The Role of Antioxidant to Counteract Oxidative Stress in Covid-19 : A Literature Review

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Abstract

Coronavirus disease 2019 (COVID-19), is an infectious disease with various clinical presentation from asymptomatic to severe pneumonia and death. It is caused by the infection of a virus belongs to the *Coronaviridae* family, which is SARS-CoV-2. One of the important mechanisms that underlies the severe respiratory syndrome of COVID-19 is the oxidant-antioxidant imbalances owing to the inflammatory response and excessive oxidative stress. The antioxidant defense system plays a role in balancing these excessive reactive species. This literature study aims to review several therapeutic approaches particularly antioxidative agents that may be favorable in the treatment of COVID-19.

Keywords : Antioxidant; Covid-19; Vitamin; Infectious Disease

1. Introduction

The Coronavirus disease itself was firstly reported in 2019 as a cluster of cases of viral pneumonia in Wuhan, Hubei Province, People's Republic of China. The disease is caused by an infection of a virus which belongs to the *Coronaviridae* family which is SARS-CoV-2 virus [1]. The virus shares characteristics with the earlier two viruses of the *Coronaviridae* family, SARS-CoV-1 and MERS-CoV. The Coronavirus is a RNA virus with single-stranded positive-sense, with approximately 80% identical genomes at a nucleotide level [2]. The mode of transmission is generally from person to person through exposure of virus-containing respiratory droplets [3]. SARS-CoV-2 primarily have 4 major structural protein-coding genes including spike glycoprotein (S), membrane protein (M),envelope protein (E), and nucleocapsid protein (N) [4]. In Coronavirus, all these proteins are coded by ORF1 [5]. The virus itself enters the host cells via the spike glycoprotein and further binds to ACE2 receptors which are widely expressed on the pulmonary alveolar epithelial cells and enterocytes of the small intestines [6]. Oncethe S glycoprotein of the virus attaches to the host receptor which is ACE2, the virus will enter the cell through endocytosis or membrane fusion. As a consequence, they undergo RNA replication and translation of the structural proteins leading to several inflammatory reactions and activation of oxidative stress [7]. Previous study had reported that the most severe form of the COVID-19 presentation is due to acute injury to the lung that is strongly

associated with overreaction of the immune system. This will lead to impaired gas exchange, hypoxia, and other mechanisms resulting in multiple organ failure and death [8]

2. Oxidative Stress in Covid-19

Reactive species, particularly reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide, and hydroxyl radical were the by-products generated from metabolic reaction of the cells [9]. In healthy individuals, reactive oxygen species (ROS) are produced in low concentration and play several physiological roles including signal transduction. Nevertheless, high concentration of ROS as seen under pathological conditions will cause an imbalance that will further damage the cells and tissues or so-called oxidative stress [10]. It has been reported that the imbalance between oxidant and antioxidant due to excessive oxidative stress and inflammation is one of the important mechanisms underlying COVID-19 derived acute respiratory distress syndrome [11]. Oxidative stress induced by SARS-CoV infection is mediated by various pathways. In COVID-19 disease, the virus provokes the hyper reaction of the immune responses in addition to the presence of inflammation [12]. Thus, it triggers abnormally large productions of reactive oxygen species (ROS) and leads to toxicity hence provoking oxidative stress. Furthermore, systemic cytokine storms exacerbated inflammatory responses and caused severe tissue damage. The increase in oxidative stress level can result in cell damage, organ failure, and ultimately, mortality due to a rapid release of free radicals and cytokines [13].

3. Antioxidant for The Treatment of Covid-19

Antioxidant is a widely used term, however the definition itself is difficult to be determined clearly. Often the term is limited to antioxidant that have activity breaking the chain reaction of inhibiting fat peroxidation, such as vitamin E [14]. Another study proposed a broad definition for an antioxidant, which is any substance presence at low concentrations can prevent or delay oxidation of the substrate compared to oxidizable substances. Or more simply, any substance that delays, prevents, or eliminates excessive oxidative agents which will potentially harming the target molecule [15]. As mentioned earlier, in the presence of COVID-19 disease, there is an abnormal excessive level of oxidative stress attributable to an increase of ROS and/or the antioxidant defenses deficiency [16]. The antioxidant defense system is thought to balance reactive species (RS) production in healthy individuals. However, antioxidant defense must remain balanced while maintaining the level of reactive species in order to function properly [15]. Several therapeutic approaches such as antioxidative agents are preferable and may be beneficial in reducing oxidative stress and preventing severe complications in COVID-19 patients [17].

There are various classifications of antioxidants. The classification of antioxidant based on their activity are divided into two broad categories which includes enzymatic and non-enzymatic antioxidants. The enzymatic-based mechanism plays a role in eradicating free radicals and also lowering oxidative stress level. In particular, antioxidant enzymes work by catalyzing oxidative metabolic products into hydrogen peroxide (H_2O_2) and water. To support the catalysis reaction, these antioxidant enzymes require several cofactors in the process such as copper, zinc, manganese, and iron. Apart from that, the mechanism that underlies the non-enzymatic antioxidants are by intercepting the chain reactions of free radicals. Some examples of these antioxidants are vitamin C, vitamin E, plant polyphenols, carotenoids, and glutathione. Another way to classify antioxidants are based on their size. It is also divided into two categories which are small-molecule and large-molecule antioxidants. Small-molecule antioxidants such as vitamin C, vitamin E, carotenoids, and glutathione acts by detoxifying and transporting reactive oxygen process in a process called radical scavenging. Equally important, large-molecule antioxidants such as SOD, CAT, GSHPx and albumin absorb ROS and prevent them from attacking other essential proteins [18].

3.1. Vitamin C

Vitamins are essential in maintaining the body's natural defenses and fighting against diseases as they carry antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant functions [19]. Vitamin C (ascorbic acid) is a water-soluble cofactor for some enzymes, catecholamine metabolism, and iron (Fe) absorption. Vitamin C is absorbed through the sodium-dependent transporter in the intestine [20]. It has antioxidant, antiviral, immunomodulating, and antithrombotic functions needed to prevent and treat infections. It can be a potent antioxidant and reducing free radicals while also helps to restore other antioxidants such as vitamin E [21].

Previous study reported that vitamin C is beneficial in repairing oxidative damage of bronchial epithelium. Another study also showed in its optimal status, dietary antioxidants such as vitamin C and sulforaphane can prevent acute inflammatory lung damage induced by reactive oxygen species (ROS). An addition of vitamin C to the treatment of COVID-19 has shown to decrease the mortality of the patients in the ICU [19]. Along with the antioxidant properties, an oral intake of high dose vitamin C can play a major role in protecting the host against viral infection in certain circumstances. Thus, vitamin C should be added in the treatment of COVID-19 as it is proven effective in the management of oxidative stress [13]. Following the Recommended Dietary Allowance (RDA), the recommended regimen of vitamin C for adults aged more than 19 years old for male is 90 mg/day and 75 mg/day for females [22].

3.2. Vitamin D

1,25-dihydroxyvitamin D or calcitriol, the active form of vitamin D, is important in maintaining bone health and regulating homeostasis of calcium. The receptors of vitamin D are widely distributed in the human airway epithelium thus protecting the airway against respiratory infections [25]. Moreover, it also functions in regulating the immune system. Oxidative stress is known to contribute in acute respiratory distress syndrome and lung injury. In COVID-19 patients where the oxidative stress is high, vitamin D has shown to increase the expression of several antioxidant genes such as glutathione reductase which will further reduce the amount of ROS due to inflammation [26]. The Recommended Dietary Allowance (RDA) of vitamin D in adults is 15-20 µg/d/day [27].

3.3. Vitamin E

Vitamin E a fat-soluble antioxidant that mainly consists of eight isoforms which includes four tocopherols and four tocotrienols. Among these various isoforms, the most important form to meet the human requirements is α-tocopherol [19]. Several studies reported that vitamin E has been proven to strengthen the immune system of patients with COVID-19. The immunomodulatory functions of vitamin E occur by the inhibition of protein kinaseC (PKC) which will affect the proliferation of macrophages, monocytes, and neutrophils and somehow reducesuperoxide free radical production. In addition, its powerful antioxidant property allows it to neutralize reactive oxygen species (ROS) and free radicals through hydrogen ions donation [23]. A study reported the combinationantioxidant therapy of vitamin E and vitamin C in COVID-19 patients is favorable particularly in reducing therisk of cardiac complications. The Recommended Dietary Allowance (RDA) of α-tocopherol in healthy adultsis 15 mg/day [24].

3.4. Zinc

Zinc (Zn^{2+}) is an essential element in maintaining the immunity of the body and reducing the risk of exposure to infectious disease. It is considered as potential treatment against SARS-CoV-2 infection since it

has an anti-inflammatory and antiviral activity as well as antioxidant functions. A previous study reported that zinc has the ability to modify the viral replication and translation of respiratory viruses. In addition, oral supplementation of zinc has been proven in several studies to reduce the risk of acute respiratory infections by 35% [25]. A deficiency of zinc can possibly cause excessive oxidative stress and increase in pro-inflammatory cytokines which can cause lung tissue injury [28]. The recommended dose of zinc in adults is 11 mg for male and 8 mg for female [29].

3.5. Carotenoid

Carotenoids are chemical compounds produced by plants and marine sources, such as seaweed which contains abundant carotenes such as α-carotene, β-carotene, and lycopene. It is known that carotenoid is useful in enhancing immunity and decreasing the risk of chronic diseases. Carotenoid serves as a powerful antioxidant which can be used to protect the body against harmful excessive oxidative stress [30]. Likewise, in cases of viral infection, carotenoids and its derivatives tend to suppress excessive production of pro-inflammatory cytokine and possibly block the ACE2 receptor. Other studies also reported that it also has an effect on developing immunity and lung function [31].

4. Conclusion

The presence of SARS-CoV-2 infection triggers inflammatory reactions and hyper reaction of immune response, and further increases reactive oxygen species (ROS). An increase in ROS causes excessive oxidative stress and leads to cell and tissue damage which can cause severe complications of COVID-19. Antioxidative agents such as vitamin C, D, E, zinc, and carotenoids can potentially protect against the harmful effects of excessive oxidative stress in COVID-19 patients. They provide immunomodulatory, anti-inflammatory, antiviral, and antioxidant properties and should be advised as an adjunctive therapy in COVID-19 patients.

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