# Food derived antioxidants and Covid-19

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## 1. Introduction

Coronaviruses (CoVs) are a large family of single-stranded RNA viruses, which can infect animals and humans, causing respiratory, gastrointestinal, hepatic, and neurologic diseases (Wu, Wu, Liu, & Yang, 2020). Nowadays, this pathogen has become the center of global attention, due to the recent spread of a new strain, named SARS-CoV-2 (previously 2019-nCoV), pathogenic agent of COVID-19 disease, which started to expand from Wuhan, China on December 2019 (C. Huang et al., 2020; C. G. Huang, Chu, & Yang, 1991; Zhu et al., 2020). Although different precautionary measures have been taken at national level in the European Union (EU) to limit and to monitor the entrance of potential COVID-19 cases from China, the first symptomatic cases have been reported on February 21$^{st}$ in Lombardy (Italy) and a few days later a number of EU countries including Spain, France, and Germany and lately UK, started to register their own enhancing cases. In this context, Italy was one of the first and hardest hit countries in Europe, with over 333,940 cases and 36,061deaths reported. On March 11$^{th}$ 2020, the WHO announced COVID-19 as a worldwide pandemic, i.e. 2 months after the official disclosure from the Chinese government of the actual cluster epidemics in Whuan. To date (08$^{th}$ October 2020), SARS-CoV-2 has affected to 36,002,827 persons and caused 1,049,810 deaths in the world ("WHO COVID19 Dashboard,"). Compared with the SARS-CoV that caused an outbreak of SARS in 2003, COVID-19 has a stronger transmission capacity by inhalation of infectious aerosols and it has an incubation period equal to 3-14 days (Backer, Klinkenberg, & Wallinga, 2020). After this incubation time, it may be responsible for disease ranging from the asymptomatic to fatal consequences. After infection, people may display symptoms i.e. fever (body temperature up to 39.0 °C), cough, myalgia, dyspnea with or without diarrhea. In addition, in the second week of infection, it progresses to hypoxemia, difficulty in breathing, and acute respiratory distress syndrome (The Lancet Infectious Diseases, 2020). In this stage, some patients require mechanical ventilation in intensive care unit and some of these severe cases show high levels of pro-inflammatory cytokines, including IL-6, IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, suggesting that the “cytokine storm syndrome”, activated by the virus, could be a clinical predictor of fatal outcome in these patients (Soy et al., 2020). Hence many evidences indicate that the immune system is the second system most affected by COVID-19 after the respiratory one. In this context,

IL-6 release plays a key role in a severe progression of COVID-19. In severe forms of COVID-19, it has been proposed that a severe widespread alveolar and interstitial inflammation extends to the pulmonary vasculature. Intra-pulmonary inflammation might negatively modulate a severe local vascular dysfunction including micro-thrombosis and hemorrhage, resulting in pulmonary intravascular coagulopathy (PIC). In addition to the inflammatory process, the mechanisms accounting for clotting and vascular changes may also include oxidative stress. In particular, NOX2-derived ROS are implicated in clotting and platelet activation, promoting thrombin generation and platelet aggregation or impairing artery dilatation and endothelial dysfunction (Guzik et al., 2020).

Therefore, COVID-19 has emerged as a multifaceted, multi-system, multi-organ disorder, which produces its pathogenic effects through a quite ubiquitous target at the level of multiple organs. Notably, all age groups are susceptible to the virus, and elderly patients with comorbidities are more likely to experience a severe illness (Infusino et al., 2020).

Scientific community are pursuing many efforts trying to quickly develop a vaccine, which may counteract the pandemic. However, despite several groups are working on this direction, it is difficult in a short time to succeed in producing and marketing a safe product. Technical time is needed also because it is an unknown virus. In fact, other efforts are actually trying to understand the pathogenesis of COVID-19, which would be extremely useful in order to identify specific and more efficient therapies. Another way to speed the process is to sort out some old drugs capable to work against this new disease threat. This is generally referred to as “drug repurposing”, which doubtless shows some advantage since researchers are not required to repeat the earlier stages of development that simply demonstrate the safety of the drug. In this context, only Remdesivir, which was originally developed for Ebola, has shown to be effective in shortening the time to recovery of hospitalized COVID-19 patients (Beigel et al., 2020). In addition, a short-term use of corticosteroids to inhibit the cytokine cascade and to prevent disease progression toward a severe form could be considered for patients with severe COVID-19 pneumonia (Song, Li, Xie, Hou, & You, 2020).

Besides the development of a pharmacological therapy, in the field of alternative and coadjutant therapeutic, the use of dietary supplements or nutraceuticals for the prevention or treatment of SARS-CoV-2 infection may be a useful strategy. In light with these observations, it is reasonable to consider oxidative stress- and inflammation-induced endothelial dysfunction as a therapeutic target for COVID-19 and many bioactive substances, which are naturally present in foods, have widely displayed potent antioxidant activities. Herein, we specifically comment some literature evidences which link the food-derived antioxidants with treatment and prevention of oxidative stress and inflammation which play a key role in the progression of COVID-19.

## 2. Food Derived Antioxidants and Covid-19

### 2.1 Polyphenols

Polyphenolic compounds found in plants that are responsible for a range of pharmacological properties, including antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral activity. Many of these polyphenolic compounds, including apigenin, luteolin, quercetin, amentoflavone, daidzein, puerarin, epigallocatechin, epigallocatechin gallate, and gallocatechin gallate, presented antiviral activity through inhibition of the proteolytic activity of SARS-CoV 3C-like protease, which is vital to viral replication (Solnier & Fladerer, 2020). Although many flavonoids may activate the transcription factor Nrf2, studies using two flavonoids, in particular, have demonstrated the great potential of these two compounds, not only as Nrf2 inducers but also because of their strong anti-viral activity. They are epigallocatechin-3-gallate (EGCG) and thymoquinone, which are already on the market and sold as dietary supplements (Mendonca & Soliman, 2020).

Among polyphenols, curcumin could be a potential treatment option for patients with Covid-19. Utomo et al. conducted a study using molecular docking with target receptors including SARS-CoV-2 protease, the receptor binding domain (RBD) of spike glycoprotein, and the protease domain (PD) of ACE, which are believed to participate in virus infection (Utomo, Ikawati, & Meiyanto). They demonstrated that curcumin could bind to the target receptors of SARS-CoV-2, supporting the use of this molecule for preventive or prophylaxis treatments of virus infections, including SARS-CoV-2. Moreover, a combination of three (phyto-) nutrients, such as vitamin C, curcumin, and glycyrrhizic acid, promotes interferons production and regulates the inflammatory response, suggesting that the combination of these molecules may be helpful in regulating the immune response to combat SARS-CoV-2 infections (L. Chen et al., 2020).

### 2.2 Carotenoids

Carotenoids, also known as tetraterpenoids, are lipid soluble plant pigments responsible for bright red, yellow, and orange colors in many fruits and vegetables. More than 750 different structures of carotenoids have so far been isolated from natural sources and different carotenoids structures naturally possess different physical, chemical and functional properties (Amengual, 2019). In particular, they are known for their antioxidant properties and quenching of ROS, such as singlet oxygen and lipid peroxides within the lipid bilayer of the cell membrane (Krinsky & Johnson, 2005). Some clear evidences suggest that low levels of α- and β-carotene, lutein/zeaxanthin, as well as total carotenoids are significantly associated with increased levels of oxidative stress and also of inflammation (Walston et al., 2006). For instance, low levels of α- and β-carotene, lutein/zeaxanthin,

and total carotenoids were significantly more likely to be associated with increased IL-6 levels in women (Walston et al., 2006). Carotenoids such as lutein, zeaxanthin, and carotene plasma concentrations have also received attention for their potential antiviral roles (Naithani et al., 2008). A higher risk of mortality has been associated with low concentrations of plasma carotenoids in patients having contracted an HIV infection (Melikian et al., 2001). Finally, some carotenoids serve as precursors for vitamin A and may thereby exert immune-modulating functions attributed directly to vitamin A status.

### 2.3 Supplementation with vitamin C and vitamin D

Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is an essential dietary component. In fact, it is involved in many physiological processes and additionally it is also an important physiological antioxidant (Iddir et al., 2020) and has been shown to regenerate other antioxidants within the body, including alpha-tocopherol (vitamin E) (Traber & Stevens, 2011). The antioxidant activity of vitamin C is accompanied to its tendency to improve the immune function. Vitamin C induce the neutrophils migration to the infection site, stimulating phagocytosis and ROS generation. Furthermore, vitamin C modulates differentiation and maturation of both T-cells and NK (Huijskens et al., 2014; Iddir et al., 2020).

Low vitamin C status has been discussed as an adjuvant measure to aid in individuals with the common cold and also pneumonia and positive effects were found in some intervention trials such as shortening the duration of colds (Hemilä, 2017). Few controlled studies found significant benefits for supplementing vitamin C in subjects with pneumonia. For example, in a double-blinded controlled trial with elderly participants, 200 mg/d of ascorbic acid for 4 weeks improved respiratory condition (Hunt, Chakravorty, Annan, Habibzadeh, & Schorah, 1994).

Among their physiological function, vitamin D, a fat-soluble vitamin, displays anti-inflammatory and immune modulator activities. More in details, vitamin D modulates nuclear factor κB (NF-kB) activity via upregulation of the NF-κB inhibitory protein (IκBα). NF-kB induces the production of many molecules which amplify the inflammatory response (IL-6, IL1-β, TNF-α), stimulate the production, mobilization, and adhesion of inflammatory cells (GM-CSF, IL-4, IL-5, VCAM-1, ICAM-1, E-selectin), and finally modulates the production of enzymes such as iNOS, COX-2, PLA2 and determine the production of free radicals causing tissue damage (Y. Chen et al., 2013). Clear evidences suggest that it is able to stimulate the immune response, reduce the risk of infections, and balance the inflammatory reaction probably in a favorable way for the body. A meta-analysis of data

of 10,933 participants from 25 randomized controlled trials showed that vitamin D administration reduces the risk of acute respiratory tract infections (Martineau et al., 2017). Moreover, evidences suggest that Vitamin D Supplementation may reduce risk of influenza and COVID-19 infections and deaths (Grant, Baggerly, & Lahore, 2020). An Italian study group has proposed a nutritional protocol for patients with COVID-19, which also includes the supplementation of 25-hydroxyvitamin D in the presence of a deficit (Caccialanza et al., 2020).

## 3. Conclusions

During the pandemic, as in all other circumstances, it is reasonable to recommend a proper diet rich in antioxidant nutrients in order to guarantee a good "strengthen of defenses". While diet, nutritional supplements, and similar interventions show great promise for preventing and managing COVID-19, it is also true that strong clinical research data are required to support any such claim.

The hypothesis that vitamin supplementation and nutraceutical consumptions can reduce the risk of COVID-19 incidence or mortality should be investigated through large-scale in randomized trials. Therefore, many efforts should focus in this direction contributing to find useful strategy for halting COVID-19.

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