Received: 24 November 2022 | Revised: 26 December 2022 | Accepted: 26 December 2022

DOI: 10.1002/fft2.207

FOOD FRONTIERS Open Access

REVIEW ARTICLE

An emerging natural antioxidant therapy for COVID-19 infection patients: Current and future directions

Amit Kumar Shrivastava[1] | Prafulla Kumar Sahu[2] | Teresa Cecchi[3] | Laxmi Shrestha[1] | Sanjay Kumar Shah[4] | Anamika Gupta[5] | Anjan Palikhey[1] | Bishal Joshi[6] | Pramodkumar P. Gupta[7] | Jitendra Upadhyaya[8] | Mahendra Paudel[9] | Dr Niranjan Koirala[10]

[1]Department of Pharmacology, Universal College of Medical Sciences Bhairahawa, Rupandehi, Nepal
Email:; sr.akshri.ucms.np@gmail.com

[2]School of Pharmacy, Centurion University of Technology and Management, Bhubaneswar, Odisha, India

[3]Chemistry Department, ITT MONTANI, Fermo, Italy

[4]Department of Reproductive Medicine, Joint Inter-national Research Laboratory of Reproduction and Development, Chongquing Medical University, Chongqing, People's Republic of China

[5]Sharjah Institute for Medical Sciences, University of Sharjah, Sharjah, United Arab Emirates
Email: malaparab@gmail.com

[6]Department of Physiology, Universal College of Medical Sciences Bhairahawa, Rupandehi, Nepal

[7]School of Biotechnology and Bioinformatics, D. Y. Patil Deemed to be University, CBD Belapur, Navi Mumbai, India

[8]Institute of Agriculture and Animal Science, Tribhuvan University, Chitwan, Nepal

[9]Department of Agri-Botany and Ecology, Institute of Agriculture and Animal Science, Tribhuvan University, Mahendranagar, Nepal

[10]Natural Products Research Facility, Gandaki Province Academy of Science and Technology, Pokhara, Gandaki Province, Nepal

Correspondence
Niranjan Koirala, Gandaki Province Academy of Science and Technology, Gandaki Province, Pokhara, Nepal.
Email: koiralaresearchfoundation@gmail.com

Abstract

Objective: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) affects millions of people worldwide. The article aims to review the therapeutic perspective on natural antioxidants, their mechanism of action, pharmacokinetics in management and cure of COVID-19/ SARS-CoV-2 infection.

Methods: We conducted a literature search including World Health Organization and National Institute of Health guidelines and clinical trials registered with ClinicalTrials.gov limited to antioxidants in COVID-19 management.

Results: Elderly, immunocompromised patients, and others with underlying health conditions or multiple comorbidities have a high mortality rate. Disrupted redox homeostasis and oxidative stress seem to be biological pathways that may increase personal vulnerability to infection. Antioxidants like vitamins C, D, E, epigallocatechin-3 gallate, and morin have been reported to protect against COVID-19 disease. Reactive oxygen species are immunological regulatory elements of viral replication. Natural

antioxidants exhibit potential action in preventing inflammation and organ dysfunction during viral infection. They also increase glutathione level, oxygenation rate, and immunological responses in the treatment of sepsis and acute respiratory distress syndrome.

Conclusion: No wonder the selection of prevention, treatment, and cure of COVID-19 and SARS-CoV-2 mainly depends upon the antiviral and immunoregulatory activity which they possess. Yet, their efficacy against COVID-19 is of great concern and demands extensive study.

KEYWORDS
antioxidant, clinical trials, epigallocatechin-3 gallate, morin, quercetin, SARS CoV-2, vitamin D

1 | INTRODUCTION

Coronavirus is an enclosed virus with only a single-stranded RNA gene and helical symmetry nucleocapsid belonging to the coronaviridae family. There are four types of coronavirus: α, β, δ, and γ coronavirus (Cherry et al., 2017; Loeffelholz & Tang, 2020). In 1931, a novel respiratory tract infection in farmed chicken was detected in North Dakota; Schalk and M.C. Hwan were the first to notice it (Fabricant, 1998). Human coronaviruses (HCoVs) are among the fastest growing viruses, with a high percentage of nucleotide substitution and recombination in the genome. Human coronavirus includes alpha coronavirus (HCoVs-229E and HCoVs-NL63) and beta coronavirus (HCoVs-OC43 and HCoVs-HKU1), which were first revealed in 2000 (Cecchini & Cecchini, 2020; Lim et al., 2016). In 2002, in the Guangdong province of China, life-threatening respiratory disease with no causative factors was reported, and in 2003 the syndrome was designated as a severe acute respiratory syndrome (Ksiazek et al., 2003). In total, 8096 people were globally affected, causing 774 death (10% death rate) (Liang et al., 2020). In 2012, the Middle East respiratory syndrome corona virus (MERS-CoV) was identified in Saudi Arabia, infecting 2506 persons worldwide and resulting in 862 deaths (35% mortality rate) (Liang et al., 2020). SARS-CoV-2, also known as 2019-nCoV, was found in late December 2019 (Tu et al., 2020).

It spreads throughout all human groups, infecting around one-third of the world's population with the typical symptoms of a common cold at the early stages of illness (Lim et al., 2016). The SARS-CoV-2 has a diameter of 60–140 nm and belongs to the β coronavirus family. The name comes from their exterior appearance, which includes spikes around the exterior appearance (Cascella et al., 2020; Sohrabi et al., 2020). In the last week of December 2019, 27 unexplained instances of pneumonia were recognized in Wuhan city of Hubei Province in China. Wuhan city is the most populated place in central China, with about 11 million residents. It caused flu-like signs such as dry cough, dyspnea, fever, and many others symptoms, putting people at risk. In most of cases, the incubation time is 1–14 days (Pascarella et al., 2020; Peng et al., 2020; Sohrabi et al., 2020; L.-s. Wang et al., 2020). It quickly spread around the world. On March 11, 2020, 71 days after the discovery of SARS-CoV-2, the World Health Organization (WHO) proclaimed COVID-19 as a pandemic (Da Silveira Cespedes & de Souza, 2020). It grew enormously via social events in various countries, on a cruise ship in Japan, religious group events in South Korea, and Ski resorts in Italy, and Austria (Petersen et al., 2020). The world outbreak mortality rate is about 3%, and frail patients who had comorbidities such as cardiovascular disease, diabetes, asthma, etc. are at high risk (Pascarella et al., 2020). Both the influenza virus and the coronavirus are deadly respiratory tract infections that cause mortality from acute respiratory distress syndrome (ARDS) (Cheng, 2020).

COVID-19 outbreak requires worldwide attention in emergency development of therapies for effective combating of the disease. Until recently, several drug candidates have been repurposed. New molecules were put forward to combat the pandemic (Alanagreh et al., 2020; Sansone et al., 2020). Due to the high rate of transmission, COVID-19 deadly infection requires successful introduction of new vaccines for reducing the mortality and spread of the pandemic. Emergency approval has been given to few of these new vaccines for public use. However, their immunological fitness and true effectiveness are yet to be established.

Therefore, in the current state of a global health pandemic, safe and inexpensive approaches with a valid biological basis should be prioritized. In this review, we describe the general antiviral properties of vitamins C, D, E, epigallocatechin-3 gallate (EGCG), and morin. Also, we define their profile of biological action and pharmacokinetics, and we discuss the approach to the management and cure of SARS-CoV-2/COVID-19 infection.

2 | MECHANISM OF SARS-COV-2 ENTRY AND IMITATION INTO THE HOST CELL

Cryoelectron tomography and cryoelectron microscopy revealed that the coronavirus is spherical in shape. Coronavirus is named from the club-shaped spikes on the virus's surface that resemble a crown. Spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein are among the structural proteins found in coronavirus (SARS-CoV-2). A large S protein generates homotrimers that adhere to the viral surface and mediates coronavirus attachment

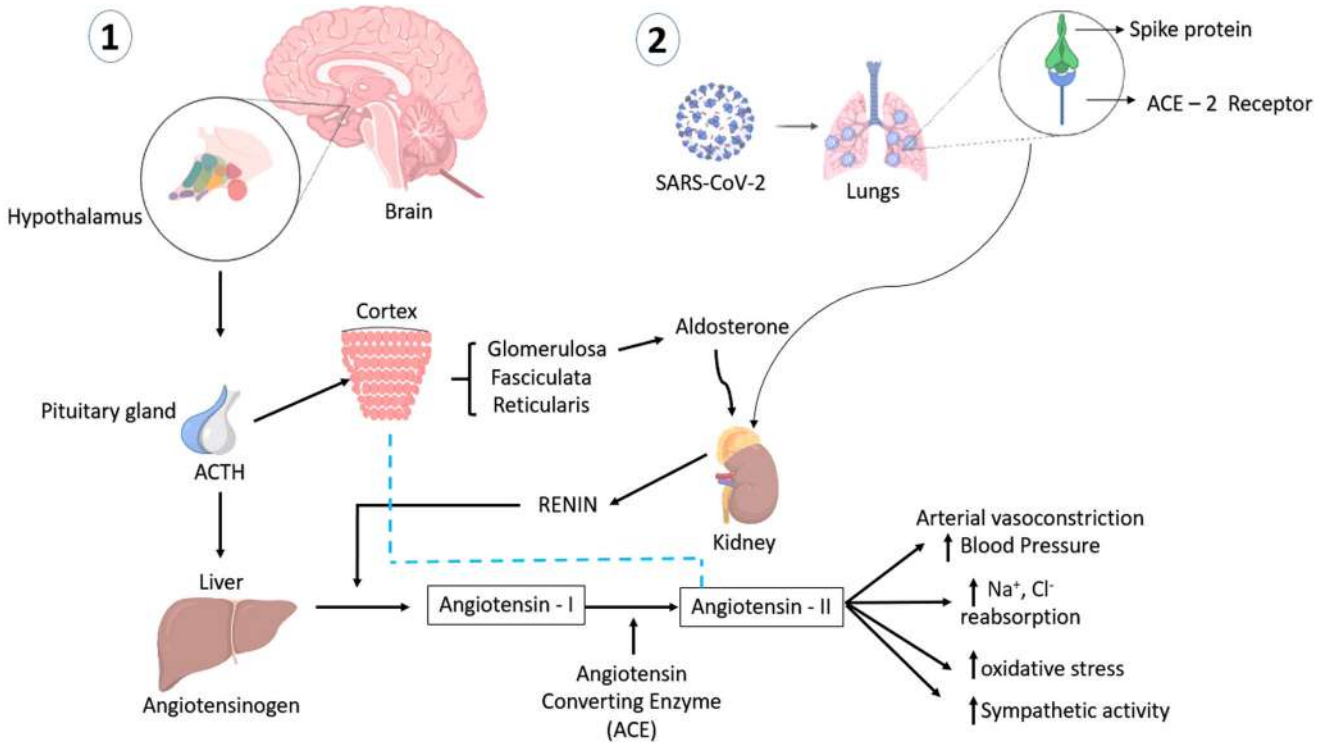

FIGURE 1 The mechanism of SARS-CoV-2 bind with the ACE-2 receptor and activate angiotensin I and II which promote the different biological function and oxidative stress in the cell. (1) The normal mechanism is how the hypothalamus and anterior pituitary gland regulate and activate angiotensin I and II to maintain blood circulation and other biological functions in the body. (2) When the SARS-CoV-2 virus enters the lungs, with the help of spike protein, it binds to the ACE-2 receptor and facilitates the entry of the viral genome through envelope protein into the host cell and promotes inflammation and congestion into the lungs. After that, the SARS-CoV-2 activates the renin, the activator ofangiotensinogen, to angiotensin I and angiotensin II and increases the production of ROS resulting from developing oxidative stress and causing cellular death.

and adhesion to human target cells (C. Huang et al., 2020; Perrotta et al., 2020). The genomic architecture of all coronaviruses has six opening reading frames (ORFs). The initial ORF is found at the end of the 5′ chromosome, about two-thirds of the total genomic sequence length, and encodes polypeptides 1a and 1b as well as other ORFs found at the end of the 3′ chromosome (Alanagreh et al., 2020). The ORF1 gene is found at a region downstream of the nucleocapsid and spikes viral replication proteins. The spike protein interacts with the angiotensin-converting enzyme-2 (ACE-2) receptor during SARS-CoV-2 replication, causing conformational changes (Figure 1). Through the endosomal pathway, the viral envelope is fused and enters the cell membrane. The virus introduces RNA into the cells, which is then replicated by the polyproteins pp1a and pp1ab. The RTCA (RNA 3′-terminal phosphate cyclase) stimulates the synthesis of full genomic length of negative RNA copies during viral replication and is utilized as a prototype for full-length of positive RNA genomes sequence. Discontinuous transcription of subgenomic mRNA is required for viral protein translation. Virions in the endoplasmic reticulum and Golgi bodies create these RNA genomes and viral proteins, which are then transferred via vesicles; finally, they get out of the cells and are released (Figure 2) (Alanagreh et al., 2020; Mirzaei et al., 2020; Shereen et al., 2020).

Several studies have shown that the viral infection causes an oxidative stress inside the host, which initiates the toll-like receptor and the interferon antiviral signaling cascade (Mendonca & Soliman, 2020). This review aims to describe antioxidant molecules that could possibly boost immune activity (Checconi et al., 2020).

3 | THE PROCESS OF ROS GENERATION IN SARS-COV-2 INFECTION

Reactive oxygen species (ROS) are oxygen-derived biomolecules such as superoxide radical anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\bullet}$), which regulate a variety of cellular mechanisms including growth factors, cytokines, transcription, apoptosis, ion transport, and immunomodulation. Viruses use a variety of strategies to alter host cell's redox state (see Figure 3). For example, subcellular oxidative stress controls the formation of ROS in cells and decreases glutathione expression (Amatore et al., 2015; Khomich et al., 2018; Narayana et al., 2019). Mitochondrial dysfunction promotes ROS production in the cells and modulates the oxidative metabolism and immune responses. ROS contributes to T-cell proliferation and T-cell-mediated immunity (Yarosz & Chang, 2018). The oxidative stress exacerbates through the imbalance between ROS creation and reclaim (Hildeman, 2004; Ray et al., 2012; Reshi et al., 2014). The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) produces ROS in a well-synchronized process (Amatore et al., 2015). The NOX consists of seven membrane proteins, including NOX1 to NOX5, and

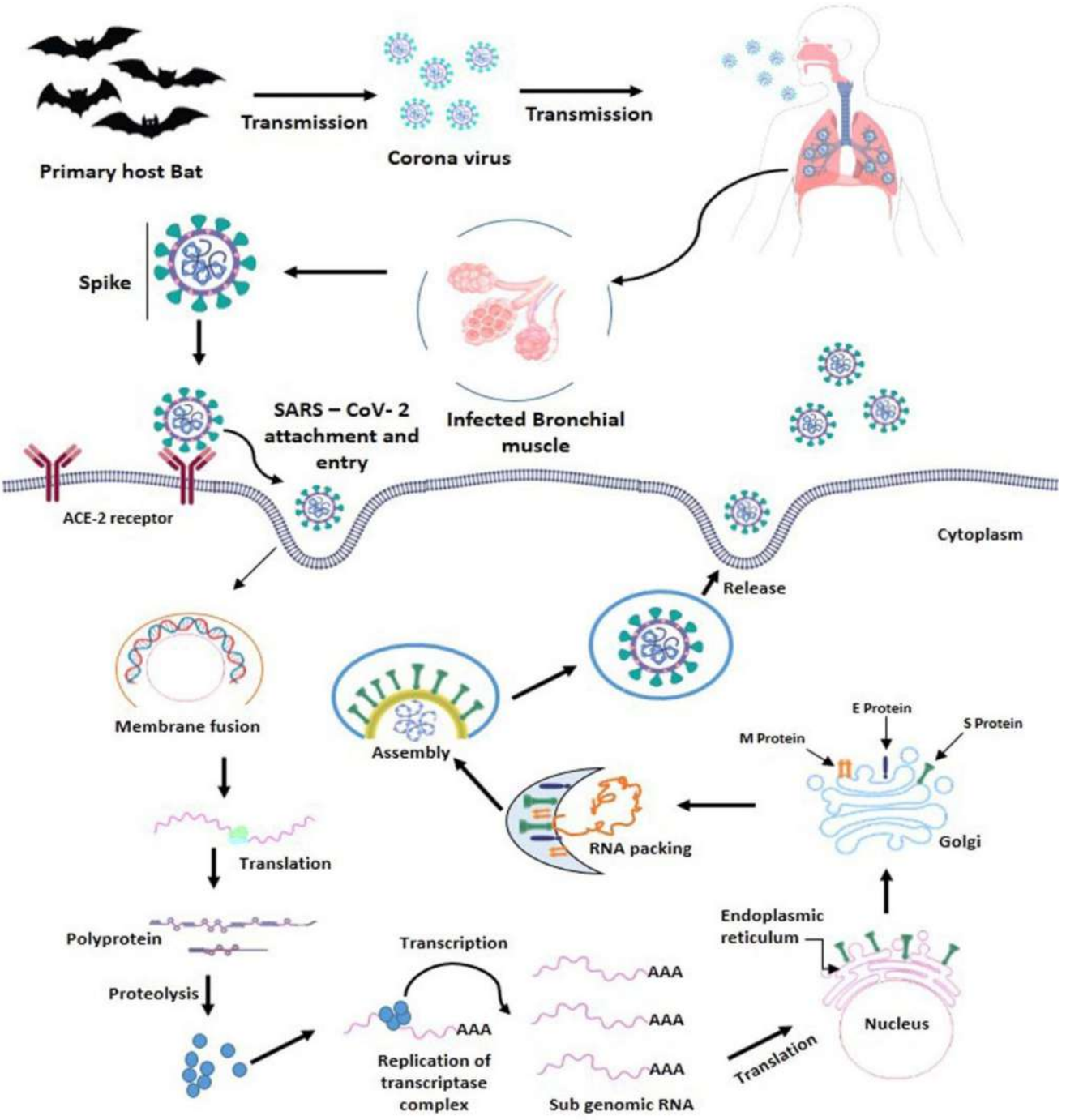

FIGURE 2 Mechanism of SARS-CoV-2 cell entry and replication into the host cell through viral spike proteins

two different oxidases, Duox1 and Duox2. The pathogens, particularly bacteria, invade the cells and are killed by NOX2-mediated ROS, but viruses are not eliminated (Checconi et al., 2020; To et al., 2017). The intermediate SARS-CoV-2 variant identifies methylated CpG inside the viral genome to replicate many RNA viruses and Toll-like receptor (TLR)-9. By altering the preserved single cysteine residue (Cys98) of TLR-7 activation, NOX2 activity decreases the antiviral transcription factor. NOX2 creates ROS in nonpathogenic cells, responsible for the stimulation of nuclear factor kappa beta (NF-κB) by the respiratory syncytial virus. NOX4, a member of the NOXs family, is essential for producing ROS in pulmonary and somatic cells during a viral illness. NOX4 stimulates the p38 and ERK1-2 genes, stimulating mitogen protein kinase (MAPKs) to increase viral replication by promoting ribonucleoprotein (Amatore et al., 2015; Fink et al., 2008; Marjuki et al., 2006; Nencioni et al., 2009). The production of ROS by NOX2 causes arterial impairment. The RNA-containing virus promotes NOX2, although the exact mechanism in COVID-19 individuals is still unknown. The researchers discovered that NOX2 expression

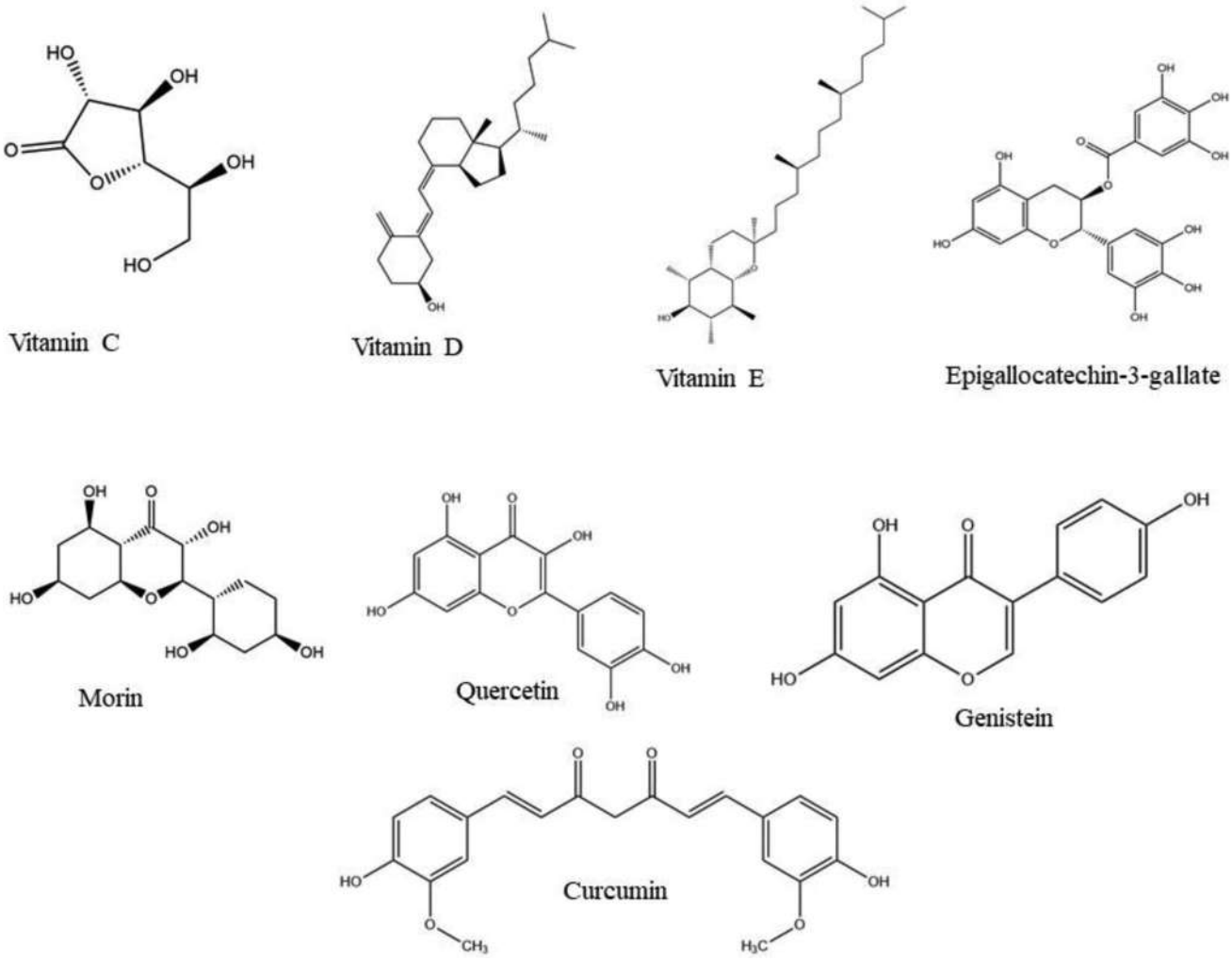

FIGURE 3 Structure of active natural antioxidants

overlaps in SARS-CoV-2 ill patients whether or not vascular complication is not a single predictor aimed at ischemic consequences. The investigators discovered that in COVID-19 patients a high serum concentration of NOX proteins and a decrease in antioxidants concentration in the plasma increase the risk of thrombotic complications (Violi et al., 2020). The ACE-2 receptor, which would be the major entry receptor for SARS-CoV-2, facilitates ROS release (Cecchini & Cecchini, 2020; Checconi et al., 2020; Hoffmann et al., 2020). Downregulation of glucose-6 phosphate dehydrogenase (G6PD) is a leading cause of oxidative stress. G6PD deficiency promotes oxidative stress susceptibility, and the amount of G6PD is regarded as an inflammatory marker (Kassi et al., 2020).

4 | CURRENT GUIDELINES FOR THE PREVENTION AND TREATMENT OF COVID-19 INFECTION

For the prevention of COVID-19 infections, the WHO living guideline concerning drugs to prevent COVID-19 is available (https://app.magicapp.org/#/guideline/nBkO1E).

The WHO (2021) and NIH guidelines concerning therapeutics for COVID-19 are available. Altered expression of genes can reveal NF-κB as a probable source of illness severity. The proinflammatory response in ARDS is substantial (Keles & Infections, 2020). ROS oxidize glycoproteins and membrane lipids, swiftly extinguishing infected cells as well as healthy ones. Interleukin receptor blockers, corticoids, antiviral medicines, anti-SARS-CoV-2 antibody products, antithrombotic drugs, antibiotics, systemic corticosteroids, anti-inflammatory medicines, and immune stimulants are among the medications to treat COVID-19 patients, but a number of uncertainties persist (Wu et al., 2020).

5 | RATIONALE FOR THE USE OF ANTIOXIDANTS

According to the literature, SARS-Cov-2 downregulates the immune system through multiple mechanisms. Vitamins C, E, D, melatonin, *N*-acetyl cysteine, iron complexing agent (deferoxamine), NF-κB inhibitor, and promoters (curcumin, resveratrol) of the nuclear factor erythroid 2–related factor 2 (Nrf2), which is an emerging regulator of cellular resistance to oxidative stress, are all potent antioxidants that can help cure COVID-19 infection via mitigation of the proinflammatory response in ARDS (Keles & Infections, 2020).

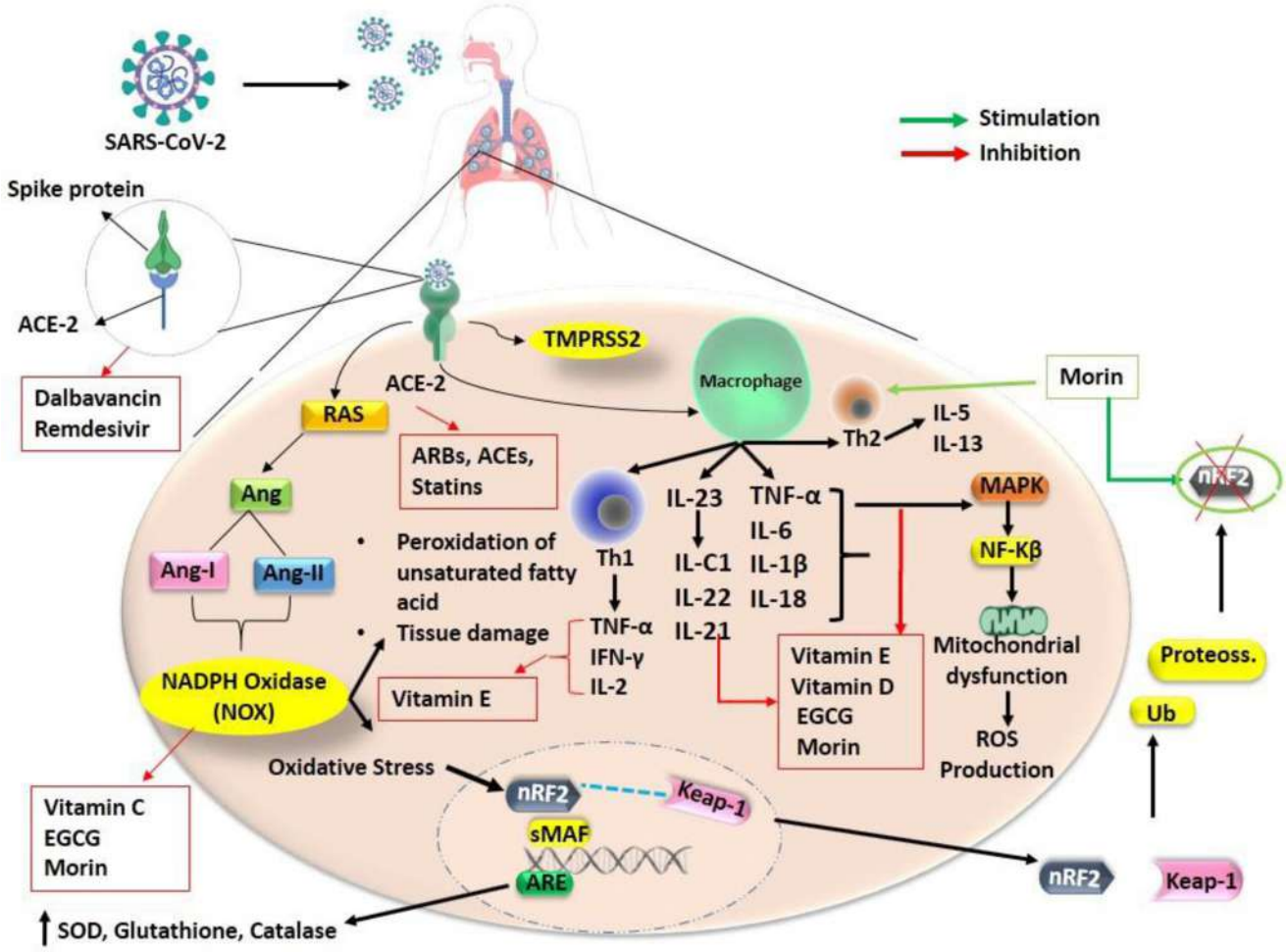

FIGURE 4 The process of ROS generation in SARS-CoV-2 infection. The virus interacts with the ACE-2/TMPRSS2 pathway and enters the host cell. The spike glycoprotein of SARS-CoV-2 interacts with the ACE-2 receptor, which is present on the cell surface. The spike protein is important for the entry of SARS-CoV-2 into the host cell through TMPRSS2. This pathway leads to the recognition of the virus by a Pathogen recognition receptors (PRR). It activates the immune cells, increases proinflammatory cytokines and ROS, and develops oxidative stress in the host cell. Similarly, the upregulation of ACE-2 activates the renin–angiotensin system, which plays an important role in increasing inflammatory mediators and ROS production. The NADPH oxidase is an important enzyme for the activation of macrophages in the cell for ROS. Increasing the ROS production through the activation of NADPH oxidase causes peroxidation of unsaturated fatty acid and tissue damage generated by oxidative stress; expression of nuclease factor (Nrf2) along with small musculoaponeurotic fibrosarcoma (sMAF) protein activates antioxidant response elements (AREs) into the cells and activates other antioxidant enzymes including superoxide dismutase and glutathione, catalase. The activation of macrophages activates different T-helper cells (Th cells); they are leased to activate different types of inflammatory cytokines. In the homeostatic condition, the Keap-1 blocks the Nrf2 activation and promotes the degradation of Nrf2 through ubiquitin-proteasome. Thus, it prevents the generation of antioxidants through Nrf2 into the cells. Morin is a unique compound; it shows multiple mechanisms for preventing oxidative stress, and it prevents the Nrf2 degradation into the host cell.

Table 1 presents the details of clinical studies of different natural antioxidants, which reveals how naturally available antioxidants can be utilized for preventing COVID-19 infection in distinct stages of clinical studies, either alone or in combination (Cecchini & Cecchini, 2020; Giménez et al., 2020; J.-Z. Wang et al., 2020). In this review, we summarize the detailed information and mechanism of some selective natural antioxidants.

Figure 4 shows the structure of active natural antioxidants possibly useful in COVID-19 management. All these natural compounds that showed strong antioxidant activity may have beneficial effects against COVID-19 infection.

6 | METHODOLOGY

6.1 | Search strategy

The purpose of this study was to conduct a methodical assessment of primary reports of pragmatic trials. We utilized a PubMed search filter to locate pragmatic trials published between 2019 and 2022 specifically those that were registered in ClinicalTrials.gov. The study also used full-text papers, ClinicalTrials.gov, and Web of Science. When downloading study information from ClinicalTrials.gov, participant's age (18 > 65), gender, inpatient (hospitalized), and intervention were

TABLE 1 Clinical trials on COVID-19 (Natural antioxidants)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
1	Ascorbic acid	Interventional (clinical trial) Confirmed SARS-CoV-2 infection, age 18+	NCT04363216	66	0.3,0.6, and 0.9 g/kg	Phase 2	Supplementation. No Study results posted on ClinicalTrials.gov	Coppock (2020)
								https://clinicaltrials.gov/ct2/show/study/NCT04363216
2	Ascorbic acid	Interventional (clinical trial) confirmed COVID-19 patients were hospitalized with mild or moderate complication	NCT04401150	800	50 mg/kg intravenous administration every 6 h	Phase 3	No study results reported on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/study/NCT04401150
3	Ascorbic acid + melatonin	Interventional (clinical trial) COVID-19 positive test, age 50+ years	NCT04530539	150	100 mg vitamin C 10 mg melatonin	Recruiting	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/study/NCT04530539
4	Melatonin	Interventional (clinical trial) taking 18 years or older people with confirmed COVID-19 infection.	NCT04474483	30	10 mg three times per day	Phase 2	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/study/NCT04474483
5	Vitamin C+ quercetin + bromelain + zinc	Interventional (clinical trial) confirmed SARS-CoV-2 infection, age 18+	NCT04468139	60	500 mg quercetin 500 mg bromelain 50 mg zinc 100 mg vitamin C	Phase 4	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT04468139
6	Masitinib + isoquercetin	Interventional (clinical trial) confirmed COVID-19 infection, age 18-year-old or above	NCT04622865	200	Masitinib 300 mg/kg/day Isoquercetin 4.5 mg/kg/day oral administration	Phase 2	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT04622865

(Continues)

TABLE 1 (Continued)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
7	Vitamin C in a complex formulation	Observationalwith the onset of COVID-19 symptoms or who have tested positive in a diagnostic test for SARS-CoV-2 age 18+	NCT04666753	40	Immuno formulation consisting of ascorbic acid 300 mg and transfer factors 100 and 800 mg anti-inflammatory natural blend, 60 mg zinc orotate, 48 mg selenium yeast, 20,000 IU cholecalciferol, 480 mg ferulic acid, 90 mg resveratrol, 800 mg spirulina, 560 mg N-acetylcysteine, 610 mg glucosamine sulfate potassium chloride, and 400 mg maltodextrin-stabilized orthosilicic acid	Completed December 2020	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/results/NCT04666753
8	Vitamin C	Interventional (clinical trial) diagnosed as serious or critical SARI , being treated in the ICU age 18+	NCT04264533	56	12 g vitamin C twice a day for 7 days by the infusion pump with a speed of 12 mL/h	Phase 2	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/study/NCT04264533
9	Vitamin C + methylene blue + N-acetyl cysteine	Interventional (clinical trial) Five confirmed case of COVID-19 admission to intensive care unit Need for intubation and mechanical ventilation Age 18–90	NCT04370288	20	Methylene blue 1 mg/kg Vitamin C 1500 mg/kg N-acetyl cysteine 1500 mg/kg	Phase-1	Preliminary results showed the treatment of severe COVID-19 with a mixture of MB, vitamin C, and N-acetyl cysteine is safe and feasible. No Study results posted on ClinicalTrials.gov	Alamdari et al. (2020), https://clinicaltrials.gov/ct2/show/results/NCT04370288

(Continues)

TABLE 1 (Continued)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
10	Glycine + N-acetyl cysteine	Interventional (clinical trial), confirmed COVID-19 infection with aged between 55- to 85-year-old were selected.	NCT04703036	64	Dietary supplement dose was not defined	Early phase 1	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/results/NCT04703036
11	Vitamin D	Observational systemic lupus erythematosus and COVID-19 infected patients age 18–80 years	NCT04709744	38	–	Completed January 14 , 2021	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/results/NCT04709744
12	Vitamin D	Interventional (clinical trial) newly diagnosed patients with COVID-19 age 18+	NCT04536298	2700	9600 IU per day	Phase 3	No study results posted on ClinicalTrials.gov	Manson et al. (2020), R. Wang et al. (2021)https://clinicaltrials.gov/ct2/show/results/NCT04536298
13	Vitamin D and/or zinc	Interventional (clinical trial) PCR confirmed COVID-19-infected patients· Oxygen saturation level of 90 or aboveage 18+	NCT04641195	700	(1) Vitamin D (180,000 IU bolus at enrollment, followed by 2000 IU daily); (2) zinc (placebo at enrollment followed by one daily dose of 40 mg); (3) vitamin D and zinc; or (4) placebo for a total of 8 weeks	Phase 3	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/results/NCT04641195
14	Vitamin D/vitamin C + vitamin B + zinc acetate/omega-3	Interventional (clinical trial) Positive SARS-CoV-2 test group with risk factors and negative SARS-CoV-2 Test group with risk factors Age 18+	NCT04828538	3600	4000 IU vitamin D 1000 mg Omega 1000 mg vitamin C Vitamin B complex (1 mg B12, 50 mg B6, 2.5 mg B9, 100 mg B1, 100 mg B2, 1 mg B3, 50 mg B7), zinc acetate 100 mg	Not applicable	No study results posted on ClinicalTrials.gov	Hathaway et al. (2020),https://clinicaltrials.gov/ct2/show/results/NCT04828538

(Continues)

TABLE 1 (Continued)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
15	Vitamin D, resveratrol	Outpatients who test positive for infection with SARS-CoV-2, mild COVID-19 Age 45+	NCT04400890	100	Vitamin D3 100,000 IU on day 1 Resveratrol 1000 mg four times per day for 15 days.	Phase 2	no study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT04400890
16	Vitamin D3	Interventional (clinical trial) Patients who confirmed COVID-19 infection with vitamin D deficiency at age 17 years or older were selected for this study.	NCT04385940	64	Vitamin D3 50,000 IU oral administration for three weeks	Phase 3	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT04385940
17	Cholecalciferol	Interventional (clinical trial) patients with confirmed COVID-19 infection in both children and adults were randomly selected for this study	NCT04552951	80	Cholecalciferol 100, 000 IU single dose	Phase 4	The administration of 100,000 IU cholecalciferol has not improved the outcome of COVID-19 disease.	Cannata-Andía et al. (2022)https://clinicaltrials.gov/ct2/show/study/NCT04552951
18	Vitamin K2	Interventional (clinical trial) COVID-19 patients with a laboratory-confirmed SARS-CoV-2 infection within the previous 96 h	NCT04770740	40	333 mcg	Phase 2	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT04770740

(Continues)

TABLE 1 (Continued)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
19	Quercetin	Interventional (clinical trial) Clinical score greater than 6 at least 40 years old.	NCT04853199	200	Each patient should receive 150 mg of one tablet twice a day 30 min before the meal	Early phase 1	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/record/NCT04853199
20	Quercetin	Interventional (Clinical Trial)	NCT04578158	152	Patients will receive standard COVID-19 care as per the hospital/physician guidelines and dietary Supplement: 400 mg of oral quercetin phytosome	Phase 3	No study results posted on Clinical Trials.gov.	https://clinicaltrials.gov/ct2/show/NCT04578158
21	Genistein	Interventional (clinical trial) Patients hospitalized with COVID-19-related acute respiratory distress and mean Average age of 18 years old	NCT04482595	66	1500 mg	Phase 2	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/study/NCT04482595
22	Curcumin	Interventional (clinical trial) Patients with moderate COVID-19 symptoms at the age of 18 years and above	NCT04802382	252	Combination of artemisinin 12 mg, curcumin 40 mg, Boswellia 30 mg, and vitamin C 120 mg in spray administration—divided into four separate doses given as an add-on therapy, four doses over 48 h (day 1 and day 2), twice a day (morning and evening).	Phase 3	No study results posted on ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/results/NCT04802382

(Continues)

TABLE 1 (Continued)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
23	Curcumin + Boswellia + vitamin C	Interventional (clinical trial) Patients hospitalized with COVID-19-related acute respiratory distress and mean average age 18 years old or older.	NCT05037162	240	Curcumin 40 mg Boswellia 30 mg and vitamin C 120 mg combination called CimetrA-1 was administered through a nasal spray.	Phase 2	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT05037162
24	Resveratrol + vitamin D3	Interventional (clinical trial) Patients tested COVID-19 positive with mild symptoms and a mean age of 45 years	NCT04400890	200	Resveratrol 1000 mg four times per day for 15 days. Vitamin D3 100,000 IU on day 1	Phase 2	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT04400890
25	Resveratrol	Interventional (clinical trial) Patients tested COVID-19 positive with mild symptoms and aged between 18- to 65-year-old.	NCT04799743	30	Resveratrol 1 g administered orally every day	Not applicable	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT04799743
26	Cannabidiol	Interventional (clinical trial) Patients were tested COVID-19 positive and 18-year-old or adult patients were selected for this study.	NCT04731116	40	Cannabidiol 150 mg (5% solution) was administered orally	Phase 2	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT04731116

(Continues)

TABLE 1 (Continued)

S.N.	Drugs	Study type and main inclusion criteria	Clinical trial number	Number of patients	Dose	Phase	Results	Reference
26	Synthetic Cannabidiol	Interventional (clinical trial) patients were tested COVID-19 positive and 18-year-old or adult patients were selected for this study.	NCT04686539	50	Cannabidiol oil was administered three times a day	Phase 1	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT04686539
28	Cannabidiol	Interventional (clinical trial) patients were tested COVID-19 positive and 18-year-old or adult patients were selected for this study.	NCT04615949	422	CardiolRx (Cannabidiol) 2.5 mg/kg to 7.5 mg/kg administered orally two times a day.	Phases 2 and 3	No study results posted on ClinicalTrials.gov.	https://clinicaltrials.gov/ct2/show/study/NCT04615949

Note: The list of natural antioxidants and their clinical trials detail was obtained from NIH clinical trial database.
Abbreviations: DHA, docosahexaenoic acid; IU, international unit; mcg, microgram; mg, milligram.

precategorized. Natural antioxidants were included in the intervention, prescribed either alone or in combination with other drugs. MERS-CoV, murine coronaviruses (MCoV) complications, and medicine prescriptions devoid of natural antioxidants were not included in the study, nor there were similar trials involving outpatients.

6.2 | Software used

The Chem Draw professional (version 16.0) was used to draw the chemical structures of a compound, and the Web-based program Biorender was utilized to create the illustrations; the citation management program Endnote 9.0 was also employed.

7 | VITAMIN C

According to NIH guidelines, at the moment, there is insufficient evidence to recommend either for or against the use of vitamin C for the treatment of COVID-19 in noncritically and critically ill patients (National Institute of Health, 2020). Ongoing studies are further evaluating this issue. Vitamins C and E seem to be the two important dietary antioxidants for human existence. Vitamin C, commonly known as ascorbic acid, is a powerful water-soluble antioxidant and electron donor. Alfa-keto glutarate dependent dehydrogenase requires it as a cofactor. It is absorbed through a sodium-dependent transporter from the gut. Vitamin C reduces NADPH oxidase activation, which creates ($O_2^{\bullet -}$) and reactive ions in mRNA expression and is essential for different cellular functions, it inhibits hypoxia-induced and transcription factors. It suppresses the hypoxia-induced factor mechanism, which provides an alternate method of infection and inflammatory regulation (Cramer et al., 1986; Milani et al., 2021). Vitamin C promotes noradrenaline biosynthesis by synthesizing catecholamine (the production of adrenaline via dopamine through the enzyme dopamine beta-hydroxylase) and, in extracellular space, it upregulates the tyrosine hydroxylase enzyme (Hernández et al., 2020). The endothelial nitric oxide synthase (eNOs), tetrahydrobiopterin, which promotes arterial elasticity and modulates blood pressure by minimizing vascular constriction, was also regenerated by vitamin C (Kang et al., 2013). Vitamin C also inhibits protein phosphatase 2A activation, and tumor necrosis factor alpha (TNF-α), and displays a defensive function for mitochondrial permeability, preventing capillary leakage (Muellner et al., 2010; Padayatty et al., 2003; Soto et al., 2020; Traber & Stevens, 2011).

Vitamin C is an important compound for the development and maturation of lymphocytes and regulates their biological function (Carr & Maggini, 2017). Lymphocytes help in maintaining adaptive immunity in the body for preventing viral and bacterial infections. Nutritional impairment does not appear to be substantially linked to vitamin C deficiency. The importance of vitamin C intake in noticed but is difficult to quantify (Bjørklund et al., 2022).

7.1 | Clinical trials and other studies on vitamin C alone or in combination with other components

A vitamin C randomized clinical trial was performed (registration number NCT04363216) by Dangan Coppock and his team at Thomas Jefferson University Philadelphia, PA. The investigators aim at determining the safety and effect of ascorbic acid administration in COVID-19-infected patients to test the hypothesis that the 0.3–0.9 g/kg administration of ascorbic acid could help to promote the lymphocyte activation in newly diagnosed COVID-19 hospitalized patients who will likely not require mechanical ventilation within 24 h of study intervention, but, to date, no data are available to support the ascorbic acid at given dose promotes the lymphocyte activation in COVID-19 patients (Dagan Coppock, 2020).

Another randomized clinical trial study of vitamin C in combination with melatonin was conducted by Corey Fogleman at Lancaster General Hospital, Lancaster, PA (registration number NCT04530539) (https://clinicaltrials.gov/ct2/show/NCT04530539). One hundred fifty participants (age 50+) are to be included in this study and experience more than 5 days of COVID-19 infection. Melatonin (10 mg) and vitamin C (1000 mg) were prescribed to infected patients; the study is in its recruiting phase and aims at studying the progression of symptoms during the treatment (ClinicalTrials.gov). Melatonin has a strong natural antioxidant and has free radical scavenging activity. It is naturally secreted into the body through the pineal gland and is also found in some fruits and vegetables that regulate circadian rhythm (Tarocco et al., 2019). Melatonin is highly lipophilic thus it easily crosses the cell membrane, and it is widely distributed in the cell. It effectively eliminates free radicals from the biological system. It scavenges free radicals and also neutralizes high toxic radical which is generated within the cells, while several more small molecules of natural antioxidants also showed direct scavenging activity through metal chelating and hydroxyl radical scavenging activity (Galano et al., 2018; Hacışevki & Baba, 2018). Melatonin can transform guanosine radical to guanosine by transferring its electrons to repair oxidized DNA into the cell (Hacışevki & Baba, 2018).

A. K. Ahmed et al. (2020a) indicated that quercetin 800 mg, bromelain 165 mg, zinc acetate 50 mg, and ascorbic acid 1 g once daily supplements were safe for patients infected with SARS-CoV-2 and may prevent poor prognosis. The clinical trial (registration number NCT04468139) (A. K. Ahmed et al., 2020b) concerning the quadruple therapy with zinc, quercetin, bromelain, and vitamin C still does not have any study results posted concerning the pharmacological effects of this multiple compositions of antioxidants. Quercetin is a water-soluble flavonoid compound that is mainly found in vegetables and fruits. It has unique pharmacological properties such as anticancer, anti-inflammatory, antiviral, antioxidant, and antipsychological activities. The most important feature of quercetin is its strong antioxidant property; it activates mitochondrial biogenesis and prevents lipid peroxidation, platelet aggregation, and capillary permeability factor (Li et al., 2016). Epigallocatechin-gallate polyphenols transport zinc cations across the plasma membrane independently of plasma

membrane zinc transporters and act as zinc ionophores (Dabbagh-Bazarbachi et al., 2014). Zinc is an element found in our cellular matrix involved in various cellular processes (Rahman & Idid, 2021; Te Velthuis et al., 2010). It has a very important role in regulating the transcription factor, in the enzymatic process, in the maintenance of the function of structural proteins, in the activation of immune response, and formation of growth factors in the body (Bagherani & Smoller, 2016). The regular use of zinc supplements increases its concentration in the cell. The zinc ion inhibits coronavirus andarterivirus RNA polymerase activity in vitro, while zinc ionophores block the replication of these viruses in cell culture (Te Velthuis et al., 2010). The pharmacological action of zinc in the COVID-19 infected patients is to prevent the replication of the viral genome into the host cell. Zinc counters the pneumonitis condition, which is caused by the SARS-CoV-2 virus. It inactivates the replicase enzyme into the cell (the enzyme replicase is responsible for replication and transcription of viral genome), activates interferon, increases the production and development of lymphocytes (T & B cells), and triggers the secretion of perforin which shows antiviral action (Rahman & Idid, 2021). Anyhow, according to NIH guidelines, to date, there is insufficient evidence to recommend either for or against the use of zinc for the treatment of COVID-19, taking into account that zinc may be harmful. One component of the drug composition used in the described clinical trial, that is bromelain, was the focus of interest of some in vitro studies. Bromelain is an enzyme and is mainly found in pineapple juice, and its stem is often used for medicinal purposes (Pavan et al., 2012). Bromelain has a wide range of pharmacological activity including inhibition of platelet aggregation factor, anti-inflammatory activity (inhibit prostaglandin E2 synthesis and other inflammatory mediators), immunomodulation, and inhibition of the production of bacterial enterotoxin (Chakraborty et al., 2021). Various studies were conducted to investigate the effect of bromelain on the inhibition of SARS-CoV-2 replication in the host cell. Bromelain inhibits the S-ectodomain, a part of the protein which provides the binding site of cell surface receptor. In SARS-CoV-2 replication, the most important cell surface receptor is ACE-2 which helps in binding the spike protein and releases the viral genome into the cell (Edwards et al., 2021). Sagar et al. (2020) determined the effect of bromelain on the VeroE6 cell line. The bromelain was used in varying concentrations such as 19, 37, and 70 μg/mL into the SARS-CoV-2–infected veroE6 cell lines. After 48 h of bromelain treatment, a significant inhibition of S-ectodomainthereby altering the S-protein binding with veroE6 cell lines was observed, and the ability to inhibit the in vitro replication of the SARS-CoV-2 genome into the cell was confirmed

Another study was conducted by Sagar et al. (2021) to evaluate the inhibition effect of bromelain in in vitro and in silico studies. It shows a dose-dependent effect on ACE-2 and transmembrane protases-2 (TMPRSS2) protein in veroE6 cells, but it shows significant inhibition of ACE-2 expression in Calu-3 cells; similarly the TMPRSS2 protein reduces the expression in the same cell. In this study, different concentrations including 5,10,15,20, and 25 μg/mL of bromelain were used to check the effect of bromelain against the s-ectodomain. The result revealed that a 25-μg/mL concentration of bromelain significantly inhibited the expression of s-ectodomain and SARS-CoV-2 in veroE6 cells. The study was also confirmed by performing a cysteine protease inhibitor assay; wherein bromelain effectively inhibited the SARS-CoV-2 binding affinity to VeroE6 cells ($p = .0021$) and hindered its replication. In the molecular docking study, the bromelain was equally bound with both proteins (ACE-2 and TMPRSS2) and showed good interaction with both proteins. Thus this study revealed that bromelain can be used as a broad-spectrum antiviral agent, but clinical trials are needed.

An observational retrospective study of an immuno-formulation recruited 40 participants with the onset of COVID-19 symptoms or who have tested positive in a diagnostic test for SARS-CoV-2 (Fagron Iberica S.A.U., 2020) but no study results were posted.

Chronic COVID-19-infected patients were administered a high dose (200 mg/kg) of parenteral vitamin C in a randomized large interventional clinical trial that is in phase 2 (registration number NCT04264533). Vitamin C is supposed to suppress cytokine storm generated by COVID-19 illness and to improve pulmonary function and reduce mortality for patients with COVID-19, but no study results were posted (F. Liu et al., 2020).

Phase 1 clinical trial (registration number NCT04370288) was performed at Mashhad University of Medical Sciences, Iran, in 2020. Preliminary results showed that the treatment of severe COVID-19 with a mixture of methylene blue, vitamin C, and *N*-acetyl cysteine is safe and feasible (Alamdari et al., 2020).

8 | VITAMIN D

According to NIH guidelines, at the moment, there is insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19; hence, further research is needed.

Vitamin D is crucial for bone metabolism and also has a beneficial effect on the immune system. It disrupts immune cells such as macrophages, T and B lymphocytes, neutrophils, and dendritic cells, encouraging biologically based systems that exhibit vitamin D receptors (VDR) and provide human infection resistance. Vitamin D would be a unique prohormone created in the skin when exposed to ultraviolet radiation (290–315 nm in the visible range, converting 7-hydroxholesterol to cholecalciferol and vitamin D D3). However, only a limited content of vitamin D is created in the skin (Beard et al., 2011; Biesalski, 2020; Hadizadeh, 2021; Lanham-New et al., 2020). Vitamin D comes in a variety of compounds, including 25-hydroxyvitamin D (25 OHD) and 1,25-dihydroxy vitamin D. 25 OHD, which is formed through vitamin D hydroxylation, is the active primary metabolite of vitamin D. VDR is triggered by a transcription factor that interacts to 25 OHD, causing heteromerization with retinoid X receptor and the formation of A, 9-cis retinoic acid, another active metabolite (Beard et al., 2011; Biesalski, 2020; Lanham-New et al., 2020) of vitamin D, may also act as an immunomodulator, lowering the risk of viral infections such as syncytial virus and influenza (Siddiqui et al., 2020).

In addition, multiple chronic disorders such as respiratory tract infection, hypertension, diabetes mellitus, and others were reduced

when 25 OHD concentration was enhanced (Arboleda & Urcuqui-Inchima, 2020; Grant et al., 2020b). An investigation on vitamin D supplementation found that it has strong antiviral effect against a variety of respiratory viruses (Ali, 2020; Berthelot et al., 2020; Grant et al., 2020b; Greiller & Martineau, 2015; Hastie et al., 2020; Khare et al., 2013; Martineau et al., 2017; Patel et al., 2019; Schögler et al., 2016). It also controls cell-mediated immunity by inducing antimicrobial peptides such as cathelicidin, IL-37, and defensins via bioactive compounds of vitamin D (1,25-dihydroxy vitamin D) (Grant et al., 2020a). Antimicrobial peptides are essential components of the innate immune system that defend the host from pathogenic bacteria by affecting the function of bacterial cell membranes and suppressing inflammatory mediators. Thus, there is an essential factor in creating novel antibiotics to combat antimicrobial resistance in bacteria (Narayana et al., 2019; Rajasekaran et al., 2019). Vitamin D supplementation boosts antioxidant ability by raising glutathione levels (glutathione reductase and glutamate ligase modulator subunits), which has antimicrobial properties and helps in fighting COVID-19 infection (Grant et al., 2020a).

8.1 | Clinical trials and other studies on vitamin D alone or in combination with other components

An observational study (registration number NCT04709744) of vitamin D included 38 participants. This study, started in January 2021 (Yasmin Adel, 2021), aims at determining the effect of vitamin D in previously diagnosed systemic lupus erythematosus patients with COVID-19 infection; the recruitment is completed, but results are still not available.

The multicentered interventional clinical trial (registration number NCT04536298) (R. Wang et al., 2021) included 2700 participants who experienced first-time COVID-19 infection. The objective of this study is to evaluate the efficacy of vitamin D3 supplementation to reduce disease severity in persons with newly diagnosed COVID-19 infection and to prevent infection in household members at the dose of 9600 IU/day on days 1 and 2 and 3200 IU/day on day 3–28 (Manson et al., 2020; R. Wang et al., 2021). Results are still not available, even if vitamin D deficiency increases the risk of COVID-19 hospitalization and/or mortality (Manson et al., 2020).

For hospitalized frail elderly patients with COVID-19, regular bolus vitamin D3 supplementation was associated with less severe COVID-19 and a better survival rate (Annweiler et al., 2020).

The interventional clinical trial (registration number NCT04641195) (Fawzi, 2020) included 700 volunteers infected with SARS-CoV-2. The randomized trial aims at determining the effect of vitamin D and zinc supplementation for improving treatment outcomes among COVID-19 patients in India. Eligible individuals randomly received: (1) vitamin D (180,000 IU bolus at enrolment, followed by 2000 IU daily); (2) zinc (placebo at enrolment followed by one daily dose of 40 mg); (3) vitamin D and zinc; or (4) placebo for a total of 8 weeks. The study will end in March 2022.

There are several studies concerning the use of vitamin D to evaluate the immunological response and therapeutic potential that may be effective in preventing SARS-CoV-2 virus replication in the cell by altering its genome sequence. In a computational study, NSP7 and spike glycoproteins of SARS-CoV-2 are envisaged as potential targets of vitamin D and ivermectin. This study hypothesized that vitamin D inhibits the viral replication in the cell (Dasgupta et al., 2020).

Another clinical research was conducted to study the influence of vitamin D sufficiency on the reduced risk of severity from a COVID-19 infection. Two hundred thirty-five patients out of 611 were included in this study because these patients have a low level of vitamin D; the authors said, "we cannot explain the cause and effect relationship of vitamin D sufficiency and the reduced risk of severity from a COVID-19 infection" and concerns were raised by the editors about the validity of results and conclusions reported in the article (Maghbooli et al., 2020).

The interventional clinical trial (registration number NCT04828538) is a randomized, double-blind, placebo-controlled study aimed at investigating the effects of 4000 IU vitamin D versus placebo, a combination of 1000 mg vitamin C, vitamin B complex and zinc acetate, 100 mg/day versus placebo, and 1000 mg omega-3 docosahexaenoic acid (DHA)/eicosapentaenoic acid (EPA) versus placebo on mortality risk, severe outcomes, and complications in patients recently diagnosed with COVID-19. EPA and DHA are precursors of resolving D and E, which inhibit the inflammatory mediators, activate macrophages leading to increase apoptosis in the cell, and subsequently decreasing the level of IL-6 in the lungs (Hathaway et al., 2020). Results of the clinical trial are still not available.

An Iranian randomized clinical trial (IRCT20151226025699N3) concerning the effect of omega-3 fatty acid supplementation (1000 mg omega-3 daily for 14 days) on clinical and biochemical parameters of critically ill patients with COVID-19 revealed that the intervention group had significantly higher 1-month survival rate and improved the levels of several parameters of respiratory and renal function (Doaei et al., 2021).

Vitamin B is a natural water-soluble compound that comprises eight subtypes of vitamin B. Vitamin B (i) maintains cellular function and enzymatic reactions, (ii) decreases the production of free radicals and inhibits the overproduction of inflammatory cytokines in the body (Kennedy, 2016; Mikkelsen & Apostolopoulos, 2019), and (iii) regulates the innate and adaptive immunity and the function of endothelial cellular integrity (Shakoor et al., 2021). A computational study suggests that methylcobalamin from vitamin B12 may serve as an effective inhibitor of the RNA-dependent-RNA polymerase activity of the nsp12 protein and the SARS-CoV-2 viral replication (Narayanan & Nair, 2020).

In a randomized double-blind placebo-controlled interventional clinal trial (registration number NCT04400890), the combination of vitamin D3 100,000 IU on day 1 and resveratrol 1000 mg four times per day for 15 days was tested to assess the possible reduction in hospitalization at 21 days from enrolment. Results of this clinical trial are still not available.

Resveratrol is a polyphenol compound and is widely found in many plant species. It has high antioxidant properties, anticarcinogenic,

cardioprotective, vasodilator, and neuroprotective activity (Salehi et al., 2018).

It may be effective for the inhibition of SARS-CoV-2 in the cell. Previous studies concluded that resveratrol is effective against viral infections like the zika virus, influenza virus, MERS-CoV, etc. (Lin et al., 2017; Mohd et al., 2019). Yang et al. (2020) analyzed the effect of resveratrol on the SARS-CoV-2-infected Vero cell. In this study, the Vero cells were infected at a multiplicity of infection of 0.01 with SARS-CoV-2 and treated with different concentrations of resveratrol; after 48 h of the treatment, the cells were examined. The result shows that 100 and 200 μg/mL concentration of resveratrol significantly inhibited the growth of SARS-CoV-2 into the Vero cell .

Another in vitro study was conducted by Pasquereau et al. (2021) to reveal the effect of seven drug compounds against HCoV-229E and SARS-COV-2 on Vero cells. Among these three drugs, resveratrol was less cytotoxic and only showed a reduction of viral titer.

9 | VITAMIN E

Vitamin E is a lipid-soluble antioxidant made up of tocopherol and tocotrienols, two distinct types of compounds. Only alfa-tocopherol has been found as a type of vitamin E that humans require. Due to pharmacokinetic differences, alfa-tocopherol is 5–10 times more widely distributed than other subtypes of vitamin E (Zabetakis et al., 2020). Vitamin E deficiency reduces the number of lymphocytes, the function of natural killer cells, and the creation of antibodies. The relationship between dendritic cells and $CD4^+$ T-cells is enhanced when vitamin E is supplemented (Calder, 2020). Numerous experiments have shown that vitamin E treatment at different doses, such as 800, 60, and 200 mg/kg/day, improves cell-mediated immunity (Th1 cell activity, lymphocyte proliferation, IL-2 production, improved phagocytosis) (De la Fuente et al., 2008; Meydani et al., 1990; World Health Organization & Tufts University Consultation on Nutritional Guidelines for the Elderly, 2002). Vitamin E is abundant in almonds, peanut butter, and sunflower seeds. In the cytoplasmic membrane, it scavenges polyunsaturated fatty acids and lipoprotein radicals (Arshad et, al., 2020). Previous investigations reported the free radical quenching activity principally modulates gene expression in the cells. It protects against exposure to UV radiation, which has a favorable effect on lipid peroxidation and prevents from skin illnesses (Keen & Hassan, 2016; Valentino et al., 2018). The in vivo study revealed that the α-tocopherol effectively transfers hydrogen atoms to lipid free radicals and forms nonradical lipid products via the α-tocopheroxyl radical (Yamauchi, 1997). Since both C and E vitamins have antioxidant properties, their combination can help to manage the condition during COVID-19 infection in individuals with cardiac problems. The Recommended Dietary Allowance (RDA) of vitamin E for healthy adults according to the NIH DRI is 15 mg/day (tolerable upper intake level 1000 mg/day), but there is little evidence to date on the utility of vitamin E as a prophylactic or therapeutic agent against COVID-19 (Zabetakis et al., 2020).

10 | VITAMIN K

Vitamin K is an important compound for the coagulation of blood. It has many important biological roles including homeostasis, cell proliferation, and differentiation, inflammation, etc. Recently, some important role of vitamin K was revealed with its cofactor γ-glutamyl carboxylase including antioxidant increases cognition and inhibits tumor progression, etc. (Simes et al., 2020). The lipid-soluble vitamin is currently a choice of supplement to maintain body functions. The main concern about vitamin K is its effectiveness in COVID-19 patients as hospitalized patients are diagnosed with multiple blood clots in the lungs (at the site of SARS-CoV-2 infection) (Ackermann et al., 2020; Guan et al., 2020; Tang et al., 2020). The infection progressively affects the endothelial cells, which play a crucial role in coagulation, resulting in imbalance of the coagulation factors after infection and thrombosis in the lungs (Kudelko et al., 2021).

10.1 | Clinical trials and other studies

Dofferhoff from Canisius-Wilhelmina Hospital, the Netherlands, is conducting a phase 2, double-blind, randomized, placebo-controlled clinical trial to investigate the safety and effectiveness of oral vitamin K2 supplementation in COVID-19 (registration number NCT04770740) (https://clinicaltrials.gov/ct2/show/study/NCT04770740). The objective of this clinical trial was to determine whether vitamin K is effective against pulmonary damage and coagulopathy in COVID-19 patients. A total of 40 participants are included in this study. Patients will take three tablets of vitamin K2 menaquinone-7 (333 mcg) per day. Patients taking vitamin k2 MK-7 will receive a total of 999 mcg per day from day 1 until day 14 or discharge, whichever occurs earlier. All subjects can be treated with prophylactic or therapeutic heparin-based (heparin or any low-molecular-weight heparin) anticoagulants, according to local hospital protocols. Respiratory distress and thromboembolism are common in COVID-19-infected patients. Matrix Gla protein is an essential factor to show anticoagulant activity and prevents pulmonary and vascular elastic fiber damage. No results were posted yet.

Dofferhoff et al. (2020) conducted clinical research and a total of 135 newly diagnosed COVID-19 infected hospitalized patients and found that reduced vitamin K status is a potentially modifiable risk factor of severe COVID-19.

11 | EPIGALLOCATECHIN-3 GALLATE

Green tea is a widely consumed drink around the world. Polyphenols, which make up 30% of the overall mass of green tea, seem to be the most important phytoconstituents. Green tea contains various polyphenols, including epicatechin, epicatechin-3 gallate, epigallocatechin, EGCG, and catechin (Chu et al., 2017; Menegazzi et al., 2001). It

has anti-inflammatory, anticancer, antimicrobial, and immunomodulatory properties, among others (Menegazzi et al., 2020). The inhibiting action of IFN-γ that evokes tyrosine phosphorylation and downregulation of DNA-binding affinity of transcription factor signal transducer and activator of transcription 1 (STAT-1α) is demonstrated by the mechanistic explanation of polyphenols found in green tea (Basiricò et al., 2019). The EGCG also inhibits the expression of inducible nitric oxide synthase II (Menegazzi et al., 2001; Tedeschi et al., 2004). Green tea extract, including polyphenols, was found to have antioxidant effects in many investigations (Annunziata et al., 2018; Das et al., 2019; S. Liu et al., 2017). EGCG suppresses proinflammatory cytokines such as TNF-α, IL-1, and IL-6 and decreases oxidative stress. Polyphenols are natural substances that significantly reduce oxidative stress and inflammation (Basiricò et al., 2019). Their known pharmacophore structures can be useful in the elaboration of new anti-COVID-19 formulation. Polyphenols including betulinic acid, indigo, aloe-emodine, luteolin, and quinomethyl triterpenoids, quercitin or gallate can be safe for patients and inhibit coronavirus enzymes, which are essential for SARS-CoV-2 virus replication and infection (Chojnacka et al., 2020). In addition, green tea polyphenols have a strong interaction with specific main protease (Mpro) residues (His41 and Cys145), indicating that polyphenols may be potent inhibitors of the SARS-CoV-2 primary proteolytic enzymes (Ghosh et al., 2020). Green tea extract containing polyphenols should have anti-inflammatory effects, according to many experimental models (Menegazzi et al., 2020). In mice with carrageenan-induced edema, 25 mg/kg green tea extract administered intraperitoneally decreased inflammation by lowering ICAM-1 and (TNF-α) (Di Paola et al., 2005). EGCG has anti-inflammatory and antioxidant properties and suppresses STAT-1 function. All cytokine receptors and STAT-3 activity are activated by the immune cells, which would be a key element in immune response and autoimmune regulation. In addition, the level of IL-6 in COVID-19 is excessive. Thus, the primary pathogenic factor and EGCG regulate the immune system and avoid hyperinflammatory reactions. Since COVID-19 promotes the generation of inflammatory mediators and ROS, the ability of EGCG to scavenge free radicals and reduce the activation of inflammatory cytokines helps to manage the respiratory distress complications (Menegazzi et al., 2020).

Few in vitro studies support the effectiveness of EGCG in SARS-CoV-2 infection. EGCG inhibits the entry of viral genome from SARS-CoV, MERS-CoV, and Vesicular stomatitis virus G (VSV-Ginto) the cell in vitro as indicated by RT-qPCR; hence, it might be suitable for developing effective anti-COVID-19 drugs (Henss et al., 2021). Another in vitro study indicated that green tea or EGCG is effective in inhibiting the SARS-CoV-2 and HCoV OC43 infection. The study shows that EGCG has a broad-spectrum in vitro antiviral activity by inhibiting spike binding to the ACE-2 receptor and also exhibiting anti-inflammatory and antioxidant potential (J. Liu et al., 2021). Other in vitro studies confirm the inhibition of the activity of SARS-CoV-2 3CL-protease by EGCG, theaflavin (Jang et al., 2020), and the inactivation of SARS-CoV-2 in vitro by green tea catechin, catechin-derivative, and black tea galloylated theaflavins (Ohgitani et al., 2021). Another previous study revealed that 100 μM concentration of EGCG shows 50% inhibition of $3CL^{pro}$ viral protein; similarly, a computational study confirms that EGCG has strong interaction with $3CL^{pro}$ protein, and the binding energy was −9.96 kcal/mol (Bahun et al., 2022).

12 | MORIN

Morin is a 3,5,7,2,4 pentahydroxyflavone phytoconstituent obtained from different members of the Moraceae family (*Maclurapomifera*, *Macluratinctoria*, and *Psidium guajava*) (Park et al., 2015; Rattanachaikunsopon & Phumkhachorn, 2007). Morin was shown to have an inhibitory activity on immunoglobulin E-mediated allergic reactions in the existing literature (Annunziata et al., 2018). It suppresses the expression of proinflammatory activities such as NF-κB, interleukins, cytokines, and activated T-helper cells 2 (Th2 cells) (Kandhare et al., 2019; Park et al., 2015). Phenolic chemicals effectively treat oxidative stress-related disorders such as cancer, cardiovascular problems, and neurological illnesses. In addition, numerous types of hydroxyl groups are able to interact with free radicals, chelate redox metals such as Cu and Fe, and endow phenolic compounds with substantial antioxidant capacity (Jomová et al., 2019). The antioxidant activity of morin was investigated in isoproterenol-induced myocardial ischemia rodents by Al-Numair et al. (2014). The increased concentrations of superoxide dismutase, catalase, glutathione peroxidase, and glutathione S transferase were dramatically normalized by pretreatment with morin 40 mg/kg as the concentrations of nonenzymatic antioxidants. Another study looked into morin's antioxidant and cytoprotective properties against hydrogen peroxide-induced oxidative stress. According to the findings, Morin would have a significant inhibitory effect on 2,2-azino-bis-3(ethylbenzothiazoline 6-6 sulfonic acid) radical and a superoxide dismutase-like activity. Antioxidant and cytoprotective effects are associated with the induction of Nrf-2-mediated heme oxygenase-1 expression in V79-4 Chinese hamster lung fibroblasts. Also, it decreases H_2O_2-induced cellular oxidative stress, inhibits mitochondrial dysfunction, and reduces H_2O_2-induced apoptosis (M. Lee et al., 2017). The antiherpes simplex virus (HSV) activity was determined using various solvent extracts. At 38.5 and 50.8 g/mL, accordingly, ethyl acetate and methanolic extracts demonstrated substantial EC_{50} potency. In addition, a biologically guided chromatographic separation approach was employed to separate morin from a petroleum ether extract of macluracochinchinensis. It had a higher antiHSV-2 action at an EC_{50} value of 53.5 μg/mL (Bunyapraphatsara et al., 2000). Because morin has a high link with antioxidant and anti-inflammatory action, a prior study revealed that the molecular mechanism of morin parallels that of vitamins C and D and EGCG.

Computational analysis showed that flavonol morin targets host ACE-2, Importin IMP-α, Poly (ADP-ribose) polymerase 1 (PARP-1), and viral proteins of SARS-CoV-2, SARS-CoV, and MERS-CoV critical for infection and survival (Gupta et al., 2021).

13 | QUERCETIN

Quercetin is a flavonoid and is commonly found in many fruits and vegetables. Quercetin has a high value of antioxidant properties and analgesics, and it strongly inhibits the Nod-like receptor protein 3 (NLRP3) inflammasome-mediated IL-1β, NRF2, and thioredoxin-interacting protein activation to the cell (Agrawal et al., 2020; Li et al., 2016). The concentration of quercetin in the body may affect mitochondrial biogenesis, increase ATP production, activate the electron transport chain resulting in decreasing the production of ROS and inhibiting cellular oxidative stress (Saeedi-Boroujeni & Mahmoudian-Sani, 2021). Quercetin activates T-helper cell (Th-1) and interferon-γ (IFN- γ) and downregulates Th-2 derived IL-4. Quercetin-3β-galactoside is an isoform of isoquercetin, which is an important glycoside form of quercetin. The SARS-CoV-2 virus quercetin-3β-galactoside contains the hydroxyl group which binds to $3CL^{pro}$ and recognized Gln184 protein and formed a complex to inhibit the proteolytic activity (Biancatelli et al., 2020; Mrityunjaya et al., 2020).

13.1 | Clinical trials and other studies on quercetin alone or in combination with other components

A quercetin clinical trial was conducted in Tunisia (registration number NCT04853199) (Risky et al., 2020). The objective of this study is to determine the effectiveness of an herbal medicine supplement in the treatment of COVID-19 infection, but no results were posted yet. Few previously published studies support the hypothesis of this clinical trial. Quercetin was used in combination with other natural compounds such as vitamin C, zinc, and bromelain for the determination of their effects on COVID-19 patients. Quercetin 800 mg, bromelain 165 mg, zinc acetate 50 mg, and ascorbic acid 1 g once daily supplements may prevent poor SARS-CoV-2 prognosis and were safe for infected patients even if randomized clinical trials are needed in the future to ensure the efficacy of the mixture (A. Ahmed et al., 2020).

A randomized, open-labeled, and controlled study aimed to investigate the adjuvant benefits of quercetin phytosome in community-based subjects with confirmed SARS-CoV-2 infection. The treatment will continue for 30 days (registration number NCT04578158) (https://clinicaltrials.gov/ct2/show/NCT04578158). No results were posted, but it is suggested that quercetin phytosome is a safe agent; in combination with standard care, at early stage of viral infection quercetin could aid in preventing the severity of COVID-19 disease. A double-blind, placebo-controlled study is, however, needed to confirm the results of our study (Di Pierro et al., 2021).

All types of polyphenols are effective to inhibit ACE functions; quercetin, like other polyphenols, was reported to have anti-SARS-CoV activity. Quercetin noncompetitively inhibits the papain-like protease and 3-chymotrypsin-like protease in the SARS-CoV-2 virus (Muchtaridi et al., 2020).

14 | GENISTEIN

Genistein is a bioflavonoid compound found in soy and soy-containing food. It is similar to flavonoids. There is interest in the potential of genistein to prevent or treat many diseases like cardiovascular disease (Andres et al., 2009), it shows antidiabetic (Gilbert & Liu, 2013), anti-inflammatory (Tuli et al., 2019), antioxidant (Mazumder & Hongsprabhas, 2016), and antiviral activity (Shawky et al., 2020).

14.1 | Clinical trials and other studies

A randomized, double-blind, placebo-controlled, two-arm study (registration number NCT04482595) (https://clinicaltrials.gov/ct2/show/study/NCT04482595) evaluates the effectiveness and safety of genistein (1500 mg) for the mitigation of impaired pulmonary function in COVID-19 patients recently discharged from the hospital. All patients received current background standard of care based on local clinical site practice. No results were posted yet.

In silico pharmacokinetic and molecular docking studies of natural flavonoids, including genistein, show anti-SARS-CoV-2 properties against their proteins, namely RNA-dependent RNA polymerase, Mpro, and spike (S) protein; in particular, genistein interacts with the spike proteins' key ribosome-binding domain and may inhibit spread to receptors, thereby limiting viral spread (Vijayakumar et al., 2020).

Another computational study also supported that the genistein highly interacted with S2 spike proteins with binding energy −8.5 kcal/mol as compared to other natural compounds. This study showed that flavonoids and bioflavonoids containing compounds were highly effective in inhibiting the viral replication of host cells (Pandey et al., 2021).

Genistein is also a phytochemical from *Camellia sinensis*. Confirming the reported antiviral activities of *Camellia sinensis*, an in silico study supports the beneficial effect of traditional Ayurvedic/herbal medicine in the management of the COVID-19 crisis by targeting SARA-CoV-2 main metalloprotease. The antiviral potential is evident not only for genistein from the predicted docking score but also for theaflavin, (−)-epigallocatechin 3-gallate, 1-O-caffeoylquinic acid, and ethyl trans-caffeate. Drug likeness characteristics and no or fewer side effects of these compounds make them interesting at least in the prophylaxis of the COVID-19 outbreak (Kanbarkar & Mishra, 2021).

15 | CURCUMIN

Curcumin is commonly obtained from the plant *Curcuma longa* and is commonly called turmeric. In Asian and South Asian countries, it is widely used. It has been widely used for pharmacological and culinary purposes. In Ayurveda, curcumin takes a special place because it is used in many chronic diseases. It is a polyphenol compound, and the role of the polyphenol compound was discussed above

(Hewlings & Kalman, 2017). Curcumin helps in treating many diseases like gastrointestinal disease, respiratory disease, central nervous system disorder, autoimmune diseases, cardiovascular complication, etc. (Pari et al., 2008).

Curcumin is a promising prophylactic, therapeutic candidate for COVID-19 because it exerts antiviral activity by multiple mechanisms: (i) direct interaction with viral membrane proteins; (ii) disruption of the viral envelope; (iii) inhibition of viral protease; and (iv) induction of host antiviral responses. Moreover, curcumin protects from ARDS via targeting NF-κB, inflammasome, IL-6 trans signal, and high mobility group box-1 (HMGB1) pathways. It is noteworthy to mention that curcumin is safe and well-tolerated (Thimmulappa et al., 2021).

15.1 | Clinical trial and other studies

A randomized clinical trial was conducted to determine the effect of curcumin and piperine on COVID-19 patients. In total 525 mg of curcumin and 2 mg of piperine were given to COVID-19 patients and determined their health complications during hospitalization. The result shows that the combination of both drugs effectively reduced the mortality and morbidity of COVID-19 patients (Pawar et al., 2021).

A randomized clinical trial was designed to evaluate the effect of a mixture comprising artemisinin, curcumin, Boswellia, and vitamin C in a nanoparticular formulation, in patients diagnosed with COVID-19 (registration number NCT04802382). Experiments performed in vitro with the formulation demonstrated the ability to reduce cytokine elevation in response to stimulation of human Peripheral blood mononuclear cells (PBMCs) preparations. The clinical trial is designed to include 252 adult patients who suffer from moderate COVID-19 infection. Safety will be assessed. No results were posted yet.

A computational study was performed to determine the interaction of the compound with specific viral proteins. In this study, a total of 10 natural compounds were selected against spike proteins. After performing the molecular docking and molecular dynamic simulation, all the natural compounds showed a good binding affinity with spike protein and could be effective in inhibiting the activation of S-protein (Pandey et al., 2021). In vitro inhibition of extracts from turmeric (*Curcuma longa*) rhizomes against SARS-CoV-2 chymotrypsin-like protease activity was demonstrated (Guijarro-Real et al., 2021).

16 | ASSAY OF SYSTEMIC OXIDATIVE STRESS STATUS OF COVID-19 PATIENTS

Owing to the key role of oxidative stress and inflammation in the development of COVID-19 symptoms, it is crucial to know the systemic oxidative stress status of COVID-19 patients hospitalized in the intensive care unit for severe pneumonia. Biomarkers of oxidative stress including antioxidants, trace elements, and oxidatively damaged lipids. An important drop in antioxidant levels was detected in COVID-19 patients, as evidenced by vitamin C, glutathione, thiol proteins, γ-tocopherol, and β-carotene levels largely below the reference interval (Pincemail et al., 2021).

17 | ANTIOXIDANT ACTIVITY ASSAYS OF PUTATIVE DRUG CANDIDATES: A CRITICAL COMPARATIVE EVALUATION

Antioxidant compounds exhibit antiviral action in models of coronavirus infections. The antiviral activity might be due not only to the inhibitory effect on the enzymatic activity of targets crucial in coronavirus replication (SARS-CoV $3CL^{pro}$, SARS-CoV papain-like protease SARS-CoV helicase protein, and MERS-CoV $3CL^{pro}$) but also to the reduction of ROS accumulation that retards the coronavirus-activated apoptotic signaling (Diniz et al., 2020).

The activity of antioxidants that could be used in the prevention and management of the SARS-CoV-2 pandemic could be measured via various antioxidant capacity assays; they can be classified as hydrogen atom transfer (HAT) or electron transfer (ET) methods.

HAT-based methods, such as twin reversed arterial perfusion (TRAP), oxygen radical absorbance capacity (ORAC), and crocin assays, generally apply a competitive reaction scheme, in which the antioxidant and an oxidable probe compete for peroxyl radicals thermally generated through the decomposition of the azo radical initiator, normally AAPH (2,20-azobis-2-methyl-propanimidamide, dihydrochloride). Unfortunately, AAPH radicals are different from the biological ones, and it was inferred that only antioxidant activity against peroxyl radicals is probably measured; moreover, the concentration of the substrate is much less than that of the antioxidants, at variance with the real situation. Since these methods lack a chain propagation step and the nature of the damaging reaction is not characterized, the relevance of these approaches to radical chain-breaking antioxidant capacity was considered low. The crocin-bleaching assays measure the inhibition capacity of antioxidants in protecting the bleaching of crocin by AAPH, but it is scarcely useful because its quantitative application is impaired by (i) the insensitivity of inhibited bleaching rates to the concentration changes of antioxidants, (ii) interferences, and (iii) the lot-to-lot variability of crocin (D. Huang et al., 2005).

ET-based assays, such as trolox equivalence antioxidant capacity (TEAC), ferric ion reducing antioxidant power (FRAP), 2,2-diphenylpicrylhydrazyl (DPPH), and Folin–Ciocalteu (FC), measure the capacity of an antioxidant to reduce an oxidant, which changes color when reduced to an extent that can be correlated with the sample's antioxidant concentrations. In the following paragraphs, we detail the drawbacks of these methods.

In the ET-based TEAC, the oxidant is $ABTS^{\cdot -}$ (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid decolorization assay). This method is not sound, since the TEAC values for pure antioxidant compounds are not correlated with the number of electrons an antioxidant can give away. Unfortunately, the reaction rate differences are not reflected in the TEAC values because the TEAC assay is an end-point assay, and this lowers the reliability of TEAC results (D. Huang et al., 2005).

In the FRAP, the FRAP values for a number of antioxidants conflict with their reductive properties, which makes test results unreliable; moreover, the test time (4 min) was demonstrated not to be long enough for polyphenols (D. Huang et al., 2005). The ET-based DPPH method uses stable and commercially available organic nitrogen radicals (2,2-diphenyl-1-picrylhydrazyl radical). The absorbance of the mixture fades as its reduction goes on, and it is monitored at 515 nm until it is stable. The percentage of the remaining DPPH is proportional to the antioxidant concentrations. Tested antioxidants never face those ROS responsible for the oxidative stress of the biological system, and this is easily predicted to impair the reliability of their estimates: in this respect, the stability of the commercially available DPPH is emblematic, since many antioxidants important from a biological point of view may be inert to it. Consequently, the antioxidant capacity is easily expected to be wrongly rated. Furthermore, the reaction kinetics between DPPH and antioxidants does not linearly depend on DPPH concentrations and reversible reactions were also observed. Finally, the ratings are pH sensitive. All these issues lower the soundness of the DPPH assay that is the most widely used antioxidant capacity assay (Diniz et al., 2020; D. Huang et al., 2005).

The most important ET-based method is the assay of total phenols by FC reagent. Obviously, the FC reagent is nonspecific to phenolic compounds as it can be reduced by many nonphenolic compounds, such as vitamin C, Cu(I), etc. Like other ET-based methods, it is an end-point method, characterized by nonlinear kinetics and reversible reaction; it has to be taken into account that the tested reducing capacity of the antioxidants may not parallel their ability to prevent oxidation of biological substrates by free radicals (D. Huang et al., 2005).

The quantitation of antioxidant capacity of putative antioxidant drug candidates usually relies on ET-based methods (DPPH, ABTS, FRAP) (Diniz et al., 2020). Taking the limitations of each assay, the comparison of different methods to obtain a fair estimate of the antioxidant activity of a drug candidate is mandatory.

The Briggs-Rauscher (BR) oscillating reaction that is triggered by mixing adequate amount of sodium iodate, hydrogen peroxide, and malonic acid in the presence of manganese sulfate as a catalyst, can be profitably used to estimate the antioxidant capacity of a sample; this method has never been used for the antioxidant capacity rating of radical scavengers that could be used in the prevention and management of SARS-CoV-2 pandemic.

Figure 5: illustrates the chemistry involved in the Briggs–Rauscher (BR) reaction.

The global BR reaction illustrated in Equation (1)

$$IO_3^- + 2H_2O_2 + CH_2(COOH)_2 + H^+ \rightarrow ICH(COOH)_2 + 2O_2 + 3H_2O \quad (1)$$

is accomplished through two-component reactions:

$$IO_3^- + 2H_2O_2 + H^+ \rightarrow HIO + 2O_2 + 2H_2O, \quad (2)$$

$$HIO + CH_2(COOH)_2 \rightarrow ICH(COOH)_2 + H_2O. \quad (3)$$

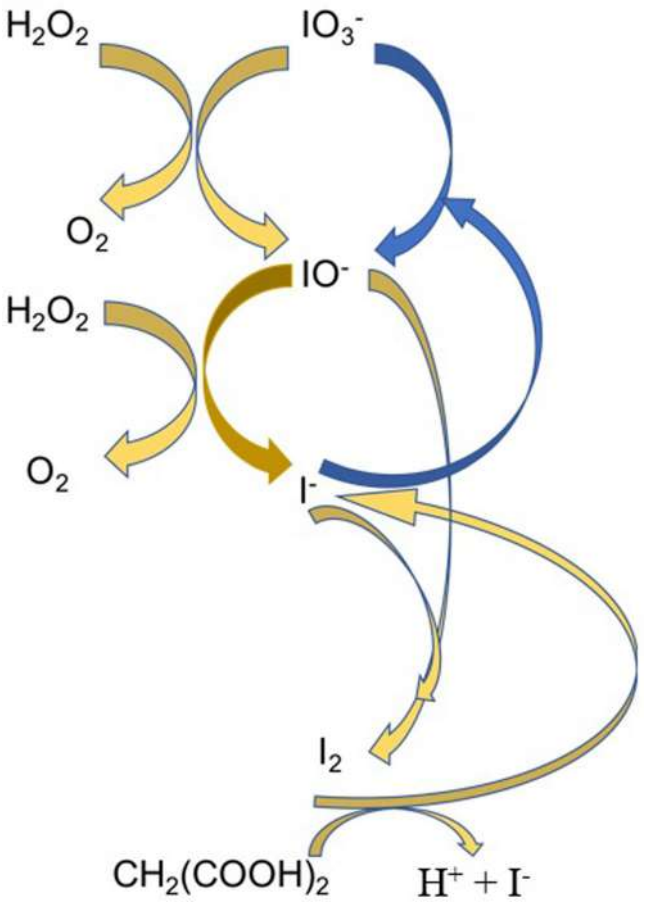

FIGURE 5 Explanation of the chemistry involved in the Briggs–Rauscher(BR) reaction

Equation (2) can follow both a fast radical path, involving the HOO• and the redox chemistry of the catalyst (Mn^{++}), or a nonradical path when the [I^-] is low and high, respectively.

Equation (3) is a two-step reaction:

$$I^- + HIO + H^+ \rightarrow I_2 + H_2O, \quad (4)$$

$$I_2 + CH_2(COOH)_2 \rightarrow ICH(COOH)_2 + H^+ + I^-. \quad (5)$$

Upon initial mixing of the solutions, IO_3^- reacts with H_2O_2 to produce, via a fast radical path, a rapidly increasing [IO^-]. IO^- is partly reduced to I^- by H_2O_2 and partly reacts with I^-, producing I_2 according to Equation (4) (amber solution, radical path). I_2 reacts slowly with malonic acid, thereby causing an increase in [I^-] according to Equation (5). Its high concentration triggers its reaction with IO_3^- and hence a slow nonradical production of IO^- (blue solution nonradical path). IO^- and I^- are consumed in the iodination of malonic acid at a faster rate compared to that of their slow production. Eventually [I^-] is reduced to such a low value that the radical process takes over again. This oscillating sequence repeats until the malonic acid or IO_3^- is depleted.

Contrary to currently used antioxidant capacity assay, according to the BR strategy, the sample antioxidants have to chemically face in the test mixture the same ROS responsible for the oxidative stress and particularly $HOO^{\bullet}$ and H_2O_2. In this respect, the BR antioxidant capacity assay is the only in vitro test that simulates an in vivo assay. Moreover, it is able to detect the activity of those polyphenolic Fe^{2+} chelators able to exert a preventive antioxidant role avoiding the formation (via the Fenton's reaction) of the most disruptive and dangerous free radical, that is the hydroxyl radical ($OH^{\bullet}$) thereby increasing the eligibility of the BR method to test their antioxidant activity. Noteworthy, the method works at pH $\leq$ 2, that is, in the pH range of human gastric fluids at which lipid peroxidation is amplified (Kanner et al., 2001). Since the oscillation period is particularly sensitive to the temperature, it is important to thermostat the reaction mixture during the test. Another disadvantage is the fact that it works in a hydrophilic environment; however, it can also be optimized for lipophilic samples, and it was actually used to estimate the antioxidant capacity of extra virgin olive oil (Cecchi et al., 2010a).

The BR assay has not only theoretical advantages but also many practical benefits: it is easy, inexpensive, and rapid, that is why it was often used to test the antioxidant activity of a wide variety of samples (Cecchi et al., 2010b, 2011; Cervellati et al., 2004; Gajdoš Kljusurić et al., 2005; Honer & Cervellati, 2003; Prenesti et al., 2005; Y.-D. Wang et al., 2013).

18 | CONCLUSION AND FUTURE ASPECTS

Cytokine storm exacerbates tissue damage and organ malfunction. SARS-CoV-2 suppresses NF-k expression, which is required for cytokine and Nrf-2 activation in infected cells, according to the research. The stimulation of antioxidant mechanisms is dependent on Nrf-2 expression, and also the control of the Nrf-2 mechanism is entirely reliant on the viral cycle and virus types. This study looks at certain potential antioxidants that would help cells fight cellular oxidative stress and inflammation. Antioxidants may stop the viral genome replication into the host cell and could control organ failure by suppressing the cellular regulatory pathway and activating immune cells. The most potent antioxidants include vitamins C and D and flavonoids, which have an identical cellular mechanism to COVID-19 and effectively reduce immune responses. The most recent studies concerning the prophylactic use of antioxidants and their use in managing COVID-19 patients are described. According to a literature review, natural antioxidants may help to reduce the complications of viral infection.

Although investigators have shown that antioxidants may be useful against COVID-19, the exact mechanism and efficacy remain uncertain. Therefore, more research is needed to investigate the precise action of possible antioxidants and their maintenance in pathogenic cells and how they combat the inflammatory process and cytokine storm. In the future, clinical studies are needed to assess the effectiveness of antioxidants in the management of COVID-19 infection.

Limitation of the study

Although the study is an overview of different natural antioxidants that were used to determine the efficacy of the patients who were infected with SARS-CoV-2 infection. The limitation of the study is to define the possibility of natural antioxidants to reduce the complications of the infection, but due to unavailability of complete information we cannot justify the finding of many clinical trial results. Thus, this review shows the possibility of many natural antioxidants showing additive or synergistic effects with other drugs.

AUTHOR CONTRIBUTION

All the Authors have equal contributions and agree with the manuscript content.

ACKNOWLEDGMENT

The assistance provided by Dr. Suryakanta Swain, The Assam Kaziranga University, Assam, India during the manuscript preparation is greatly acknowledged.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

Amit Kumar Shrivastava https://orcid.org/0000-0002-8915-9186
Prafulla Kumar Sahu https://orcid.org/0000-0002-5199-3861
Teresa Cecchi https://orcid.org/0000-0003-1940-864X
Laxmi Shrestha https://orcid.org/0000-0002-2489-4278
Sanjay Kumar Shah https://orcid.org/0000-0003-2180-7076
Anamika Gupta https://orcid.org/0000-0003-2334-7958
Anjan Palikhey https://orcid.org/0000-0002-0224-0791
Bishal Joshi https://orcid.org/0000-0001-9096-4660
Jitendra Upadhyaya https://orcid.org/0000-0002-0036-2015
Dr Niranjan Koirala https://orcid.org/0000-0002-7777-1191

REFERENCES

Ackermann, M., Verleden, S E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, H., Tzankov, A., Li, W W., Li, V W., Mentzer, S J., & Jonigk, D. (2020). Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *New England Journal of Medicine*, *383*(2), 120–128.[CrossRef].

Agrawal, P. K., Agrawal, C., & Blunden, G. (2020). Quercetin: Antiviral significance and possible COVID-19 integrative considerations. *Natural Product Communications*, *15*(12), 1934578X2097629.[CrossRef].

Ahmed, A., Abdelseed, H., Albalawi, Y., Almutairi, Y., Alsalameen, E., & Alkattan, A. (2020). Evaluation of the effect of zinc, quercetin, bromelain and vitamin C on COVID-19 patients. medRxiv. https://doi.org/10.1101/2020.12.22.20245993

Ahmed, A. K., Albalawi, Y. S., Shora, H. A., Abdelseed, H. K., & Al-Kattan, A. N. (2020a). Effects of quadruple therapy: Zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients infected with COVID-19. *Research International Journal of Endocrinology and Diabetes*, *1*, 18–21.

Ahmed, A. K., Albalawi, Y. S., Shora, H. A., Abdelseed, H. K., & Al-Kattan, A. N. (2020). Effects of quadruple therapy: zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients infected with COVID-19. *Research International Journal of Endocrinology and Diabetes*, *1*(1), 018–021..

Al-Numair, K., Chandramohan, G., Alsaif, M., Veeramani, C., & Newehy, A. (2014). Morin, a flavonoid, on lipid peroxidation and antioxidant status in experimental myocardial ischemic rats. *African Journal of Traditional, Complementary and Alternative Medicines*, *11*(3), 14–20.[CrossRef].

Alamdari, D. H., Moghaddam, A. B., Amini, S., Keramati, M. R., Zarmehri, A. M., Alamdari, A. H., Damsaz, M., Banpour, H., Yarahamadi, A., & Koliakos, G. (2020). Application of methylene blue-vitamin C–N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial. *European Journal of Pharmacology*, *885*, 173494..

Alanagreh, L. A., Alzoughool, F., & Atoum, M. J. P. (2020). The human coronavirus disease COVID-19: its origin, characteristics, and insights into potential drugs and its mechanisms. *Pathogens*, *9*(5), 331.

Ali, N. (2020). Role of vitamin D in preventing of COVID-19 infection, progression and severity. *Journal of Infection and Public Health*, *13*(10), 1373–1380.[CrossRef].

Amatore, D., Sgarbanti, R., Aquilano, K., Baldelli, S., Limongi, D., Civitelli, L., Nencioni, L., Garaci, E., Ciriolo, M. R., & Palamara, A. T. (2015). Influenza virus replication in lung epithelial cells depends on redox-sensitive pathways activated by NOX4-derived ROS. *Cellular Microbiology*, *17*(1), 131–145.[CrossRef].

Andres, A., Donovan, S M., & Kuhlenschmidt, M S. (2009). Soy isoflavones and virus infections. *The Journal of Nutritional Biochemistry*, *20*(8), 563–569.[CrossRef].

Annunziata, G., Maisto, M., Schisano, C., Ciampaglia, R., Daliu, P., Narciso, V., Tenore, G., & Novellino, E. (2018). Colon bioaccessibility and antioxidant activity of white, green and black tea polyphenols extract after in vitro simulated gastrointestinal digestion. *Nutrients*, *10*(11), 1711.[CrossRef].

Annweiler, G., Corvaisier, M., Gautier, J., Dubée, V., Legrand, E., Sacco, G., & Annweiler, C. (2020). Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: The GERIA-COVID quasi-experimental study. *Nutrients*, *12*(11), 3377.

Arboleda, J. F., & Urcuqui-Inchima, S. (2020). Vitamin D supplementation: A potential approach for coronavirus/COVID-19 therapeutics? *Frontiers in Immunology*, *11*, 1523.[CrossRef].

Arshad, M. S., Khan, U., Sadiq, A., Khalid, W., Hussain, M., Yasmeen, A., Asghar, Z., & Rehana, H. (2020). Coronavirus disease (COVID-19) and immunity booster green foods: A mini-review. *Food Science & Nutrition*, *8*(8), 3971–3976.

Bagherani, N., & R Smoller, B. (2016). An overview of zinc and its importance in dermatology-Part I: Importance and function of zinc in human beings. *Global Dermatology*, *3*, 330–336.[CrossRef].

Bahun, M., Jukić, M., Oblak, D., Kranjc, L., Bajc, G., Butala, M., Bozovičar, K., Bratkovič, T. E., Podlipnik, Č., & Poklar Ulrih, N. (2022). Inhibition of the SARS-CoV-2 $3CL^{pro}$ main protease by plant polyphenols. *Food Chemistry*, *373*, 131594.[CrossRef].

Basiricò, L., Morera, P., Dipasquale, D., Bernini, R., Santi, L., Romani, A., Lacetera, N., & Bernabucci, U. (2019). (–)-Epigallocatechin-3-gallate and hydroxytyrosol improved antioxidative and anti-inflammatory responses in bovine mammary epithelial cells. *Animal*, *13*(12), 2847–2856.[CrossRef].

Beard, J A., Bearden, A., & Striker, R. (2011). Vitamin D and the anti-viral state. *Journal of Clinical Virology*, *50*(3), 194–200.[CrossRef].

Berthelot, J.- M., Drouet, L., & Lioté, F. (2020). Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? *Emerging Microbes & Infections*, *9*(1), 1514–1522.

Biancatelli, C., L, R. M., Berrill, M., Catravas, J. D., & Marik, P. E. (2020). Quercetin and vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). *Frontiers in Immunology*, *11*, 1451.

Biesalski, H. K. (2020). Vitamin D deficiency and co-morbidities in COVID-19 patients—A fatal relationship? *NFS Journal*, *20*, 10.[CrossRef].

Bjørklund, G., Shanaida, M., Lysiuk, R., Butnariu, M., Peana, M., Sarac, I., Strus, O., Smetanina, K., & Chirumbolo, S. (2022). Natural compounds and products from an anti-aging perspective. *Molecules (Basel, Switzerland)*, *27*(20), 7084.[CrossRef].

Bunyapraphatsara, N., Dechsree, S., Yoosook, C., Herunsalee, A., & Panpisutchai, Y. (2000). Anti-herpes simplex virus component isolated from *Maclura cochinchinensis*. *Phytomedicine*, *6*(6), 421–424.[CrossRef].

Calder, P. C. (2020). Nutrition, immunity and Covid-19. *BMJ Nutrition, Prevention & Health*, 2020. bmjnph-2020-000085.

Camini, F. C., Da Silva Caetano, C. C., Almeida, L. T., & De Brito Magalhães, C. L. (2017). Implications of oxidative stress on viral pathogenesis. *Archives of Virology*, *162*(4), 907–917.[CrossRef].

Cannata-Andía, J. B., Díaz-Sottolano, A., Fernández, P., Palomo-Antequera, C., Herrero-Puente, P., Mouzo, R., Carrillo-López, N., Panizo, S., Ibañez, G. H., Ballarino, C., Sánchez-Polo, V., Pefaur-Penna, J., Maderuelo-Riesco, I., Calviño-Varela, J., Gómez, M. D., Gómez-Alonso, C., Cunningham, J., Naves-Díaz, M., … Cusumano, C. A. (2022). A single-oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve outcomes in the COVID-19 disease: the COVID-VIT-D—a randomised multicentre international clinical trial. *BMC Medicine*, *20*(1), 83.

Carr, A. C., & Maggini, S. (2017). Vitamin C and immune function. *Nutrients*, *9*(11), 1211.

Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S. C., & Di Napoli, R. (2020). Features, evaluation and treatment coronavirus (COVID-19). In *Statpearls [Internet]*. StatPearls Publishing.

Cecchi, T., Cecchi, P., & Passamonti, P. (2011). The first quantitative rating system of the antioxidant capacity of beauty creams via the Briggs–Rauscher reaction: a crucial step towards evidence-based cosmetics. *Analyst*, *136*(3), 613–618.

Cecchi, T., Passamonti, P., & Cecchi, P. J. (2010a). Optimization of the measurement of Italian mono cultivar extra virgin olive oil antioxidant power via the Briggs–Rauscher reaction. *Food Analytical Methods*, *3*(1), 1–6.

Cecchi, T., Passamonti, P., & Cecchi, P. J. (2010b). Study of the quality of extra virgin olive oil stored in PET bottles with or without an oxygen scavenger. *Food Chemistry*, *120*(3), 730–735.

Cecchini, R., & Cecchini, A. L. (2020). SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Medical Hypotheses*, *143*, 110102.[CrossRef].

Cervellati, R., Höner, K., Furrow, S. D., Mazzanti, F., & Costa, S. (2004). An experimental and mechanistic investigation of the complexities arising during inhibition of the Briggs–Rauscher reaction by antioxidants. *Helvetica Chimica Acta*, *87*(1), 133–155.

Chakraborty, A. J., Mitra, S., Tallei, T E., Tareq, A. M., Nainu, F., Cicia, D., Dhama, K., Emran, T. B., Simal-Gandara, J., & Capasso, R. (2021). Bromelain a potential bioactive compound: a comprehensive overview from a pharmacological perspective. *Life*, *11*(4), 317.[CrossRef].

Checconi, P., De Angelis, M., Marcocci, M. E., Fraternale, A., Magnani, M., Palamara, A. T., & Nencioni, L. (2020). Redox-modulating agents in the treatment of viral infections. *International Journal of Molecular Sciences*, *21*(11), 4084.[CrossRef].

Cheng, R Z. (2020). Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? *Medicine in Drug Discovery*, *5*, 100028.[CrossRef].

Cherry, J., Demmler-Harrison, G. J., Kaplan, S. L., Steinbach, W. J., & Hotez, P. J. (2017). *Feigin and Cherry's textbook of pediatric infectious diseases* [E-Book]. Elsevier Health Sciences.

Chojnacka, K., Witek-Krowiak, A., Skrzypczak, D., Mikula, K., & Młynarz, P. (2020). Phytochemicals containing biologically active polyphenols as

an effective agent against Covid-19-inducing coronavirus. *Journal of Functional Foods*, *73*, 104146.[CrossRef].

Chu, C., Deng, J., Man, Y., & Qu, Y. (2017). Green tea extracts epigallocatechin-3-gallate for different treatments. *BioMed Research International*, *2017*, 1–9.[CrossRef].

ClinicalTrials.gov. *The effect of melatonin and vitamin C on COVID-19*. https://clinicaltrials.gov/ct2/show/NCT04530539?term=melatonin&cond=Covid19&draw=1&rank=5

Cramer, D W. (1986). The relation of endometriosis to menstrual characteristics, smoking, and exercise. *JAMA*, *255*(14), 1904–1908. [CrossRef].

Coppock, D., M, D., & Jefferson, T. (2020). Pharmacologic ascorbic acid as an activator of lymphocyte signaling for COVID-19 Treatment. https://clinicaltrials.gov/ct2/show/NCT04363216?cond=NCT04363216&draw=2&rank=1

Dabbagh-Bazarbachi, H., Clergeaud, G., Quesada, I M., Ortiz, M., O'sullivan, C K., & Fernández-Larrea, J. B. (2014). Zinc ionophore activity of quercetin and epigallocatechin-gallate: From Hepa 1-6 cells to a liposome model. *Journal of Agricultural and Food Chemistry*, *62*(32), 8085–8093.[CrossRef].

Das, A., Kalita, A., Raychaiudhuri, U., & Chakraborty, R. (2019). Synergistic effect of herbal plant extract (*Hibiscus sabdariffa*) in maintain the antioxidant activity of decaffeinated green tea from various parts of Assam. *Journal of Food Science and Technology*, *56*(11), 5009–5016.[CrossRef].

Dasgupta, J., Sen, U., Bakshi, A., Dasgupta, A., Manna, K., Saha, C., De, R. K., Mukhopadhyay, S., & Bhattacharyya, N. P. (2020). Nsp7 and spike glycoprotein of SARS-CoV-2 are envisaged as potential targets of vitamin D and ivermectin. *MDPI Preprint*, 2020050084. https://doi.org/10.20944/preprints202005.0084.v1

Da Silveira Cespedes, M., & de Souza, J C. R. P. (2020). Sars-CoV-2: A clinical update-II. *Revista da Associação Médica Brasileira*, *66*(4), 547–557.[CrossRef].

De La Fuente, M., Hernanz, A., Guayerbas, N., Manuel Victor, V., & Arnalich, F. (2008). Vitamin E ingestion improves several immune functions in elderly men and women. *Free Radical Research*, *42*(3), 272–280.[CrossRef].

Di Paola, R., Mazzon, E., Muià, C., Genovese, T., Menegazzi, M., Zaffini, R., Suzuki, H., & Cuzzocrea, S. (2005). Green tea polyphenol extract attenuates lung injury in experimental model of carrageenan-induced pleurisy in mice. *Respiratory Research*, *6*(1), 66.[CrossRef].

Di Pierro, F., Derosa, G., Maffioli, P., Bertuccioli, A., Togni, S., Riva, A., Allegrini, P., Khan, A., Khan, S., Altaf, N., Zahid, M., Ujjan, I. D., Nigar, R., Khushk, M. I., Phulpoto, M., Lail, A., Devrajani, B. R., Ahmed, S., & Khan, B. A. (2021). Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: A prospective, randomized, controlled, and open-label study. *International Journal of General Medicine*, *14*, 2359–2366.

Diniz, L. R. L., da Silva Maia Bezerra Filho, C., Fielding, B. C., & De Sousa, D. P. (2020). Natural antioxidants: A review of studies on human and animal coronavirus. *Oxidative Medicine and Cellular Longevity*, *2020*, 3173281.

Doaei, S., Gholami, S., Rastgoo, S., Gholamalizadeh, M., Bourbour, F., Bagheri, S. E., Samipoor, F., Akbari, M. E., Shadnoush, M., Ghorat, F., Mosavi Jarrahi, S. A., Ashouri Mirsadeghi, N., Hajipour, A., Joola, P., Moslem, A., & Ghorat, F. J. (2021). The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *Journal of Translational Medicine*, *19*(1), 128.

Dofferhoff, A. S., Piscaer, I., Schurgers, L. J., Visser, M. P., van den Ouweland, J. M., de Jong, P. A., Gosens, R., Hackeng, T. M., van Daal, H., Maassen, C., Karssemeijer, E. G. A., Vermeer, C., Wouters, E. F. M., Kistemaker, L. E. M., Walk, J., Janssen, R., & Lux, P. (2020). Reduced vitamin K status as a potentially modifiable risk factor of severe COVID-19. *Clinical Infectious Diseases*, *73*(11), e4039–e4046.

Edwards, R. J., Mansouri, K., Stalls, V., Manne, K., Watts, B., Parks, R., Janowska, K., Gobeil, S. M. C., Kopp, M., Lu, X., Mu, Z., Deyton, M., Oguin, T. H., Sprenz, J., Williams, W., Saunders, K. O., Montefiori, D., Sempowski, G. D., Acharya, P., … Li, D. (2021). Cold sensitivity of the SARS-CoV-2 spike ectodomain. *Nature Structural & Molecular Biology*, *28*(2), 128–131.

Fabricant, J. (1998). The early history of infectious bronchitis. *Avian Diseases*, *42*(4), 648–650.[CrossRef].

Fawzi, W. (2020). *Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India*. https://clinicaltrials.gov/ct2/show/NCT04641195

Fink, K., Duval, A., Martel, A., Soucy-Faulkner, A., & Grandvaux, N. (2008). Dual role of NOX2 in respiratory syncytial virus-and Sendai virus-induced activation of NF-κB in airway epithelial cells. *The Journal of Immunology*, *180*(10), 6911–6922.[CrossRef].

Gajdoš Kljusurić, J., Djaković, S., Kruhak, I., Kovačević Ganić, K., Komes, D., & Kurtanjek, Ž. (2005). Application of Briggs-Rauscher reaction for measurement of antioxidant capacity of Croatian wines. *Acta Alimentaria*, *34*(4), 483–492.

Galano, A., Tan, D.-X., & Reiter, R. (2018). Melatonin: A versatile protector against oxidative DNA damage. *Molecules (Basel, Switzerland)*, *23*(3), 530.[CrossRef].

Ghosh, R., Chakraborty, A., Biswas, A., & Chowdhuri, S. (2020). Evaluation of green tea polyphenols as novel coronavirus (SARS CoV-2) main protease (Mpro) inhibitors—An in silico docking and molecular dynamics simulation study. *Journal of Biomolecular Structure & Dynamics*, *39*, 4362–4374. https://doi.org/10.1080/07391102.2020.1779818

Gilbert, E. R., & Liu, D. (2013). Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic β-cell function. *Food & Function*, *4*(2), 200–212.

Grant, W., Lahore, H., Mcdonnell, S., Baggerly, C., French, C., Aliano, J., & Bhattoa, H. (2020a). Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*, *12*(4), 988.[CrossRef].

Grant, W. B., Lahore, H., McDonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J. L., & Bhattoa, H. P. (2020b). Vitamin D supplementation could prevent and treat influenza, coronavirus, and pneumonia infections. *MDPI Preprint*, 2020030235. https://doi.org/10.20944/preprints202003.0235.v1

Greiller, C., & Martineau, A. (2015). Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients*, *7*(6), 4240–4270.[CrossRef].

Guan, W.-J., Ni, Z. -Y., Hu, Y., Liang, W. -H., Ou, C. -Q., He, J.-X., Liu, L., Shan, H., Lei, C. -L., Hui, D. S. C., Du, B., Li, L. -J., Zeng, G., Yuen, K. -Y., Chen, R. -C., Tang, C. L., Wang, T., Chen, P. -Y., Xiang, J., … & Zhong, N. -S. (2020). Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*, *382*(18), 1708–1720.[CrossRef].

Guijarro-Real, C., Plazas, M., Rodríguez-Burruezo, A., Prohens, J., & Fita, A. (2021). Potential in vitro inhibition of selected plant extracts against SARS-CoV-2 chymotripsin-like protease (3CLPro) activity. *Foods*, *10*(7), 1503.

Gupta, A., Ahmad, R., Siddiqui, S., Yadav, K., Srivastava, A., Trivedi, A., Ahmad, B., Khan, M. A., Shrivastava, A. K., & Singh, G. K. (2021). Flavonol morin targets host ACE2, IMP-α, PARP-1 and viral proteins of SARS-CoV-2, SARS-CoV and MERS-CoV critical for infection and survival: a computational analysis. *Journal of Biomolecular Structure & Dynamics*, *40*(12), 5515–5546.

Hacışevki, A., & Baba, B. (2018). An overview of melatonin as an antioxidant molecule: a biochemical approach. In C. M. Drăgoi, & A. C. Nicolae (Eds.), *Melatonin: Molecular biology, clinical and pharmaceutical approaches* (pp. 59–85). IntechOpen.

& Hadizadeh, F. (2021). Supplementation with vitamin D in the COVID-19 pandemic? *Nutrition Reviews*, *79*(2), 200–208.[CrossRef].

Hastie, C. E., Mackay, D. F., Ho, F., Celis-Morales, C. A., Katikireddi, S. V., Niedzwiedz, C. L., Jani, B. D., Welsh, P., Mair, F. S., O'Donnell, C. A., Gill, J. M. R., Sattar, N., Pell, J. P., & Gray, S. R. (2020). Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(4), 561–565.

Hathaway, D. III, Pandav, K., Patel, M., Riva-Moscoso, A., Singh, B. M., Patel, A., Min, Z. C., Singh-Makkar, S., Sana, M. K., Sanchez-Dopazo, R., Desir, R.,

Fahem, M. M. M., Manella, S., Rodriguez, I., Alvarez, A., & Abreu, R. (2020). Omega 3 fatty acids and COVID-19: a comprehensive review. *Infection & Chemotherapy*, *52*(4), 478.

Henss, L., Auste, A., Schürmann, C., Schmidt, C., Von Rhein, C., Mühlebach, M D., & Schnierle, B S. (2021). The green tea catechin epigallocatechin gallate inhibits SARS-CoV-2 infection. *Journal of General Virology*, *102*(4), 001574.[CrossRef].

Hernández, A., Papadakos, P. J., Torres, A., González, D. A., Vives, M., Ferrando, C., & Baeza, J. (2020). Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19. *Revista Española de Anestesiología y Reanimación (English Edition)*, *67*(5), 245–252.[CrossRef].

Hewlings, S., & Kalman, D. (2017). Curcumin: A review of its effects on human health. *Foods*, *6*(10), 92.[CrossRef].

& Hildeman, D A. (2004). Regulation of T-cell apoptosis by reactive oxygen species. *Free Radical Biology and Medicine*, *36*(12), 1496–1504.[CrossRef].

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*, 271–280.e8. [CrossRef].

Honer, K., & Cervellati, R. (2003). Determination of the antioxidative capacity of apples using the Briggs-Rauscher method. *Ernährungs Umschau*, *50*(1), 13–15.

Huang, C., Liang, Y., Zeng, X., Yang, X., Xu, D., Gou, X., Sathiaseelan, R., Senavirathna, L. K., Wang, P., & Liu, L. (2020). Long noncoding RNA FENDRR exhibits antifibrotic activity in pulmonary fibrosis. *American Journal of Respiratory Cell and Molecular Biology*, *62*(4), 440–453.

Huang, D., Ou, B., Prior, R. J. A., & Chem, F. (2005). The chemistry behind antioxidant capacity assay. *Journal of Agricultural and Food Chemistry*, *53*, 1841–1856..

Jang, M., Park, Y. - I., Cha, Y. - E., Park, R., Namkoong, S., Lee, J. I., & Park, J. (2020). Tea polyphenols EGCG and theaflavin inhibit the activity of SARS-CoV-2 3CL-protease in vitro. *Evidence-Based Complementary and Alternative Medicine*, *2020*, 5630838.

Jomová, K., Hudecova, L., Lauro, P., Simunkova, M., Alwasel, S H., Alhazza, I M., & Valko, M. (2019). A switch between antioxidant and prooxidant properties of the phenolic compounds myricetin, morin, 3′,4′-dihydroxyflavone, taxifolin and 4-hydroxy-coumarin in the presence of copper (II) ions: a spectroscopic, absorption titration and DNA damage study. *Molecules (Basel, Switzerland)*, *24*(23), 4335.[CrossRef].

Kanbarkar, N., & Mishra, S. (2021). Matrix metalloproteinase inhibitors identified from Camellia sinensis for COVID-19 prophylaxis: an in silico approach. *Advances in Traditional Medicine*, *21*(1), 173–188..

Kandhare, A. D., Liu, Z., Mukherjee, A. A., & Bodhankar, S. L. (2019). Therapeutic potential of morin in ovalbumin-induced allergic asthma via modulation of SUMF2/IL-13 and BLT2/NF-κB signaling pathway. *Current Molecular Pharmacology*, *12*(2), 122–138.

Kang, Z., Zhu, H., Jiang, W., & Zhang, S. (2013). Protocatechuic acid induces angiogenesis through P I3 K-A kt-e NOS-VEGF signalling pathway. *Basic & Clinical Pharmacology & Toxicology*, *113*(4), 221–227.

Kanner, J., & Lapidot, T. (2001). The stomach as a bioreactor: dietary lipid peroxidation in the gastric fluid and the effects of plant-derived antioxidants. *Free Radical Biology & Medicine*, *31*(11), 1388–1395.

Kassi, E N., Papavassiliou, K A., & Papavassiliou, A G. (2020). Defective antioxidant system: An aggravating factor for COVID-19 patients outcome? *Archives of Medical Research*, *51*, 726–727. [CrossRef].

Kaul, P., Biagioli, M C., Singh, I., & Turner, R B. (2000). Rhinovirus-induced oxidative stress and interleukin-8 elaboration involves p47-phox but is independent of attachment to intercellular adhesion molecule-1 and viral replication. *Journal of Infectious Diseases*, *181*(6), 1885–1890.[CrossRef].

Keen, M., & Hassan, I. (2016). Vitamin E in dermatology. *Indian Dermatology Online Journal*, *7*(4), 311.[CrossRef].

& Keles, E. S. (2020). Mild SARS-CoV-2 infections in children might be based on evolutionary biology and linked with host reactive oxidative stress and antioxidant capabilities. *New Microbes and New Infections*, *36*, 100723.

& Kennedy, D. (2016). B vitamins and the brain: mechanisms, dose and efficacy—a review. *Nutrients*, *8*(2), 68.[CrossRef].

Khare, D., Godbole, N M., Pawar, S D., Mohan, V., Pandey, G., Gupta, S., Kumar, D., Dhole, T N., & Godbole, M M. (2013). Calcitriol [1, 25 [OH] 2 D3] pre-and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung A549 epithelial cells. *European Journal of Nutrition*, *52*(4), 1405–1415.[CrossRef].

Khomich, O., Kochetkov, S., Bartosch, B., & Ivanov, A. (2018). Redox biology of respiratory viral infections. *Viruses*, *10*(8), 392.[CrossRef].

Ksiazek, T G., Erdman, D., Goldsmith, C. S., Zaki, S. R., Peret, T., Emery, S., Tong, S., Urbani, C., Comer, J. A., Lim, W., Rollin, P. E., Dowell, S. F., Ling, A. -E., Humphrey, C. D., Shieh, W. -J., Guarner, J., Paddock, C. D., Rota, P., Fields, B., … & Anderson, L. J. (2003). A novel coronavirus associated with severe acute respiratory syndrome. *New England Journal of Medicine*, *348*(20), 1953–1966.[CrossRef].

Kudelko, M., Yip, T. F., Hei Law, G. C., & Lee, S. M. Y. (2021). Potential beneficial effects of vitamin K in SARS-CoV-2 induced vascular disease? *Immuno*, *1*(1), 17–29.[CrossRef].

Lanham-New, S. A., Webb, A. R., Cashman, K. D., Buttriss, J. L., Fallowfield, J. L., Masud, T., Hewison, M., Mathers, J. C., Kiely, M., Ward, K. A., Magee, P., Darling, A. L., Hill, T. R., Greig, C., Smith, C. P., Murphy, R., Leyland, S., Bouillon, R., Kohlmeier, M., … & Welch, A. A. (2020). Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJ Nutrition, Prevention & Health*, *3*(1), 106.

& Lee, C. (2018). Therapeutic modulation of virus-induced oxidative stress via the Nrf2-dependent antioxidative pathway. *Oxidative Medicine and Cellular Longevity*, *2018*, 6208067. [CrossRef].

Lee, M. H., Cha, H. -J., Choi, E. O., Han, M. H., Kim, S. O., Kim, G. -Y., Hong, S. H., Park, C., Moon, S. -K., Jeong, S. -J., Jeong, M. -J., Kim, W. -J., & Choi, Y. H. (2017). Antioxidant and cytoprotective effects of morin against hydrogen peroxide-induced oxidative stress are associated with the induction of Nrf-2-mediated HO-1 expression in V79-4 Chinese hamster lung fibroblasts. *International Journal of Molecular Medicine*, *39*(3), 672–680.[CrossRef].

Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M., Wang, S., Liu, H., & Yin, Y. (2016). Quercetin, inflammation and immunity. *Nutrients*, *8*(3), 167.[CrossRef].

Liang, Y., Wang, M.-L., Chien, C. -S., Yarmishyn, A. A., Yang, Y. -P., Lai, W. -Y., Luo, Y. -H., Lin, Y. -T., Chen, Y. -J., Chang, P. -C., & Chiou, S. -H. (2020). Highlight of immune pathogenic response and hematopathologic effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 infection. *Frontiers in Immunology*, *11*, 1022.[CrossRef].

Lim, Y., Ng, Y., Tam, J., & Liu, D. (2016). Human coronaviruses: A review of virus–host interactions. *Diseases*, *4*(3), 26.[CrossRef].

Lin, S. -C., Ho, C. -T., Chuo, W. -H., Li, S., Wang, T. T., & Lin, C. -C. (2017). Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infectious Diseases*, *17*(1), 1–10.[CrossRef].

Liu, F., Zhu, Y., Zhang, J., Li, Y., & Peng, Z. (2020). Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. *BMJ Open*, *10*(7), e039519.[CrossRef].

Liu, J., Bodnar, B. H., Meng, F. - Z., Khan, A., Wang, X., Luo, G. G., Saribas, S., Wang, T., Lohani, S. C., Wei, Z., Luo, J., Zhou, L., Wu, J., Li, Q., Hu, W., & Ho, W., & Wang, P. (2021). Epigallocatechin gallate from green tea effectively blocks infection of SARS-CoV-2 and new variants by inhibiting spike binding to ACE2 receptor. *BioRxiv*, *11*(1), 1–5. https://doi.org/10.1186/s13578-021-00680-8

Liu, S., Ai, Z., Qu, F., Chen, Y., & Ni, D. (2017). Effect of steeping temperature on antioxidant and inhibitory activities of green tea extracts against α-amylase, α-glucosidase and intestinal glucose uptake. *Food Chemistry*, *234*, 168–173.[CrossRef].

Loeffelholz, M. J., & Tang, Y. -W. (2020). Laboratory diagnosis of emerging human coronavirus infections—The state of the art. *Emerging Microbes & Infections*, *9*(1), 747–756.

Martín Giménez, V. M., Inserra, F., Tajer, C D., Mariani, J., Ferder, L., Reiter, R J., & Manucha, W. (2020). Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. *Life Sciences*, *254*, 117808.[CrossRef].

Maghbooli, Z., Sahraian, M. A., Ebrahimi, M., Pazoki, M., Kafan, S., Tabriz, H. M., Hadadi, A., Montazeri, M., Nasiri, M., Shirvani, A., & Holick, M. F. (2020). Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. *PLoS ONE*, *15*(9), e0239799.[CrossRef].

Manson, J. E., & Bassuk, S. (2020). Commentary. Eliminating vitamin D deficiency during the COVID-19 pandemic: A call to action. *Metabolism*, *112*, 154322.

Marjuki, H., Alam, M I., Ehrhardt, C., Wagner, R., Planz, O., Klenk, H - D., Ludwig, S., & Pleschka, S. (2006). Membrane accumulation of influenza A virus hemagglutinin triggers nuclear export of the viral genome via protein kinase Cα-mediated activation of ERK signaling. *Journal of Biological Chemistry*, *281*(24), 16707–16715.[CrossRef].

Martineau, A. R., Jolliffe, D. A., Hooper, R. L., Greenberg, L., Aloia, J. F., Bergman, P., Dubnov-Raz, G., Esposito, S., Ganmaa, D., Goodall, E. C., Grant, C. C., Griffiths, C. J., Janssens, W., Laaksi, I., Manaseki-Holland, S., Mauger, D., Murdoch, D. R., Neale, R., Camargo, C. A., … & Ginde, A. A. (2017). Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*, *356*, i6583.

Mazumder, M. A. R., & Hongsprabhas, P. (2016). Genistein as antioxidant and antibrowning agents in in vivo and in vitro: A review. *Biomedicine & Pharmacotherapy*, *82*, 379–392.

Mendonca, P., & Soliman, K. F. A. (2020). Flavonoids activation of the transcription factor Nrf2 as a hypothesis approach for the prevention and modulation of SARS-CoV-2 infection severity. *Antioxidants*, *9*(8), 659.[CrossRef].

Menegazzi, M., Campagnari, R., Bertoldi, M., Crupi, R., Di Paola, R., & Cuzzocrea, S. (2020). Protective effect of epigallocatechin-3-gallate (EGCG) in diseases with uncontrolled immune activation: Could such a scenario Be helpful to counteract COVID-19? *International Journal of Molecular Sciences*, *21*(14), 5171.[CrossRef].

Menegazzi, M., Tedeschi, E., Dussin, D., Prati, A. C., Cavalieri, E., Mariotto, S., & Suzuki, H. (2001). Anti-interferon-γ action of epigallocatechin-3-gallate mediated by specific inhibition of STAT1 activation. *The FASEB Journal*, *15*(7), 1309–1311.[CrossRef].

Meydani, S. N., Barklund, M. P., Liu, S., Meydani, M., Miller, R. A., Cannon, J. G., Morrow, F. D., Rocklin, R., & Blumberg, J. B. (1990). Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. *The American Journal of Clinical Nutrition*, *52*(3), 557–563.[CrossRef].

Mikkelsen, K., & Apostolopoulos, V. (2019). Vitamin B1, B2, B3, B5, and B6 and the immune system. In M. Mahmoudi & N. Rezaei (Eds.), *Nutrition and immunity* (pp. 115–125). Springer.

Milani, G. P., Macchi, M., & Guz-Mark, A. (2021). Vitamin C in the treatment of COVID-19. *Nutrients*, *13*(4), 1172.[CrossRef].

Mirzaei, R., Karampoor, S., Sholeh, M., Moradi, P., Ranjbar, R., & Ghasemi, F. (2020). A contemporary review on pathogenesis and immunity of COVID-19 infection. *Molecular Biology Reports*, *47*(7), 5365–5376.

Mohd, A., Zainal, N., Tan, K.-K., & Abubakar, S. (2019). Resveratrol affects Zika virus replication in vitro. *Scientific Reports*, *9*(1), 1–11.[CrossRef].

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

Muchtaridi, M., Fauzi, M., Khairul Ikram, N. K., Mohd Gazzali, A., & Wahab, H. A. (2020). Natural flavonoids as potential angiotensin-converting enzyme 2 inhibitors for anti-SARS-CoV-2. *Molecules (Basel, Switzerland)*, *25*(17), 3980.[CrossRef].

Muellner, M K., Schreier, S M., Schmidbauer, B., Moser, M., Quehenberger, P., Kapiotis, S., Goldenberg, H., & Laggner, H. (2010). Vitamin C inhibits NO-induced stabilization of HIF-1α in HUVECs. *Free Radical Research*, *44*(7), 783–791.[CrossRef].

Narayana, J. L., Mishra, B., Lushnikova, T., Golla, R. M., & Wang, G. (2019). Modulation of antimicrobial potency of human cathelicidin peptides against the ESKAPE pathogens and in vivo efficacy in a murine catheter-associated biofilm model. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1861*(9), 1592–1602.[CrossRef].

Narayanan, N., & Nair, D. T. (2020). Vitamin B12 may inhibit RNA-dependent-RNA polymerase activity of nsp12 from the SARS-CoV-2 virus. *IUBMB Life*, *72*(10), 2112–2120.[CrossRef].

National Institute of Health. (2020). Coronavirus disease 2019 treatment guidelines. https://pubmed.ncbi.nlm.nih.gov/34003615/

Nencioni, L., De Chiara, G., Sgarbanti, R., Amatore, D., Aquilano, K., Marcocci, M. E., Serafino, A., Torcia, M., Cozzolino, F., Ciriolo, M. R., Garaci, E., & Palamara, A. T. (2009). Bcl-2 expression and p38MAPK activity in cells infected with influenza a virus impact on virally induced apoptosis and viral replication. *Journal of Biological Chemistry*, *284*(23), 16004–16015.[CrossRef].

Ohgitani, E., Shin-Ya, M., Ichitani, M., Kobayashi, M., Takihara, T., Kawamoto, M., Kinugasa, H., & Mazda, O. (2021). Significant inactivation of SARS-CoV-2 in vitro by a green tea catechin, a catechin-derivative, and black tea galloylated theaflavins. *Molecules*, *26*(12), 3572.

Padayatty, S. J., Katz, A., Wang, Y., Eck, P., Kwon, O., Lee, J. -H., Chen, S., Corpe, C., Dutta, A., Dutta, S. K., & Levine, M. (2003). Vitamin C as an antioxidant: evaluation of its role in disease prevention. *Journal of the American College of Nutrition*, *22*(1), 18–35.[CrossRef].

Pandey, P., Rane, J. S., Chatterjee, A., Kumar, A., Khan, R., Prakash, A., & Ray, S. (2021). Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An in silico study for drug development. *Journal of Biomolecular Structure and Dynamics*, *39*(16), 6306–6316.

Pari, L., Tewas, D., & Eckel, J. (2008). Role of curcumin in health and disease. *Archives of Physiology and Biochemistry*, *114*(2), 127–149.[CrossRef].

Park, C., Lee, W. S., Go, S. - I., Nagappan, A., Han, M. H., Hong, S. H., Kim, G., Kim, G., Kwon, T., Ryu, C., Shin, S., & Choi, Y. (2015). Morin, a flavonoid from Moraceae, induces apoptosis by induction of BAD protein in human leukemic cells. *International Journal of Molecular Sciences*, *16*(1), 645–659.

Pascarella, G., Strumia, A., Piliego, C., Bruno, F., Del Buono, R., Costa, F., Scarlata, S., & Agrò, F. E. (2020). COVID-19 diagnosis and management: a comprehensive review. *Journal of Internal Medicine*, *288*, 192–206.[CrossRef].

Pasquereau, S., Nehme, Z., Haidar Ahmad, S., Daouad, F., Van Assche, J., Wallet, C., Schwartz, C., Rohr, O., Morot-Bizot, S., & Herbein, G. (2021). Resveratrol inhibits HCoV-229E and SARS-CoV-2 coronavirus replication in vitro. *Viruses*, *13*(2), 354.[CrossRef].

Patel, N., Penkert, R. R., Jones, B. G., Sealy, R. E., Surman, S. L., Sun, Y., Tang, L., DeBeauchamp, J., Webb, A., Heine, R., Dallas, R. H., Ross, A. C., Webby, R., Hurwitz, J. L., & Richardson, J. (2019). Baseline serum vitamin A and D levels determine benefit of oral vitamin A&D supplements to humoral immune responses following pediatric influenza vaccination. *Viruses*, *11*(10), 907.

Pavan, R., Jain, S., Shraddha, & Kumar, A. (2012). Properties and therapeutic application of bromelain: a review. *Biotechnology Research International*, *2012*, 976203.[CrossRef].

Pawar, K. S., Mastud, R. N., Pawar, S. K., Pawar, S. S., Bhoite, R. R., Bhoite, R. R., Kulkarni, M. V., & Deshpande, A. R. (2021). Oral curcumin with piperine as adjuvant therapy for the treatment of COVID-19: A randomized clinical trial. *Frontiers in Pharmacology*, *12*, 1056.

Peng, F., Tu, L., Yang, Y., Hu, P., Wang, R., Hu, Q., Cao, F., Jiang, T., Sun, J., Xu, G., & Chang, C. (2020). Management and treatment of COVID-19:

the Chinese experience. *Canadian Journal of Cardiology*, *36*, 915–930. [CrossRef].

Perrotta, F., Matera, M. G., Cazzola, M., & Bianco, A. (2020). Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter? *Respiratory Medicine*, *168*, 105996.[CrossRef].

Petersen, E., Koopmans, M., Go, U., Hamer, D. H., Petrosillo, N., Castelli, F., Storgaard, M., Al Khalili, S., & Simonsen, L. (2020). Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *The Lancet Infectious Diseases*, *20*(9), E238–E244.

Pincemail, J., Cavalier, E., Charlier, C., Cheramy–Bien, J. -P., Brevers, E., Courtois, A., Fadeur, M., Meziane, S., Goff, C. L., Albert, A., Defraigne, J. -O., Rousseau, A. -F., & Misset, B. (2021). Oxidative stress status in COVID-19 patients hospitalized in intensive care unit for severe pneumonia. A pilot study. *Antioxidents (Basel)*, *10*(2), 257.

Prenesti, E., Toso, S., & Berto, S. J. (2005). Redox chemistry of red wine. Quantification by an oscillating reaction of the overall antioxidant power as a function of the temperature. *Journal of Agricultural and Food Chemistry*, *53*(10), 4220–4227.

Rahman, M. T., & Idid, S. Z. (2021). Can Zn be a critical element in COVID-19 treatment? *Biological Trace Element Research*, *199*, 550–558.[CrossRef].

Rajasekaran, G., Kumar, S. D, Yang, S., & Shin, S. Y. (2019). The design of a cell-selective fowlicidin-1-derived peptide with both antimicrobial and anti-inflammatory activities. *European Journal of Medicinal Chemistry*, *182*, 111623.[CrossRef].

Rattanachaikunsopon, P., & Phumkhachorn, P. (2007). Bacteriostatic effect of flavonoids isolated from leaves of *Psidium guajava* on fish pathogens. *Fitoterapia*, *78*(6), 434–436.[CrossRef].

Ray, P D., Huang, B. -W., & Tsuji, Y. (2012). Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cellular Signalling*, *24*(5), 981–990.[CrossRef].

Reshi, M. L., Su, Y. -C., Hong, & J. -R. (2014). RNA viruses: ROS-mediated cell death. *International Journal of Cell Biology*, *2014*, 1–16. 2014.[CrossRef].

Risky, W., Jihwaprani, M. C., Kindi, A., Ansori, A. N. M., & Mustaq, M. (2020). The pharmacological mechanism of quercetin as adjuvant therapy of COVID-19. *Traditional Medicinal Research*, *22*, 1–9.

Saeedi-Boroujeni, A., & Mahmoudian-Sani, M. -R. (2021). Anti-inflammatory potential of quercetin in COVID-19 treatment. *Journal of Inflammation*, *18*(1), 1–9.[CrossRef].

Sagar, S., Rathinavel, A. K., Lutz, W. E., Struble, L. R., Khurana, S., Schnaubelt, A. T., Mishra, N. K., Guda, C., Broadhurst, M. J., Bayles, K. W., Borgstahl, G. E. O., & Radhakrishnan, P., & Reid, S. P. M. (2020). Bromelain inhibits SARS-CoV-2 infection in VeroE6 cells. BioRxiv. https://doi.org/10.1101/2020.09.16.297366

Sagar, S., Rathinavel, A. K., Lutz, W. E., Struble, L. R., Khurana, S., Schnaubelt, A. T., Mishra, N. K., Guda, C., Palermo, N Y., Broadhurst, M J., Hoffmann, T., Bayles, K W., Reid, St. P M., Borgstahl, G E. O., & Radhakrishnan, P. (2021). Bromelain inhibits SARS-CoV-2 infection via targeting ACE-2, TMPRSS2, and spike protein. *Clinical and Translational Medicine*, *11*(2), e281. [CrossRef].

Salehi, B., Mishra, A., Nigam, M., Sener, B., Kilic, M., Sharifi-Rad, M., Fokou, P., Martins, N., & Sharifi-Rad, J. (2018). Resveratrol: A double-edged sword in health benefits. *Biomedicines*, *6*(3), 91.[CrossRef].

Sansone, C., Brunet, C., Noonan, D. M., & Albini, A. J. A. (2020). Marine algal antioxidants as potential vectors for controlling viral diseases. *9*(5), 392.

Fagron Iberica SAU. (2020). Retrospective study of immunoformulation for COVID-19. https://clinicaltrials.gov/ct2/show/NCT04666753

Schögler, A., Muster, R J., Kieninger, E., Casaulta, C., Tapparel, C., Jung, A., Moeller, A., Geiser, T., Regamey, N., & Alves, M. P. (2016). Vitamin D represses rhinovirus replication in cystic fibrosis cells by inducing LL-37. *European Respiratory Journal*, *47*(2), 520–530.[CrossRef].

Schwarz, K B. (1996). Oxidative stress during viral infection: a review. *Free Radical Biology and Medicine*, *21*(5), 641–649.[CrossRef].

Shakoor, H., Feehan, J., Mikkelsen, K., Al Dhaheri, A S., Ali, H I., Platat, C., Ismail, L. C., Stojanovska, L., & Apostolopoulos, V. (2021). Be well: A potential role for vitamin B in COVID-19. *Maturitas*, *144*, 108–111.[CrossRef].

Shawky, E., Nada, A A., & Ibrahim, R S. (2020). Potential role of medicinal plants and their constituents in the mitigation of SARS-CoV-2: identifying related therapeutic targets using network pharmacology and molecular docking analyses. *RSC Advances*, *10*(47), 27961–27983. [CrossRef].

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique, R. (2020). COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*, *24*, 91–98. [CrossRef].

Siddiqui, M., Manansala, J. S., Abdulrahman, H. A., Nasrallah, G. K., Smatti, M. K., Younes, N., Althani, A. A., & Yassine, H. M. (2020). Immune modulatory effects of vitamin D on viral infections. *Nutrients*, *12*(9), 2879.[CrossRef].

Simes, D. C., Viegas, C. S. B., & Araújo, N., Marreiros, C. (2020). Vitamin K as a diet supplement with impact in human health: current evidence in age-related diseases. *Nutrients*, *12*(1), 138.[CrossRef].

Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*, *76*, 71–76.

Soto, M. E., Guarner-Lans, V., Soria-Castro, E., Manzano Pech, L., & Pérez-Torres, I. (2020). Is antioxidant therapy a useful complementary measure for Covid-19 Treatment? An algorithm for its application. *Medicina*, *56*(8), 386.[CrossRef].

Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*, *18*(4), 844–847. https://doi.org/10.1111/jth.14768[CrossRef]

Tarocco, A., Caroccia, N., Morciano, G., Wieckowski, M. R., Ancora, G., Garani, G., & Pinton, P. (2019). Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care. *Cell Death & Disease*, *10*(4), 1–12.

Te Velthuis, A. J. W., Van Den Worm, S. H. E., Sims, A. C., Baric, R. S., Snijder, E. J., & Van Hemert, M. J. (2010). Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathogens*, *6*(11), e1001176.[CrossRef].

Tedeschi, E., Menegazzi, M., Yao, Y., Suzuki, H., Förstermann, U., & Kleinert, H. (2004). Green tea inhibits human inducible nitric-oxide synthase expression by down-regulating signal transducer and activator of transcription-1α activation. *Molecular Pharmacology*, *65*(1), 111–120.[CrossRef].

Thimmulappa, R. K., Kumar, M. N. K., Shivamallu, C., Subramaniam, K. T., Radhakrishnan, A., Suresh, B., & Kuppusamy, G. (2021). Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19. *Heliyon*, *7*, e06350.

To, E. E., Vlahos, R., Luong, R., Halls, M. L., Reading, P. C., King, P. T., Chan, C., Drummond, G. R., Sobey, C. G., Broughton, B. R. S., Starkey, M. R., Van Der Sluis, R., Lewin, S. R., Bozinovski, S., O'Neill, L. A. J., Quach, T., Porter, C. J. H., Brooks, D. A., O'Leary, J. J., & Selemidis, S. (2017). Endosomal NOX2 oxidase exacerbates virus pathogenicity and is a target for antiviral therapy. *Nature Communications*, *8*(1), 1–17.[CrossRef].

Traber, M. G., & Stevens, J. F. (2011). Vitamins C and E: beneficial effects from a mechanistic perspective. *Free Radical Biology and Medicine*, *51*(5), 1000–1013.[CrossRef].

Tu, Y. -F., Chien, C. -S., Yarmishyn, A A., Lin, Y. -Y., Luo, Y. -H., Lin, Y. -T., Lai, W. -Y., Yang, D. -M., Chou, S. -J., Yang, Y. -P., Wang, M. -L., & Chiou, S. -H. (2020). A review of SARS-CoV-2 and the ongoing clinical trials. *International Journal of Molecular Sciences*, *21*(7), 2657.[CrossRef].

Tuli, H. S., Tuorkey, M. J., Thakral, F., Sak, K., Kumar, M., Sharma, A. K., Sharma, U., Jain, A., Aggarwal, V., & Bishayee, A. (2019). Molecular mechanisms of action of genistein in cancer: Recent advances. *Frontiers in Pharmacology*, *10*, 1336.[CrossRef].

Valentino, S., Ghelfi, M., Zunica, E., Stamper, M., Hickman, S., Hwang, S., Young, E., Atkinson, J., & Manor, D. (2018). Antioxidant independent actions of vitamin E in modulating gene expression. *Free Radical Biology and Medicine*, *128*, S58–S59.[CrossRef].

Vijayakumar, B. G., Ramesh, D., Joji, A., Jayachandra Prakasan, J., & Kannan, T. (2020). In silico pharmacokinetic and molecular docking studies of natural flavonoids and synthetic indole chalcones against essential proteins of SARS-CoV-2. *European Journal of Pharmacology*, *886*, 173448.[CrossRef].

Violi, F., Oliva, A., Cangemi, R., Ceccarelli, G., Pignatelli, P., Carnevale, R., Cammisotto, V., Lichtner, M., Alessandri, F., De Angelis, M., Miele, M. C., D'ettorre, G., Ruberto, F., Venditti, M., Pugliese, F., & Mastroianni, C. M. (2020). Nox2 activation in Covid-19. *Redox Biology*, *36*, 101655.[CrossRef].

World Health Organization. (2021). *Therapeutics and COVID-19: living guideline, 31 March 2021*.

World Health Organization & Tufts University Consultation on Nutritional Guidelines for the Elderly (2002). *Keep fit for life: meeting the nutritional needs of older persons*. World Health Organization. https://apps.who.int/iris/handle/10665/42515

Wang, J. -Z., Zhang, R. -Y., & Bai, J. (2020). An anti-oxidative therapy for ameliorating cardiac injuries of critically ill COVID-19-infected patients. *International Journal of Cardiology*, *312*, 137–138. [CrossRef].

Wang, L., Wang, Y., Ye, D., & Liu, Q.-q. (2020). A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. *International Journal of Antimicrobial Agents*, *55*, 105948.[CrossRef].

Wang, M. M., Lu, M., Zhang, C. L., Wu, X., Chen, J. X., Lv, W. W., Sun, T., Qiu, H., & Huang, S. H. (2018). Oxidative stress modulates the expression of toll-like receptor 3 during respiratory syncytial virus infection in human lung epithelial A549 cells. *Molecular Medicine Reports*, *18*(2), 1867–1877.

Wang, R., DeGruttola, V., Lei, Q., Mayer, K. H., Redline, S., Hazra, A., Mora, S., Willett, W. C., Ganmaa, D., & Manson, J. E. (2021). The vitamin D for COVID-19 (VIVID) trial: A pragmatic cluster-randomized design. *Contemporary Clinical Trials*, *100*, 106176.

Wang, Y. -D., Wang, X., & Wong, Y.-S. (2013). Generation of selenium-enriched rice with enhanced grain yield, selenium content and bioavailability through fertilisation with selenite. *Food Chemistry*, *141*(3), 2385–2393.

Wu, R., Wang, L., Kuo, H.-C. D., Shannar, A., Peter, R., Chou, P. J., Li, S., Hudlikar, R., Liu, X., Poiani, G. J., Amorosa, L., Brunetti, L., Kong, A. -N., & Liu, Z. (2020). An update on current therapeutic drugs treating COVID-19. *Current Pharmacology Reports*, *6*(3), 56–70.

Yamauchi, R. (1997). Vitamin E: mechanism of its antioxidant activity. *Food Science and Technology International, Tokyo*, *3*(4), 301–309.[CrossRef].

Yang, M., Wei, J., Huang, T., Lei, L., Shen, C., Lai, J., Yang, M., Liu, L., Yang, Y., Liu, G., & Liu, G. (2020). Resveratrol inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cultured Vero cells. *Phytotherapy Research*, *35*(3), 1127–1129.

Yarosz, E. L., & Chang, C. -H. (2018). The role of reactive oxygen species in regulating T cell-mediated immunity and disease. *Immune Network*, *18*(1), e14.

Yasmin Adel, A. H. y. (2021). Impact of Vitamin D level and supplement on SLE patients during COVID-19 pandemic. Available from: https://clinicaltrials.gov/ct2/show/NCT04709744

Zabetakis, I., Lordan, R., Norton, C., & Tsoupras, A. (2020). COVID-19: The inflammation link and the role of nutrition in potential mitigation. *Nutrients*, *12*(5), 1466.[CrossRef].

How to cite this article: Shrivastava, A. K., Sahu, P. K., Cecchi, T., Shrestha, L., Shah, S. K., Gupta, A., Palikhey, A., Joshi, B., Gupta, P. P., Upadhyaya, J., Paudel, M., & Koirala, N. (2023). An emerging natural antioxidant therapy for COVID-19 infection patients: Current and future directions. *Food Frontiers*, 1–28. https://doi.org/10.1002/fft2.207