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The role of natural bioactive compounds and functional foods for fighting coronavirus infections in humans with special focus on covid-19: A systematic review

Mona Miran[1]; Mohammad Amin Aliyari[1]; Maryam Salami[1,2]*; Fatemeh Ghamari[3]; Zahra Emam-Djomeh[1,2]; Salwa Karboune[4]; Harpal S Buttar[5]*

[1]Transfer Phenomena Laboratory (TPL), Department of Food Science and Engineering, College of Agriculture and Natural Resources, University of Tehran, Karaj campus, Iran.

[2]Functional Food Research Core, College of Agriculture and Natural Resources, University of Tehran, Karaj, Iran.

[3]Department of Science Payame Noor University, P.O box 19395-4697 Tehran, Iran.

[4]Department of Food Science and Agricultural Chemistry, Macdonald Campus, Mc Gill University 21111 lakeshore, Sainte Anne de Bellevue, Quebec, H9X 3V9, Canada.

[5]Department of Pathology and Laboratory Medicine, University of Ottawa, Faculty of Medicine, Ottawa, Ontario, Canada.

***Corresponding Author:** Maryam Salami
Functional Food Research Core, College of Agriculture and Natural Resources, University of Tehran, Karaj, Iran.
Email: msalami@ut.ac.ir

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Abstract

Coronaviruses are a group of enveloped viruses with the RNA genome. Several strains infectious to humans have been identified in this group. Some of the coronaviruses, like SARS-CoV and MERS-CoV, are highly pathogenic and have caused fatal pneumonia, while some of them have caused mild diseases. Increasingly it seems that the immune system is a suitable approach in fighting against coronavirus infection. Enhancing the quality of nutrition can be considered an effective method in the prevention and treatment of diseases caused by coronaviruses. Bioactive compounds and functional foods that have anti-inflammatory and antioxidant properties can boost the immune system, with some having anti-coronaviruses properties. Of note, the host's hyperactive immune response results in an excessive inflammatory response. COVID-19 as well as MERS-CoV and SARS-CoV can lead to cytokine storm, which is a hyperinflammatory condition due to the overproduction of proinflammatory cytokines by an unregulated immune system. The results of several studies of cytokine profiles of COVID-19 patients showed that cytokine storm is directly related to lung injury and multi-organ failure in severe COVID-19, hence, anti-inflammatory bioactive compounds might be helpful. This article reviews the possible mechanisms of coronaviruses' effects on the body as well as the effects of plant-derived bioactive compounds and functional foods from three perspectives: reducing oxidative stress, decreasing inflammation, and inhibiting viral proteins.

Abbreviations: ABTS: 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); ABTS+: 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radical; ACE2: Angiotensin-converting enzyme two; AhR: Aryl hydrocarbon receptor; ARE: Antioxidant response element; 3CLpro: 3-chymotrypsin-like protease; COX: Cyclooxygenase; DPPH: 2,2′-diphenyl-1-picryl-hydrazyl; FRAP: Ferric reducing antioxidant power; HCoV: Human coronaviruses; iNOS: Inducible nitric oxide synthase; IFN: Interferon; IL: Interleukin; IP-10: IFN-γ inducible protein 10; MAPK: Mitogen-activated protein kinase; MCP: Monocyte chemoattractant protein; MERS: Middle East respiratory syndrome; MIP: Macrophage inflammatory protein; NF-κB: Nuclear factor kappa B; NOS: Nitrogen species; Nrf2: Nuclear factor-erythroid-related factor 2; NRS: Nutritional Risk Screening; ORFs: Open reading frames; PLpro: Papain-like protease; PGE: Prostaglandin E; ROS: Reactive oxygen species; SARS-CoV: Severe Acute Respiratory Syndrome-Corona virus; SCFA: Short chain fatty acid; TAS2Rs: Type 2 taste receptors; TNF-α: Tumor necrosis factor-α.

Introduction

The major viral infections which are responsible for a large percentage of the morbidities and mortalities all around the world are influenza, rhinovirus, adenovirus, and coronavirus [1,2]. Virus entry is the initial step of the viral replication cycle; prevention of viral entry leads to suppression of viral infectivity and is an attractive antiviral strategy. Coronaviruses, a genus of the Coronaviridae family, are enveloped viruses group with a pulse-stranded RNA genome [3,4] named such due to their crown or coronet appearance (Latin corona) [5]. They are surrounded by an external lipid membrane that makes them sensitive to detergents and alcohol [6]. Coronaviruses have been identified in humans and some animals and may cause severe diseases such as neurological, respiratory [5], and cardiovascular disorders. From the mid-1960s to the early 21st century, human coronaviruses (HCoV) have been considered almost harmless (HCoV-229E and HCoV-OC43). However, since the occurrence of SARS-CoV (Severe Acute Respiratory Syndrome-Corona virus) in 2002/2003, this general attitude has been changed. Shortly after the outbreak of SARS-CoV, HCoV-HKU1, and HCoV-NL63 were identified, which caused mild respiratory illnesses compared to SARS [4]. Then MERS (Middle East respiratory syndrome)-CoV was identified in 2012 [7] and together with SARS-CoV, they are highly pathogenic coronaviruses, causing fatal pneumonia [3]. The recent coronavirus, which has spread from Wuhan in China in December 2019 [8], is the seventh known strain of this group of viruses which are infectious to humans [3]. It has a complex genomic organization consisting of single stranded-positive sense RNA, which codes for several structural and non-structural proteins [8]. The epidemic of COVID-19 was declared a pandemic on 12th of March 2020 by the World Health Organization [9].

Reactive oxygen species (ROS) are responsible for the oxidative damage of lipid membranes and mitochondrial respiratory chain. The antiviral innate immunity of human body is considered to be the responsibility of the mitochondria. Mitochondrial antiviral signaling involves the activation of the retinoic acid-inducible gene I-like receptors, which requires oxidative phosphorylation activity. The cells with respiratory defects exhibited strictly impaired virus-induced induction of interferons and pro-inflammatory cytokines. Hence, antiviral drugs with antioxidant potential would protect cells by inhibiting lipid peroxidation and/or preventing the oxidative damage of mitochondrial respiratory chain. The antiviral function of the antioxidant may also involve modulation of multiple signaling pathways/targets beneficial to viral replication [10].

In a few months after the outbreak of COVID-19, various theories were proposed about the pathogenic mechanism of the virus; the most important of which is the binding of the virus to Angiotensin-converting enzyme two (ACE2) receptors [11] in vital organs such as the heart, arteries, kidneys, and most importantly, the respiratory system [12]. The unique spike protein of new coronavirus has a powerful affinity for the human ACE2 receptors. Moreover, coronavirus makes small polypeptide chains by proteolytic enzymes during transcription to form some non-structural proteins that are in charge of viral replication. The main proteolytic enzymes are 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro) [13]. 3CLpro is a proven medicinal target for MERS-CoV and SARS-CoV [14]. Therefore, it seems that the spike protein that complexes with the human ACE2 receptor, and these two main proteases may be the important targets to identify and develop therapeutic agents for COVID-19 [13]. On the other hand, patients who are infected with RNA viruses are suffering from chronic oxidative stress [15]. The oxidative stress which occurs in different viral infections [15], might affect T lymphocytes and exacerbated virus replication and transmission [16]. The complex role of free radicals in various viral diseases should be considered including their influence on the host cells' metabolism, viral replication, viruses inactivation effects, and toxic effects on host tissues. Therefore, antioxidants utilization could be used at many levels in viral disease treatment. Virus control has been shown to reduce ROS [15].

Some researchers have suggested that the virus may also infect some other cells (red blood cells and immune cells like plasma cells [17], as well as lymphocytes, especially T cells). Hence, the important role of lymphocytes should be considered [18] which might be an essential factor in the severity of the disease. Moreover, infection of the red blood cell results in immune hemolysis, thus losing the ability to carry oxygen [17] and the release of heme and free iron weakens the immune system [18]. Coronavirus includes structural proteins (i.e. envelope proteins, spike proteins, nucleocapsid phosphoproteins, and membrane proteins) and some transcribed non-structural proteins. ORF10, ORF3a, and orf1ab as transcribed non-structural proteins of the virus can attack the 1-beta chain of the hemoglobin in a coordinated manner, and release iron ions to form the porphyrin, while ORF8 as a transcribed non-structural protein and surface glycoproteins can interact with porphyrin to form a complex. Therefore, the normal metabolic pathway of heme is inhibited. A faulty cycle causes pneumonia due to the accumulation of carbon dioxide [17].

In Corona Infectious Diseases, lung cell damage occurs via oxidation of vital molecules as a result of the production of superoxide and hydrogen peroxide in addition to the overproduction of cytokines [3,19]. A study of viral families close to Corona has shown that those infected had drastically reduced levels of antioxidants such as vitamin E and glutathione IV [15], and increased levels of enzymes that produce free radicals [16]. In SARS-CoV2 a ground-glass opacity and a decrease in lung volume [2,17] due to the infiltration of inflammatory cells were observed; antioxidants can prevent the permeability of capillaries by free radicals [20].

In terms of Coronaviruses, there is no approved specific antiviral treatment up to now. Some antiviral drugs are used across the world; but their efficiency is yet to be completely determined in human body [21,22]. Generally, anti-coronavirus therapies can be divided into two categories, either destroying the coronavirus itself or acting on the human immune system or human cells [23]. Regarding antiviral activities, anticoronaviral strategies can be categorized as follows:

- Cell entry, which includes inhibition of cell attachment, inhibition of virus-cell fusion, nucleoside analogs, polymerase inhibitors, helicase inhibitors, and coronaviral transcription.

- Agents targeting translation and protein processing strategies. These include main proteinase inhibitors and papain-like proteinase (PLpro) inhibitors.

- Small interfering RNA and antisense phosphorodiamidate morpholino oligomers.

- Antiviral agents with an unexpected mode of action such as several components of herbal origin, interferons, steroids, calpain inhibitors, nitric oxide, and antibiotics [4].

Oxidative stress occurs due to an imbalance of the antioxidant defense system and diet-derived antioxidants can play a significant role in prevention of oxidative stress and human diseases. Antioxidants work in coordination, therefore, deficiency in one might affect the efficiency of others [15]. Allard et al. [24] reported α-tocopherol, β-carotene, vitamin C, and selenium concentrations were remarkably lower in plasma of HIV-positive patients. The reduction in the antioxidant defense systems and the increase in oxidative stress were observed too [24]. In a research by Ko et al [25], the concentration of selenium and zinc in plasma of hepatitis C patients were markedly lower and copper contents were notably higher. The results showed that in chronic hepatitis the blood micronutrient levels and oxidative stress have an important effect on the viral factors [25]. Accordingly, oxidative stress caused by deficiencies of micronutrients is considerable during disease or infection [15]. Functional foods and bioactive components may have a controlling or preventative role in the diseases caused by coronaviruses. Bioactive compounds (for example curcumin, quercetin, compounds from green tea, ginger, etc.) can have a positive effect on boosting the immune system due to the polyphenol compounds they contain which have antioxidant and anti-inflammatory effects. Furthermore, bitter substances in tea, coffee, chocolate, dandelions, and bitter vegetables such as bitter gourds may be effective against COVID-19 since type 2 taste receptors (TAS2Rs) might play an essential role in the host defense mechanisms. Functional foods and bioactive components can have a synergistic effect on enhancing the vaccination or drug responses in affected patients or enhance the immune system to prevent infections [26,29]. While the exact mechanism of the bioactive components against viruses is still not precise, some research has demonstrated the antiviral activities of some functional compounds such as bioactive peptides, lipids, polysaccharides [30,32]. Some polysaccharides and oligosaccharides have immunomodulatory and antiviral activities. Significant antiviral properties of some polysaccharides such as chitosan, carrageenan, and β-glucan have been confirmed. In a review, polyphenols, glucosinolates, carotenoids, bioactive peptides, essential oils, polysaccharides, oligosaccharides, and probiotics were investigated for their potential effectiveness against COVID-19. Strengthening of the immune system as well as the antiviral activity of these bioactive compounds by inhibiting the entry of the coronavirus into the host cell and the replication of the virus in human cells, were reviewed. Generally, these bioactive compounds and their functional foods were declared natural alternatives for enhancing the immune system and potentially fighting coronavirus [21].

Two primary types of the immune system as human defense against infection are as follows:

- Innate immunity (rapid response) which is leading, nonspecific, and first the first line of defense against pathogens including physical barriers (e.g., mucus and skin), chemical substances (e.g., tear), phagocyte cells (macrophages and dendritic cells), granulocytes (neutrophils, eosinophils, and basophils), mast cells, invariant natural killer cells (e.g., NK cell).

- Adaptive immunity (slow response) which plays a role in the inflammation's formation, including lymphoid cell (T-and B-cell) and humeral (antibody and immunoglobulin.)) [33-35] . Figure 1 shows organs of humman immune system.

It is worth mentioning, that functional food definition is "natural or processed foods that contains known or unknown biologically-active compounds; the foods, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease" according to the Functional Food Center (FFC) [132].

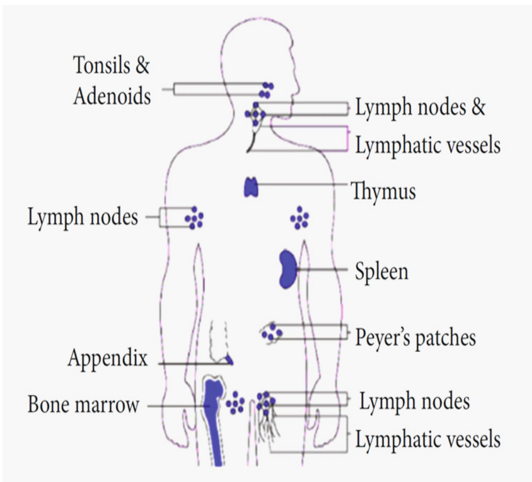


Figure 1: Organs of the human immune system (adapted from reference [33].

Two types of immunity-related disorders can be classified as immunodeficiency disease (primary and secondary (e.g. SARS and COVID-19)) and autoimmunity disease (systemic and organ-specific). Furthermore, immunity-enhancing methods contain eight strategies including immunization, vaccine, immunomodulators, probiotic food, nutrition, regular exercise, good sleep, and hygiene. Compounds that catalyze immune reactions are immunomodulators such as polyphenols, terpenoids, and alkaloids, which are noticeable bioactive molecules in modulation of the immune system. The immunomodulatory medicinal plant and plant-derived molecules affect immunity by inducing cytokines and phagocyte cells and inhibiting the synthesis of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and prostaglandin (PGE). The immunomodulators are classified as follows:

- Immunostimulants: The effectiveness of the immune system can be boosted by these kinds of bioactives via different modes of action, mainly oxidation reactions (e.g Curcumin and Genistein).

- Immunosuppressants: Blocking the immune response, such as quercetin, resveratrol, epigallocatechin-3-gallate, capsaicin, and colchicine.

- Immunoadjuvant: A chemical substance combined with an antigen to enhance the immune response by stabilization of the antigen, which increases the vaccine's effectiveness [33].

Protective factors for COVID-19 infection and disease progression may include a healthy diet and proper nutrition, vaccination, and atopy. On the other hand, some potential risk factors for COVID-19 infection that contribute to increased complications of COVID-19 in adults include older age, male gender, pre-existing comorbidities (such as cardiovascular disease and diabetes), and racial/ethnic inequlities. Generally, infection is less common and severe in children, but younger children and pre-existing comorbidities like obesity may predispose them to critical disease after infection with COVID-19 [36]. A systematic review and meta-analysis resulted (120 studies, involving 125, 446 patients) that the most common comorbidity was hypertension, obesity, diabetes, and cardiovascular disease, respectively, among other COVID-19 patients; however, chronic kidney disease or other renal diseases, cerebrovascular accident, and cardiovascular disease patients had higher severity and mortality rates [37]. It is worth mentioning that enhancing immunity for the prevention of COVID-19 by balanced nutrition seems to be crucial. In a systematic review of the role of nutrition on viral respiratory infections vitamin A, vitamin D, zinc, selenium, several nutraceuticals, and probiotics have shown suitable immune-modulatory effects. Therefore it was concluded that they may also be helpful in COVID-19 prevention and management [38]. Another review showed that foods rich in vitamins A, B (B6 and B9), C, D, and E, which are responsible for immune reactions, as well as zinc and selenium can help reduce the risks of COVID-19, and foods rich in copper can strengthen human immunity [21,39]. Some of the rich sources of these nutrients are including garlic, mushroom, cauliflower, cabbage, friuts, spices, grains, nuts, and herbs. In addition to the vital nutrients, the immune system can be boosted by other factors, such as exercise, sufficient sleep, and low-stress levels [39]. In addition, omega-3 fatty acids can boost the immune system, which are present in seafood, flaxseed, walnuts, etc. that create specialized lipid mediators (resolvins, protectins, and maresins) as potent anti-inflammatory agents [35]. High-vitamin, high protein, and carbohydrate-containing diets are recommended based on the condition of COVID-19 patients. Nutritional recommendations have been provided for hospitalized patients using their NRS-2002 (Nutritional Risk Screening) score. For patients with a score of fewer than 3 points, a diet rich in carbohydrates and proteins such as dairy products, fish, lean meat and eggs, with an energy intake of 25-30 kcal per kg is recommended. In patients with a score of 3 or more points, it is recommended to take oral protein supplements 2-3 times a day or to add protein powder to their diet. For patients with acute respiratory distress syndrome, omega-3 fatty acids and antioxidants supplements are not recommended [2].

Some flavonoids have shown antiviral activity against SARS-CoV due to presumably directly inhibiting 3CLpro [40]. Litchi seed flavonoids, quercetin, epigallocatechin gallate, and gallocatechin gallate inhibited SARS-3CLpro activity [41]. The antiviral activity of epigallocatechin gallate, which is the main polyphenol in green tea, has been determined in some studies. It can inhibit the maturation, replication, infectivity, and activity of coronavirus [42]. Furthermore, quercetin, kaempferol, and naringenin have been determined as remarkable anti-SARS-CoV2 agents by molecular docking study [13,43]. Quercetin 3-β-D-glucoside, herbacetin, helichrysetin, and isobavaschalcone, which are flavonoids inhibited cleavage property of MERS-3CLpro enzyme and therefore blocked the enzymatic activity [41]. Resveratrol was found as an effective anti-MERS agent in vitro. Resveratrol remarkably inhibited MERS-CoV infection, and after virus infection, the cellular survival rate was extended. Moreover, after resveratrol treatment, the expression of nucleocapsid protein (necessary for MERS-CoV replication) was reduced. It also down-regulated the apoptosis induced by MERS-CoV in vitro [7]. Park et al. 2013 [44] isolated Dieckol from the edible brown algae Ecklonia cava displaying SARS-CoV 3CLpro inhibition. In another study phenolic phytochemical from the seeds of Psoralea corylifolia was declared as a SARS-CoV papain-like protease inhibitor [45]. Several bioactive compounds by molecular docking as a potential inhibitor of SARS-CoV2 main protease were studied. Curcumin, demethoxycurcumin, catechin, oleuropein, luteolin-7-glucoside, apigenin-7-glucoside, and epicatechin-gallate have been identified as proper SARS-CoV2 3CLpro inhibitors [43]. Some phytochemicals including flavonoids and non-flavonoids, which have fundamental antiviral activities by a molecular docking study against the two main domains of the SARS-CoV-2 spike protein, were surveyed. C-terminal of S1 domain was intercted by curcumin, kamferol, and pterostilbene, while S2 domain of spike protein was interected by resveratrol, quercetin, apigenin, genistein, fisetin, luteolin, and isorhamnetin. Interstingly, these compounds have higher binding affinity compared to drug hydroxychloroquine [46]. Wu et al 2020 [23], analyzed the SARS-CoV-2 therapeutic targets of natural products by computational methods. They reported that hesperidin and neohesperidin from Citrus aurantium showed potential affinity as ACE2 binding compounds. Hesperidin was targeting the binding between human ACE2 and spike protein receptor-binding domain [23]. Several anti-coronavirus compounds have been identified although the mechanisms of action of some of them have not been determined yet [41] such as Leek, Stinging nettle, Black mulberry tree, Ramsons, Tabacco plant, Tulip, Daffodil, Amaryllis, Iris, Snowdrop, Red spider lily, Cymbidium orchid, Twayblade, Broad-leaved helleborine, Yellowwood, Mistletoe, and Solomon's Seal [47]. Table 1 shows some dietary sources of bioactives with anti-SARS-Cov potency. Figure 2 shows a two-way strategy of using bioactive compounds as inhibitors of viral S protein and hosts ACE2 receptor.

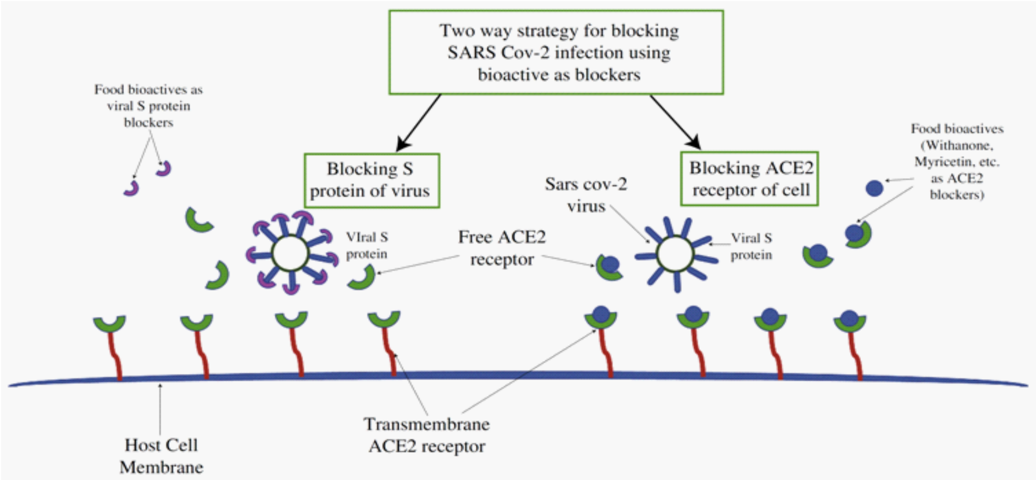


Figure 2: Two-way strategy showing the use of food bioactive compounds as inhibitors of viral S protein and host ACE2 receptor (adapted from reference [51]).

Table 1: Some dietary sources of bioactives with anti-SARS-CoV potency.

Compounds	Chemical family	Sources	Species name	Ref.
Kaempferol	Flavonoid (Flavonol)	Spinach	Spinacia oleracea	[43]
		Cabbage	Brassica oleracea	
		Dill	Anethum graveolens	
Quercetin	Flavonoid (Flavonol)	Dill	Anethum graveolens	[13,43]
		Fennel leaves	Foeniculum vulgare	
		Onion	Allium cepa	
		Oregano	Oregano vulgare	
		Chili pepper	Capsicum annum	
Luteolin-7-glucoside	Flavonoid (Flavone)	Olive	Olea Europaea L	[43]
		Star fruit	Averrhoa belimbi	
		Chili pepper	Capsicum annum	
		Welsh onion / Leek	Allium fistulosum	
Demethoxycurcumine	Phenolic compounds	Turmeric	Curcuma longa	[43]
		Curcuma	Curcuma xanthorriza	
Naringenin	Flavonoid (Flavanone)	Citrus fruit	Citrus sinensis	[43]
Apigenine-7-glucoside (Cynaroside)	Flavonoid (Flavone)	Star fruit	Averrhoa belimbi	[13,43]
		Goji berries	Lycium chinense	
		Celery	Apium graveolens	
		Olive	Olea Europaea L	
Oleuropein	Phenolic compound	Olive	Olea Europaea L	[43]
Catechin	Flavonoid (Flavanol)	Green tea	Camellia sinesis	[43]
Curcumin	Phenolic compound	Turmeric	Curcuma longa	[13,43]
		Curcuma	Curcuma xanthorriza	
Epicatechin gallate	Flavonoid (Flavanol)	Green tea	Camellia sinesis	[42,43]

Black seed or black cumin (Nigella sativa) has therapeutic benefits like immunomodulatory, antiviral, anti-inflammatory, and antioxidant properties. It is rich in some bioactive compounds such as thymoquinone, nigellidine, and α-hederin, hence, it has been suggested as a potential resource for treating COVID-19 [48]. In a study, the effect of Nigella sativa oil treatment was investigated in 173 patients with mild COVID-19 in a randomized clinical trial. The treatment group received 500 mg of the oil twice daily for ten days. The results showed that 36% of the patients in the control group recovered compared to 62% of the oil-treated one. In addition, the recovery duration was also longer in the control group (9.5-15.1 days) compared to the Nigella sativa oil treatment group (7.5 to 13.9 days) [49]. Moreover, pumpkin is rich in minerals, vitamins, polysaccharides, carotenoids, essential oils, phenolic acids, and peptides, which can be considered for boosting immunity and might be able to fight COVID-19 owing to immunomodulatory, antiviral, anti-inflammatory, and antioxidant activities [50].

Human gut bacteria and their metabolites have the ability to regulate the host's immune system [48,52]. Some studies have described that the composition of the gut microbiota is altered in COVID-19 patients compared to normal subjects. This dysbiosis can affect the manifestations, development, and severity of the disease via intestinal barrier dysfunction, changed ACE2 expression, and effects on the gut-lung axis. This dysbiosis can play a role in modulating the entry of SARS-CoV-2 and inflammation's modulation. The gut microbiota may be involved in the body's response to SARS-CoV-2 infections due to immunomodulatory influences and interactions with different organs. Moreover, the gut microbiota may also modulate the immune response to COVID-19 vaccines. Of note, probiotic bacteria and their metabolites, such as short chain fatty acids (SCFAs), are of particular importance in modulating the immune system [53] (Figure 3). Innate and adaptive immunity might be enhanced through elevating the activity of T-cells, immunoglobulin A, Th 1 cytokines, and macrophages as well as modulation of gut-associated lymphoid tissue, and natural killer cells [52,54]. The consumption of probiotic bacteria might remarkably affect respiratory viral diseases to boost immunity due to their anti-inflammatory, antiviral, and anti-allergic activities. Synanthropic bacteria vastly influence mucosal immunity by interacting with cytokines, chemokines, T regulatory lymphocytes, and nuclear factor kappa B (NF-κB) expression. Bacterial metabolites such as SCFA can directly affect epithelial and immune cells by activating NF-κB and tumor necrosis factor-α (TNF-α) and reducing stimulation of pattern recognition receptors. Research has shown that some strains of probiotic bacteria can protect against upper respiratory tract infection, improve mucosal immune system function, reduce respiratory infection during colds and strengthen the immune system, induce antiviral response against respiratory viral infection by increasing lung immune response. Therefore, these species may help to reduce COVID-19 infection due to having one or more properties mentioned above. These probiotic bacteria include Lactobacillus delbrueckii ssp. Bulgaricus, L. lactis, L. casei, L. paracasei, L. rhamnosus, L. plantarum, L. reuteri, Enterococcus faecalis, and Saccharomyces boulardii [51].

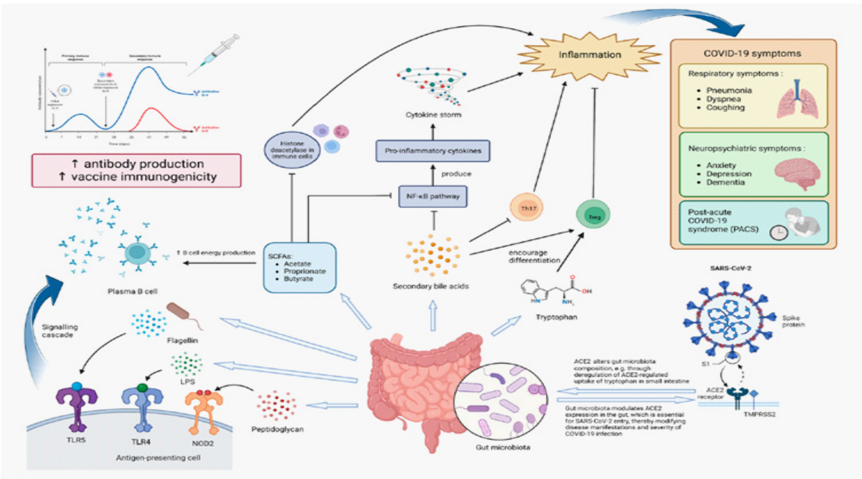


Figure 3: Potential mechanisms underlying the effect of gut microbiota on SARS-CoV-2 infection and vaccine immunogenicity (adapted from reference [53]).

The effects of plant-derived bioactive compounds and functional foods against coronaviruses occurs through two purported mechanisms as follows:

1. By decreasing inflammation and a cytokine storm.

2. By reducing of oxidative stress due to their antioxidant, anti-inflammation and ROS scavenging properties.

Anti-inflammatory effects of natural bioactive compounds and functional foods against cytokine storm and regulation of host's immune response: Inflammation is an essential response of the immune system to chemical, physical, or biological stimuli that acts as a defense mechanism to remove harmful stimuli and lead to the healing process [55]. Pro-inflammatory mediators initiate and maintain inflammation, and their activity is balanced by anti-inflammatory mediators, which are responsible for limiting inflammation after the removal of the triggering factor [56]. Overall, cellular and molecular events and interactions during acute inflammatory responses effectively reduce the risk of infection or injury [55], resulting in restoring tissue homeostasis and resolving acute inflammation [57]. However, uncontrolled acute inflammation can lead to chronic inflammation, which plays a significant role in many chronic inflammatory diseases [58]. Innate immune cells and normal cells release chemicals called cytokines when fighting pathogens. As a result, adaptive immunity is activated, which leads to the production of antibodies [33]. While pro-inflammatory cytokines facilitate inflammation, anti-inflammatory cytokines inhibit it [58]. Therefore, the use of anti-inflammatory natural compounds such as spices, medicinal plants, plant extracts, and their isolated bioactive compounds, can be effective in preventing and treating chronic inflammation due to their anti-inflammatory and antioxidant property, which some have a significant regulatory effect on cellular biomarkers related to inflammation and oxidative stress [59, 60].

The pathophysiology of coronaviruses-induced cytokine storm is complicated and not fully understood as yet. Hyperstimulation of the immune system generally results in a cytokine storm. It was observed that the progression of COVID-19 infection is fast, and the fatality rate is vast as well [19, 61, 63]. The over activation of immune cells play a key role in the inflammatory response and the excessive release of pro-inflammatory cytokines [64]. During the inflammatory response phase, pathogens are first recognized by leucocytes and macrophages, and then eliminated by the action of phagocytic immune cells which ultimately results in tissue repair and restoration of homeostasis. Successful elimination of infections is impossible without inflammation [19]. The host immune system is essential to combat viral infections, but severe immune responses can result in damage [63]. Cytokine storm is recognized as a complication of inflammatory diseases or infectious [61,63]. MERS-CoV and SARS-CoV can lead to fatal pneumonia due to the rapid replication of the virus, extensive infiltration of inflammatory cells, and high pro-inflammatory cytokine/chemokine responses. High levels of pro-inflammatory cytokines (IP-10, IL-1β, IL-6, IL-12, MCP-1, and IFN-γ) have been detected in the serum of these patients [3]. Furthermore, increased levels of some pro-inflammatory cytokines e.g., IL-1β, IL-2, IL-6, IL-10, TNF-α, and IFN-γ were observed in COVID-19 patients associated with the severity of the disease [36,65]. As a result, the cytokine storm has a significant role in fatal pneumonia [3]. Consequently, the function of multiple organs had been disrupted, which caused physiological deterioration and, eventually, death [19]. Moreover, COVID-19 can cause a cytokine storm that develops a rapid inflammatory signaling cascade. It is potentially life-threatening and might lead to rapid deterioration, coagulopathy, multi-organ failure, and death in severe cases [61,63,65]. Therefore, control of the initial stages of cytokine storm via cytokine antagonists, immunomodulators, and decreasing the cell infiltration of lung inflammatory can play a prominent role in the treatment and reduction of mortality in these patients [19].

TNF-α can activate neutrophils, which along with interleukin-1β are involved in inflammatory responses via the activation of the endothelial cells. Interleukin-2 participates in the proliferation and activation of B and T lymphocytes. B-lymphocytes and macrophages can also be activated by Interferon-γ [66]. Therefore, anti-inflammatory agents may be able to decrease the severity and mortality rate of these patients. Previous studies have shown that some phytochemicals might have beneficial effects on the immune system and may be effective in preventing viral infections, such as SARS-CoV. The combination of three effective SARS-CoV-2 inhibitors, including Fructus forsythiae, Lonicerae japonicae Flos, and Scutellariae radix, which have anti-inflammatory and immune-modulating effects [41], markedly inhibited lipopolysaccharide-induced NF-κB activity in THP-1 cells and also staphylococcal toxic shock syndrome toxin1-stimulated production of cytokines (TNF-α, IFN-γ, IL-1β, IL-6,) and chemokines (MCP-1, MIP-1α, and MIP-1β) by peripheral blood mononuclear cell [67]. It also significantly decreased the levels of transcription and translation of inflammatory cytokines, including IL-1β, IL-6, and TNF-α in alveolar macrophages of lipopolysaccharide-stimulated murine [41] Lianhuaqingwen has a potential effect in regulating host immune response. Runfeng et al. (2020) [3] investigated the antiviral and anti-inflammatory activity of Lianhuaqingwen against SARS-CoV-2. Pro-inflammatory cytokines release such as IL-6, TNF-α, CXCL-10/IP-10, and CCL-2/MCP-1 were increased after infection with HCoV-229E and SARS-CoV-2 in host cells. Lianhuaqingwen remarkably inhibited SARS-CoV-2 replication in Vero E6 cells as well as significantly decreased the production of the pro-inflammatory cytokines at the mRNA expression levels in a dose-dependent manner [3].

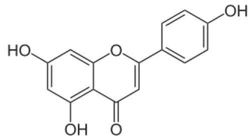
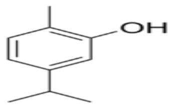
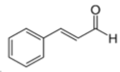
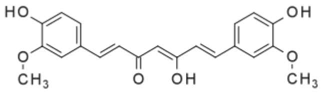
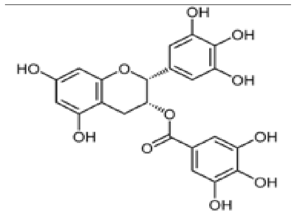
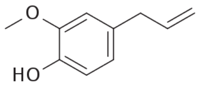
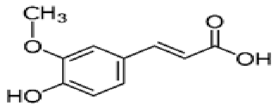
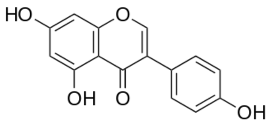
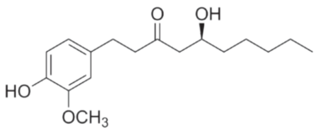
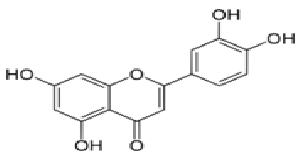
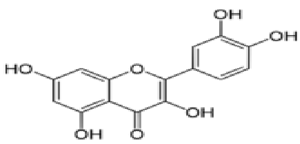
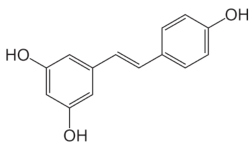
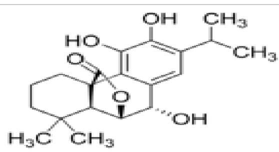
Polyphenolic compounds are able to decrease inflammatory responses through interfering with NF-κB and mitogen-activated protein kinase (MAPK) controlled inflammatory signaling cascades, which consequently lead to suppuration of oxidative stress. These cellular processes activation increases regulatory immune responses. Many polyphenols have exhibited regulatory property on the decreasing of pro-inflammatory biomarkers, including TNF-α, IFN-g, IL-1β, IL-6, and IL-8 [68]. Anti-inflammatory effects of flavonoids are demonstrated in numerous in vitro and animal models studies. They have the potential to inhibit the onset and progression of inflammatory diseases due to the inhibition of regulatory enzymes and transcription factors, which plays an essential role in controlling mediators involved in inflammation. Certain Flavonoids can reduce the release of prostaglandin, histamine and inhibit the production of pro-inflammatory cytokines or chemokines from mast cells, neutrophils, and other immune cells. Moreover, they can bind to cytokine receptors at the site of inflammation and reduce cell signaling [69]. Curcumin alleviates inflammatory responses due to inhibiting the production of NF-κB, lipoxygenase, cyclooxygenase-2, nitrite oxide, and inducible nitric oxide synthase in IFN-γ-, TNF-α- or lipopolysaccharide- activated macrophages and NK cells. It also inhibits the expression of pro-inflammatory cytokines IL-1β, IL-6, IL-12, IFN-γ-, and TNF-α, by phorbol 12-myristate 13-acetate or lipopolysaccharide-stimulated splenic lymphocytes, macrophages, dendritic cells, and monocytes [64]. Immune stimulation property of fungal b-glucans is due to their ability to bind to some membrane receptors on immune cells. Then, multiple signaling pathways are activated, which might involve T cells, B cells, monocyte dendritic cells, macrophages, neutrophils, and natural killer cells. The release of cytokines, such as TNF-α and several ILs, also be stimulated by b-glucans [70] Table 2 indicates some bioactives compounds with anti-inflammatory activity.

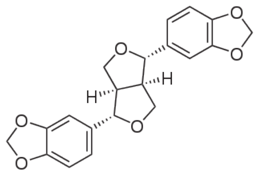
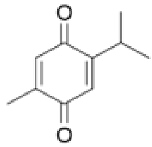
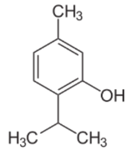
Coronaviruses-induced oxidative stress and vital organ protective effects of functional foods from ROS

Oxidative stress occurs as a result of an imbalance between the biological antioxidant defense mechanisms and production of highly reactive free radicals from the mitochondria leading to the excessive production of ROS and nitrogen species (NOS) [71,72] Due to this unabated imbalance of ROS and NOS, considerable pathological damage can occur to the cell membrane and DNA, different essential biomolecules such as proteins, nucleic acids, carbohydrates, and lipids, as well as enzymes, which can consequently result in cell necrosis and death [71,73,75]. It is now well recognized that oxidative stress plays a significant role in causing various diseases such as diabetes, cancer, rheumatoid arthritis, atherosclerosis, cardiovascular diseases, neurodegenerative disorders, and chronic obstructive pulmonary disease [75,76]. The antioxidant defense systems found in all aerobic organisms include antioxidant enzymes and antioxidant food compounds that remove or repair damaged molecules [74]. Oxidative stress can be reduced through endogenous and exogenous antioxidants by directly scavenging ROS or suppressing NF-κB activated pro-inflammatory signal transduction [68] The NF-κB family, which regulates inflammatory and immune responses, is a group of inducible transcription factors. It also inhibits cells from undergoing apoptosis in response to oxidative stress [77]. The cellular enzymatic defense mechanism that maintains oxidative balance include superoxide dismutase, catalase, peroxiredoxins, glutathione reductase, and glutathione peroxidase, which is deficient during oxidative stress caused by the excessive accumulation of ROS [68] Glutathione behaves as a remarkable antioxidant in the cells of the human body and protects cellular components against damages that are a result of ROS including free radicals such as superoxide anion radicals (O2•−) and hydroxyl radicals (OH•), and non-free radical species such as heavy metals, hydrogen peroxide (H2O2), singlet oxygen (1O2), and peroxides [74,75] .

When SARS-CoV-2 binds to its receptor (i.e., ACE2), it leads to a downregulation in ACE2, which in turn increases the angiotensin II receptor type 1 axis, which is related to oxidative stress. It can result in insulin resistance in addition to lung and endothelial damage, which are two acute consequences of COVID-19 (Figure 4). Cabbage might be useful due to containing precursors of sulforaphane, an organic sulfur isothiocyanate

Table 2: Some bioactive compounds with anti-inflammatory activitiy.

Bioactive Compounds	Class & groups	Sources	Structures	Ref.
Apigenin	Flavonoid: flavone	Lemons, parsley, fruit skins, red pepper		[102,103]
Carvacrol	Monoterpenoid phenol	Thyme (Thymus vulgaris)		[104,105]
Cinnamaldehyde		Cinnamon		[106,107]
Curcumin	Curcuminoid	Turmeric (Curcuma longa)		[108]
Epigallocatechin gallate	Flavonoid (flavanol or flavan-3-ols)	Green tea		[109,110]
Eugenol	Phenylpropanoid	Clove		[106,107]
Ferulic acid	Hydroxycinnamic acid	Tomato, grain		[111–113]
Genistein	Flavonoid (isoflavones)	Soybean		[102,114]
Gingerols	Phenolic components	Ginger (Zingiber officinale)		[115,116]
Luteolin	Flavone			[102]
Quercetin	Flavonoid (Flavonol)	Onion, apple, teas		[117,118]
Resveratrol	Flavonoid	Grapes, peanuts, and berries		[119]
Rosmanol	Polyphenol	Rosemary (Salvia rosmarinus)		[120,121]

Sesamin	Lignan	Sesame (Sesamum indicum L.)		[122,123]
Thymoquinone	1, 4-Benzoquinone (ρ-quinone)	Black seed (Nigella sativa)		[124]
Thymol	Monoterpenoid phenol	Thyme (Thymus vulgaris)		[104,105]

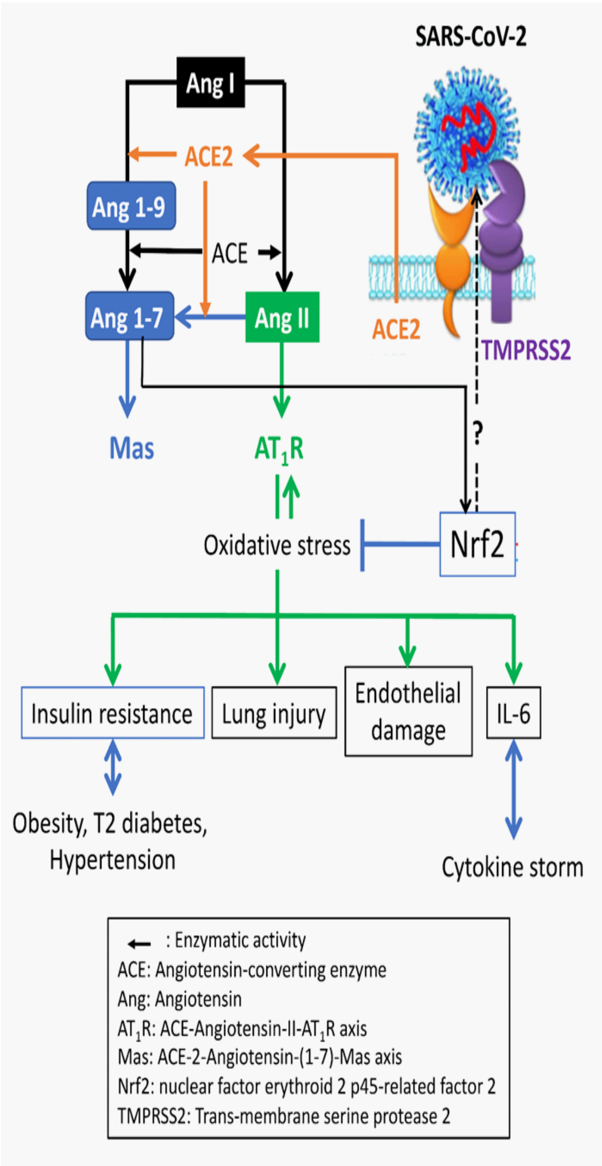


Figure 4: Oxidative stress induced by SARS-CoV-2 after its binding to ACE2 (adapted from reference [78]).

compound, which is the most active natural nuclear factor erythroid-related factor (Nrf2) activator. Moreover, fermented vegetables such as Kimchi have many lactobacilli that are strong Nrf2 activators, also. Hence, fermented cabbage might boost Nrf2-associated antioxidant effects that are beneficial in reducing the severity of COVID-19 [78].

Antioxidants can protect the body against free radicals and reduce the effects of ROS, and they can also postpone lipid peroxidation and the progression of many chronic diseases [74] Antioxidants can act through a variety of mechanisms, such as chelating metals that catalyze free radicals formation and free radicals scavenging. Heavy deposition of iron, which is a metal needed for growth and survival of all mammalian cells, can increase oxidative stress in the liver and lead to further damage, including inflammation, cancer, fibrosis, and, hepatocellular necrosis. Chelation therapy is an effective strategy to remove iron for the treatment of diseases caused by overloaded iron. Therefore, utilizing bioactive or natural raw material that acts as an antioxidant and an iron-chelating agent without side effects is a proper strategy [79].

Phenolic compounds, including flavonoids and phenolic acids, are the biggest group of natural antioxidants of human diets [80]. Effects of the interaction between Aryl hydrocarbon receptor (AhR) and Nrf2 signaling pathways are the important molecular mechanism in the ability of polyphenols to enhance endogenous antioxidant defense system to restore hemostasis of the cellular redox [68,81]. Expression of a series of antioxidant response element (ARE) genes are controlled by Nrf2 for regulating the physiological and pathophysiological effects of oxidative stress [76]. The direct and indirect antioxidant and anti-inflammatory properties of polyphenols have been confirmed, which help to alleviate the oxidative stress at the cellular level. Plant polyphenols' chemical structure make them suitable for scavenging reactive species [73], but such actions might have some disadvantages as phenolic compounds can act as prooxidants at high doses [68]. As a result of some in vitro studies, the efficacy antioxidant property of polyphenols is more than tocopherols and ascorbate [73]. Modulating cellular signaling transductions ability of polyphenols and their metabolites results in vivo anti-inflammatory and antioxidant properties. The modulatory effect of polyphenols on cellular inflammation-related biomarkers and oxidative stress are remarkable. Results of in vitro and in vivo researches have shown that low concentrations of phenolic compounds inhibit pro-inflammatory cytokines, boost antioxidant enzyme properties, and directly alleviate NF-κB or oxidative stress-induced inflammatory signaling pathways [68]. The richest natural sources of dietary polyphenols are spices, herbs, grains, fruits, and vegetables. Phenolic compounds from fruit extracts such as blueberries can inhibit Nf-kB activation [77]. Flavonoids include flavanols, chalcones, flavonols, flavanones, flavones, and isoflavones [82]. The antioxidant properties of flavonoids are due to their inhibitory effects on the production of free radicals and the scavenging activity on the ROS, and other reactive species. The antioxidant properties are a result of the chemical structure of flavonoids and special substitution patterns in their structure as well as acting as hydrogen-donating molecules cause of phenolic hydrogens [69]. Antioxidant activity of hesperidin, naringin, naringenin, rutin, and quercetin are due to their in vitro anti-lipid oxidation, in vivo reduction of peroxide formation, scavenging ROS directly, inhibition of the body's oxidant enzymes and antioxidant enzyme activity improvement [77]. Quercetin is a powerful free radical scavenger that exists at high levels in onions. It has antioxidants, antiviral, and anti-inflammatory activities [83]. It shows an antioxidant response through the activation of Nrf2 [77]. Hence, diet or supplements that are rich in flavonoids are broadly recommended to enhance health situations and prevent chronic diseases. Flavonoids due to metal chelating properties and significant free radical scavenger ability might be useful in metal-overload diseases and all oxidative stress-related diseases and dysfunction [84]. Honey and propolis have bioactive compounds consisting of flavonoids such as naringin, rutin, luteolin, and caffeic acid phenyl ester, hence have antiviral, immune system-modulating, antioxidant, and anti-inflammatory properties [85]. In a study, it has been reported that propolis could inhibit the binding of SARS-CoV-2 to the human host cell receptors. A possible mechanism of tackling COVID-19 is blocking viral-host protein interactions that induce acute inflammation—the key cause of tissue damage and disease fatalities. Additionally, it has been reported that the flavonoids presnt in propolis can significantly interrupt the life cycle of the virus. Those mechanisms have been also evaluated using the supplements rich in major flavonoid groups from honey in patients suffering from mild symptoms of COVID-19. As a result, a 59% reduction in time of the recovey in a group of 313 patients (210 in moderate situation of the disease and 103 in severe situation) was observed. Moreover, the rate of death in people who received the supplement were reduced by 4-folds compared to the control group (who did not receive the supplement [86].

Ferrous ions produce radicals from peroxides tenfold more than ferric ions. Therefore, efficient ferrous ion chelators might be more useful than ferric ion chelators to remove iron and protect the body against oxidative [74]. In a study, the antioxidant properties of some popular water-soluble phenols were investigated by the FRAP (ferric reducing antioxidant power) test and ABTS (2, 2'-azinobis 3-ethylbenzothiazoline-6-sulfonate) radical scavenging capacity assay. The strongest antioxidant activities which have been identified by the FRAP assay belong to 3, 4 dihydroxyphenylacetic acid, pyrogallol, and o-pyrocatechuic acid [87]. In an another study, some plants, such as persimmon and pear, were investigated. The highest iron-chelating activity and the largest amount of phenolic compounds were determined in Yellow Melilot [88]. Phenolic content and antioxidant activity of cereals, legumes, and berries were determined. The result of antioxidant properties measured by FRAP assay is as follows:

Cereals: Buckwheat> Barley> Wheat> Rye; Legumes: Black bean> Lentil> Black soybean> Red kidney> Yellow pea > Green pea > Chickpea; Berries: Blackcurrants > Blueberries > Raspberries > Red currants > Cranberries [89]. Table 3 shows the antioxidant properties of some functional foods and their mechanism of action.

Table 3: Antioxidant properties of some functional foods and their mechanism of action.

Dietary source		***Name of flavonoids***	***Antioxidant activity***		***Ref.***
			in vitro- in vivo assays	**Result**	
Citrus (aurantium, Limon, reticulate, & sinensis)	Fresh juices		DPPH free radical scavenging assay & Ferric reducing assay	Antioxidant property directly correlated with the content of total phenolics & ascorbic acid (except: C. aurantium)	[125]
Grapefruit	Dried & fresh peel	13 flavonoids: Main: naringin & isonaringin	DPPH, FRAP, & ABTS	Values of DPPH, FRAP & ABTS increased in dried grapefruit peels	[126]
Bergamot, Calamondin, Clementine, Kumquat, Lemon, Mandarins, Oranges, Pamplemousses, Satsumah, Tangelos, & Tangor	Flavedo extracts of 21 varieties of Citrus fruits	Poncirin, didymin, diosmin, isorhoifolin & narirutin: present in all extracts Hesperidin: present at the highest concentrations in all extracts (except pamplemousses) Naringin: only in 1 variety.	FRAP	Total phenolics significantly related to FRAP assay Flavedos were able to chelate metal ions Tangor: most effective.	[127]
Bergamot, Orange juices	Citrus flavonoids-rich extracts			As natural iron chelators: -Decreased generation of Ros -Reduced membrane lipid peroxidation -prevented DNA-oxidative damage in iron-exposed cells -Improved mitochondrial functionality	[128]

Citrus fruits	Hesperetin-treated diabetic rats	Hesperetin	-Activity of the antioxidant enzyme -FRAP assay	-Decrease levels of ROS -Increase FRAP -Improved superoxide dismutase, catalase, & glutathione peroxidase -Reduce caspase 3 activity as specific biomarkers of oxidative stress -Increase mitochondrial membrane potential	[129]
Thyme	methanol extracts		DPPH, FRAP, & Trolox equivalent antioxidant capacity	-effective free radical scavenging -strong antioxidant activity in both assays. -Positive relation between the antioxidant activity and total phenolic content	[130]
23 edible flowers			DPPH, FRAP, & ABTS	FRAP value: Lour > Paeonia lactiflora Pall > Rosa rugosa Thunb (purple) > and Perennial chamomile	[131]

Spices including saffron (Crocus sativus L.), turmeric (Curcuma longa), ginger (Zingiber officinale), and cinnamon (Cinnamomum species) have antioxidant and anti-inflammatory properties as well as reducing oxidative stress [90,91]. FRAP is a useful method to measure antioxidant activity in spices. Antioxidant and anti-apoptotic activities of saffron extract, saffron essential oil, safranal, and crocin in endothelial cells are mediated via MAPK signaling [71]. In a study, extracts of saffron stigmas and high-quality by-products (tepals + anthers) were examined. The antioxidant activity through ROS level evaluation and chelating action was obtained. As a result of the in vitro and ex vivo assays, protective effects on inflammation and oxidative stress were observed [92]. The total antioxidant activity of saffron, crocin, and crocetin was determined by FRAP assay [72]. The antioxidant activity of cold-pressed saffron floral by-product extracts by FRAP and DPPH (1, 1-diphenyl-2-picrylhydrazyl) assays were measured. Moreover, as a result, high levels of kaempferol derivatives and anthocyanins were found [93]. Turmeric and curcumin, due to the reduction of oxidative stress, antioxidant and anti-inflammatory activities, have therapeutic applications on oxidative stress-related diseases and chronic inflammation. Enzyme activity assay and FRAP in vitro antioxidant assays of Turmeric were evaluated [94]. Curcumin had an effective activity on chealting ferrous ion (Fe2+), ferric ion (Fe3+) reducing power, ABTS•+ scavenging, and DPPH• scavenging properties [74]. It can protect the human body from ROS and other free radicals that can potentially damage DNA due to its anti-oxidative activities, including radical scavenging, hydrogen peroxide scavenging, and metal chelating [95]. Cinnamaldehyde has been stated to have anti-oxidative stress ability. Furthermore, Nrf2 activators protecting tissues against oxidative stress due to lignan PRO (lignan pinoresinol) and flavonoid MFO (flavonol (-)-(2R, 3R)-5, 7-dimethoxy-3′, 4′-methylenedioxy-flavan-3-ol) as constituents of cinnamon were observed in a study [76]. Effective anti-inflammatory, immunomodulatory and anti-oxidative activities of ginger have been proven in various researches owing to its constituents such as paradols, shogaols, and zingerone [96]. Ginger modulates antioxidant enzymes, including glutathione, as well as protein oxidation, downregulating lipid, and also inhibits genotoxicity in a dose-response manner [97]. Zingerone decreased the levels of the inflammatory markers IL-6, TNF-α, NF-κB, IL-1β, iNOS, and COX-2 in cisplatin-induced damages in ovarian and uterine in another study. It suppressed the age-related inflammation and oxidative stress through the inhibition of the MAPK/NF-κB pathway as well as controlled oxidative stress through boosting the expression of antioxidant [96].

Another major source of unique polyphenolic compounds is olive leaves. It has been reported that a chemical compound named oleuropein, is the most polyphenolic compound of the olive leaf. It has been proved that this compound has several pharmacological and biological effects; such as antiviral, anticancer, antimicrobial, and anti-inflammatory effects. The multiple beneficial impacts of this compound are mostly due to the ability of this compound to scavenge free radicals. Different mechanisms mediate the antioxidant effect of oleuropein, which boosts antioxidant responses. The oleuropein's antioxidant activity is predominately dependent on its capability to improve radical stability through the formation of an intramolecular hydrogen bond between the free hydrogen of the hydroxyl group and its phenoxyl radicals [22,98,100]. For instance, Zhao and coworkers [99] surveyed the effect of oleuropein on hepatitis B virus replication in the HepG2.2.15 cell line in vitro and duck hepatitis B virus replication in ducklings in vivo. Oleuropein remarkably inhibited HBsAg secretion in HepG2.2.15 cells in a dose-dependent manner and decreased viremia in duck hepatitis B virus-infected ducks.

Polysaccharides extracted from some edible mushrooms have remarkable antioxidant activities owing to chelating properties, which could inhibit lipid oxidation. Ganoderma glucans have been demonstrated to act as free radical scavengers in food and inhibit the peroxidation of lipids. The methanolic extracts of Ganoderma tsugae and Ganoderma lucidum glucans and proteoglucans have antioxidant properties as ROS scavenging property. One study reported that glucans from Flammulina velutipes, Auricularia auricula, Lentinus edodes, and Ganoderma lucidum had significant free radical scavenging potential and antioxidant capacity [70].

Various studies have shown the antioxidant activities of milk protein-derived peptides and hydrolysates, which are consist of 5-11 amino acids, including hydrophobic one in the sequence. Different methods are used to evaluate the antioxidant activity of milk protein-derived bioactive peptides. Typical in vitro methods are radical scavenging assays that determine the ability of a potent antioxidant to prevent specific radicals such as ABTS+ and DPPH through the transfer of electrons or hydrogen donation. Although measuring the electron-donating abil¬ity of antioxidants by reducing power assay is considered to be the best method. Different peptide fragments of milk proteins have radical scaveng¬ing activity due to the prevalence of hydrophobic amino acids and aromatic residues in sequences of amino [75]. Piccolomini et al. [101] reported the reduction in the production of intracellular ROS and an increase in ferric reduction, which increased the antioxidant capacity of intestinal epithelial cells treated with whey protein hydrolysate. Furthermore, increasing the activity of antioxidant enzymes by milk hydrolysate, especially cysteine-rich whey protein, was also reported [101].

Conclusion and future directions

Some coronaviruses, including SARS-CoV1 and COVID-19 bind via the spike protein to human ACE2 receptors in vital organs, especially lungs, heart, and kidneys. However, it seems the recent coronavirus which causes COVID-19 does not target only these receptors, and other cells, especially lymphocytes and red blood cells, are also infected. Lymphocytes infection and the destruction of red blood cells and the release of heme and free iron in the form of ferrin and the cycle of oxidative stress in the blood reduces the strength of the immune system. On the other hand, the severe deterioration of some infected people is associated with cytokine storms (excessive and prolonged cytokine/chemokine response) in their bodies. Inflammatory cytokines released from active immune cells play a key role in the inflammatory response. Enhancing the immune system can be an appropriate way against coronaviruses infectious. Bioactive compounds and functional foods, including bioactive peptides and phytochemicals, especially polyphenols, can be useful due to their antioxidant and anti-inflammatory activities. On the other hand, some bioactive components and functional foods have directly antiviral properties against coronaviruses proteins including spike protein complexed with human ACE2 receptor and main proteinase inhibitors. Antioxidant, anti-inflammatory, and antiviral properties of some bioactive components and functional foods such as quercetin, curcumin, rutin, hesperidin, apigenin, luteolin, epigallocatechin gallate, naringenin, etc. have been proven against coronaviruses infection in in vitro testing. However, more research is needed, especially in in vivo testing and clinical trials to prove the use of bioactive compounds and functional foods on different coronaviruses, especially the highly patoghenic ones.

Declarations

Conflicts of interest: Authors declare no conflicts of interest.

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Author contributions: MM and MS conceived the idea and developed the initial manuscript. MM collected the data and wrote the original draft. HSB revised the manuscript and suggested editorial changes. All authors provided scientific advice and critically reviewed and approved the final submission.

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