considered for inclusion in combinatorial administration of anti-SARS-CoV-2 therapeutic agents.[318]

Overall, given the confirmed anti-inflammatory and immunomodulatory potential of curcumin, as well as the pulmonoprotective and antifibrotic effects of this phytochemical on the lung tissue, it can be included in the treatment of COVID-19. Curcumin inhibits NF-κB and some proinflammatory cytokines, contributing to reversing the detrimental impact of the cytokine storm. By intervention on the NF-κB pathway, curcumin lowers the inflammatory response by alleviating the cytokine/chemokine expression. Also, curcumin lowers fibrotic response by attenuation of the TGF-β signaling pathway in viral-induced acute respiratory distress syndrome in a mouse model.[319,320] Curcumin-based nanoformulations can regulate both the secretion and expression of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-6, and IL-1β;[321] by activation of the adenosine monophosphate-activated protein kinase pathway, curcumin can impact both oxidative burst and inflammatory response related to COX-2, mTOR, p53, or p38.[322] Through IL-10

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

activation, curcumin boosts the heme oxygenase-1 expression and modulates immune response.[323] By activating transcription factors like Nrf2, curcumin supports the antioxidant defense and the activity of phase II enzymes.[324] Moreover, curcumin has the ability to interfere with key steps in the virus life cycle such as genome replication or viral attachment.[319,320] It modulates signaling cascades, such as NF-κB and PI3K/Akt signaling, that are exploited by the virus to achieve efficient replication in the cell. It also impacts post-transcriptional and post-translational modifications, hindering the multiplication of the virus in the cell.[320,325−328] It has been reported that curcumin can alter the structure of the surface protein of viruses by that blocking access in the host and multiplication.[320]

Catechin. The computational studies show that catechin and curcumin, not only possess high binding afinity toward the spike protein and ACE2 host receptor but also to the complex formed between the receptor binding domain of the viral spike protein and ACE2; the values obtained for the binding affinity of catechin with the spike protein, ACE2 receptor, and receptor binding domain of spike protein−ACE2 receptor complex were −10.5, −7.8, and −9.1 kcal/mol, respectively. Those calculated for curcumin were −7.9, −8.9, and −7.6 kcal/mol, respectively. Molecular computational simulations performed for 100 ns confirmed that the direct interaction of curcumin with the receptor binding domain site of the spike protein takes place within 40−100 ns. Both compounds bind to the interface between the receptor binding domain of the viral spike protein and ACE2, resulting in fluctuations in the alpha helices and beta strands of the protein complex. Particularly catechin presents affinity for the amino acid residues located near the receptor binding domain site of the spike protein, causing alterations in the amino acid residues in the receptor binding domain and its vicinity. The efficiency of both phenolic compounds in impeding the formation of the complex spike protein−ACE2 receptor was further confirmed by protein−protein interaction assessment. The results of this computational study represents a premise to use these compunds as therapeutic alternative.[329]

Detailed computational approaches revealed that catechin possesses enhanced the ability to target five viral proteins: spike protein (at the receptor binding domain), cathepsin L, nucleocapsid protein, 3-chymotrypsin-like protease, and non-structural protein 6, that are vital for virus access in the host cell and infectivity.[330]

Epicatechin Gallates and Epigallocatechin Gallates. Hydrogen bonds have received much attention in investigation, given their ability to sustain the binding affinity of a ligand by displacing the water molecules that are bound to the protein. Computational studies have been applied to characterize intermolecular interactions underlying the formation of complexes such as protein−ligand, protein−nucleic acid, and protein−protein. Molecular docking and molecular dynamics approaches aimed at describing the interaction of epicatechin gallates, epigallocatechin gallates from tea, as well as antivirals remdesivir and favipiravir with the RNA-dependent RNA polymerase of SARS-CoV-2. Epicatechin-3,5-di-*O*-gallate yielded the largest number of hydrogen bonds with the residues of viral RdRp. Epigallocatechin-3,4-di-*O*-gallate, epicatechin-3,5-di-*O*-gallate, and epigallocatechin-3,5-di-*O*-gallate generated a larger number of hydrogen bonds with the viral RNA at the active site of RNA-dependent RNA polymerase than remdesivir and favipiravir.[331] Epigallocatechin gallate from green tea has been also reported for its ability to impact cell signaling and contributes to lowering the endothelial cell inflammatory processes by a decrease in cyclooxygenase-2 and caveolin-1 expressions and by suppressing Akt kinase and ERK 1/2 kinases of the MAPK (mitogen-activated protein kinase) signaling pathway.[301,332]

Theaflavins. Theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, and theaflavin-3,3′-digallate from black tea have been investigated for their bioactive virtues. Theaflavins, particularly theaflavin-3′-gallate and theaflavin-3,3′-digallate, can impart prophylactic potential, being able to attach to the receptor-binding domain of spike protein. Epigallocatechin gallate and its lipophilic derivatives can dock to the active sites of SARS-CoV-2 and are also likely to impart prophylactic effect and act as therapeutic alternatives. Hydrophobic interactions and hydrogen bonds are formed by theaflavins with the viral spike protein, impacting the receptor binding domain. Inhibition of 3-chymotrypsin-like protease by theaflavins takes place at a smaller concentration when compared to other catechins, including epigallocatechin gallate, with a good affinity of the investigated bioactive principles for the target.[333]

A comparative evaluation has been performed on the ability of epicatechin gallate and gallocatechin-3-gallate to impact 3-chymotrypsin-like protease. The affinity in the case of gallocatechin-3-gallate proved the smallest, and that exhibited by epigallocatechin gallate, the highest.[334] The inhibitory activity of high concentrations of epigallocatechin gallate exerted on viral neuraminidase and genomic RNA synthesis, better than that of epicatechin gallate and much higher than that of epigallocatechin, was ascribed to the 3-galloyl moiety belonging to catechin, while the 5′-OH group present on the trihydroxybenzyl moiety at 2-position had not a significant role.[335,336]

Theaflavin-3,3′-digallate possesses the best inhibitory activity against viral neuraminidase among the three gallate derivatives formed by theaflavin. Further comparative assessment proved that dimeric molecules, such as theaflavin and procyanidin B-2, generally displayed more enhanced antiviral activity against influenza viruses than catechin monomers.[337]

Quercetin (3,3′,4′,5,7-pentahydroxyflavone occurring in large amounts in fruits and vegetables: berries, grains, kale, onion) is well-known for its antioxidant abilility that relies on its capacity to neutralize free radical species by hydrogen donation.[299] This flavonol acts against COVID-19-associated inflammation by modulating NF-kB activation.[338,339] Quercetin and luteolin (3′,4′,5,7-tetrahydroxyflavone) lower IL-6 expression in mast cells[340] and can be considered as a secure alternative to the therapy based on corticosteroids. Results obtained on mouse alveolar macrophages showed that luteolin inhibits lipopolysaccharide-induced inflammation, encompassing the expressions of TNF-α, IL-6, cyclooxygenase-2, and inducible nitric oxide synthase. The generation of reactive oxidative species was hampered by lowering NF-κB and AP-1 (activator protein 1) activation mechanisms. So, luteolin can be incorporated in the therapy against lung inflammatory diseases.[58] Computational simulations aim to test such molecules for their capacity to act as ACE2 receptor blockers, hampering the ability of the virus to exploit cellular mechanisms and subsequently replicate.[299,341]

In a study dealing with a comparison between flavonoids and classical antivirals, it has been proved that polyphenolics are able to bind to the C-terminus of either S1 or S2 domains of SARS-CoV-2 spike protein, this interaction being stronger than

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

that involving hydroxychloroquine. Flavonols like quercetin and *fisetin* exhibited the smallest and equal binding energy of −8.5 kcal/mol, pointing toward an identical and strong predilection for binding to S2 domain of the spike protein. In spite of this comparable propensity for the S2 domain, the additional 5-OH group present on the chromone ring of quercetin conferred a distinct manner of establishing hydrogen bonding interactions when compared to fisetin, which consisted of interaction with different residues of the S2 domain. In the case of kamferol, the lack of one −OH group at the 3′-C position of the phenyl ring led to a reduction in the binding affinity (−7.4 kcal/mol) and to a preference to bind to S1 domain, rather than to S2 domain, noticed also in the case of other investigated flavonols: quercetin, fisetin, and isorhamnetin (3′-methoxylated derivative of quercetin). Among other natural phenolics investigated in this research, pterostilbene and curcumin, both bound to the C-terminal of the S1 domain, with curcumin exhibiting better affinity.[296] Clinical studies for which diminished risk of error is reported, showed that oral quercetin can lower the prevalence and period of respiratory tract infections in some populations; nevertheless, further researches are needed to ascertain the ability of quercetin to lower the frequency of occurrence and duration of respiratory infections.[342]

In vitro and in silico studies proved that quercetin has the ability to interfere with the activity of compounds responsible for different steps of the coronavirus access to the target and replication cycle such as 3-chymotrypsin like protease, papain-like protease, and NTPase/helicase. Being characterized by a pleiotropic activiity and the lack of toxic potential, quercetin and its derivatives may be included in clinical trials to fight against the coronavirus.[339]

Quercetin has confirmed its ability to interfere with a series steps related to the viral capacity of the pathogen, virus access, replication, or protein assembly, therapeutic features enhanced in combination with vitamin C. Furthermore, given the absence of side effects, the coadministration of these unexpensive antioxidant compounds plays a role in the prophylaxis and the early therapy of respiratory infections like that caused by COVID-19. The reported synergetic antiviral capacity was ascribed to a sum of immunomodulatory and antiviral properties and to the ability of ascorbate of recycling quercetin, boosting efficacy. These inexpensive and secure alternatives should be considered for experimental use. Populations at high risk should benefit from the inclusion of quercetin and vitamin C, alongside convalescent plasma and remdesivir.[343]

Kaempferol. Kaempferol (3,4′,5,7-tetrahydroxyflavone) endowed with high bioavailability can inhibit the 3a ion channel of the coronavirus. The interference of this flavonol with the steps of the virus life cycle makes such a bioactive principle a multitarget one.[299] The presence of one −OH group at the C-4′ position on the B ring of the flavinic structure, the C2−C3 double bond, and the keto group at the C-4 position promotes its activity as a neuraminidase inhibitor.[337] *Baicalein* (5,6,7-trihydroxyflavone) and more actively *baicalin* (7-*O*-glucuronide of baicalein) inhibit the RNA-dependent RNA polymerase of SARS-CoV-2. Given their antiviral potential, these safe phytocompounds are recommended for further studies, aiming at incorporation, either as such or combined with remdesivir (classical antiviral nucleoside analogue of adenine), in anti-COVID-19 therapy.[344] Also, baicalein and baicalin, alongside terpenes and peptides, are inhibitors of transmembrane serine protease 2. These compounds interact with distinct binding sites of the virus, and this leads to an increase of their bioactivity. Molecular docking results show the ability of baicalein to act as ACE2 receptor inhibitor.[289,345]

Naringenin, a trihydroxy flavanone, suppresses mitogen activated protein kinase phosphorylation by lowering both NF-κB and activator protein 1 translocation as well as their attachment to DNA, hindering the generation of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, or IL-33.[346] Naringenin confirmed its ability to suppress lung/respiratory overexpression and eosinophilic inflammation of airways in asthma. The counteraction of acute neutrophilic inflammation of airways was also achieved by the previously reported suppression of the NF-κB pathway.[347]

A recent study aimed at evaluating the activities of a series of phenolics belonging to flavonoid and nonflavonoid classes and alkaloids (benzoic acid, gallic acid, resveratrol, oleuropein, ellagic acid, quercetin, naringenin, and caffeine) to act as inhibitors of RNA-dependent RNA polymerase in severe acute respiratory syndrome linked to SARS-CoV-2 pathology. These activities were compared to those noted for nucleoside analogues ribavirin or remdesivir. The docking studies resulted in a ranking based on the values of the binding energy, established with SARS-CoV-2 polymerase: remdesivir > gallic acid > quercetin > caffeine > ribavirin > resveratrol > naringenin > benzoic acid > oleuropein > ellagic acid. Computational simulations by molecular docking showed that all investigated polyphenols could establish hydrogen bonds with some of the nucleotide triphosphate entry channels, namely at ARG 553, ARG 555, or LYS 545, except for oleuropein and caffeine. It was inferred that this may impact the access of the substrate or of divalent cations to the central active site cavity, resulting in inhibition of enzyme activity. Gallic acid and quercetin proved to have higher affinity than ribavirin for SARS-CoV-2 polymerase and exhibited drug-like behavior and pharmacokinetic features. Moreover, resveratrol, benzoic acid, ellagic acid, and naringenin also showed some potential as polymerase inhibitors. Further research is nonetheless necessary to explore the efficacy of these phenolic compounds in treating COVID-19.[348]

STUDIES DEALING WITH NONFLAVONOIDS, FLAVONOID, AND FLAVONOID-GLYCOSIDES

Other in vitro and in silico studies proved the ability of phenolics to impede either coronavirus access or replication. Gallocatechin gallate, epigallocatechin gallate, quercetin, baicalin, hesperetin, luteolin, as well as more rarely investigated flavonoids (amentoflavone, papyriflavonol A, scutellarein), as plant-sourced secondary metabolites confirmed for their anti-inflammatory and antioxidant activity can impact 3-chymotrypsin like protease, papain-like protease and NTPase, and essential proteins for the infective potential of the coronavirus. Recently, the ability of flavonoids to inhibit two promotors of the infective potential of the virus that dissociate spike protein in its subunits (transmembrane serine protease 2 and furin) has been subject to investigation. Their pleitropic features are also corroborated with the absence of systemic toxicity, enabling further development of the therapeutic strategies against the coronavirus.[349]

Molecular docking studies were applied to explore the antiviral potential of rutin (quercetin-3-*O*-rutinoside), myricitrin (3,3′,4′,5,5′,7-hexahydroxyflavone 3-*O*-rhamnoside or

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

myricetin 3-*O*-rhamnoside), and other members of flavonoid glycosides group such as mearnsitrin (myricetin 4′-methyl ether-3-*O*-rhamnoside) and quercetin 3-*O*-*b*-D-glucoside (isoquercitrin). Rutin, a flavonoid glycoside found mainly in citrus fruits, berries, apple, peaches, grape seeds, and red pepper, presented the best potential to inhibit main SARS-CoV-2 protease, followed by isoquercitrin, mearnsitrin, and myricitrin, isolated from vegetables, fruits, nuts, and spices. The antiviral activity of rutin is complemented by the anti-inflammatory potential, so this compound is recommended for confirmatory in vivo studies as a therapeutic agent.[350]

Methoxylated flavonoids (tangeretin, nobiletin, hesperetin) and naringenin proved the ability to strongly bind to the three essential receptors: receptor binding domain of spike glycoprotein, the protease domain of ACE-2 receptor, and SARS-CoV-2 protease. The interaction was more efficient when compared to that established by the reference tested ligands, namely protease inhibitors lopinavir and nafamostat used in classical antiviral therapy. Considering the three main proteic targets involved in the viral infection (the SARS-CoV-2 protease, the receptor binding domain of spike glycoprotein, and the ACE2 receptor), hesperidin could bind the most efficiently, as revealed by docking scores. This glycoside of hesperetin (the methoxylated derivative of eriodictyol, a flavanone) establishes with the SARS-CoV-2 protease a stronger interaction than lopinavir (classical antiretroviral behaving as protease inhibitor). Alongside hesperidin, other flavonoids present in oranges in smaller a amount, naringenin and tangeretin, also proved to have better affinity than lopinavir and nafamostat for the three key aforementioned targets, so it was suggested that these interactions can also impart inhibitory activity against the viral infection.[351]

Other computational simulations independently performed on hesperidin showed a small binding energy, both with the S protein and the main protease (Mpro) that converts the early viral proteins, pp1a and ppa1b, into the complex important for viral replication.[352] By targeting viral main protease, hesperidin renders more difficult the processing of the early proteins that are part of the viral genome (pp1a and pp1ab) into functional proteins into the host cell. The obtained binding energy of hesperidin is smaller than that proper to ritonavir, lopinavir, and indinavir, proving high affinity. Also, by overlapping the complex ACE2-receptor binding domain and the complex hesperidin−receptor binding domain, a specific superposition of hesperidin with the interface of ACE2 receptor could be noticed, pointing out that hesperidin may obstruct the interaction of the ACE2−receptor binding domain of the S protein.[353] Moreover, for both hesperidin and ascorbic acid, the antiviral activity is potentiated by the anti-inflammatory activity and by the ability to neutralize the impairment induced by the reactive oxygenated species.[352]

A molecular docking-based investigation performed on 26 phenolic compounds showed that hesperidin also exhibited one of the highest affinities for the crystallized form of the main protease of SARS-CoV-2.[352,354] This flavanone glycoside impacts some of the amino acids of the protein by hydrogen bonding. Hesperidin and rutin were more efficient in impacting main protease than nelfinavir, with reported scores of −178.59 and −176.27.[354]

Molecular docking determinations enabled establishing a ranking by affinity: hesperidin > rutin > diosmin > apiin > diacetylcurcumin. Moreover, these investigated flavonoids were more efficient in impacting Mpro than the classical antiretroviral drug nelfinavir. The potential to target key proteins and the biologically secure profile recommend these compounds for incorporation in anti-COVID-19 therapy. Nevertheless, confirmation is required by studies performed in vitro and in vivo to ascertain the medicinal viability.[352,354]

CAROTENOIDS

Astaxanthin. Astaxanthin (Figure 6) was a confirmed for its safety in use, antioxidative, anti-inflammatory, and immunomodulatory features.

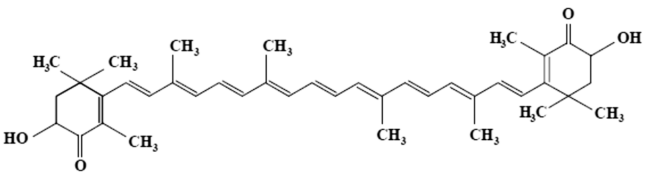


Figure 6. Astaxanthin, a carotenoid belonging to the class of xanthophylls.

Preclinical studies sustain the preventative potential in acute lung injury and acute respiratory distress syndrome. The protective influence is exerted by modulating the expression of pro-inflammatory cytokines IL-6, IL-8, IL-1β, and TNF-α. Also, astaxanthin modulates peroxisome proliferator-activated receptors activity. Astaxanthin hampers oxidative impairment and alleviates overexpression of inflammatory responses by control over signaling pathways like NF-κB, NLRP3 inflammasome, as well as Janus kinase-signal transducer and activator of transcription (JAK/STAT). So, given this potential to alleviate inflammation, astaxanthin can be included in therapy as adjunctive supplement. Nevertheless, its intervention in COVID-19 would need further validation in clinical studies.[355]

A novel in silico study approached the interaction of carotenoids commonly present in food with common therapeutic targets of SARS-CoV-2: spike protein (including mutant S proteins corresponding to the variants of concern), main protease, helicase, replication complex of RNA-dependent RNA polymerases, and ADP-ribose phosphatase. Molecular docking investigations showed that some of the compounds had high affinities toward target receptors. Crocin especially binds robustly to the replication complex of RNA-dependent RNA polymerases, with the lowest binding energy of −10.5 kcal/mol. This interaction is established via van der Waals forces, hydrogen bridges, carbon−hydrogen bonds, and π-alkyl interactions. It was reported that the strong interaction with the RNA-binding site of the replication complex is the main underlying antiviral activity. Also, crocin proved to have low binding energy values and high affinity for the other aforementioned targets. The results were confirmed by molecular dynamics simulations that revealed that crocin binds to several key amino acid residues of the investigated receptors. α-Carotene, capsanthin, and neoxanthin bound to the ADP-ribose phosphatase were proved by the lowest values of binding energies of −9.6, −9.4, and −9.4 kcal/mol, respectively, indicating the high affinity of the discussed carotenoids. Hence, crocin and other carotenoids can be included in prophylaxis and therapy against SARS-CoV-2.[356]

Molecular docking simulations were applied to assess the affinity of marine carotenoids for SARS-CoV-2 S glycoprotein. The inhibitory activity against SARS-CoV-2 pseudovirus was reported in studies on HEK293 cells, with overexpressed

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

angiotensin converting enzyme 2. Siphonaxanthin isolated from *Codium fragile* exhibited an important inhibitory potential against SARS-CoV-2 pseudovirus entry portal, proved by a value of IC_{50} of 87.4 μM, whereas fucoxanthin isolated from *Undaria pinnatifida* sporophyll did not. Although further investigations would be required to enlighten the inhibitory mechanisms followed by siphonaxanthin against SARS-CoV-2 infection and to thorougly describe the biological activities of siphonaxanthin in vitro and in vivo in the presence of SARS-CoV-2, this study points toward the benefits of the application of marine carotenoids.[357]

OTHER PLANT SECONDARY METABOLITES

Glycyrrhizin. Glycyrrhizin (Figure 7) is known for its pharmacological virtues, so the therapeutic potential of glycyrrhizin in the treatment of COVID-19 was investigated.

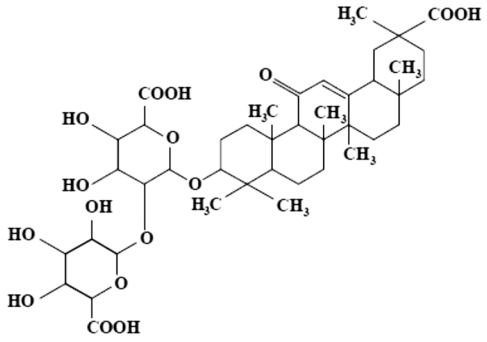


Figure 7. Glycyrrhizin, a saponin with a triterpene skeleton as aglycone.

Its actions encompass: inhibition of reactive oxygenated species accumulation, inhibition of overproduction of airway droplets, inhibition of thrombin, hampering of proinflammatory cytokine release, induction of endogenous interferon,[358] and disruption of the interaction between the receptor-binding domain of SARS-COV2 and ACE2 through binding to angiotensin converting enzyme II.[358,359] Also, glycyrrhizin strongly inhibits the viral main protease, as proved in experiments using a fluorogenic 3-chymotrypsin like protease activity kit based on infected Vero E6 cells.[360]

Alkaloids. Alkaloids inhibit targets that are necessary for the virus life cycle and related to SARS-CoV infective potential and pathogenicity. Alkaloids impact structural proteins of the virus (spike glycoprotein and nucleocapsid protein), as well as the ACE2 receptor. Moreover, inhibition of the enzymes responsible for virus replication, such as RNA dependent RNA polymerase and 3-chymotrypsin-like protease, was reported.[361−364] It has been suggested that alkaloids that interact with DNA, such as berberine, berbamine, berberrubine, chelerythrine, chelidonine, coptisine, dicentrine, jatrorrhizine, palmatine, and sanguinarine, could also be exploited for their anti-SARS-CoV-2 potential.[362,364]

CRITICAL CONCLUSIONS AND FUTURE PROSPECTS

The overactivation of the immune response in viral pathologies implies the release of reactive oxygen species and proinflammatory cytokines. Enhanced inflammation can activate coagulation, increase the number of airway droplets, and eventually is likely to give rise to multiple organ failure and anoxia. So the anti-inflammatory and immunomodulatory role of endogenous and exogenous are welcome in the complex context of cytokine burst.[8,11]

Antioxidant impairment and illness severity are tightly related, where antioxidant deficiency amplifies viral load but also has been identified as possible repercussion of progression of COVID-19 from mild to severe illness. Antioxidant deficiency triggers oxidative burst and the expression of pro-inflammatory markers. The interaction pathogen Toll-like receptor triggers prooxidative pathways, giving rise to TNF-α-induced activation of nicotinamide adenine dinucleotide phosphate oxidase, a major ROS source in macrophages. Viral pathologies imply a vicious cycle-like mechanism, oxidative stress promoting inflammatory responses by activating transcription factors linked to inflammation. On the other hand, cytokine storm itself triggers oxidative stress via inflammatory mediators.[8]

Antioxidant impairment accelerates viral mutation and replication. Moreover, the virus hijacks the host's antioxidant profile, hence the importance in avoiding deficiency. The immunomodulatory potential of antioxidants encompasses suppression of pro-inflammatory cytokine release and control on the release and function of T and B cells.[280] Direct antiviral mechanisms of action of antioxidants encompass interference on virus access in the host cell and multiplication: impact on S protein affecting binding to receptor and membrane fusion or direct interference with the activity of the ACE2 receptor by blocking its interface.[69,291]

In the last two years, efforts have been directed toward determining the most efficacious antioxidant(s) in anti-SARS-CoV-2 therapy. Low molecular weight thiol impairment (mainly glutathione, key contributor to the endogenous antioxidant profile) has been recognized as a source of illness severity.[38,39,43]

Pro-oxidative effects in SARS-CoV-2 are linked to alterations occurring in the cell's metabolism and transmembranar fluxes of glutathione and cysteine. It is considered that these represent the repercussions of an enhanced cysteine utilization in viral protein synthesis and endoplasmic reticulum stress activation that impacts the expressions of both Nrf2 and NF-kB, transcription factors responsible for the modulation of oxidative stress and glutathione metabolism, with relevance for the control of the pro-inflammatory impact of the virus. Perturbations of the thiol−disulfide redox balance in the lung tissue and lining fluids promotes the risk of infection and lowers the host's ability to react to pathogens and hamper complications.[365]

As proved in the case of other viral pathologies,[366,367] pro-oxidative factors are promotors of the virus−host cell interaction, enhancing the affinity of the spike protein for the ACE2 receptor.[74] It was stressed out that this binding is impacted by the cell's redox equilibrium, ensured by the low molecular weight thiols present in the extracellular fluids and by the cysteine residues present in the extracellular domains of membrane proteins.[365,368] A chronically lowered reduced glutathione/oxidized glutathione ratio defines a high oxidative stress level related to the occurrence of low-molecular oxidation products such as lipid peroxides and cysteine disulfides (present in protein or nonprotein conjugate forms) in blood plasma.[369]

Glutathione levels diminish with age and become lower in chronic medical conditions associated with both oxidative stress and infectious disease severity such as diabetes,

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

hypertension, and chronic obstructive pulmonary disease.[370] It was asserted that glutathione amounts in tissues other than blood cells are likely to be more severely impacted by oxidative stress because erythrocytes are lacking mitochondria that represent the main ROS source. It was asserted that glutathione amount should be corroborated with additional biomarkers assessed in blood and urine to determine more accurately discrepancies that may occur in the levels of oxidative stress in subjects generally healthy: F2-isoprostanes, malondialdehyde, and total cysteine disulfide.[370] Glutathione status was not correlated with malonyl dialdehyde levels nor with total cysteine, the authors of the clinical study suggesting that the glutathione buffering capacity does not necessarily constitute a limiting protective factor against oxidative stress in an analyzed cohort of healthy elderly.[370] Nevertheless, oxidative stress as an impairing condition provoked by reactive oxygen species overproduction is counteracted by antioxidants, glutathione being one of the most abounding.[66]

Post-hoc analyses of a randomized control trial[370] showed that administration of medium to high GlyNAC (glycine-*N*-acetylcysteine) doses to subjects characterized by elevated oxidative stress (revealed by higher than median values of malonyl dialdehyde, as lipid peroxidation marker) and lowered the glutathione profile (below the median level), resulted in efficacious glutathione restoration, proving that glutathione replenishment from dietary cysteine and glycine occurs on the basis of cellular requirements. Importantly, comparable results were noticed when total cysteine was considered as a high oxidative stress marker.[370]

Glycine (present in the structure of glutathione tripeptide), on the other hand, is a one-carbon metabolite and functions as $-CH_3$ donor, required for DNA synthesis, cellular reactions and cartilage, brain, and cellular health. Moreover, methyl group impairment was identified as an aspect responsible for COVID-related complications.[371] Glycine levels were found to be significantly lower in older adults, when compared to those of young subjects, and were inversely correlated with insulin resistance.[370] Glycine levels are also decreased in obesity, a condition associated with illness severity.[372] GlyNAC supplementation proved safe, boosting glutathione levels in older healthy adults with pronounced glutathione deficiency and elevated oxidative stress. In subjects without enhanced oxidative impairment, the circulating glutathione level was kept stable.[370]

A pilot study focused on GlyNAC supplementation in patients hospitalized for acute COVID-19 infection, and having high oxidative stress and impaired glutathione levels proved that cysteine (from *N*-acetylcysteine) supports mitochondrial metabolism and is a sulfhydryl group donor, required for maintaining redox homeostasis and for biosynthesis of various metabolites.[66] In the context of viral pathology, mainly during the first stages, there is an increased cysteine uptake to sustain viral replication, while the enhanced viral protein synthesis leads to thiol depletion and oxidative stress activation.[365] The corresponding oxidized form, cysteine disulfide, at concentrations higher than 300 μM in the elderly, is associated with an increased cardiovascular risk,[373] a condition tightly linked to COVID-19 severity. Benefits imparted by GlyNAC supplementation encompass: amelioration of glutathione deficiency, of glycine and cysteine profile, control on oxidative stress and inflammation, and correction of mitochondrial, endothelial vascular dysfunction, and insulin resistance, as proved in human clinical trials.[66,374,375] Improvement of T lymphocyte proliferative response, modulation of the inflammatory pathway, blockage of NF-κB activation, and alleviation of respiratory distress have also been reported.[75,376]

In a two-center cohort study dealing with moderate or severe COVID-19 pneumonia, *N*-acetylcysteine administration (1200 mg daily), lowered the risk for mechanical ventilation and mortality.[377] Poly(lactic-coglycolic acid) nanoparticles encapsulating *N*-acetylcysteine have proved their efficiency in hampering the damaging effects of reactive oxygen species, inflammation, and acute lung injury. The nanoformulation enables the targeted release of *N*-acetylcysteine to the lungs with improved pulmonary deposition and increased pulmonary concentrations at lower *N*-acetylcysteine dose.[378]

Maintaining the endogenous antioxidant profile is therefore pivotal, as pre-existing oxidative stress is a strong promoter of the affinity of the spike protein for the ACE2 receptor. If already bound, the conversion of disulfides to thiols in the receptor binding domain exerts a restricted influence on the binding affinity of the spike protein for the ACE2 receptor. Importantly, if the influence of reductive agents is exerted before the binding, a remarkable conformational change occurs in the receptor binding domain of the spike protein that negatively impacts this binding.[74]

These findings enable the exploitation of novel therapeutic targets and are in line with previous reports showing that appropriate cellular redox status, preserved mainly via the thiol−disulfide balance, impedes both viral fusion and entry processes.[379,380] Conversely, disulfides, formed during oxidation of cysteine thiols, enable folding and conformational alterations in the spike protein, prone to viral entry into host cells.[381,382]

So, as the affinity of the virus for the ACE2 receptor is promoted by the oxidation of the cysteine moieties present in the receptor binding domain of the S protein and in the peptidase domain of ACE2, the reductive ability imparted by antioxidant molecules helps in hampering the infective potential of the virus.[77,84,382] The particular modulative antioxidant intervention on the renin−angiotensin system, and the control on ACE2 expression is controversially debated. The capacity to promote ACE2 expression was first viewed as a factor enabling virus entry in the host cell. Nevertheless, it has also been found that ACE2 activity can impart protection in critical stages of the disease, which is consistent with the results of animal studies.[305−307] In the particular case of the adipose tissue, polyphenols like resveratrol can lower ACE-2 overexpression. This effect, alongside a reduction in lepin, can reduce pro-inflammatory activity and illness severity.[308,309]

Recent studies aiming at delineating and solving the above-mentioned controversies focused on the largely debated impact of ACE2 activation. When the spike protein of SARS-CoV-2 interacts with the ACE2 receptor, transmembrane serine protease 2 proteolytically dissociates ACE2 and allows viral particles to access the host cell, replicate, and undergo cell-to-cell transmission. Moroever, as spike glycoprotein attaches to the ACE2 receptor, this interaction impairs angiotensin II conversion to angiotensin 1−7. The accumulation of angiotensin II, a reactive oxygenated species promotor results in lung injury and pneumonia.[383] In vitro studies proved the existence of a direct correlation between the ACE2 expression and SARS-CoV-2 infectivity in the lungs and other tissues.[383] Renin−angiotensin−aldosterone system inhibitors were developed, aiming at impeding ACE2 receptor attachment to S protein and viral entry into the lungs and heart.[383,384]

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

Nevertheless, it has been recently asserted that the renin−angiotensin−aldosterone system inhibitors can induce a feedback mechanism that results in ACE2 receptor activation, promoting S protein binding and eventually favoring viral entry in the lung and heart.[46,383] Recently, ACE inhibitors have been investigated for their ability to enhance disease severity due to ACE2 expression activation. It was asserted that zinc impairment provoked by chronic use of ACE inhibitors may increase COVID-19 pathogenicity in susceptible subjects.[218] A multicenter study is nevertheless required to thoroughly determine the real impact on zinc amounts in COVID-19 patients who are taking ACE inhibitors or other pharmaceuticals likely to result in low zinc amounts.[218]

Critical discussions were also directed toward the role of soluble ACE2 results after shedding. It has been asserted that ACE2 cleaved by transmembrane protease serine 2 allows SARS-CoV-2 access in the host cell and damage, whereas ACE2 cleaved by ADAM17 imparts rather protective effect, mainly against detrimental influence of *angiotensin II*. Shedding by transmembrane protease serine 2 is followed by membrane fusion, RNA release into the cytoplasm, and replication. Soluble ACE2 is able to bind the virus, but an intracellular environment is required for virus replication. With the contribution of transmembrane protease serine 2, ectodomain shedding of ACE2 modulated by ADAM17 could promote SARS-CoV cell access via endocytosis. Nevertheless, ADAM17 activity is not considered a prerequisite for viral entry through fusion, which is a more effective way than endocytosis to achive viral replication.[385] Soluble ACE2 resulting after shedding, at high concentrations, was particularly correlated to disease severity. Nevertheless, clinical-grade recombinant human ACE2, a soluble, exogenous form of ACE2 can bind to SARS-COV-2 lowering the infective potential, as shown by studies performed on engineered human tissues.[86]

Alongside the impact on the viral spike protein and the ACE2 receptor, other reported mechanisms followed by antioxidants are inhibition of dipeptidyl peptidase 4 (viral coreceptor) of transmembrane protease serine 2 or furin that also enable virus access by promoting S protein cleavage, inhibition of helicase, impact on papain like protease, 3-chyomotrypsin like protease, or RNA-dependent RNA polymerase that promote viral replication.

Not all of the reports converge toward the same conclusions with respect to the clinical benefits of nonvitamin antioxidants as therapeutic agents. Appropriate timing and dosage, cautious supplementation meant to avoid deficiency, impact of overload and pro-oxidative activities, mutual influences of these micronutrients, as well as their complex relationship with other antioxidant species or other therapeutic agents, are essential factors that should be considered.

Certain mutual influences are highly relevant in anti-SARS-CoV-2 antioxidant/micronutrient administration. It was asserted that glutathione biosynthesis is modulated similarly to a rheostat system, developed to preserve adequate antioxidant capacity, at the same time hampering an over-generation of low molecular antioxidants that could negatively impact on the significant roles of reactive oxygenated species as signaling chemical species.[386] Glutathione and vitamin D contribute to the replenishment of each other's level to restoring the antioxidant profile, and both deficiencies lead to illness severity.[38,39,43] While glutathione boosts Th1-related immune response,[58] vitamin D triggers the activity of Th2 and T regulatory lymphocytes but inhibits Th1 lymphocytes, modulating inhibitory and inflammatory cytokines.[54] Zinc triggers glutamate−cysteine ligase expression, promoting de novo glutathione synthesis.[155] Moreover, zinc absorption is promoted by glutathione.[218,387] Excessive zinc amounts, exceeding the recommended daily allowances, can convert zinc into a pro-oxidant, with pro-inflammatory and pro-apoptotic effects. The copper deficiency induced by zinc excess may result in impaired expression of copper-dependent enzymes.[155,203,204] The consideration of the complex role of antioxidants in anti-SARS-CoV-2 therapy enable the development of strategic research directions and the exploitation of novel therapeutic targets.

Antioxidant supplementation is not meant to replace classical antiviral and anti-inflammatory treatment, but it can be considered as auxiliary therapy, at least to prevent deficiencies related to an impaired immune system. Nutrition represents one of the key factors influencing the antioxidant/oxidant balance and inflammation.

AUTHOR INFORMATION

Corresponding Author

Aurelia Magdalena Pisoschi − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania;* orcid.org/0000-0002-9697-4429; Email: aureliamagdalenapisoschi@yahoo.ro

Authors

Florin Iordache − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania*

Loredana Stanca − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania*

Iuliana Gajaila − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania*

Oana Margarita Ghimpeteanu − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania*

Ovidiu Ionut Geicu − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania; Faculty of Biology, Department Biochemistry and Molecular Biology, University of Bucharest, 050095 Bucharest, Romania*

Liviu Bilteanu − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania; Molecular Nanotechnology Laboratory, National Institute for Research and Development in Microtechnologies, 077190 Bucharest, Romania*

Andreea Iren Serban − *Faculty of Veterinary Medicine, Department Preclinical Sciences, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 050097 Bucharest, Romania; Faculty of Biology, Department Biochemistry and Molecular Biology, University of Bucharest, 050095 Bucharest, Romania;* orcid.org/0000-0003-1862-3524

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jmedchem.2c01134

Author Contributions

The authors have contributed equally.

Notes

The authors declare no competing financial interest.

Biographies

Aurelia Magdalena Pisoschi got her B.Sc. degree in Chemistry, her M.Sc. degree in Organic Chemistry and Physical Chemistry, her Ph.D. degree in Chemistry (University of Bucharest), and finalized postdoctoral studies in Biochemistry and Biotechnology. She is Associate Professor at the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine, titular of the courses in Chemistry (sections in English and French language), Additives and Ingredients in Food Industry and Food Chemistry. Her research interest encompasses food chemistry, antioxidants, and analytical chemistry: electroanalysis, enzyme sensors, and UV−vis spectrometry. The publications (more than 80 works: articles, books, and communications) resulted in a high number of citations (over 4500 in Google Scholar), with Hirsch indexes of 16 (Google Scholar), 14 (Web of Science), and 14 (Scopus), in August 2022.

Florin Iordache got his B.Sc. in Biology followed by a M.Sc. degree in Biochemistry and Molecular Biology. His Ph.D. degree was obtained in the field of Biology, and his Thesis defense (2013), was entitled "Epigenetic Mechanisms Involved in Stem Cell Differentiation". At present, is a lecturer at the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine, titular of the courses in Biochemistry (section in English language IInd year of study), and Enzymatic and Immunological Techniques used for food analysis. His research interest encompasses cell biology, stem cells, food biochemistry, antioxidants, essential oils, and natural products used for food preservation. He published over 80 articles and five books, participating in four international and six national projects, and coordinating two projects as project director.

Loredana Stanca got her B.Sc. degree in Biology (specialization in Biochemistry), her M.Sc. degree in Biochemistry and Molecular Biology, and her Ph.D. Degree in Biology (University of Bucharest). She is a Lecturer at the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine, titular of the courses Molecular Biology Techniques applied in Veterinary Medicine (section in English language), and Biochemistry (section of Food Control and Expertise). Her research interest encompasses food biochemistry, glycation end-products toxicity, colorectal cancer, nanotoxicology. The publications (about 45 works: articles, book chapters, and communications) resulted in a high number of citations (over 435 in Google Scholar), with Hirsch indexes of 11 (Google Scholar), 9 (Web of Science) and 9 (Scopus), in August 2022.

Iuliana Gajaila got her B.Sc. degree in Chemical Engineering (Polytechnic Institute of Bucharest), her M.Sc. degree in Biostatistics (University of Bucharest), her Ph.D. degree in Agrochemistry, and finalized postdoctoral studies in Food Hygiene and Public Health (University of Agronomic Sciences and Veterinary Medicine of Bucharest). She is a lecturer at the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine, titular of the course in Chemistry (Control and Food Expertise specialization). Her research interest encompasses food chemistry, food preservation, microbiological sensors, analytical chemistry, and biostatistics. The publications (more than 40 works: articles, books, and communications) resulted in over 80 citations in Google Scholar, with Hirsch indexes of 3 (Google Scholar), 3 (Web of Science), and 3 (Scopus), in August 2022.

Oana-Margarita Ghimpeteanu, 37 years old, is an engineer in the field of Food Engineering and a lecturer at the Faculty of Veterinary Medicine, University of Agronomic Sciences and Veterinary Medicine in Bucharest. She has a Ph.D. Degree in the field of Veterinary Medicine since 2013. Her professional experience is expressed through continuous research in the field of food control of products of both animal and plant origin. It started during her doctorate and postdoctorate and continues during her teaching activity in specialized disciplines. The experience in the field of quality and safety of agrifood products is materialized in the publication of four books, 80 scientific papers (articles and communications), member in three research projects, and seven educational projects. Citations: 74 (Hirsch index), 4 (Google Scholar), and 2 (Web of Science).

Ovidiu Ionut Geicu, postdoctoral researcher, has obtained his Ph.D. degree in Biology in 2019 (University of Bucharest). Since 2016, he has been a member in three research projects in the field of inflammation, oxidative stress, and AGEs pathological effects, carried out within the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine. His skills include techniques such as cell culture, molecular biology techniques (qRT-PCR, ddPCR, Southern and Northern blotting), 2-DE, Western blot, ELISA, etc. The publications (more than 28 works: articles, books, and communications) are highlighted in a Hirsch index of 7 (Google Scholar), 6 (Web of Science), and 6 (Scopus).

Liviu Bilteanu holds a B.Sc. degree in Physics, a B.Sc. degree in Mathematics, a M.Sc. degree in Theoretical Physics, and a Ph.D. degree in Physics. He is a medical doctor specializing in Radiation Oncology at the Oncological Institute in Bucharest. Dr. Bilteanu is an Associate Professor at the University of Agronomic Sciences and Veterinary Medicine, where he teaches Biophysics and Applied Mathematics in Life Sciences. He is also an associate researcher at the National Institute for Research and Development in Micro-technologies in Bucharest. His research interests are related to atomic scale calculations, silicon and graphene-based bionanotechnologies, biostatistics, cancer molecular biology, clinical research in oncology, and medical image analysis by machine learning algorithm.

Andreea Iren Serban got her B.Sc. degree in Biochemistry, her M.Sc. degree in Neurobiology, and her Ph.D. degree in Biology. Since 2017, she is a Ph.D. advisor at University of Bucharest in the field of Biology. She is Full Professor at the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Faculty of Veterinary Medicine, titular of Biochemistry and Molecular biology techniques applied in veterinary medicine courses. She has over 20 years of experience in the field of diabetes and cancer and their link with inflammation and oxidative stress and in vitro and in vivo biocompatibility of nanoparticles assessment. The publications (more than 75 works: articles, books, and communications) are highlighted in a Hirsch index of 15 (Google Scholar), 14 (Web of Science), and 14 (Scopus).

■ ABBREVIATIONS USED

ACE, angiotensin-converting enzyme; 3CLpro, 3-chyomotrypsin like protease; CC, chemokine family; COX, cyclooxygenase; CXC, chemokine (C-X-C motif) ligand; DPP-4, dipeptidyl peptidase 4; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GPx, glutathione peroxidase; GlyNAC, glycine-*N*-acetylcysteine; HIF1α, hypoxia-inducible factor 1 α; ICAM-1, intercellular

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

adhesion molecule 1; IL, interleukin family; JAK/STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NRF2, nuclear factor-erythroid factor 2-related factor 2; NF-κB, nuclear factor-κB; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; ROS, reactive oxygen species; SELENOP, selenoprotein P; SELENOF, selenoprotein F; TGF-β, transforming growth factor β; TLR, toll-like receptor; TMPRSS2, transmembrane protease serine 2; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1

REFERENCES

(1) Lammi, C.; Arnoldi, A. Food-derived antioxidants and COVID-19. *J. Food Biochem.* **2021**, *45*, No. e13557.

(2) Bakadia, B. M.; Boni, B. O. O.; Ahmed, A. A. Q.; Yang, G. The impact of oxidative stress damage induced by the environmental stressors on COVID-19. *Life Sci.* **2021**, *264*, 118653.

(3) Fu, Y. S.; Ho, W. Y.; Kang, N.; Tsai, M. J.; Wu, J.; Huang, L.; Weng, C. F. Pharmaceutical prospects of curcuminoids for the remedy of COVID-19: Truth or myth. *Front. Pharmacol.* **2022**, *13*, 863082.

(4) Mrityunjaya, M.; Pavithra, V.; Neelam, R.; Janhavi, P.; Halami, P. M.; Ravindra, P. V. Immune-boosting, antioxidant and anti-inflammatory food supplements targeting pathogenesis of COVID-19. *Front. Immunol.* **2020**, *11*, 570122.

(5) Agod, Z.; Fekete, T.; Budai, M. M.; Varga, A.; Szabo, A.; Moon, H.; Boldogh, I.; Biro, T.; Lanyi, A.; Bacsi, A.; Pazmandi, K. Regulation of type I interferon responses by mitochondria-derived reactive oxygen species in plasmacytoid dendritic cells. *Redox Biol.* **2017**, *13*, 633−645.

(6) Sena, L. A.; Chandel, N. S. Physiological roles of mitochondrial reactive oxygen species. *Mol. Cell* **2012**, *48* (2), 158−167.

(7) Pisoschi, A. M.; Pop, A.; Iordache, F.; Stanca, L.; Predoi, G.; Serban, A. I. Oxidative stress mitigation by antioxidants - an overview on their chemistry and influences on health status. *Eur. J. Med. Chem.* **2021**, *209*, 112891.

(8) Pisoschi, A. M.; Pop, A.; Iordache, F.; Stanca, L.; Geicu, O. I.; Bilteanu, L.; Serban, A. I. Antioxidant, anti-inflammatory and immunomodulatory roles of vitamins in COVID-19 therapy. *Eur. J. Med. Chem.* **2022**, *232*, 114175.

(9) Leite Diniz, L. R.; Bezerra Filho, C.d.S.M.; Fielding, B. C.; Pergentino de Sousa, D. P. Natural antioxidants: A review of studies on human and animal coronavirus. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 3173281.

(10) Zhang, Z.; Rong, L.; Li, Y.-P. Flaviviridae viruses and oxidative stress: Implications for viral pathogenesis. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 1409582.

(11) Lee, J.; Jang, J.; Park, S. M.; Yang, S. R. An update on the role of Nrf2 in respiratory disease: Molecular mechanisms and therapeutic approaches. *Int. J. Mol. Sci.* **2021**, *22* (16), 8406.

(12) Osterholm, M. T. Preparing for the next pandemic. *N. Engl. J. Med.* **2005**, *352* (18), 1839−1842.

(13) Teijaro, J. R.; Walsh, K. B.; Rice, S.; Rosen, H.; Oldstone, M. B. Mapping the innate signaling cascade essential for cytokine storm during influenza virus infection. *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111* (10), 3799−3804.

(14) Sun, X.; Wang, T.; Cai, D.; Hu, Z.; Chen, J.; Liao, H.; Zhi, L.; Wei, H.; Zhang, Z.; Qiu, Y.; Wang, J.; Wang, A. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev.* **2020**, *53*, 38−42.

(15) Kong, R.; Yang, G.; Xue, R.; Liu, M.; Wang, F.; Hu, J.; Guo, X.; Chang, S. COVID-19 Docking Server: an interactive server for docking small molecules, peptides and antibodies against potential targets of COVID-19. *Bioinformatics.* **2020**, *36* (20), 5109−5111.

(16) Dietz, W.; Santos-Burgoa, C. Obesity and its implications for COVID-19 mortality. *Obesity.* **2020**, *28* (6), 1005.

(17) Muhammad, Y.; Kani, Y. A.; Iliya, S.; Muhammad, J. B.; Binji, A.; El-Fulaty Ahmad, A.; Kabir, M. B.; Umar Bindawa, K.; Ahmed, A. Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: A cross-sectional comparative study in Jigawa, Northwestern Nigeria. *SAGE Open Med.* **2021**, *9*, 205031212199124.

(18) Chien, J. Y.; Hsueh, P. R.; Cheng, W. C.; Yu, C. J.; Yang, P. C. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. *Respirology.* **2006**, *11* (6), 715−722.

(19) Reghunathan, R.; Jayapal, M.; Hsu, L. Y.; Chng, H.-H.; Tai, D.; Leung, B. P.; Melendez, A. J. Expression profile of immune response genes in patients with severe acute respiratory syndrome. *BMC Immunol.* **2005**, *6*, 2.

(20) Shimabukuro-Vornhagen, A.; Godel, P.; Subklewe, M.; Stemmler, H. J.; Schlößer, H. A.; Schlaak, M.; Kochanek, M.; Böll, B.; von Bergwelt-Baildon, M. S. Cytokine release syndrome. *J. Immunother. Cancer.* **2018**, *6*, 56.

(21) Tanaka, T.; Narazaki, M.; Kishimoto, T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy.* **2016**, *8* (8), 959−970.

(22) Hunter, C. A.; Jones, S. A. IL-6 as a keystone cytokine in health and disease. *Nat. Immunol.* **2015**, *16* (5), 448−457.

(23) Pathan, N.; Hemingway, C. A.; Alizadeh, A. A.; Stephens, A. C.; Boldrick, J. C.; Oragui, E. E.; McCabe, C.; Welch, S. B.; Whitney, A.; O'Gara, P.; Nadel, S.; Relman, D. A.; Harding, S. E.; Levin, M. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. *Lancet.* **2004**, *363* (9404), 203−209.

(24) Heid, M. E.; Keyel, P. A.; Kamga, C.; Shiva, S.; Watkins, S. C.; Salter, R. D. Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. *J. Immunol.* **2013**, *191*, 5230−5238.

(25) Kelley, N.; Jeltema, D.; Duan, Y.; He, Y. The NLRP3 inflammasome: An overview of mechanisms of activation and regulation. *Int. J. Mol. Sci.* **2019**, *20*, 3328.

(26) Lara, P. C.; Macías-Verde, D.; Burgos-Burgos, J. Age-induced NLRP3 inflammasome over-activation increases lethality of SARS-CoV-2 pneumonia in elderly patients. *Aging Dis.* **2020**, *11*, 756−762.

(27) Pisoschi, A. M.; Pop, A.; Cimpeanu, C.; Turcuş, V.; Predoi, G.; Iordache, F. Nanoencapsulation techniques for compounds and products with antioxidant and antimicrobial activity - a critical view. *Eur. J. Med. Chem.* **2018**, *157*, 1326−1345.

(28) Pisoschi, A. M.; Pop, A.; Cimpeanu, C.; Predoi, G. Antioxidant capacity determination in plants and plant-derived products: a review. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 9130976.

(29) Pisoschi, A. M.; Pop, A. The role of antioxidants in the chemistry of oxidative stress: a Review. *Eur. J. Med. Chem.* **2015**, *97*, 55−74.

(30) Samadi, M.; Shirvani, H.; Rahmati-Ahmadabad, S. A study of possible role of exercise and some antioxidant supplements against coronavirus disease 2019 (COVID-19): A cytokines related perspective. *Apunts Sports Med.* **2020**, *55* (207), 115−117.

(31) Silvagno, F.; Vernone, A.; Pescarmona, G. P. The role of glutathione in protecting against the severe inflammatory response triggered by COVID-19. *Antioxidants.* **2020**, *9* (7), 624.

(32) Gropper, S. S.; Smith, J. L.; Carr, T. P. *Advanced Nutrition and Human Metabolism*, 7th ed.; Cengage Learning Inc.: Wadsworth, 2017.

(33) Niki, E.; Tsuchiya, J.; Tanimura, R.; Kamiya, Y. Regeneration of vitamin E from a chromanoxyl radical by glutathione and vitamin C. *Chem. Lett. Jpn.* **1982**, *11* (6), 789−792.

(34) Pehlivan, F. E. Vitamin C: an Antioxidant Agent, In *Vitamin C*; Hamza, A. H., Ed.; IntechOpen, 2017; pp 23−35.

(35) Dzik, K.; Skrobot, W.; Flis, D. J.; Karnia, M.; Libionka, W.; Kloc, W.; Kaczor, J. J. Vitamin D supplementation attenuates oxidative stress in paraspinal skeletal muscles in patients with low back pain. *Eur. J. Appl. Physiol.* **2018**, *118* (1), 143−151.

(36) Jain, S. K.; Micinski, D. Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and gsh formation, and decreases ros and mcp-1 and il-8 secretion in high-glucose exposed u937 monocytes. *Biochem. Biophys. Res. Commun.* **2013**, *437* (1), 7−11.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(37) Lee, W. C.; Mokhtar, S. S.; Munisamy, S.; Yahaya, S.; Rasool, A. Vitamin D status and oxidative stress in diabetes mellitus. *Cell. Mol. Biol. (Noisy-le-Grand).* **2018**, *64* (7), 60−69.
(38) Jain, S. K.; Parsanathan, R. Can Vitamin D and L-Cysteine co-supplementation reduce 25 (OH)-Vitamin D deficiency and the mortality associated with COVID-19 in African Americans? *J. Am. Coll. Nutr.* **2020**, *39* (8), 694−699.
(39) Jain, S. K.; Parsanathan, R.; Achari, A. E.; Kanikarla-Marie, P.; Bocchini, J. A., Jr. Glutathione stimulates vitamin D regulatory and glucose metabolism genes, lowers oxidative stress and inflammation, and increases 25-hydroxy-vitamin d levels in blood: A novel approach to treat 25-hydroxyvitamin D deficiency. *Antioxid. Redox Signal.* **2018**, *29* (17), 1792−1807.
(40) Alvarez, J. A.; Chowdhury, R.; Jones, D. P.; Martin, G. S.; Brigham, K. L.; Binongo, J. N.; Ziegler, T. R.; Tangpricha, V. Vitamin D status is independently associated with plasma glutathione and cysteine thiol/ disulphide redox status in adults. *Clin Endocrinol.* **2014**, *81* (3), 458−466.
(41) Jain, S. K.; Micinski, D.; Huning, L.; Kahlon, G.; Bass, P. F.; Levine, S. N. Vitamin D and l-cysteine levels correlate positively with gsh and negatively with insulin resistance levels in the blood of type 2 diabetic patients. *Eur. J. Clin. Nutr.* **2014**, *68* (10), 1148−1153.
(42) Parsanathan, R.; Jain, S. K. Glutathione deficiency induces epigenetic alterations of vitamin D metabolism genes in the livers of high-fat diet-fed obese mice. *Sci. Rep.* **2019**, *9*, 14784.
(43) Polonikov, A. Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in COVID-19 patients. *ACS Infect. Dis.* **2020**, *6* (7), 1558−1562.
(44) Jain, S. K.; Parsanathan, R.; Levine, S. N.; Bocchini, J. A.; Holick, M. F.; Vanchiere, J. A. The potential link between inherited G6PD deficiency, oxidative stress, and vitamin D deficiency and the racial inequities in mortality associated with COVID-19. *Free Radic. Biol. Med.* **2020**, *161*, 84−91.
(45) Wimalawansa, S. J. Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. *Biology (Basel).* **2019**, *8*, 30.
(46) Abdrabbo, M.; Birch, C. M.; Brandt, M.; Cicigoi, K. A.; Coffey, S. J.; Dolan, C. C.; Dvorak, H.; Gehrke, A. C.; Gerzema, A. E. L.; Hansen, A.; Henseler, E. J.; Huelsbeck, A. C.; LaBerge, B.; Leavens, C. M.; Le, C. N.; Lindquist, A. C.; Ludwig, R. K.; Reynolds, J. H.; Severson, N. J.; Sherman, B. A.; Sillman, H. W.; Smith, M. A.; Smith, M. A.; Snortheim, M. J.; Svaren, L. M.; Vanderpas, E. C.; Wackett, M. J.; Wozney, A. J.; Bhattacharyya, S.; Hati, S. Vitamin D and COVID-19: A review on the role of vitamin D in preventing and reducing the severity of COVID-19 infection. *Protein Sci.* **2021**, *30* (11), 2206−2220.
(47) Razzaque, M. S. The FGF23-Klotho axis: Endocrine regulation of phosphate homeostasis. *Nat. Rev. Endocrin.* **2009**, *5* (11), 611−619.
(48) Berridge, M. J. Vitamin D, reactive oxygen species and calcium signalling in ageing and disease. *Philos. Trans. Royal Soc. B Biol. Sci.* **2016**, *371* (1700), 20150434.
(49) Antelmann, H.; Helmann, J. D. Thiol-based redox switches and gene regulation. *Antiox Redox Signal.* **2011**, *14*, 1049−1063.
(50) Ma, Q. Role of Nrf2 in oxidative stress and toxicity. *Annu. Rev. Pharmacol. Toxicol.* **2013**, *53*, 401−426.
(51) Nguyen, T.; Nioi, P.; Pickett, C. B. The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. *J. Biol. Chem.* **2009**, *284* (20), 13291−13295.
(52) Wen, H.; Gwathmey, J. K.; Xie, L. H. Oxidative stress-mediated effects of angiotensin II in the cardiovascular system. *World J. Hypertens.* **2012**, *2* (4), 34−44.
(53) Sassi, F.; Tamone, C.; D'Amelio, P. Vitamin D: Nutrient, hormone, and immunomodulator. *Nutrients.* **2018**, *10* (11), 1656.
(54) Alhassan Mohammed, H.; Mirshafiey, A.; Vahedi, H.; Hemmasi, G.; Moussavi Nasl Khameneh, A.; Parastouei, K.; Saboor-Yaraghi, A. A. Immunoregulation of inflammatory and inhibitory cytokines by Vitamin D3 in patients with inflammatory bowel diseases. *Scand. J. Immunol.* **2017**, *85* (6), 386−394.
(55) Schwalfenberg, G. K. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Mol. Nutrit. Food. Res.* **2011**, *55* (1), 96−108.
(56) Sherbet, G. V. Tumour Suppression and Inhibition of Angiogenesis by TXNIP (Thioredoxin Interacting Protein). In *Molecular Approach to Cancer Management*; Academic Press: Cambridge, MA, 2017; pp 101−103.
(57) Taylor, E. W.; Radding, W. Understanding selenium and glutathione as antiviral factors in COVID-19: Does the viral M (pro)protease target host selenoproteins and glutathione synthesis? *Front. Nutr.* **2020**, *7*, 143.
(58) Pérez de la Lastra, J. M.; Andrés-Juan, C.; Plou, F. J.; Pérez-Lebeña, E. Impact of Zinc, Glutathione, and Polyphenols as antioxidants in the immune response against SARS-CoV-2. *Processes.* **2021**, *9* (3), 506.
(59) Coric, V.; Milosevic, I.; Djukic, T.; Bukumiric, Z.; Savic-Radojevic, A.; Matic, M.; Jerotic, D.; Todorovic, N.; Asanin, M.; Ercegovac, M.; Ranin, J.; Stevanovic, G.; Pljesa-Ercegovac, M.; Simic, T. GSTP1 and GSTM3 variant alleles affect susceptibility and severity of COVID-19. *Front. Mol. Biosci.* **2021**, *8*, 747493.
(60) Khanfar, A.; Al Qaroot, B. Could glutathione depletion be the Trojan horse of COVID-19 mortality? *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 12500−12509.
(61) Santos Duarte Lana, J. F.; Santos Duarte Lana, A. V.; Souza Rodrigues, Q.; Silva Santos, G.; Navani, R.; Navani, A.; Furtado da Fonseca, L.; Marques Azzini, G. O.; Setti, T.; Mosaner, T.; Lopes Simplicio, C.; Mazzini Setti, T. Nebulization of glutathione and N-Acetylcysteine as an adjuvant therapy for COVID-19 onset. *Adv. Redox Res.* **2021**, *3*, 100015.
(62) Jaiswal, N.; Bhatnagar, M.; Shah, H. N-acetycysteine: A potential therapeutic agent in COVID-19 infection. *Med. Hypotheses.* **2020**, *144*, 110133.
(63) Zhang, Q.; Ju, Y.; Ma, Y.; Wang, T. N-acetylcysteine improves oxidative stress and inflammatory response in patients with community acquired pneumonia. A randomized controlled trial. *Medicine (Baltimore)* **2018**, *97* (45), No. e13087.
(64) Ibrahim, H.; Perl, A.; Smith, D.; Lewis, T.; Kon, Z.; Goldenberg, R.; Yarta, K.; Staniloae, C.; Williams, M. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. *Clin. Immunol.* **2020**, *219*, 108544.
(65) Sadowska, A. M. N-Acetylcysteine mucolysis in the management of chronic obstructive pulmonary disease. *Ther. Adv. Respir. Dis.* **2012**, *6* (3), 127−135.
(66) Kumar, P.; Osahon, O.; Vides, D. B.; Hanania, N.; Minard, C. G.; Sekhar, R. V. Severe glutathione deficiency, oxidative stress and oxidant damage in adults hospitalized with COVID-19: Implications for GlyNAC (Glycine and N-Acetylcysteine) supplementation. *Antioxidants.* **2022**, *11* (1), 50.
(67) Cazzola, M.; Calzetta, L.; Facciolo, F.; Rogliani, P.; Matera, M. G. Pharmacological investigation on the anti-oxidant and anti-inflammatory activity of N-acetylcysteine in an ex vivo model of COPD exacerbation. *Respir. Res.* **2017**, *18*, 26.
(68) Hui, D. S. C.; Lee, N. Adjunctive therapies and immunomodulating agents for severe influenza. *Influenza Other Respir Viruses* . **2013**, *7*, 52−59.
(69) Jorge-Aarón, R. M.; Rosa-Ester, M. P. N-acetylcysteine as a potential treatment for novel coronavirus disease 2019. *Future Microbiol.* **2020**, *15*, 959−962.
(70) De Flora, S.; Balansky, R.; La Maestra, S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. *FASEB J.* **2020**, *34* (10), 13185−13193.
(71) Hati, S.; Bhattacharyya, S. Impact of thiol-disulfide balance on the binding of Covid-19 spike protein with angiotensin-converting enzyme 2 receptor. *ACS Omega.* **2020**, *5* (26), 16292−16298.
(72) Boesgaard, S.; Aldershvile, J.; Poulsen, H. E.; Christensen, S.; Dige-Petersen, H.; Giese, J. *N*-Acetylcysteine inhibits angiotensin converting enzyme in vivo. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 1239−1244.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(73) Schoeman, D.; Fielding, B. C. Coronavirus envelope protein: current knowledge. *Virol. J.* **2019**, *16*, 69.
(74) Fossum, C. J.; Laatsch, B. F.; Lowater, H. R.; Narkiewicz-Jodko, A. W.; Lonzarich, L.; Hati, S.; Bhattacharyya, S. Pre-existing oxidative stress creates a docking-ready conformation of the SARS-CoV-2 receptor-binding domain. *ACS Bio. Med. Chem. Au.* **2022**, *2* (1), 84−93.
(75) Horowitz, R. I.; Freeman, P. R.; Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. *Respir. Med. Case Rep.* **2020**, *30*, 101063.
(76) Guloyan, V.; Oganesian, B.; Baghdasaryan, N.; Yeh, C.; Singh, M.; Guilford, F.; Ting, Y. S.; Venketaraman, V. Glutathione supplementation as an adjunctive therapy in COVID-19. *Antioxidants (Basel).* **2020**, *9* (10), 914.
(77) Dragomanova, S.; Miteva, S.; Nicoletti, F.; Mangano, K.; Fagone, P.; Pricoco, S.; Staykov, H.; Tancheva, L. Therapeutic potential of alpha-lipoic acid in viral infections, including COVID-19. *Antioxidants (Basel).* **2021**, *10* (8), 1294.
(78) Lavoie, J. C.; Chessex, P. Consider optimizing glutathione levels in COVID-19 symptomatic patients. *Free Radic. Biol. Med.* **2020**, *159*, S44.
(79) Pagano, G.; Manfredi, C.; Pallardo, F. V.; Lyakhovich, A.; Tiano, L.; Trifuoggi, M. Potential roles of mitochondrial cofactors in the adjuvant mitigation of proinflammatory acute infections, as in the case of sepsis and COVID-19 pneumonia. *Inflamm. Res.* **2021**, *70* (2), 159−170.
(80) Bustamante, J.; Lodge, J. K.; Marcocci, L.; Tritschler, H. J.; Packer, L.; Rihn, B. H. Alpha-lipoic acid in liver metabolism and disease. *Free Radic. Biol. Med.* **1998**, *24* (6), 1023−1039.
(81) Rochette, L.; Ghibu, S. Mechanics insights of alpha-lipoic acid against cardiovascular diseases during COVID-19 infection. *Int. J. Mol. Sci.* **2021**, *22* (15), 7979.
(82) Zhong, M.; Sun, A.; Xiao, T.; Yao, G.; Sang, L.; Zheng, X.; Zhang, J.; Jin, X.; Xu, L.; Yang, W.; Wang, P.; Hu, K.; Zhang, D.; Ge, J. A randomized, single-blind, group sequential, active-controlled study to evaluate the clinical efficacy and safety of α-lipoic acid for critically Ill patients with Coronavirus Disease 2019 (COVID-19). *Front. Med. (Lausanne).* **2022**, *8*, 566609.
(83) Sayıner, S.; Şehirli, A.Ö.; Serakıncı, N. Alpha lipoic acid as a potential treatment for COVID-19 - A hypothesis. *Curr. Top. Nutraceutical Res.* **2021**, *19*, 172−175.
(84) Suhail, S.; Zajac, J.; Fossum, C.; Lowater, H.; McCracken, C.; Severson, N.; Laatsch, B.; Narkiewicz-Jodko, A.; Johnson, B.; Liebau, J.; Bhattacharyya, S.; Hati, S. Role of oxidative stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) infection: A Review. *Protein J.* **2020**, *39* (6), 644−656.
(85) de Queiroz, T. M.; Xia, H.; Filipeanu, C. M.; Braga, V. A.; Lazartigues, E. α-Lipoic acid reduces neurogenic hypertension by blunting oxidative stress-mediated increase in ADAM17. *Am. J. Physiol. Heart Circ. Physiol.* **2015**, *309* (5), H926−H934.
(86) Wang, J.; Zhao, H.; An, Y. ACE2 shedding and the role in COVID-19. *Front. Cell Infect. Microbiol.* **2022**, *11*, 789180.
(87) Venkataraman, T.; Frieman, M. B. The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis. *Antiviral Res.* **2017**, *143*, 142−150.
(88) Cure, E.; Cumhur Cure, M. Alpha-lipoic acid may protect patients with diabetes against COVID-19 infection. *Med. Hypotheses.* **2020**, *143*, 110185.
(89) Razaghi, A.; Poorebrahim, M.; Sarhan, D.; Björnstedt, M. Selenium stimulates the antitumour immunity: Insights to future research. *Eur. J. Cancer.* **2021**, *155*, 256−267.
(90) Brigelius-Flohé, R.; Banning, A.; Schnurr, K. Selenium-dependent enzymes in endothelial cell function. *Antioxid. Redox Signal.* **2003**, *5* (2), 205−215.
(91) Khatiwada, S.; Subedi, A. A mechanistic link between selenium and Coronavirus Disease 2019 (COVID-19). *Curr. Nutr. Rep.* **2021**, *10*, 125−136.
(92) Avery, J. C.; Hoffmann, P. R. Selenium, selenoproteins, and immunity. *Nutrients.* **2018**, *10* (9), 1203.
(93) Ivory, K.; Prieto, E.; Spinks, C.; Armah, C. N.; Goldson, A. J.; Dainty, J. R.; Nicoletti, C. Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults. *Clin. Nutr.* **2017**, *36* (2), 407−415.
(94) Steinbrenner, H.; Al-Quraishy, S.; Dkhil, M. A.; Wunderlich, F.; Sies, H. Dietary selenium in adjuvant therapy of viral and bacterial infections. *Adv. Nutr.* **2015**, *6* (1), 73−82.
(95) Zhang, J.; Taylor, E. W.; Bennett, K.; Saad, R.; Rayman, M. P. Association between regional selenium status and reported outcome of COVID-19 cases in China. *Am. J. Clin. Nutr.* **2020**, *111* (6), 1297−1299.
(96) Fedele, D.; De Francesco, A.; Riso, S.; Collo, A. Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: An overview. *Nutrition.* **2021**, *81*, 111016.
(97) Shreenath, A. P.; Ameer, M. A.; Dooley, J. Selenium Deficiency. In *StatPearls*; StatPearls Publishing LLC: Treasure Island, FL, 2022; https://www.ncbi.nlm.nih.gov/books/NBK482260/.
(98) Kiremidjian-Schumacher, L.; Roy, M. Selenium and Immune Function. *Z. Ernahrung Swiss.* **1998**, *37*, 50−56https://pubmed.ncbi.nlm.nih.gov/9558729/.
(99) Qian, F.; Misra, S.; Prabhu, K. S. Selenium and selenoproteins in prostanoid metabolism and immunity. *Crit. Rev. Biochem. Mol. Biol.* **2019**, *54* (6), 484−516.
(100) Rayman, M. P. Selenium and Adverse Conditions of Human Pregnancy. In *Selenium: Its Molecular Biology and Role in Human Health*; Hatfield, D. L., Berry, M. J., Gladyshev, V. N., Eds.; Springer Science+Business Media, LLC, New York, 2011.
(101) Zhang, J.; Saad, R.; Taylor, E. W.; Rayman, M. P. Selenium and selenoproteins in viral infection with potential relevance to COVID-19. *Redox Biol.* **2020**, *37*, 101715.
(102) Harthill, M. Micronutrient selenium deficiency influences evolution of some viral infectious diseases. *Biol. Trace Elem. Res.* **2011**, *143* (3), 1325−1336.
(103) Gao, X.; Zhang, Z.; Xing, H.; Yu, J.; Zhang, N.; Xu, S. Selenium deficiency-induced inflammation and increased expression of regulating inflammatory cytokines in the chicken gastrointestinal tract. *Biol. Trace Elem Res.* **2016**, *173* (1), 210−218.
(104) Zeng, J.; Zhou, J.; Huang, K. Effect of selenium on pancreatic proinflammatory cytokines in streptozotocin-induced diabetic mice. *J. Nutr. Biochem.* **2009**, *20* (7), 530−536.
(105) Mahmoodpoor, A.; Hamishehkar, H.; Shadvar, K.; Ostadi, Z.; Sanaie, S.; Saghaleini, S. H.; Nader, N. D. The effect of intravenous selenium on oxidative stress in critically Ill patients with acute respiratory distress syndrome. *Immunol. Invest.* **2019**, *48* (2), 147−159.
(106) Dhanjal, N. I. K.; Sharma, S.; Prabhu, K. S.; Prakash, N. T. Selenium supplementation through Se-rich dietary matrices can upregulate the anti-inflammatory responses in lipopolysaccharide-stimulated murine macrophages. *Food Agric. Immunol.* **2017**, *28*, 1374−1392.
(107) Stone, C. A.; Kawai, K.; Kupka, R.; Fawzi, W. W. Role of Selenium in HIV infection. *Nutr. Rev.* **2010**, *68* (11), 671−681.
(108) Dworkin, B. M. Selenium deficiency in HIV infection and the acquired immunodeficiency syndrome (AIDS). *Chem. Biol. Interact.* **1994**, *91* (2−3), 181−186.
(109) Wood, S. M.; Beckham, C.; Yosioka, A.; Darban, H.; Watson, R. R. β-Carotene and selenium supplementation enhances immune response in aged humans. *Integr. Med.* **2000**, *2* (2), 85−92.
(110) Broome, C. S.; McArdle, F.; Kyle, J. A.; Andrews, F.; Lowe, N. M.; Hart, C. A.; Arthur, J. R.; Jackson, M. J. An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. *Am. J. Clin. Nutr.* **2004**, *80* (1), 154−162.
(111) Jayawardena, R.; Sooriyaarachchi, P.; Chourdakis, M.; Jeewandara, C.; Ranasinghe, P. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. *Diabetes Metab. Syndr.* **2020**, *14* (4), 367−382.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(112) Hoffmann, F. W.; Hashimoto, A. C.; Shafer, L. A.; Dow, S.; Berry, M. J.; Hoffmann, P. R. Dietary selenium modulates activation and differentiation of CD4+ T cells in mice through a mechanism involving cellular free thiols. *J. Nutr.* **2010**, *140* (6), 1155−1161.
(113) Rayman, M. P. Selenium and human health. *Lancet.* **2012**, *379* (9822), 1256−1268.
(114) Taheri, S.; Asadi, S.; Nilashi, M.; Ali Abumalloh, R.; Ghabban, N. M. A.; Mohd Yusuf, S. Y.; Supriyanto, E.; Samad, S. A literature review on beneficial role of vitamins and trace elements: Evidence from published clinical studies. *J. Trace Elem. Med. Biol.* **2021**, *67*, 126789.
(115) Guillin, O. M.; Vindry, C.; Ohlmann, T.; Chavatte, L. Selenium, selenoproteins and viral infection. *Nutrients.* **2019**, *11* (9), 2101.
(116) Bermano, G.; Méplan, C.; Mercer, D. K.; Hesketh, J. E. Selenium and viral infection: are there lessons for COVID-19? *Br. J. Nutr.* **2021**, *125* (6), 618−627.
(117) Hiffler, L.; Rakotoambinina, B. Selenium and RNA virus interactions: Potential implications for SARS-CoV-2 infection (COVID-19). *Front. Nutr.* **2020**, *7*, 164.
(118) Wang, Y.; Huang, J.; Sun, Y.; Stubbs, D.; He, J.; Li, W.; Wang, F.; Liu, Z.; Ruzicka, J. A.; Taylor, E. W.; Rayman, M. P.; Wan, X.; Zhang, J. SARS-CoV-2 suppresses mRNA expression of selenoproteins associated with ferroptosis, endoplasmic reticulum stress and DNA synthesis. *Food. Chem. Toxicol.* **2021**, *153*, 112286.
(119) Zhang, H. Y.; Zhang, A. R.; Lu, Q. B.; Zhang, X. A.; Zhang, Z. J.; Guan, X. G.; Che, T. L.; Yang, Y.; Li, H.; Liu, W.; Fang, L. Q. Association between fatality rate of COVID-19 and selenium deficiency in China. *BMC Infect. Dis.* **2021**, *21*, 452.
(120) Sies, H.; Parnham, M. J. Potential therapeutic use of ebselen for COVID-19 and other respiratory viral infections. *Free Radic. Biol. Med.* **2020**, *156*, 107−112.
(121) Ren, X.; Zou, L.; Lu, J.; Holmgren, A. Selenocysteine in mammalian thioredoxinreductase and application of ebselen as a therapeutic. *Free Radic. Biol. Med.* **2018**, *127*, 238−247.
(122) Jin, Z.; Du, X.; Xu, Y.; Deng, Y.; Liu, M.; Zhao, Y.; Zhang, B.; Li, X.; Zhang, L.; Peng, C.; Duan, Y.; Yu, J.; Wang, L.; Yang, K.; Liu, F.; Jiang, R.; Yang, X.; You, T.; Liu, X.; Yang, X.; Bai, F.; Liu, H.; Liu, X.; Guddat, L. W.; Xu, W.; Xiao, G.; Qin, C.; Shi, Z.; Jiang, H.; Rao, Z.; Yang, H. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature.* **2020**, *582* (7811), 289−293.
(123) Kunwar, A.; Priyadarsini, K. I. Selenium, a micronutrient can modulate viral diseases including COVID-19. *Indian J. Biochem. Biol.* **2020**, *57*, 713−723.
(124) Kieliszek, M.; Lipinski, B. Selenium supplementation in the prevention of coronavirus infections (COVID-19). *Med. Hypoteses.* **2020**, *143*, 109878.
(125) Miller, S.; Walker, S. W.; Arthur, J. R.; Nicol, F.; Pickard, K.; Lewin, M. H.; Howie, A. F.; Beckett, G. J. Selenite protects human endothelial cells from oxidative damage and induces thioredoxinreductase. *Clin. Sci. (London).* **2001**, *100* (5), 543−550.
(126) Lewin, M. H; Arthur, J. R; Riemersma, R. A; Nicol, F.; Walker, S. W; Millar, E.M.; Howie, A. F; Beckett, G. J Selenium supplementation acting through the induction of thioredoxinreductase and glutathione peroxidase protects the human endothelial cell, line EAhy926 from damage by lipid hydroperoxides. *Biochim. Biophys. Acta* **2002**, *1593*, 85−92.
(127) Berggren, M.; Gallegos, A.; Gasdaska, J.; Powis, G. Cellular thioedoxinreductase activity is regulated by selenium. *Anticancer Res.* **1997**, *17*, 3377−3380.
(128) Kaźmierczak-Barańska, J.; Boguszewska, K.; Karwowski, B. T. Nutrition can help DNA repair in the case of aging. *Nutrients.* **2020**, *12* (11), 3364.
(129) Park, H. S.; Huh, S. H.; Kim, Y.; Shim, J.; Lee, S. H.; Park, I. S.; Jung, Y. K.; Kim, I. Y.; Choi, E. J. Selenite negatively regulates caspase-3 through a redox mechanism. *J. Biol. Chem.* **2000**, *275* (12), 8487−8491.
(130) Zhang, L.; Liu, Y. Potential interventions for novel coronavirus in China: a systematic review. *J. Med. Virol.* **2020**, *92* (5), 479−490.
(131) Chelkeba, L.; Ahmadi, A.; Abdollahi, M.; Najafi, A.; Ghadimi, M. H.; Mosaed, R.; Mojtahedzadeh, M. The effect of parenteral selenium on outcomes of mechanically ventilated patients following sepsis: a prospective randomized clinical trial. *Ann. Intensive Care* **2015**, *5*, 29.
(132) Manzanares, W.; Biestro, A.; Torre, M. H.; Galusso, F.; Facchin, G.; Hardy, G. High-dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation. *Intensive Care Med.* **2011**, *37* (7), 1120−1127.
(133) Mahmoodpoor, A.; Hamishehkar, H.; Sanaie, S.; Behruzizad, N.; Iranpour, A.; Koleini, E.; Nader, N. D. Antioxidant reserve of the lungs and ventilator-associated pneumonia: a clinical trial of high dose selenium in critically ill patients. *J. Crit. Care.* **2018**, *44*, 357−362.
(134) Landucci, F.; Mancinelli, P.; De Gaudio, A. R.; Virgili, G. Selenium supplementation in critically ill patients: a systematic review and meta-analysis. *J. Crit. Care.* **2014**, *29* (1), 150−156.
(135) Demircan, K.; Chillon, T. S.; Sun, Q.; Heller, R. A.; Klingenberg, G. J.; Hirschbil-Bremer, I. M.; Seemann, P.; Diegmann, J.; Bachmann, M.; Moghaddam, A.; Schomburg, L. Humoral immune response to COVID-19 mRNA vaccination in relation to selenium status. *Redox Biol.* **2022**, *50*, 102242.
(136) Huang, Z.; Rose, A. H.; Hoffmann, P. R. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. *Antioxid. Redox Signal.* **2012**, *16* (7), 705−743.
(137) Romagnani, S. T-cell subsets (Th1 versus Th2). *Ann. Allergy Asthma Immunol.* **2000**, *85* (1), 9−18.
(138) Nelson, S. M.; Lei, X.; Prabhu, K. S. Selenium levels affect the IL-4-induced expression of alternative activation markers in murine macrophages. *J. Nutr.* **2011**, *141* (9), 1754−1761.
(139) Pedrosa, L. F. C.; Barros, A. N. A. B.; Leite-Lais, L. Nutritional risk of vitamin D, vitamin C, zinc, and selenium deficiency on risk and clinical outcomes of COVID-19: A narrative review. *Clin. Nutr. ESPEN.* **2022**, *47*, 9−27.
(140) Vavougios, G. D.; Ntoskas, K. T.; Doskas, T. K. Impairment in selenocysteine synthesis as a candidate mechanism of inducible coagulopathy in COVID-19 patients. *Med. Hypotheses.* **2021**, *147*, 110475.
(141) Younesian, O.; Khodabakhshi, B.; Abdolahi, N.; Norouzi, A.; Behnampour, N.; Hosseinzadeh, S.; Alarzi, S. S. H.; Joshaghani, H. Decreased serum Selenium levels of COVID-19 patients in comparison with healthy individuals. *Biol. Trace Elem. Res.* **2022**, *200* (4), 1562−1567.
(142) Majeed, M.; Nagabhushanam, K.; Gowda, S.; Mundkur, L. An exploratory study of selenium status in healthy individuals and in patients with COVID-19 in a south Indian population: The case for adequate selenium status. *Nutrition.* **2021**, *82*, 111053.
(143) Fakhrolmobasheri, M.; Mazaheri-Tehrani, S.; Kieliszek, M.; Zeinalian, M.; Abbasi, M.; Karimi, F.; Mozafari, A. M. COVID-19 and Selenium deficiency: a systematic review. *Biol. Trace Elem. Res.* **2022**, *200* (9), 3945−3956.
(144) Skesters, A.; Kustovs, D.; Lece, A.; Moreino, E.; Petrosina, E.; Rainsford, K. D. Selenium, selenoprotein P, and oxidative stress levels in SARS-CoV-2 patients during illness and recovery. *Inflammopharmacology.* **2022**, *30* (2), 499−503.
(145) Manzanares, W.; Moreira, E.; Hardy, G. Pharmaconutrition revisited for critically ill patients with coronavirus disease 2019 (COVID-19): Does selenium have a place? *Nutrition* **2021**, *81*, 110989.
(146) Forceville, X.; Mostert, V.; Pierantoni, A.; Vitoux, D.; Le Toumelin, P.; Plouvier, E.; Dehoux, M.; Thuillier, F.; Combes, A. Selenoprotein P, rather than glutathione peroxidase, as a potential marker of septic shock related syndromes. *Eur. Surg. Res.* **2009**, *43* (4), 338−347.
(147) Manzanares, W.; Biestro, A.; Galusso, F.; Torre, M. H.; Manay, N.; Pittini, G.; Facchin, G.; Hardy, G. Serum selenium and

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

glutathione peroxidase-3 activity: biomarkers of systemic inflammation in the critically ill? *Intensive Care Med.* **2009**, *35* (5), 882−889.
(148) Bodnar, M.; Szczyglowska, M.; Konieczka, P.; Namiesnik, J. Methods of selenium supplementation: bioavailability and determination of selenium compounds. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 36−55.
(149) Vinceti, M.; Filippini, T.; Rothman, K. J. Selenium exposure and the risk of type 2 diabetes: a systematic review and meta-analysis. *Eur. J. Epidemiol.* **2018**, *33* (9), 789−810.
(150) He, L.; Zhao, J.; Wang, L.; Liu, Q.; Fan, Y.; Li, B.; Yu, Y. L.; Chen, C.; Li, Y. F. Using nano-selenium to combat Coronavirus Disease 2019 (COVID-19)? *Nano Today* **2021**, *36*, 101037.
(151) Corrao, S.; Mallaci Bocchio, R.; Lo Monaco, M.; Natoli, G.; Cavezzi, A.; Troiani, E.; Argano, C. Does evidence exist to blunt inflammatory response by nutraceutical supplementation during COVID-19 pandemic? An overview of systematic reviews of Vitamin D, Vitamin C, Melatonin, and Zinc. *Nutrients.* **2021**, *13* (4), 1261.
(152) Wu, D.; Lewis, E. D.; Pae, M.; Meydani, S. N. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. *Front. Immunol.* **2019**, *9*, 3160.
(153) Kardos, J.; Héja, L.; Simon, A.; Jablonkai, I.; Kovacs, R.; Jemnitz, K. Copper signalling: causes and consequences. *Cell Commun. Signal.* **2018**, *16*, 71.
(154) Lee, S. R. Critical role of zinc as either an antioxidant or a prooxidant in cellular systems. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 9156285.
(155) Marreiro, D. D.; Cruz, K. J. C.; Morais, J. B. S.; Beserra, J. B.; Severo, J. S.; de Oliveira, A. R. S. Zinc and oxidative stress: Current mechanisms. *Antioxidants (Basel)* **2017**, *6* (2), 24.
(156) Ruz, M.; Carrasco, F.; Rojas, P.; Codoceo, J.; Inostroza, J.; Basfi-fer, K.; Valencia, A.; Vásquez, K.; Galgani, J.; Pérez, A.; Lopez, G.; Arredondo, M.; Perez-Bravo, F. Zinc as a potential coadjuvant in therapy for type 2 diabetes. *Food. Nutr. Bull.* **2013**, *34* (2), 215−221.
(157) Chasapis, C. T.; Loutsidou, A. C.; Spiliopoulou, C. A.; Stefanidou, M. E. Zinc and human health: An update. *Arch. Toxicol.* **2012**, *86* (4), 521−534.
(158) Faghfouri, A. H.; Zarezadeh, M.; Aghapour, B.; Izadi, A.; Rostamkhani, H.; Majnouni, A.; Abu-Zaid, A.; Varkaneh, H. K.; Ghoreishi, Z.; Ostadrahimi, A. Clinical efficacy of zinc supplementation in improving antioxidant defense system: A comprehensive systematic review and time-response meta-analysis of controlled clinical trials. *Eur. J. Pharmacol.* **2021**, *907*, 174243.
(159) Wessels, I.; Maywald, M.; Rink, L. Zinc as a gatekeeper of immune function. *Nutrients.* **2017**, *9* (12), 1286.
(160) Jarosz, M.; Olbert, M.; Wyszogrodzka, G.; Młyniec, K.; Librowski, T. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. *Inflammopharmacology.* **2017**, *25* (1), 11−24.
(161) de Almeida Brasiel, P. G. The key role of zinc in elderly immunity: A possible approach in the COVID-19 crisis. *Clin. Nutr. Espen.* **2020**, *38*, 65−66.
(162) Hojyo, S.; Fukada, T. Roles of Zinc signaling in the immune system. *J. Immunol. Res.* **2016**, *2016*, 6762343.
(163) Bonaventura, P.; Benedetti, G.; Albarède, F.; Miossec, P. Zinc and its role in immunity and inflammation. *Autoimmun. Rev.* **2015**, *14*, 277−285.
(164) Kloubert, V.; Rink, L. Zinc as a micronutrient and its preventive role of oxidative damage in cells. *Food Funct.* **2015**, *6* (10), 3195−3204.
(165) Mousavi, S. M.; Hajishafiee, M.; Clark, C. C. T.; Borges do Nascimento, I. J.; Milajerdi, A.; Amini, M. R.; Esmaillzadeh, A. Clinical effectiveness of zinc supplementation on the biomarkers of oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* **2020**, *161*, 105166.
(166) Pincemail, J.; Cavalier, E.; Charlier, C.; Cheramy-Bien, J. P.; Brevers, E.; Courtois, A.; Fadeur, M.; Meziane, S.; Goff, C. L.; Misset, B.; Albert, A.; Defraigne, J. O.; Rousseau, A. F. Oxidative stress status in COVID-19 patients hospitalized in intensive care unit for severe pneumonia, A pilot study. *Antioxidants (Basel).* **2021**, *10* (2), 257.
(167) Karmaker, S.; Saha, T. K.; Yoshikawa, Y.; Sakurai, H. A zinc (II)/Poly (γ-glutamic acid) complex as an oral therapeutic for the treatment of Type-2 diabetic KKAy mice. *Macromol. Biosci.* **2009**, *9* (3), 279−286.
(168) Shakoor, H.; Feehan, J.; Al Dhaheri, A. S.; Ali, H. I.; Platat, C.; Ismail, L. C.; Apostolopoulos, V.; Stojanovska, L. Immune-boosting role of vitamins D, C, E, Zinc, Selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas* **2021**, *143*, 1−9.
(169) Alam, S.; Bhuiyan, F. R.; Emon, T. H.; Hasan, M. Prospects of nutritional interventions in the care of COVID-19 patients. *Heliyon* **2021**, *7* (2), No. e06285.
(170) Axelrod, A. E. Role of the B Vitamins in the Immune Response. In: *Diet and Resistance to Disease*; Phillips, M., Baetz, A., Eds.; Springer: Boston, 1981.
(171) Ifhar, L. S.; D. Ben-Shachar, D. Heme Metabolism, Mitochondria, And Complex I in Neuropsychiatric Disorders. In *Neuroprotectionin Autism, Schizophrenia and Alzheimer's Disease*; Gozes, I., Levine, J., Eds.; Academic Press, 2020; pp 173−207.
(172) Gammoh, N. Z.; Rink, L. Zinc in infection and inflammation. *Nutrients.* **2017**, *9* (6), 624.
(173) Pal, A.; Squitti, R.; Picozza, M.; Pawar, A.; Rongioletti, M.; Dutta, A. K.; Sahoo, S.; Goswami, K.; Sharma, P.; Prasad, R. Zinc and COVID-19: basis of current clinical trials. *Biol. Trace Elem. Res.* **2021**, *199* (8), 2882−2892.
(174) Biaggio, V. S.; Pérez Chaca, M. V.; Valdéz, S. R.; Gómez, N. N.; Gimenez, M. S. Alteration in the expression of inflammatory parameters as a result of oxidative stress produced by moderate zinc deficiency in rat lung. *Exp. Lung. Res.* **2010**, *36* (1), 31−44.
(175) Bao, S.; Knoell, D. L. Zinc modulates cytokine-induced lung epithelial cell barrier permeability. *Am. J. Physiol. Lung. Cell. Mol. Physiol.* **2006**, *291* (6), L1132−L1141.
(176) Liu, M. J.; Bao, S.; Napolitano, J. R.; Burris, D. L.; Yu, L.; Tridandapani, S.; Knoell, D. L. Zinc regulates the acute phase response and serum amyloid a production in response to sepsis through JAKSTAT3 signaling. *PLoS One* **2014**, *9* (4), No. e94934.
(177) Mayor-Ibarguren, A.; Busca-Arenzana, C.; Robles-Marhuenda, Á. A Hypothesis for the possible role of zinc in the immunological pathways related to COVID-19 infection. *Front. Immunol.* **2020**, *11*, 1736.
(178) Shankar, A. H.; Prasad, A. S. Zinc and immune function: The biological basis of altered resistance to infection. *Am. J. Clin. Nutr.* **1998**, *68*, 447S−463S.
(179) Tomita, H. Zinc in Taste and Smell Disorder. In *Trace Elements in Clinical Medicine*; Tomita, H., Ed.; Springer: Tokyo, 1990; pp 15−37.
(180) Barazzoni, R.; Bischoff, S. C.; Breda, J.; Wickramasinghe, K.; Krznaric, Z.; Nitzan, D.; Pirlich, M.; Singer, P. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin. Nutr.* **2020**, *39*, 1631−1638.
(181) Skalny, A. V.; Rink, L.; Ajsuvakova, O. P.; Aschner, M.; Gritsenko, V. A.; Alekseenko, S. I.; Svistunov, A. A.; Petrakis, D.; Spandidos, D. A.; Aaseth, J.; Tsatsakis, A.; Tinkov, A. A. Zinc and respiratory tract infections: perspectives for COVID-19. *Int. J. Mol. Med.* **2020**, *46*, 17−26.
(182) te Velthuis, A. J.; van den Worm, S. H.; Sims, A. C.; Baric, R. S.; Snijder, E. J.; van Hemert, M. J. Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* **2010**, *6* (11), No. e1001176.
(183) Gasmi, A.; Tippairote, T.; Mujawdiya, P. K.; Peana, M.; Menzel, A.; Dadar, M.; Gasmi Benahmed, A.; Bjørklund, G. Micronutrients as immunomodulatory tools for COVID-19 management. *Clin. Immunol.* **2020**, *220*, 108545.
(184) Read, S. A.; Obeid, S.; Ahlenstiel, C.; Ahlenstiel, G. The role of zinc in antiviral immunity. *Adv. Nutr.* **2019**, *10* (4), 696−710.
(185) Wessels, I.; Rolles, B.; Rink, L. The potential impact of zinc supplementation on COVID-19 pathogenesis. *Front Immunol.* **2020**, *11*, 1712.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(186) Muscogiuri, G.; Barrea, L.; Savastano, S.; Colao, A. Nutritional recommendations for CoVID-19 quarantine. *Eur. J. Clin. Nutr.* **2020**, *74* (6), 850−851.
(187) Speth, R.; Carrera, E.; Jean-Baptiste, M.; Joachim, A.; Linares, A. Concentration-dependent effects of zinc on angiotensin converting enzyme-2 activity (1067.4). *FASEB J.* **2014**, *28*, 1067.4.
(188) Chinni, V.; El-Khoury, J.; Perera, M.; Bellomo, R.; Jones, D.; Bolton, D.; Ischia, J.; Patel, O. Zinc supplementation as an adjunct therapy for COVID-19: Challenges and opportunities. *Br. J. Clin. Pharmacol.* **2021**, *87* (10), 3737−3746.
(189) Yasui, Y.; Yasui, H.; Suzuki, K.; Saitou, T.; Yamamoto, Y.; Ishizaka, T.; Nishida, K.; Yoshihara, S.; Gohma, I.; Ogawa, Y. Analysis of the predictive factors for a critical illness of COVID-19 during treatment-relationship between serum zinc level and critical illness of COVID-19. *Int. J. Infect. Dis.* **2020**, *100*, 230−236.
(190) Taheri, M.; Bahrami, A.; Habibi, P.; Nouri, F. A review on the serum electrolytes and trace elements role in the pathophysiology of COVID-19. *Biol. Trace Elem. Res.* **2021**, *199* (7), 2475−2481.
(191) Hemilä, H.; Fitzgerald, J. T.; Petrus, E. J.; Prasad, A. Zinc acetate lozenges may improve the recovery rate of common cold patients: an individual patient data meta-analysis. *Open Forum Infect. Dis.* **2017**, *4* (2), ofx059.
(192) Zinc. *NIH Covid-19 Treatment Guidelines*; National Institutes of Health, 2022; https://www.covid19treatmentguidelines.nih.gov/therapies/supplements/zinc/ (accessed 2022-05-22).
(193) Kiabi, F. H.; Alipour, A.; Darvishi-Khezri, H.; Aliasgharian, A.; Zeydi, A. E. Zinc supplementation in adult mechanically ventilated trauma patients is associated with decreased occurrence of ventilator-associated pneumonia: A secondary analysis of a prospective. Observational study. *Indian J. Crit. Care Med.* **2017**, *21*, 34−39.
(194) Rozga, M.; Cheng, F. W.; Moloney, L.; Handu, D. Effects of micronutrients or conditional amino acids on COVID-19-related outcomes: An evidence analysis center scoping review. *J. Acad. Nutr. Diet.* **2021**, *121* (7), 1354−1363.
(195) Fatima, S.; Zaidi, S. S.; Alsharidah, A. S.; Aljaser, F. S.; Banu, N. Possible prophylactic approach for SARS-CoV-2 infection by combination of melatonin, Vitamin C and Zinc in animals. *Front. Vet. Sci.* **2020**, *7*, 585789.
(196) Derwand, R.; Scholz, M.; Zelenko, V. COVID-19 outpatients: Early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: A retrospective case series study. *Int. J. Antimicrob. Agents.* **2020**, *56* (6), 106214.
(197) Thomas, S.; Patel, D.; Bittel, B.; Wolski, K.; Wang, Q.; Kumar, A.; Il'Giovine, Z. J.; Mehra, R.; McWilliams, C.; Nissen, S. E.; Desai, M. Z. Effect of high-dose Zinc and Ascorbic Acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection. *JAMA Netw. Open.* **2021**, *4* (2), No. e210369.
(198) Derwand, R.; Scholz, M. Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19? *Med. Hypotheses.* **2020**, *142*, 109815.
(199) Lentini, G.; Cavalluzzi, M. M.; Habtemariam, S. COVID-19, chloroquine repurposing, and cardiac safety concern: chirality might help. *Molecules.* **2020**, *25* (8), 1834.
(200) Tonnesmann, E.; Kandolf, R.; Lewalter, T. Chloroquine cardiomyopathy a review of the literature. *Immunopharmacol. Immunotoxicol.* **2013**, *35* (3), 434−442.
(201) Myint, Z. W.; Oo, T. H.; Thein, K. Z.; Tun, A. M.; Saeed, H. Copper deficiency anemia. *Ann. Hematol.* **2018**, *97* (9), 1527−1534.
(202) Scartoni, D.; Desideri, I.; Giacomelli, I.; Di Cataldo, V.; Di Brina, L.; Mancuso, A.; Furfaro, I.; Bonomo, P.; Simontacchi, G.; Livi, L. Nutritional supplement based on zinc, prebiotics, probiotics and vitamins to prevent radiation-related gastrointestinal disorders. *Anticancer Res.* **2015**, *35*, 5687−5692.
(203) Maret, W. Zinc biochemistry: From a single zinc enzyme to a key element of life. *Adv. Nutr.* **2013**, *4* (1), 82−91.
(204) Maret, W.; Sandstead, H. H. Zinc requirements and the and the risks and benefits of zinc supplementation. *J. Trace Elem. Med. Biol.* **2006**, *20* (1), 3−18.
(205) Jothimani, D.; Kailasam, E.; Danielraj, S.; Nallathambi, B.; Ramachandran, H.; Sekar, P.; Manoharan, S.; Ramani, V.; Narasimhan, G.; Kaliamoorthy, I.; Rela, M. COVID-19: poor outcomes in patients with zinc deficiency. *Int. J. Infect. Dis.* **2020**, *100*, 343−349.
(206) Rahman, M. T.; Idid, S. Z. Can Zn be a critical element in COVID-19 treatment? *Biol. Trace Elem. Res.* **2021**, *199* (2), 550−558.
(207) Boretti, A. Zinc augments the antiviral potential of HCQ/CQ and ivermectin to reduce the risks of more serious outcomes from COVID-19 infection. *J. Trace Elem. Med. Biol.* **2022**, *71*, 126954.
(208) Dhawan, M.; Emran, T. B.; Priyanaka; Choudhary, O. P. Immunomodulatory effects of zinc and its impact on COVID-19 severity. *Ann. Med. Surg. (London).* **2022**, *77*, 103638.
(209) Moratin, H.; Ickrath, P.; Scherzad, A.; Meyer, T. J.; Naczenski, S.; Hagen, R.; Hackenberg, S. Investigation of the immune modulatory potential of Zinc oxide nanoparticles in human lymphocytes. *Nanomaterials (Basel)* **2021**, *11* (3), 629.
(210) Wong, C. P.; Rinaldi, N. A.; Ho, E. Zinc deficiency enhanced inflammatory response by increasing immune cell activation and inducing IL6 promoter demethylation. *Mol. Nutr. Food Res.* **2015**, *59* (5), 991−999.
(211) Maares, M.; Hackler, J.; Haupt, A.; Heller, R. A.; Bachmann, M.; Diegmann, J.; Moghaddam, A.; Schomburg, L.; Haase, H. Free Zinc as a predictive marker for COVID-19 mortality risk. *Nutrients.* **2022**, *14* (7), 1407.
(212) Balboni, E.; Zagnoli, F.; Filippini, T.; Fairweather-Tait, S. J.; Vinceti, M. Zinc and selenium supplementation in COVID-19 prevention and treatment: a systematic review of the experimental studies. *J. Trace Elem. Med. Biol.* **2022**, *71*, 126956.
(213) Fosmire, G. J. Zinc toxicity. *Am. J. Clin. Nutr.* **1990**, *51* (2), 225−227.
(214) Lazarczyk, M.; Favre, M. Role of Zn2+ ions in host-virus interactions. *J. Virol.* **2008**, *82* (23), 11486−11494.
(215) Nath, S.; Baidya, D. K. Mucormycosis in COVID-19: Is zinc a silent killer in India? *Indian J. Crit. Care Med.* **2021**, *25* (9), 1079−1080.
(216) Imran, M.; Alshrari, A. S.; Tauseef, M.; Khan, S. A.; Hudu, S. A.; Abida. Mucormycosis medications: A patent review. *Expert Opin. Ther. Pat.* **2021**, *31*, 1059−1074.
(217) Imran, M.; Fatima, W.; Alzahrani, A. K.; Suhail, N.; Alshammari, M. K.; Alghitran, A. A.; Alshammari, F. N.; Ghoneim, M. M.; Alshehri, S.; Shakeel, F. Development of therapeutic and prophylactic zinc compositions for use against COVID-19: A glimpse of the trends, inventions, and patents. *Nutrients.* **2022**, *14* (6), 1227.
(218) Khiatah, B.; Amos, A.; Carlson, D. Association between COVID-19 and angiotensin-converting enzyme inhibitors with the spotlight on zinc: an opinion. *Ann. Med.* **2021**, *53* (1), 1673−1675.
(219) Li, C.; Li, Y.; Ding, C. The role of copper homeostasis at the host-pathogen axis: from bacteria to fungi. *Int. J. Mol. Sci.* **2019**, *20* (1), 175.
(220) Gombart, A. F.; Pierre, A.; Maggini, S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients.* **2020**, *12* (1), 236.
(221) Calder, P. C. Nutrition, immunity and COVID-19. *BMJ. Nutr. Prevent. Health.* **2020**, *3* (1), 74−92.
(222) Turnlund, J. R.; Jacob, R. A.; Keen, C. L.; Strain, J. J.; Kelley, D. S.; Domek, J. M.; Keyes, W. R.; Ensunsa, J. L.; Lykkesfeldt, J.; Coulter, J. Long-term high copper intake: effects on indexes of copper status, antioxidant status, and immune function in young men. *Am. J. Clin. Nutr.* **2004**, *79* (6), 1037−1044.
(223) Kelley, D. S.; Daudu, P. A.; Taylor, P. C.; Mackey, B. E.; Turnlund, J. R. Effects of low-copper diets on human immune response. *Am. J. Clin. Nutr.* **1995**, *62* (2), 412−416.
(224) Rupp, J. C.; Locatelli, M.; Grieser, A.; Ramos, A.; Campbell, P. J.; Yi, H.; Steel, J.; Burkhead, J. L.; Bortz, E. Host cell copper transporters CTR1 and ATP7A are important for influenza A virus replication. *Virol. J.* **2017**, *14*, 11.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(225) Sharma, L. Management against Covid-19 through nutritional supplementation to build adaptive immunity—a systematic review. *Int. J. Pharm. Sci. Res.* **2020**, *11*, 4114−4122.
(226) Baez-Santos, Y. M.; St John, S. E.; Mesecar, A. D. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. *Antiviral Res.* **2015**, *115*, 21−38.
(227) Han, Y. S.; Chang, G. G.; Juo, C. G.; Lee, H. J.; Yeh, S. H.; Hsu, J. T.; Chen, X. Papain-like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): expression, purification, characterization, and inhibition. *Biochemistry.* **2005**, *44* (30), 10349−10359.
(228) Raha, S.; Mallick, R.; Basak, S.; Duttaroy, A. K. Is copper beneficial for COVID-19 patients? *Med. Hypotheses.* **2020**, *142*, 109814.
(229) Yan, Z.; Spaulding, H. R. Extracellular superoxide dismutase, a molecular transducer of health benefits of exercise. *Redox Biol.* **2020**, *32*, 101508.
(230) Arrieta, F.; Martinez-Vaello, V.; Bengoa, N.; Jiménez-Mendiguchia, L.; Rosillo, M.; de Pablo, A.; Voguel, C.; Martinez-Barros, H.; Pintor, R.; Belanger-Quintana, A.; Mateo, R.; Candela, A.; Botella-Carretero, J. I. Serum zinc and copper in people with COVID-19 and zinc supplementation in parenteral nutrition. *Nutrition.* **2021**, *91−92*, 111467.
(231) Bala, S.; Failla, M. L. Copper deficiency reversibly impairs DNA synthesis in activated T lymphocytes by limiting interleukin 2 activity. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89* (15), 6794−6797.
(232) Hopkins, R. G.; Failla, M. L. Copper deficiency reduces interleukin-2 (IL-2) production and IL-2 mRNA in human T-lymphocytes. *J. Nutr.* **1997**, *127* (2), 257−262.
(233) Francis, Z.; Book, G.; Litvin, C.; Kalivas, B. The COVID-19 pandemic & Zinc-induced copper deficiency an important link. *Am. J. Med.* **2022**, *135*, E290−E291.
(234) Heller, R. A.; Sun, Q.; Hackler, J.; Seelig, J.; Seibert, L.; Cherkezov, A.; Minich, W. B.; Seemann, P.; Diegmann, J.; Pilz, M.; Bachmann, M.; Ranjbar, A.; Moghaddam, A.; Schomburg, L. Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker. *Redox Biol.* **2021**, *38*, 101764.
(235) Ivanova, I. D.; Pal, A.; Simonelli, I.; Atanasova, B.; Ventriglia, M.; Rongioletti, M.; Squitti, R. Evaluation of zinc, copper, and Cu:Zn ratio in serum, and their implications in the course of COVID-19. *J. Trace. Elem. Med. Biol.* **2022**, *71*, 126944.
(236) Skalny, A. V.; Timashev, P. S.; Aschner, M.; Aaseth, J.; Chernova, L. N.; Belyaev, V. E.; Grabeklis, A. R.; Notova, S. V.; Lobinski, R.; Tsatsakis, A.; Svistunov, A. A.; Fomin, V. V.; Tinkov, A. A.; Glybochko, P. V. Serum zinc, copper, and other biometals are associated with COVID-19 severity markers. *Metabolites.* **2021**, *11* (4), 244.
(237) Govind, V.; Bharadwaj, S.; Sai Ganesh, M. R.; Vishnu, J.; Shankar, K. V.; Shankar, B.; Rajesh, R. Antiviral properties of copper and its alloys to inactivate covid-19 virus: a review. *Biometals.* **2021**, *34* (6), 1217−1235.
(238) Zuniga, J. M.; Cortes, A. The role of additive manufacturing and antimicrobial polymers in the COVID-19 pandemic. *Expert Rev. Med. Devices.* **2020**, *17* (6), 477−481.
(239) Amin, A. H.; El-Missiry, M. A.; Othman, A. I. Melatonin ameliorates metabolic risk factors, modulates apoptotic proteins, and protects the rat heart against diabetes-induced apoptosis. *Eur. J. Pharmacol.* **2015**, *747*, 166−173.
(240) El-Missiry, M. A.; El-Missiry, Z. M. A.; Othman, A. I. Melatonin is a potential adjuvant to improve clinical outcomes in individuals with obesity and diabetes with coexistence of Covid-19. *Eur. J. Pharmacol.* **2020**, *882*, 173329.
(241) Muniyappa, R.; Gubbi, S. COVID-19 pandemic, corona viruses, and diabetes mellitus. *Am. J. Physiol. Endocrinol. Metab.* **2020**, *318* (5), E736−E741.
(242) Boga, J. A.; Coto-Montes, A.; Rosales-Corral, S. A.; Tan, D. X.; Reiter, R. J. Beneficial actions of melatonin in the management of viral infections: a new use for this "molecular handyman? *Rev. Med. Virol.* **2012**, *22* (5), 323−338.
(243) Reiter, R. J.; Ma, Q.; Sharma, R. Treatment of Ebola and other infectious diseases: melatonin "goes viral. *Melatonin Res.* **2020**, *3* (1), 43−57.
(244) Colunga Biancatelli, R. M. L.; Berrill, M.; Mohammed, Y. H.; Marik, P. E. Melatonin for the treatment of sepsis: the scientific rationale. *J. Thorac. Dis.* **2020**, *12*, S54.
(245) Hardeland, R. Melatonin and inflammation-Story of a double-edged blade. *J. Pineal Res.* **2018**, *65* (4), No. e12525.
(246) Garcia, J. A.; Volt, H.; Venegas, C.; Doerrier, C.; Escames, G.; Lopez, L. C.; Acuña-Castroviejo, D. Disruption of the NF-kappaB/NLRP3 connection by melatonin requires retinoid-related orphan receptor-alpha and blocks the septic response in mice. *FASEB J.* **2015**, *29* (9), 3863−3875.
(247) Acuña-Castroviejo, D.; Escames, G.; Figueira, J. C.; de la Oliva, P.; Borobia, A. M.; Acuña-Fernández, C. Clinical trial to test the efficacy of melatonin in COVID-19. *J. Pineal Res.* **2020**, *69*, No. e12683.
(248) Miller, S. C.; Pandi, P. S.; Esquifino, A. I.; Cardinali, D. P.; Maestroni, G. J. The role of melatonin in immuno-enhancement: potential application in cancer. *Int. J. Exp. Pathol.* **2006**, *87* (2), 81−87.
(249) Juybari, K. B.; Pourhanifeh, M. H.; Hosseinzadeh, A.; Hemati, K.; Mehrzadi, S. Melatonin potentials against viral infections including COVID-19: Current evidence and new findings. *Virus Res.* **2020**, *287*, 198108.
(250) Yu, G.-M.; Kubota, H.; Okita, M.; Maeda, T. The anti-inflammatory and antioxidant effects of melatonin on LPS-stimulated bovine mammary epithelial cells. *PLoS One.* **2017**, *12* (5), No. e0178525.
(251) Heo, J. S.; Pyo, S.; Lim, J. Y.; Yoon, D. W.; Kim, B. Y.; Kim, J. H.; Kim, G. J.; Lee, S. G.; Kim, J. Biological effects of melatonin on human adipose-derived mesenchymal stem cells. *Int. J. Mol. Med.* **2019**, *44*, 2234−2244.
(252) Gilad, E.; Wong, H. R.; Zingarelli, B.; Virág, L.; O'Connor, M.; Salzman, A. L.; Szabó, C. Melatonin inhibits expression of the inducible isoform of nitric oxide synthase in murine macrophages: role of inhibition of NFkappaB activation. *FASEB J.* **1998**, *12* (9), 685−693.
(253) Galley, H. F.; Lowes, D.; Allen, L.; Cameron, G.; Aucott, L. S.; Webster, N. R. Melatonin as a potential therapy for sepsis: a phase I dose escalation study and an ex vivo whole blood model under conditions of sepsis. *J. Pineal Res.* **2014**, *56* (4), 427−438.
(254) Reiter, R. J.; Sharma, R.; Ma, Q.; Dominquez-Rodriguez, A.; Marik, P. E.; Abreu-Gonzalez, P. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. *Med. Drug Discovery* **2020**, *6*, 100044.
(255) Acuna-Castroviejo, D.; Noguiera-Navarro, M. T.; Reiter, R. J.; Escames, G. Melatonin actions in the heart: more than a hormone. *Melatonin Res.* **2018**, *1* (1), 21−26.
(256) Zhang, R.; Wang, X.; Ni, L.; Di, X.; Ma, B.; Niu, S.; Liu, C.; Reiter, R. J. COVID-19: melatonin as a potential adjuvant treatment. *Life Sci.* **2020**, *250*, 117583.
(257) Feitosa, E. L.; Júnior, F.T.D.S.S.; Nery Neto, J. A. O.; Matos, L. F. L.; Moura, M. H. S.; Rosales, T. O.; De Freitas, G. B. L. COVID-19: Rational discovery of the therapeutic potential of Melatonin as a SARS-CoV-2 main protease inhibitor. *Int. J. Med. Sci.* **2020**, *17* (14), 2133−2146.
(258) Reynolds, J. L.; Dubocovich, M. L. Melatonin multifaceted pharmacological actions on melatonin receptors converging to abrogate COVID-19. *J. Pineal Res.* **2021**, *71*, No. e12732.
(259) Zhou, Y.; Hou, Y.; Shen, J.; Mehra, R.; Kallianpur, A.; Culver, D. A.; Gack, M. U.; Farha, S.; Zein, J.; Comhair, S.; Fiocchi, C.; Stappenbeck, T.; Chan, T.; Eng, C.; Jung, J. U.; Jehi, L.; Erzurum, S.; Cheng, F. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. *PLoS Biol.* **2020**, *18* (11), No. e3000970.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(260) Zhou, Y.; Hou, Y.; Shen, J.; Huang, Y.; Martin, W.; Cheng, F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery* **2020**, *6*, 14.
(261) del Río, B. D.; Pedrero, J. M.; Martínez-Campa, C.; Zuazua, P.; Lazo, P. S.; Ramos, S. Melatonin, an endogenous-specific inhibitor of estrogen receptor α via calmodulin. *J. Biol. Chem.* **2004**, *279* (37), 38294−38302.
(262) Ui-Tei, K.; Nagano, M.; Sato, S.; Miyata, Y. Calmodulin-dependent and-independent apoptosis in cells of a drosophila neuronal cell line. *Apoptosis.* **2000**, *5* (2), 133−140.
(263) Annunziata, G.; Sanduzzi Zamparelli, M.; Santoro, C.; Ciampaglia, R.; Stornaiuolo, M.; Tenore, G. C.; Sanduzzi, A.; Novellino, E. May polyphenols have a role against coronavirus infection? An overview of in vitro evidence. *Front. Med. (Laussane)* **2020**, *7*, 240.
(264) Levy, E.; Delvin, E.; Marcil, V.; Spahis, S. Can phytotherapy with polyphenols serve as a powerful approach for the prevention and therapy tool of novel coronavirus disease 2019 (COVID-19)? *Am. J. Physiol. Endocrinol. Metab.* **2020**, *319* (4), E689−E708.
(265) Paraiso, I. L.; Revel, J. S.; Stevens, J. F. Potential use of polyphenols in the battle against COVID-19. *Curr. Opin. Food Sci.* **2020**, *32*, 149−155.
(266) Brgiez Mojzer, E. B.; Knez Hrncic, M. K.; Škerget, M.; Knez, Ž.; Bren, U. Polyphenols: Extraction methods, antioxidative action, bioavailability and anticarcinogenic effects. *Molecules* **2016**, *21*, 901.
(267) Gonzalez-Alfonso, J. L.; Peñalver, P.; Ballesteros, A. O.; Morales, J. C.; Plou, F. J. Effect of α-glucosylation on the stability, antioxidant properties, toxicity, and neuroprotective activity of (−)-epigallocatechin gallate. *Front. Nutr.* **2019**, *6*, 30.
(268) Rasouli, H.; Farzaei, M. H.; Khodarahmi, R. Polyphenols and their benefits: A review. *Int. J. Food Prop.* **2017**, *20*, 1700−1741.
(269) Hong, M.; Cheng, L.; Liu, Y.; Wu, Z.; Zhang, P.; Zhang, X. A natural plant source-tea polyphenols, a potential drug for improving immunity and combating virus. *Nutrients.* **2022**, *14* (3), 550.
(270) Sroka, Z.; Cisowski, W. Hydrogen peroxide scavenging, antioxidant and antiradical activity of some phenolic acids. *Food Chem. Toxicol.* **2003**, *41* (6), 753−758.
(271) Zheng, Y. Z.; Deng, G.; Zhang, Y. C. Multiple free radical scavenging reactions of flavonoids. *Dyes Pigm.* **2022**, *198*, 109877.
(272) Scalbert, A.; Johnson, I. T.; Saltmarsh, M. Polyphenols: antioxidants and beyond. *Am. J. Clin. Nutr.* **2005**, *81*, 215S−217S.
(273) Sivanantham, A.; Pattarayan, D.; Rajasekar, N.; Kannan, A.; Loganathan, L.; Bethunaickan, R.; Mahapatra, S. K.; Palanichamy, R.; Muthusamy, K.; Rajasekaran, S. Tannic acid prevents macrophage-induced pro-fibrotic response in lung epithelial cells via suppressing TLR4-mediated macro-phage polarization. *Inflamm. Res.* **2019**, *68* (12), 1011−1024.
(274) Tsai, M. J.; Chang, W. A.; Liao, S. H.; Chang, K. F.; Sheu, C. C.; Kuo, P. L. The effects of epigallocatechin gallate (EGCG) on pulmonary fibroblasts of id-iopathic pulmonary fibrosis (IPF)-a next-generation sequencing and bio-informatic approach. *Int. J. Mol. Sci.* **2019**, *20*, 1958.
(275) Jasso-Miranda, C.; Herrera-Camacho, I.; Flores-Mendoza, L. K.; Dominguez, F.; Vallejo-Ruiz, V.; Sanchez-Burgos, G. G.; Pando-Robles, V.; Santos-Lopez, G.; Reyes-Leyva, J. Antiviral and immunomodulatory effects of polyphenols on macrophages infected with dengue virus serotypes 2 and 3 enhanced or not with antibodies. *Infect. Drug. Resist.* **2019**, *12*, 1833−1852.
(276) Park, J. Y.; Yuk, H. J.; Ryu, H. W.; Lim, S. H.; Kim, K. S.; Park, K. H.; Ryu, Y. B.; Lee, W. S. Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. *J. Enzyme Inhib. Med. Chem.* **2017**, *32* (1), 504−515.
(277) Augusti, P. R.; Conterato, G. M. M.; Denardin, C. C.; Prazeres, I. D.; Serra, A. T.; Bronze, M. R.; Emanuelli, T. Bioactivity, bioavailability, and gut microbiota transformations of dietary phenolic compounds: implications for COVID-19. *J. Nutr Biochem.* **2021**, *97*, 108787.
(278) Yahfoufi, N.; Alsadi, N.; Jambi, M.; Matar, C. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients.* **2018**, *10* (11), 1618.
(279) Kelley, D. S.; Adkins, Y.; Laugero, K. D. A review of the health benefits of cherries. *Nutrients.* **2018**, *10* (3), 368.
(280) Shakoor, H.; Feehan, J.; Apostolopoulos, V.; Platat, C.; Al Dhaheri, A. S.; Ali, H. I.; Ismail, L. C.; Bosevski, M.; Stojanovska, L. Immunomodulatory effects of dietary polyphenols. *Nutrients.* **2021**, *13* (3), 728.
(281) Wang, K.; Ping, S.; Huang, S.; Hu, L.; Xuan, H.; Zhang, C.; Hu, F. Molecular mechanisms underlying the in vitro anti-inflammatory effects of a flavonoid-rich ethanol extract from chinese propolis (poplar type). *Evid. Based Complement. Alternat. Med.* **2013**, *2013*, 127672.
(282) Giovinazzo, G.; Gerardi, C.; Uberti-Foppa, C.; Lopalco, L. Can natural polyphenols help in reducing cytokine storm in COVID-19 patients? *Molecules.* **2020**, *25* (24), 5888.
(283) Gupta, S. C.; Prasad, S.; Kim, J. H.; Patchva, S.; Webb, L. J.; Priyadarsini, I. K.; Aggarwal, B. B. Multitargeting by curcumin as revealed by molecular interaction studies. *Nat. Prod. Rep.* **2011**, *28* (12), 1937−1955.
(284) Shukla, M.; Gupta, K.; Rasheed, Z.; Khan, K. A.; Haqqi, T. M. Bioavailable constituents/metabolites of pomegranate (Punica granatum L) preferentially inhibit COX2 activity ex vivo and IL-1beta-induced PGE2 production in human chondrocytes in vitro. *J. Inflamm. (London).* **2008**, *5*, 9.
(285) Jung, H. A.; Karki, S.; Ehom, N. Y.; Yoon, M. H.; Kim, E. J.; Choi, J. S. Anti-diabetic and anti-inflammatory effects of green and red kohlrabi cultivars (Brassica oleracea var. gongylodes). *Prev. Nutr. Food Sci.* **2014**, *19*, 281−290.
(286) Ambriz-Pérez, D. L.; Leyva-López, N.; Gutierrez-Grijalva, E. P.; Heredia, J. B. Phenolic compounds: Natural alternative in inflammation treatment. A review. *Cogent Food Agric.* **2016**, *2*, 1131412.
(287) Hämäläinen, M.; Nieminen, R.; Vuorela, P.; Heinonen, M.; Moilanen, E. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-κB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-κB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators Inflamm.* **2007**, *2007*, 45673.
(288) Rowe, C. A.; Nantz, M. P.; Bukowski, J. F.; Percival, S. S. Specific formulation of Camellia sinensis prevents cold and flu symptoms and enhances gamma, delta T cell function: A randomized, double-blind, placebo-controlled study. *J. Am. Coll. Nutr.* **2007**, *26* (5), 445−452.
(289) El-Missiry, M. A.; Fekri, A.; Kesar, L. A.; Othman, A. I. Polyphenols are potential nutritional adjuvants for targeting COVID-19. *Phytother. Res.* **2021**, *35* (6), 2879−2889.
(290) Chojnacka, K.; Skrzypczak, D.; Izydorczyk, G.; Mikula, K.; Szopa, D.; Witek-Krowiak, A. Antiviral properties of polyphenols from plants. *Foods.* **2021**, *10* (10), 2277.
(291) Hasan, A.; Paray, B. A.; Hussain, A.; Qadir, F. A.; Attar, F.; Aziz, F. M.; Sharifi, M.; Derakhshankhah, H.; Rasti, B.; Mehrabi, M.; Shahpasand, K.; Saboury, A. A.; Falahati, M. A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin. *J. Biomol. Struct. Dyn.* **2021**, *39* (8), 3025−3033.
(292) Khan, R. J.; Jha, R. K.; Amera, G. M.; Jain, M.; Singh, E.; Pathak, A.; Singh, R. P.; Muthukumaran, J.; Singh, A. K. Targeting SARS-CoV-2: A systematic drug repurposing approach to identify promising inhibitors against 3C-like proteinase and 2′-O-ribose methyltransferase. *J. Biomol. Struct. Dyn.* **2021**, *39* (8), 2679−2692.
(293) Zhou, Y.; Simmons, G. Development of novel entry inhibitors targeting emerging viruses. *Expert. Rev. Anti. Infect. Ther.* **2012**, *10* (10), 1129−1138.
(294) Tripet, B.; Howard, M. W.; Jobling, M.; Holmes, R. K.; Holmes, K. V.; Hodges, R. S. Structural characterization of the SARS-coronavirus spike S fusion protein core. *J. Biol. Chem.* **2004**, *279* (20), 20836−20849.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(295) Steinmann, J.; Buer, J.; Pietschmann, T.; Steinmann, E. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. *Br. J. Pharmacol.* **2013**, *168* (5), 1059−1073.
(296) Vellingiri, B.; Jayaramayya, K.; Iyer, M.; Narayanasamy, A.; Govindasamy, V.; Giridharan, B.; Ganesan, S.; Venugopal, A.; Venkatesan, D.; Ganesan, H.; Rajagopalan, K.; Rahman, P. K. S. M.; Cho, S. G.; Kumar, N. S.; Subramaniam, M. D. COVID-19: A promising cure for the global panic. *Sci. Total Environ.* **2020**, *725*, 138277.
(297) Pandey, P.; Rane, J. S.; Chatterjee, A.; Kumar, A.; Khan, R.; Prakash, A.; Ray, S. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. *J. Biomol. Struct. Dyn.* **2021**, *39* (16), 6306−6316.
(298) Belouzard, S.; Millet, J. K.; Licitra, B. N.; Whittaker, G. R. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses.* **2012**, *4* (6), 1011−1033.
(299) Jain, R.; Shukla, S.; Nema, N.; Panday, A. A systemic review: Structural mechanism of SARS CoV-2A and promising preventive cure by phytochemicals. *Int. J. Immunol. Immunother.* **2020**, *7*, 051.
(300) Walls, A. C.; Park, Y. J.; Tortorici, M. A.; Wall, A.; McGuire, A. T.; Veesler, D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell.* **2020**, *181*, 281−292.
(301) Kiani, A. K.; Dhuli, K.; Anpilogov, K.; Bressan, S.; Dautaj, A.; Dundar, M.; Beccari, T.; Ergoren, M. C.; Bertelli, M. Natural compounds as inhibitors of SARS-CoV-2 endocytosis: A promising approach against COVID-19. *Acta Biomed.* **2020**, *91*, No. e2020008.
(302) Baglivo, M.; Baronio, M.; Natalini, G.; Beccari, T.; Chiurazzi, P.; Fulcheri, E.; Petralia, P. P.; Michelini, S.; Fiorentini, G.; Miggiano, G. A.; Morresi, A.; Tonini, G.; Bertelli, M. Natural small molecules as inhibitors of coronavirus lipid-dependent attachment to host cells: a possible strategy for reducing SARS-COV-2 infectivity? *Acta Biomed.* **2020**, *91*, 161−164.
(303) Imai, Y.; Kuba, K.; Ohto-Nakanishi, T.; Penninger, J. M. Angiotensin-con-verting enzyme 2 (ACE2) in disease pathogenesis. *Circ. J.* **2010**, *74* (3), 405−410.
(304) Kuba, K.; Imai, Y.; Rao, S.; Gao, H.; Guo, F.; Guan, B.; Huan, Y.; Yang, P.; Zhang, Y.; Deng, W.; Bao, L.; Zhang, B.; Liu, G.; Wang, Z.; Chappell, M.; Liu, Y.; Zheng, D.; Leibbrandt, A.; Wada, T.; Slutsky, A. S.; Liu, D.; Qin, C.; Jiang, C.; Penninger, J. M. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* **2005**, *11*, 875−879.
(305) Imai, Y.; Kuba, K.; Rao, S.; Huan, Y.; Guo, F.; Guan, B.; Yang, P.; Sarao, R.; Wada, T.; Leong-Poi, H.; Crackower, M. A.; Fukamizu, A.; Hui, C. C.; Hein, L.; Uhlig, S.; Slutsky, A. S.; Jiang, C.; Penninger, J. M. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature.* **2005**, *436* (7047), 112−116.
(306) Bao, H.; Gao, F.; Xie, G.; Liu, Z. Angiotensin-converting enzyme 2 inhibits apoptosis of pulmonary endothelial cells during acute lung injury through suppressing MiR-4262. *Cell Physiol. Biochem.* **2015**, *37* (2), 759−767.
(307) Min, F.; Gao, F.; Li, Q.; Liu, Z. Therapeutic effect of human umbilical cord mesenchymal stem cells modified by angiotensin-converting enzyme 2 gene on bleomycin-induced lung fibrosis injury. *Mol. Med. Rep.* **2015**, *11* (4), 2387−2396.
(308) de Ligt, M.; Hesselink, M. K. C.; Jorgensen, J.; Hoebers, N.; Blaak, E. E.; Goossens, G. H. Resveratrol supplementation reduces ACE2 expression in human adipose tissue. *Adipocyte.* **2021**, *10* (1), 408−411.
(309) van Brummelen, R.; van Brummelen, A. C. The potential role of resveratrol as supportive antiviral in treating conditions such as COVID-19 - A formulator's perspective. *Biomed. Pharmacother.* **2022**, *148*, 112767.
(310) Kelleni, M. T. Resveratrol-zinc nanoparticles or pterostilbene-zinc: Potential COVID-19 mono and adjuvant therapy. *Biomed. Pharmacother.* **2021**, *139*, 111626.
(311) Rahman, M. H.; Akter, R.; Bhattacharya, T.; Abdel-Daim, M. M.; Alkahtani, S.; Arafah, M. W.; Al-Johani, N. S.; Alhoshani, N. M.; Alkeraishan, N.; Alhenaky, A.; Abd-Elkader, O. H.; El-Seedi, H. R.; Kaushik, D.; Mittal, V. Resveratrol and neuroprotection: Impact and its therapeutic potential in Alzheimer's disease. *Front. Pharmacol.* **2020**, *11*, 619024.
(312) Mehany, T.; Khalifa, I.; Barakat, H.; Althwab, S. A.; Alharbi, Y. M.; El-Sohaimy, S. Polyphenols as promising biologically active substances for preventing SARS-CoV-2: A review with research evidence and underlying mechanisms. *Food Biosci.* **2021**, *40*, 100891.
(313) Mody, V.; Ho, J.; Wills, S.; Mawri, A.; Lawson, L.; Ebert, M.C.C.J.C.; Fortin, G. M.; Rayalam, S.; Taval, S. Identification of 3-chymotrypsin like protease (3CLPro) inhibitors as potential anti-SARS-CoV-2 agents. *Commun. Biol.* **2021**, *4*, 93.
(314) Xu, H.; LI, J.; Song, S.; Xiao, Z.; Chen, X.; Huang, B.; Sun, M.; Su, G.; Zhou, D.; Wang, G.; Hao, R.; Wang, N. Effective inhibition of coronavirus replication by Polygonum cuspidatum. *Front. Biosci. (Landmark Ed.).* **2021**, *26*, 789−798.
(315) Yamada, K.; Ogawa, H.; Hara, A.; Yoshida, Y.; Yonezawa, Y.; Karibe, K.; Nghia, V. B.; Yoshimura, H.; Yamamoto, Y.; Yamada, M.; Nakamura, K.; Imai, K. Mechanism of the antiviral effect of hydroxytyrosol on influenza virus appears to involve morphological change of the virus. *Antiviral Res.* **2009**, *83* (1), 35−44.
(316) Paolacci, S.; Kiani, A. K.; Shree, P.; Tripathi, D.; Tripathi, Y. B.; Tripathi, P.; Tartaglia, G. M.; Farronato, M.; Farronato, G.; Connelly, S. T.; Ceccarini, M. R.; Coatto, M.; Ergoren, M. C.; Sanlidag, T.; Dautaj, A.; Bertelli, M. Scoping review on the role and interactions of hydroxytyrosol and alpha-cyclodextrin in lipid-raft-mediated endocytosis of SARS-CoV-2 and bioinformatic molecular docking studies. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 90−100.
(317) Goc, A.; Sumera, W.; Rath, M.; Niedzwiecki, A. Phenolic compounds disrupt spike-mediated receptor-binding and entry of SARS-CoV-2 pseudo-virions. *PLoS One.* **2021**, *16* (6), No. e0253489.
(318) Suravajhala, R.; Parashar, A.; Choudhir, G.; Kumar, A.; Malik, B.; Nagaraj, V. A.; Padmanaban, G.; Polavarapu, R.; Suravajhala, P.; Kishor, P. B. K. Molecular docking and dynamics studies of curcumin with COVID-19 proteins. *Netw. Model. Anal. Health Inform. Bioinform.* **2021**, *10*, 44.
(319) Avasarala, S.; Zhang, F.; Liu, G.; Wang, R.; London, S. D.; London, L. Curcumin modulates the inflammatory response and inhibits subsequent fibrosis in a mouse model of viral-induced acute respiratory distress syndrome. *PLoS One.* **2013**, *8* (2), No. e57285.
(320) Zahedipour, F.; Hosseini, S. A.; Sathyapalan, T.; Majeed, M.; Jamialahmadi, T.; Al-Rasadi, K.; Banach, M.; Sahebkar, A. Potential effects of curcumin in the treatment of COVID-19 infection. *Phytother Res.* **2020**, *34* (11), 2911−2920.
(321) Asadirad, A.; Nashibi, R.; Khodadadi, A.; Ghadiri, A. A.; Sadeghi, M.; Aminian, A.; Dehnavi, S. Antiinflammatory potential of nano-curcumin as an alternative therapeutic agent for the treatment of mild-to-moderate hospitalized COVID-19 patients in a placebo-controlled clinical trial. *Phytotherapy Res.* **2022**, *36* (2), 1023−1031.
(322) Soltani, A.; Salmaninejad, A.; Jalili-Nik, M.; Soleimani, A.; Javid, H.; Hashemy, S. I.; Sahebkar, A. 5′-adenosine monophosphate-activated protein kinase: A potential target for disease prevention by curcumin. *J. Cell Physiol.* **2019**, *234* (3), 2241−2251.
(323) Naito, Y.; Takagi, T.; Higashimura, Y. Heme oxygenase-1 and anti-inflammatory M2 macrophages. *Arch. Biochem. Biophys.* **2014**, *564*, 83−88.
(324) Dai, J.; Gu, L.; Su, Y.; Wang, Q.; Zhao, Y.; Chen, X.; Deng, H.; Li, W.; Wang, G.; Li, K. Inhibition of curcumin on influenza A virus infection and influenzal pneumonia via oxidative stress, TLR2/4, p38/JNK MAPK and NF-Kb pathways. *Int. Immunopharmacol.* **2018**, *54*, 177−187.
(325) Ahn, K. S.; Sethi, G.; Jain, A. K.; Jaiswal, A. K.; Aggarwal, B. B. Genetic deletion of NAD (P)H:Quinone oxidoreductase 1 abrogates activation of nuclear factor-kappaB, IkappaBalpha kinase, c-Jun N-terminal kinase, Akt, p38, and p44/42 mitogen-activated protein kinases and potentiates apoptosis. *J. Biol. Chem.* **2006**, *281* (29), 19798−19808.
(326) Mathew, D.; Hsu, W.-L. Antiviral potential of curcumin. *J. Funct.Foods.* **2018**, *40*, 692−699.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(327) Praditya, D.; Kirchhoff, L.; Brüning, J.; Rachmawati, H.; Steinmann, J.; Steinmann, E. Anti-infective properties of the golden spice curcumin. *Front. Microbiol.* **2019**, *10*, 912.
(328) Puar, Y. R.; Shanmugam, M. K.; Fan, L.; Arfuso, F.; Sethi, G.; Tergaonkar, V. Evidence for the involvement of the master transcription factor NF-κB in cancer initiation and progression. *Biomedicines.* **2018**, *6* (3), 82.
(329) Jena, A. B.; Kanungo, N.; Nayak, V.; Chainy, G. B. N.; Dandapat, J. Catechin and curcumin interact with S protein of SARS-CoV2 and ACE2 of human cell membrane: insights from computational studies. *Sci. Rep.* **2021**, *11*, 2043.
(330) Mishra, C. B.; Pandey, P.; Sharma, R. D.; Malik, M. Z.; Mongre, R. K.; Lynn, A. M.; Prasad, R.; Jeon, R.; Prakash, A. Identifying the natural polyphenol catechin as a multi-targeted agent against SARS-CoV-2 for the plausible therapy of COVID-19: an integrated computational approach. *Brief. Bioinform.* **2021**, *22* (2), 1346−1360.
(331) Bhardwaj, V. K.; Singh, R.; Sharma, J.; Rajendran, V.; Purohit, R.; Kumar, S. Bioactive molecules of tea as potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2. *Front. Med. (Lausanne).* **2021**, *8*, 684020.
(332) Zheng, Y.; Lim, E. J.; Wang, L.; Smart, E. J.; Toborek, M.; Hennig, B. Role of caveolin-1 in EGCG-mediated protection against linoleic-acid-induced endothelial cell activation. *J. Nutr. Biochem.* **2009**, *20* (3), 202−209.
(333) Mhatre, S.; Srivastava, T.; Naik, S.; Patravale, V. Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. *Phytomedicine.* **2021**, *85*, 153286.
(334) Ghosh, R.; Chakraborty, A.; Biswas, A.; Chowdhuri, S. Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors-An in silico docking and molecular dynamics simulation study. *J. Biomol. Struct. Dyn.* **2021**, *39*, 4362−4374.
(335) Song, J. M.; Lee, K. H.; Seong, B. L. Antiviral effect of catechins in green tea on influenza virus. *Antivir. Res.* **2005**, *68*, 66−74.
(336) Xu, J.; Xu, Z.; Zheng, W. A review of the antiviral role of green tea catechins. *Molecules.* **2017**, *22* (8), 1337.
(337) Yang, Z. F.; Bai, L. P.; Huang, W. B.; Li, X. Z.; Zhao, S. S.; Zhong, N. S.; Jiang, Z. H. Comparison of in vitro antiviral activity of tea polyphenols against influenza A and B viruses and structure-activity relationship analysis. *Fitoterapia.* **2014**, *93*, 47−53.
(338) Mehta, P.; McAuley, D. F.; Brown, M.; Sanchez, E.; Tattersall, R. S.; Manson, J. J. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* **2020**, *395* (10229), 1033−1034.
(339) Pawan, K.; Agrawal, A. C.; Blunden, G. Quercetin: antiviral significance and possible COVID-19 integrative considerations. *Nat. Prod. Commun.* **2020**, *15*, 1934578X20976293.
(340) Kandere-Grzybowska, K.; Kempuraj, D.; Cao, J.; Cetrulo, C. L.; Theoharides, T. C. Regulation of IL-1-induced selective IL-6 release from human mast cells and inhibition by quercetin. *Br. J. Pharmacol.* **2006**, *148*, 208−215.
(341) Lin, L. T.; Hsu, W. C.; Lin, C. C. Antiviral natural products and herbal medicines. *J. Tradit. Complement. Med.* **2014**, *4* (1), 24−35.
(342) Aucoin, M.; Cooley, K.; Saunders, P. R.; Cardozo, V.; Remy, D.; Cramer, H.; Neyre Abad, C.; Hannan, N. The effect of quercetin on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. *Adv. Integr. Med.* **2020**, *7* (4), 247−251.
(343) Colunga Biancatelli, R. M. L.; Berrill, M.; Catravas, J. D.; Marik, P. E. Quercetin and Vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). *Front Immunol.* **2020**, *11*, 1451.
(344) Zandi, K.; Musall, K.; Oo, A.; Cao, D.; Liang, B.; Hassandarvish, P.; Lan, S.; Slack, R. L.; Kirby, K. A.; Bassit, L.; Amblard, F.; Kim, B.; AbuBakar, S.; Sarafianos, S. G.; Schinazi, R. F. Baicalein and Baicalin Inhibit SARS-CoV-2 RNA-Dependent-RNA Polymerase. *Microorganisms.* **2021**, *9* (5), 893.
(345) da Silva Antonio, A.; Moreira Wiedemann, L. S.; Veiga-Junior, V. F. Natural products' role against COVID-19. *RSC Adv.* **2020**, *10*, 23379−23393.
(346) Khalil, A.; Tazeddinova, D. The upshot of polyphenolic compounds on immunity amid COVID-19 pandemic and other emerging communicable diseases: an appraisal. *Nat. Prod. Bioprospect.* **2020**, *10* (6), 411−429.
(347) Shi, Y.; Dai, J.; Liu, H.; Li, R. R.; Sun, P. L.; Du, Q.; Pang, L. L.; Chen, Z.; Yin, K. S. Naringenin inhibits allergen-induced airway inflammation and airway responsiveness and inhibits NF-κB activity in a murine model of asthma. *Can. J. Physiol. Pharmacol.* **2009**, *87* (9), 729−735.
(348) Abdo, N.; Moheyeldin, O.; Shehata, M.; El Sohaimy, S. Inhibition of the SARS-CoV-2 RNA-dependent RNA polymerase by natural bioactive compounds: Molecular docking analysis. *Egypt. J. Chem.* **2021**, *64*, 1989−2001.
(349) Russo, M.; Moccia, S.; Spagnuolo, C.; Tedesco, I.; Russo, G. L. Roles of flavonoids against coronavirus infection. *Chem. Biol. Interact.* **2020**, *328*, 109211.
(350) Abd El-Mordy, F. M.; El-Hamouly, M. M.; Ibrahim, M. T.; Abd El-Rheem, G.; Aly, O. M.; Abd El-kader, A. M.; Youssif, K. A.; Abdelmohsen, U. R. Inhibition of SARS-CoV-2 main protease by phenolic compounds from Manilkara hexandra (Roxb.) Dubard assisted by metabolite profiling and in silico virtual screening. *RSC Adv.* **2020**, *10*, 32148−32155.
(351) Utomo, R. Y.; Ikawati, M.; Meiyanto, E. Revealing the potency of Citrus and Galangal constituents to halt SARS-CoV-2 infection. *Preprints* **2020**, *2020*, 2020030214.
(352) Bellavite, P.; Donzelli, A. Hesperidin and SARS-CoV-2: New light on the healthy function of citrus fruits. *Antioxidants (Basel).* **2020**, *9* (8), 742.
(353) Wu, C.; Liu, Y.; Yang, Y.; Zhang, P.; Zhong, W.; Wang, Y.; Wang, Q.; Xu, Y.; Li, M.; Li, X.; Zheng, M.; Chen, L.; Li, H. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm. Sin. B* **2020**, *10* (5), 766−788.
(354) Adem, S.; Eyupoglu, V.; Sarfraz, I.; Rasul, A.; Ali, M. Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: an in silico strategy unveils a hope against CORONA. *Preprints* **2020**, *2020*, 2020030333.
(355) Talukdar, J.; Bhadra, B.; Dattaroy, T.; Nagle, V.; Dasgupta, S. Potential of natural astaxanthin in alleviating the risk of cytokine storm in COVID-19. *Biomed. Pharmacother.* **2020**, *132*, 110886.
(356) Mujwar, S.; Sun, L.; Fidan, O. In silico evaluation of food-derived carotenoids against SARS-CoV-2 drug targets: Crocin is a promising dietary supplement candidate for COVID-19. *J. Food Biochem.* **2022**, *46*, e14219.
(357) Yim, S.-K.; Kim, I.; Warren, B.; Kim, J.; Jung, K.; Ku, B. Antiviral activity of two marine carotenoids against SARS-CoV-2 Virus entry in silico and in vitro. *Int. J. Mol. Sci.* **2021**, *22* (12), 6481.
(358) Luo, P.; Liu, D.; Li, J. Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. *Int. J. Antimicrob. Agents.* **2020**, *55* (6), 105995.
(359) Gomaa, A. A.; Abdel-Wadood, Y. A. The potential of glycyrrhizin and licorice extract in combating COVID-19 and associated conditions. *Phytomed. Plus.* **2021**, *1* (3), 100043.
(360) van de Sand, L.; Bormann, M.; Alt, M.; Schipper, L.; Heilingloh, C. S.; Steinmann, E.; Todt, D.; Dittmer, U.; Elsner, C.; Witzke, O.; Krawczyk, A. Glycyrrhizin effectively inhibits SARS-CoV-2 replication by inhibiting the viral main protease. *Viruses.* **2021**, *13* (4), 609.
(361) Majnooni, M. B.; Fakhri, S.; Bahrami, G.; Naseri, M.; Farzaei, M. H.; Echeverria, J. Alkaloids as potential phytochemicals against SARS-CoV-2: Approaches to the associated pivotal mechanisms. *Evid. Based Complement. Alternat. Med.* **2021**, *2021*, 6632623.
(362) Wink, M. Potential of DNA intercalating alkaloids and other plant secondary metabolites against SARS-CoV-2 causing COVID-19. *Diversity.* **2020**, *12* (5), 175.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX

(363) Pandeya, K. B.; Ganeshpurkar, A.; Mishra, M. K. Natural RNA dependent RNA polymerase inhibitors: molecular docking studies of some biologically active alkaloids of *Argemone mexicana*. *Med. Hypotheses.* **2020**, *144*, 109905.
(364) Maurya, V. K.; Kumar, S.; Prasad, A. K.; Bhatt, M. L.; Saxena, S. K. Structure-based drug designing for potential antiviral activity of selected natural products from Ayurveda against SARS-CoV-2 spike glycoprotein and its cellular receptor. *Virus disease.* **2020**, *31* (2), 179−193.
(365) Galli, F.; Marcantonini, G.; Giustarini, D.; Albertini, M. C.; Migni, A.; Zatini, L.; Gioiello, A.; Rossi, R.; Bartolini, D. How aging and oxidative stress influence the cytopathic and inflammatory effects of SARS-CoV-2 infection: The role of cellular glutathione and cysteine metabolism. *Antioxidants (Basel).* **2022**, *11* (7), 1366.
(366) Fenouillet, E.; Barbouche, R.; Jones, I. M. Cell entry by enveloped viruses: redox considerations for HIV and SARS-coronavirus. *Antioxid. Redox Signal.* **2007**, *9* (8), 1009−1034.
(367) Lavillette, D.; Barbouche, R.; Yao, Y.; Boson, B.; Cosset, F. L.; Jones, I. M.; Fenouillet, E. Significant redox insensitivity of the functions of the SARS-CoV spike glycoprotein: Comparison with hiv envelope. *J. Biol. Chem.* **2006**, *281* (14), 9200−9204.
(368) Giustarini, D.; Santucci, A.; Bartolini, D.; Galli, F.; Rossi, R. The age-dependent decline of the extracellular thiol-disulfide balance and its role in SARS-CoV-2 infection. *Redox Biol.* **2021**, *41*, 101902.
(369) Fu, X.; Cate, S. A.; Dominguez, M.; Osborn, W.; Ozpolat, T.; Konkle, B. A.; Chen, J.; Lopez, J. A. Cysteine disulfides (Cys-ss-X) as sensitive plasma biomarkers of oxidative stress. *Sci. Rep.* **2019**, *9*, 115.
(370) Lizzo, G.; Migliavacca, E.; Lamers, D.; Frézal, A.; Corthesy, J.; Vinyes-Parès, G.; Bosco, N.; Karagounis, L. G.; Hövelmann, U.; Heise, T.; von Eynatten, M.; Gut, P. A randomized controlled clinical trial in healthy older adults to determine efficacy of glycine and N-acetylcysteine supplementation on glutathione redox status and oxidative damage. *Front Aging.* **2022**, *3*, 852569.
(371) McCaddon, A.; Regland, B. COVID-19: A methyl-group assault? *Med. Hypotheses.* **2021**, *149*, 110543.
(372) Newgard, C. B.; An, J.; Bain, J. R.; Muehlbauer, M. J.; Stevens, R. D.; Lien, L. F.; Haqq, A. M.; Shah, S. H.; Arlotto, M.; Slentz, C. A.; Rochon, J.; Gallup, D.; Ilkayeva, O.; Wenner, B. R.; Yancy, W. S., Jr.; Eisenson, H.; Musante, G.; Surwit, R. S.; Millington, D. S.; Butler, M. D.; Svetkey, L. P. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab.* **2009**, *9* (4), 311−326 Erratum in *Cell Metab.* **2009** *9* (6) 565−566..
(373) El-Khairy, L.; Ueland, P. M.; Refsum, H.; Graham, I. M.; Vollset, S. E. European Concerted Action Project. Plasma Total Cysteine as a Risk Factor for Vascular Disease: The European Concerted Action Project. *Circulation.* **2001**, *103*, 2544−2549.
(374) Kumar, P.; Liu, C.; Suliburk, J. W.; Minard, C. G.; Muthupillai, R.; Chacko, S.; Hsu, J. W.; Jahoor, F.; Sekhar, R. V. Supplementing glycine and N-acetylcysteine (GlyNAC) in aging HIV patients improves oxidative stress, mitochondrial dysfunction, inflammation, endothelial dysfunction, insulin resistance, genotoxicity, strength, and cognition: Results of an open-label clinical trial. *Biomedicines.* **2020**, *8* (10), 390.
(375) Sekhar, R. V. GlyNAC supplementation improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, aging hallmarks, metabolic defects, muscle strength, cognitive decline, and body composition: Implications for healthy aging. *J. Nutr.* **2021**, *151* (12), 3606−3616.
(376) Wong, K. K.; Lee, S. W. H.; Kua, K. P. N-Acetylcysteine as adjuvant therapy for COVID-19 - A perspective on the current state of the evidence. *J. Inflamm Res.* **2021**, *14*, 2993−3013.
(377) Assimakopoulos, S. F.; Aretha, D.; Komninos, D.; Dimitropoulou, D.; Lagadinou, M.; Leonidou, L.; Oikonomou, I.; Mouzaki, A.; Marangos, M. N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study. *Infect. Dis. (Lond).* **2021**, *53* (11), 847−854.
(378) Karimi Zarchi, A. A.; Faramarzi, M. A.; Gilani, K.; Ghazi-Khansari, M.; Ghamami, G.; Amani, A. N-acetylcysteine-loaded PLGA nanoparticles outperform conventional N-acetylcysteine in acute lung injuries in vivo. *Int. J. Polymeric Mater. Polymeric Biomaterials.* **2017**, *66* (9), 443−454.
(379) Fenouillet, E.; Barbouche, R.; Jones, I. M. Cell entry by enveloped viruses: Redox considerations for HIV and SARS-coronavirus. *Antioxid. Redox Signal.* **2007**, *9* (8), 1009−1034.
(380) Mathys, L.; Balzarini, J. The role of cellular oxidoreductases in viral entry and virus infection-associated oxidative stress: potential therapeutic applications. *Expert Opin. Ther. Targets.* **2016**, *20* (1), 123−143.
(381) Meirson, T.; Bomze, D.; Markel, G. Structural basis of SARS-CoV-2 spike protein induced by ACE2. *Bioinformatics.* **2021**, *37* (7), 929−936.
(382) Manček-Keber, M.; Hafner-Bratkovič, I.; Lainšček, D.; Benčina, M.; Govednik, T.; Orehek, S.; Plaper, T.; Jazbec, V.; Bergant, V.; Grass, V.; Pichlmair, A.; Jerala, R. Disruption of disulfides within RBD of SARS-CoV-2 spike protein prevents fusion and represents a target for viral entry inhibition by registered drugs. *FASEB J.* **2021**, *35*, No. e21651.
(383) Albashir, A. A. D. Renin-angiotensin-aldosterone system (RAAS) inhibitors and coronavirus disease 2019 (COVID-19). *South Med. J.* **2021**, *114* (1), 51−56.
(384) Fountain, J. H.; Lappin, S. L. Physiology, Renin Angiotensin System. In *StatPearls* StatPearls Publishing: Treasure Island, FL, 2021 https://www.ncbi.nlm.nih.gov/books/NBK470410/.
(385) Xiao, L.; Sakagami, H.; Miwa, N. ACE2: The key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: Demon or angel? *Viruses.* **2020**, *12* (5), 491.
(386) Ristow, M. Unraveling the truth about antioxidants: mitohormesis explains ROS-induced health benefits. *Nat. Med.* **2014**, *20*, 709−711.
(387) Cohen, N.; Golik, A. Zinc balance and medications commonly used in the management of heart failure. *Heart Fail Rev.* **2006**, *11* (1), 19−24.

https://doi.org/10.1021/acs.jmedchem.2c01134
J. Med. Chem. XXXX, XXX, XXX−XXX