Section A-Research paper

Impact of Antioxidants on the immune system in infectious disease caused by the severe acute respiratory syndrome coronavirus 2

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Abstract

The coronavirus (Covid-19) has infected over 60 million people with over 1.5 million deaths worldwide. Saudi Arabia is one of the infected countries where 357,000 cases were recorded, 347,000 were discharged or cured and 5,907 deaths were reported as per the World Health Organization by the first of December 2020. While discussing the crisis COVID-19 we must mention the immune system and how it is supporting us. The immune system is a complex and sophisticated network of specialized organs, tissues, cells, proteins, and chemicals that have been established to defend the host against several pathogens, including viruses, bacteria, fungi, parasites, and cancer cells. Antioxidants are one of these immune promoters. They're often referred to as free radical removal." To promote a wide range of positive results, nutrition practitioners advise a high intake of antioxidants regularly in the form of food. Vegetables and fruits are considered to be healthy, they are rich sources of antioxidants.

This is a systematic review of clinical and laboratory research assessing the effect of antioxidants in the coronavirus disease crisis of 2019 on the immune system. We used the "Immune system"," COVID-19", "Oxidative stress" and "Antioxidants" keywords and collected the data from PubMed. And Abstracts were initially screened to include only articles that examined the association between Immunity and Antioxidants.

So, as we recognize from the articles, antioxidants may help in preventing this mechanism and lead to reducing the free radicals and enhancing the functioning of immune cells to fight the virus.

Keywords: Immune system, randomized controlled trials, Antioxidants, Oxidative stress, COVID-19, free radicals, and plant resources.

INTRODUCTION

Oxygen is an essential part of life. As cells use oxygen to generate energy, free radicals are produced by mitochondria as a result of ATP (adenosine triphosphate) synthesis. In general, the reactive oxygen species (ROS) and reactive nitrogen species (RNS) are free radicals typically derived from the cellular oxidation and reduction process as both harmful and beneficial compounds, these species play a dual role (Lien et al., 2008). Whether from endogenous metabolic processes or foreign sources, free radicals and other ROS are derived (Hajashemi et al., 2010).

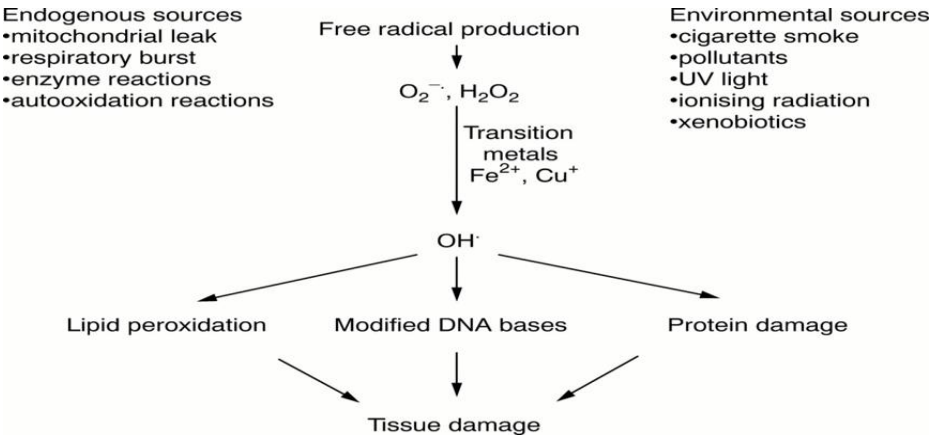


Figure 1. The key sources of free radicals in the body as well as the effects of free radicals

(This picture was adapted from jcp.bmj.com)

For optimal functioning, the immune system is highly dependent on precise cell-cell communication, and any disruption to the signaling systems involved would result in impaired immune responsiveness. The free radicals damage the tissues which results from a threat to the immune system. Since the phagocytic cells produce reactive oxygen species, during defense to the infection. Immune cells use ROS to sustain their functions and thus need sufficient amounts of antioxidant defenses to prevent the harmful effects of extreme ROS output (Hughes, 1999). When we get older or particularly nervous, high levels of ROS increase, promoting oxidative stress and inflammation in the body in this circumstance, natural body functions, especially immune systems, are significantly impaired by excessive oxygen radicals and pro-inflammatory molecules. For this purpose, preventing the side effects of ROS by antioxidants can help us boost the effectiveness of our immune system (Pangrazzi and Luca, 2019). A variety of disorders, including atherosclerosis, Alzheimer's disease, cancer, eye disease, diabetes, rheumatoid arthritis, and motor neuron disease, are associated with oxidative damage and free radicals in humans. The advantage of antioxidants in stopping or halting the progression of these diseases has been seen in several studies (Hajashemi et al., 2010).

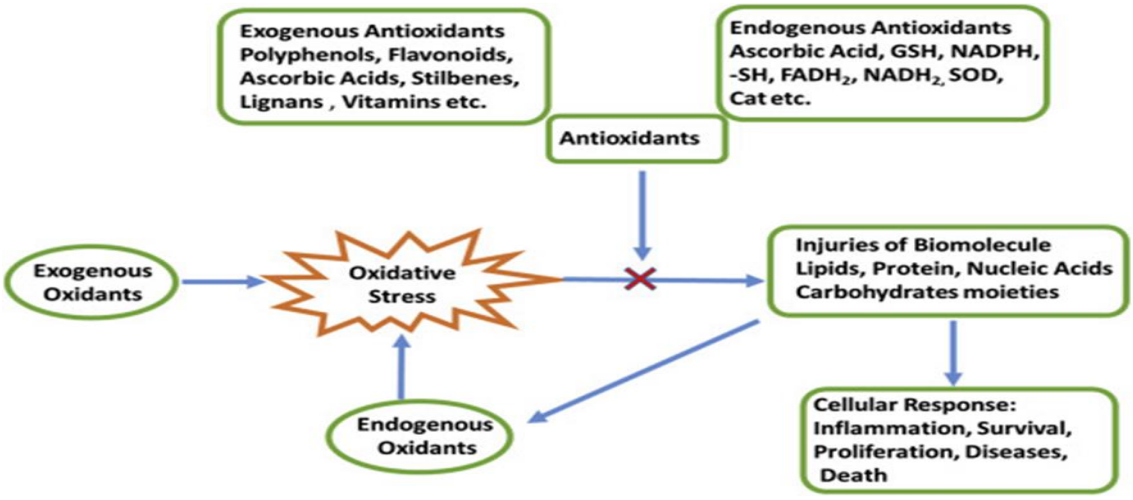


Figure 2. Exogenous and endogenous antioxidants and how antioxidants work

In Wuhan City, China, a cluster of cases of pneumonia caused by a previously identified virus was noted in December 2019 (Weston and Frieman, 2020). This virus is now known as the coronavirus-2 severe acute respiratory syndrome (SARS-CoV-2), contributing to the 2019 coronavirus disease (COVID-19) growth (Lake, 2020). The

coronavirus disease has spread globally and has been recognized by the WHO (Lake, 2020; Rothan and Byrareddy, 2020). The main sign and symptoms of SARS-CoV-2 are coughing, fever, and shortness of breath or without symptoms or mild to severe Rothan and Byrareddy, 2020). In the more serious patients complications can include respiratory failure, acute heart problems, multiple organ dysfunction, septic shock, and even fatal in more critical conditions (Bansal, 2020; Singhal, 2020; Zhou et al., 2020; Kochi et al., 2020). These complications are suspected to be related to the cytokine storm in which viral replication results in the release of cytokines and other immune-based stimuli to be abnormally high, resulting in hyper-inflammation Xie, et al., 2020)

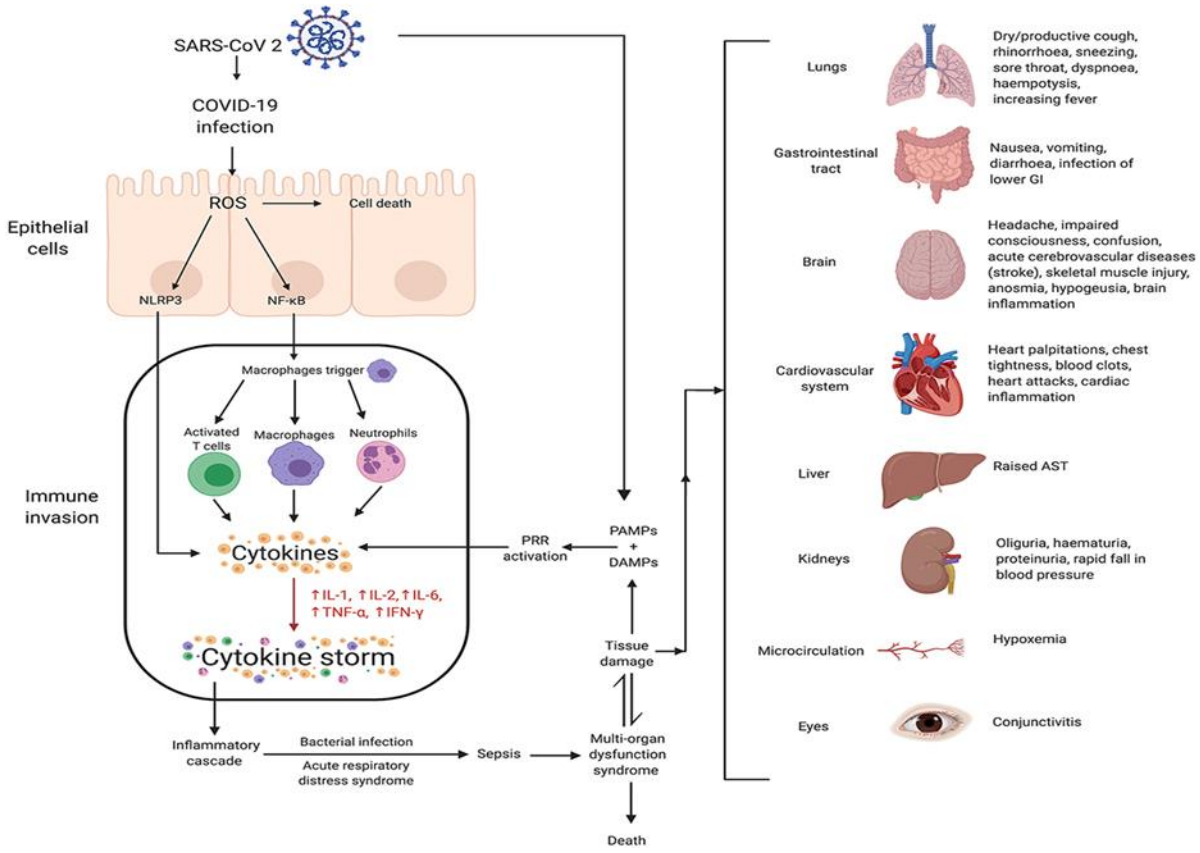


Figure 3. Diagram indicating how COVID-19 can cause cytokine storm.

The spread of this new infectious disease has been rapidly developing. Strict national disease control policies, including policies to practice social distancing and to allow or even compel people to stay at home, have been introduced. To remain healthy, people are often at a loss about appropriate dietary habits and adequate nutrient status, particularly during this self-confinement, frequently viewed as stressful. A stable functioning immune

system is paramount in avoiding infection, and an effective and nutritious diet is a significant basis for an efficient immune response (Chacko et al., 2010; George et al., 2010; Ma et al., 2008; Mozaffarian et al., 2004; North et al., 2009: Jahns et al., 2018). In the development of the anti-inflammatory dietary index, for example, the essential notion of the relationship between dietary elements, metabolism, inflammation, and oxidative stress is well-regarded and emphasized (Shivappa et al., 2014). Omega-3 fatty acids (Calder, 2010), vitamin A (Rubim et al., 2017), and vitamin C (Wannamethee et al., 2006), provide dietary and therapeutic constituents believed to exert anti-inflammatory and antioxidant effects. A broad range of viral infections, including HIV 1, viral hepatitis B, C, and D viruses, herpes viruses, respiratory viruses, and most RNA viruses, are known to cause oxidative stress (Zhang et al., 2019: Ivano et al., 2016). Coronaviruses belonging to this family are also probable. Let us remember that coronaviruses are RNA viruses encapsulated in various types: classic coronaviruses, usually responsible for minor respiratory infections, SARS-CoV and MERS-CoV, which are implicated in more serious respiratory infection epidemics (Jean et al., 2006). Viral infections normally lead to increased production of free radicals and antioxidant degradation (Camini et al., 2016).

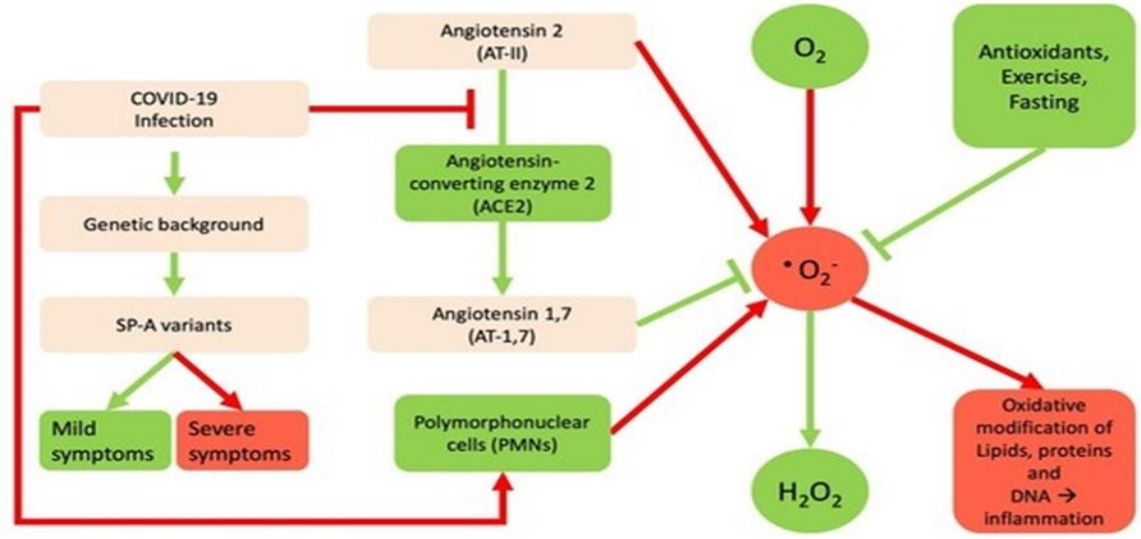


Figure 4. Diagram indicating how COVID-19 may contribute to the generation of free radicals.

Therefore, our research aims to find out the effect of some antioxidants on the immune system and their effect in preventing coronavirus infection by strengthening the immune

system. Thus, the objective of the research is to identify what are antioxidants and their sources, how antioxidants will affect the immune system, what is the relationship of the immune system with coronavirus infection, and how antioxidants preventing coronavirus infection.

MATERIALS AND METHODS

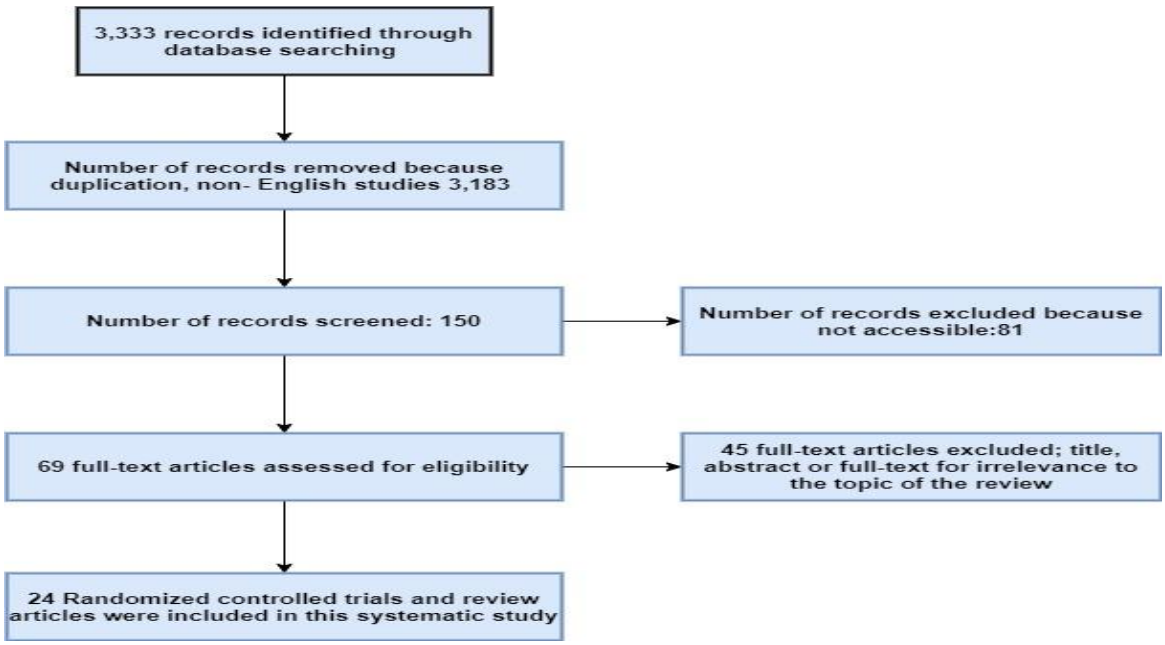
This is a systematic review of clinical and laboratory research assessing the effect of antioxidants in the coronavirus disease crisis of 2019 on the immune system. We used the "Immune system"," COVID-19", "Oxidative stress" and "Antioxidants" keywords and collected the data from PubMed. And Abstracts were initially screened to include only articles that examined the association between Immunity and Antioxidants. Table 1

Table 1. The search terms were entered into the PubMed search engines to identify the studies used in this systematic review.

Number	Search term	strategy	No. of studies
1	Antioxidants	antioxidant s""[All Fields] OR ""antioxidants""[Pharmacological Action] OR ""antioxidants""[MeSH Terms] OR ""antioxidants""[All Fields] OR ""antioxidant""[All Fields] OR ""antioxidating""[All Fields] OR ""antioxidation""[All Fields] OR ""antioxidative""[All Fields] OR ""antioxidative""[All Fields] OR ""antioxidative""[All Fields] OR ""antioxidizing""[All Fields	607,928
2	Oxidative stress	oxidative stress""[MeSH Terms] OR (""oxidative""[All Fields] AND ""stress""[All Fields]) OR ""oxidative stress""[All Fields]	242,588
3	Immune system	immune system""[MeSH Terms] OR (""immune""[All Fields] AND ""system""[All Fields]) OR ""immune system""[All Fields]	1,296,589

4	COVID-19	severe acute respiratory syndrome coronavirus 2""[Supplementary Concept] OR ""severe acute respiratory syndrome coronavirus 2""[All Fields] OR ""scov""[All Fields] OR ""2019 scov""[All Fields] OR ""covid 19""[All Fields] OR ""sarscov 2""[All Fields] OR (((""coronavirus""[All Fields] OR ""cov""[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])	77,287
5	1 AND 3	Antioxidants"[All Fields] AND "Immune system"[All Fields]	3,333
6	1 AND 4	Antioxidants"[All Fields] AND "COVID-19"[All Fields]	218

Methodology Flowchart



1. **Study Selection**

Articles included in the review followed these

Inclusion criteria: 1. English language 2. Explicit reference to the evaluation of the association between Immunity and OS through their effect by antioxidants. Instead, articles were excluded by title, abstract, or full text for irrelevance to the topic of the review. Further

Exclusion criteria are books and lexicomp.

2. **Data Extraction**

We performed the initial search and selected the articles based on the inclusion and exclusion criteria. The data extracted included (I) a study of systematic review articles, randomized controlled trials, and review articles (II) sample size, (III) clinical and biological factors, and (IV) the outcome of interest of the study. The principal outcome of interest included studies about the effect of antioxidants on the immune system during the COVID-19 crisis.

RESULTS AND DISCUSSION

Upon review of the literature, we tabulated the results based on a list of antioxidants.

Vitamin A

For a group of retinoids that is fat-soluble, the common terminology used was Vitamin A which includes retinol, retinal, and retinyl esters (Johnson et.al, 2010; Ross, 2010: Ross, 2006), it has an important role in immune function, reproduction, eyes, and cellular communication (Johnson et.al., 2010; Solomons, 2006: Institute of Medicine (US) panel on micronutrients, 2001). Vitamin A also promotes the development and division of cells and plays a key role in the regular formation and stabilization of the heart, lungs, kidneys, and other organs (Ross, 2010). Mainly there are two types of vitamin A are present in humans nutritional products: vitamin A pre-formed (retinol, retinol ester) and provitamin A carotenoids (Johnson et.al., 2010; Ross, 2010: Ross, 2006; Solomons, 2006: Institute of Medicine (US) panel on micronutrients, 2001). Preformed vitamin A is present in animal foods such as cheese, fish, and beef. (Ross, 2010). Plants are the primary source of dietary provitamin A (Dawson, 2000). Vitamin A has a wide role in immunity, the innate and adaptive affected of lack of vitamin A (Spinas et al., 2015).

Table 2. Impact of Vitamin A on the immune system.

Antioxidants	Type of Study	No. of patients	Duration of study	Result	Ref.
Vitamin A	Review article	NA	NA	Retinoic Acid has previously been shown to facilitate both the development and regulation of	(Kiss et al., 2008)

				thymocyte apoptosis.	
	Randomized controlled trials	94 patients were hospitalized, with a respiratory infection and diarrhea	15 months	Vit. A about innate immune responses show that it is significantly different in both vitamin A-treated groups compared to the control group. And show anti-infective properties.	(35Thurnham et al., 2000)
	Randomized controlled trials	60 patients	42 days	Vit. A supplementation greatly increased the total lymphocyte count in babies from South Africa.	(Coutsoudis et al., 1992)
	Randomized controlled trials	NA	NA	Little evidence of the potential impact of Vit.A. Supplementation on the development or activation of B lymphocytes.	(Decicco et al., 2001)
	Review article	NA	NA	Retinoid acid plays a significant function in the regulation of the innate immune system's cell growth, maturation, and activity.	(Huang et al., 2018)

Glutathione reductase:

Glutathione reductase has a role in maintaining the supply of diminished glutathione. Glutathione is one of the most common substances that decrease thiols in the cells; it plays a crucial role in the cellular control of reactive oxygen species (Couto et al., 2016). GSH removes superoxide and hydroxyl radicals non-enzymatically or acts as an electron donor to many enzymes (Dalmizrak et al., 2019). GSH is created by the body. It consists mostly of three amino acids: glycine, cysteine, and glutamine. glutathione level may become reduced for a lot of reasons like insufficient diet, stress, infections, and chronic disease (Pizzorno, 2014). Sulfur is needed for glutathione synthesis and must consume a sufficient amount from foods rich in sulfur like meat, fish and poultry, allium, and

cruciferous vegetables (Moore et al., 2007; Bogaards et al., 1994; Bahadoran et al., 2011).

Table 3. Impact of Glutathione on the immune system.

Antioxidants	**Type of Study**	**No. of patients**	**Duration of study**	**Result**	**Ref.**
Glutathione reductase	Review article	NA	NA	It plays a critical role in decreasing oxidative stress, trying to maintain redox balance, improving metabolic detoxification, and organizing the immune system.	(Pizzorno, 2014)
	Randomized controlled trial	33	21 days	Glutathione reductase activity was diminished when large levels of oxidative markers were expressed by Neutrophils and lymphocytes.	(Carrera et al., 2014)
	Randomized controlled trial	15	21 days	Glutathione Reductase shows neutrophil increase activity	(Funes et al., 2010)
	Review article	NA	NA	The potential of increased risk of infection when there is a reduction in glutathione level	(Droge and Breitkreutz, 2000)
	Review article	NA	NA	In tissue regeneration, glutathione is used and makes up chemicals and proteins present in the immune system	(Arshad et al., 2020)

Vitamin E:

(Multi-formed fat-soluble vitamin) Four tocopherols and four tocotrienols contain natural vitamin E. The most abundant type in nature is R alpha-tocopherol, and it has the highest biological activity. Although the key lipid-soluble antioxidant in the body is vitamin E, this action cannot be assigned to all its properties. Vitamin E functions as an antioxidant in cell membranes, preventing the proliferation of free radical reactions (Herrera and Barbas, 2001).

Table 4. Impact of Vitamin E on the immune system.

Antioxidants	Type of Study	No. of patients	Duration of study	Result	Ref.
Vitamin E	Review article	NA	NA	The functions of both T and B cells are impaired by vitamin E deficiency and are essential for normal immune cell function. Although immune cells are vitamin E enriched due to higher content of polyunsaturated fatty acids, they are particularly at high risk of oxidative damage at this stage	(Pekmezci, 2011)
	Review article	NA	NA	In mouse models of peritonitis and asthma, Vitamin E effectively inhibits inflammation and bronchial hyper-reactivity by selectively inhibiting the biosynthesis of lipid mediators derived from 5-lipoxygenase in vitro and in vivo.	(Pein et al., 2018)
	Randomized control trial	32 elderly patients	30 days	The research exhibits that vitamin E may increase the immune response when it was used by the Elderly as supplementation.	(Meyadani et al., 1990)
	Randomized control	88	4 months	No adverse effects were observed with vitamin E supplementation in elderly people. This study also revealed that	(Meyadani et al., 1997)

	trial			vitamin E levels higher than currently recommended may improve some of the clinically relevant in vivo T-cell mediated functions indicated in healthy elderly people.	

Selenium:

Selenium, the essential trace mineral, is of vital significance to human health. Selenium has structural and enzymatic functions as a constituent of selenoproteins, becoming best known as an antioxidant and a catalyst for the synthesis of active thyroid hormone in the latter sense. For the proper functioning of the immune system, selenium is required and appears to be a key nutrient in counteracting virulence production and inhibiting the progression of HIV to AIDS (Rayman, 2000).

Table 5. Impact of Selenium on the immune system.

Antioxidants	Type of Study	No. of patients	Duration of study	Result	Ref.
SELENIUM	Systematic Review	NA	NA	Dietary selenium (Se), plays a key role in inflammation and immunity. sufficient levels of Se are important for initiating the immune system, but they are also involved in adjusting the increase in immune responses and chronic inflammation	(Huang et al., 2012)
	Randomized Control trial	Three groups 1st group take (topical corticosteroid) 2nd group take (topical Se) 3rd group take (systemic Se)	6-12 weeks	Oral lichen planus (OLP) is a chronic disease with immune-mediated pathogenesis. Selenium (Se), an antioxidant, plays a vital role in controlling the immunity	(Lassi et al., 2020)

	Meta-analysis	NA	NA	Selenium aids to enhance the immune system and also protects other tissues from impairing and safeguard thyroid functions.	(Avenell et al., 2004)

Zinc:

Zinc is a vital trace element, it manages oxidative stress and supports the immune system by managing inflammatory cytokines (Kiyani et al., 2019). Zinc is extensively used in industry and cosmetic products with favorable investment in medical diagnosis and treatment (Almansour et al., 2017). The body requires zinc for DNA, protein synthesis, and during pregnancy (Maggini et al., 2012).

Table 6. Impact of Zinc on the immune system.

Antioxidants	Type of Study	No. of patients	Duration of study	Result	Ref.
ZINC	Systemic Review	NA	NA	Zinc has a foremost role in immune function. Immune cells are decreased by zinc insufficiency, essential to altered host defense, higher risk of inflammation, and even death	(Maares and Haase, 2016)
	Randomized Control trial	31	3 months	The improvements in the activity of T cells are associated with an increase in the concentration of serum zinc.	(Barnett et al., 2016)
	Meta-analysis	NA	NA	Zinc insufficiency is associated with slower physical, cognitive, and sexual development, causing skin disorders, lowering immunity, growing the incidence of acute	(Lassi et. al., 2020)

				diseases in infants and children, and leading to Stunting for children.	

Vitamin C:

Vitamin C is commonly known as ascorbic acid and it is a water-soluble vitamin. This implies that it dissolves in water and is supplied to the tissues of the body but is not well preserved. It should also be taken regularly with food or supplements. Vitamin C performs an essential part in infection control and wound healing. It has antioxidant properties and can neutralize the immoderate free radicals. Also helps in making several hormones and chemical messengers used in the brain and nerves (Huang et al., 2015).

Table 7. Impact of Vitamin C on the immune system.

Antioxidants	Type of Study	No. of patients	Duration of study	Result	Ref.
Vitamin C	Review article	NA	NA	Increasing the different cellular roles of both the natural and adaptive immune system, helps to immune response.	(Webb and Villamor, 2007)
	Randomized Control Trial	41	18 days	By blockading the activation and aggregation of neutrophils and lowering alveolar epithelial water channel destruction all through COVID-19, vitamin C can assist to dispose of alveolar fluid.	(Liu et al., 2020)
	Randomized control trial	28	72 days	A meta-analysis of both trials suggested that intravenous vitamin C monotherapy may	(Garland et al., 2015)

				reduce mortality	
	Randomized Control Trial	total of 1185 patients	within 24 h	Administration of Vit. C raised the reservoir of antioxidants, decreased reactive oxygen species, and minimized inflammatory markers.	(Khan et al., 2020)

In this systematic review, we collected data from twenty-four articles found to be in our inclusion criteria and we evaluated the relationship between specific antioxidants and the immune system.

Five articles focused on the relationship between Vitamin A and its effect on immunity. And five more articles illustrated the relationship of Glutathione reductase and its influence on the immune system, whereas four studies emphasized Vitamin E's effect on immunity, three studies described the effect of selenium on the immune system and seven studies reported the role of Zinc and Vitamin C on the immune system.

Emerging proof recommends that Antioxidants appear to play a most important function in immune function (Hughes, 1999), and in preventing oxidative stress in the body (Pangrazzi and Luca, 2019). Antioxidants may help in preventing viral infections by decreasing their formation of oxidative stress (Zhang et al., 2019: Ivano et al., 2016). Five studies analyzed the important role of Vitamin A and show that retinoic acid helps in the regulation of thymocyte apoptosis Kiss et al., 2008). Few other studies show that Vitamin A has Anti-infection properties Coutsoudis et al., 1992).

Moreover, two studies conducted as randomized controlled trials exhibit the effect of glutathione reductase on 48 patients, and the results show a decrease in glutathione level when there is an increase in oxidative markers expressed by neutrophils and lymphocytes. One study also showed an increase in the potential of infection when there is a decrease in glutathione Pizzorno, 2014; Carrera et al., 2014; Funes et al., 2010).

About two studies were Vitamin E Randomized Clinical Trials conducted on 120 people, 32 of them (elderly patients) exhibit an enhancement in their immunity response, and 88

of healthy elderly people show that Vitamin E has an important role in vivo indexes of T-cell-mediated function (Pein et al., 2018; Meydani et al., 1990). Three studies were conducted on the effect of selenium and the result of the studies confirm that selenium has a role in initiating and modulating immunity (Lassi et al., 2020).

A systematic review article shows a significant role of Zinc in immunity. When Zinc is decreased in the body will result in altered host defense and make the body more susceptible to inflammations and even death. The rise in serum zinc would enhance the feature of T-cells (Barnett et al., 2016).

Three more randomized controlled trials show that Vitamin C prevents the activation and accumulation of neutrophils in the lung during COVID-19, as monotherapy may reduce mortality and eliminate oxidative stress activity (Khan et al., 2020).

Finally, this systematic review concludes that the effect of oxidative stress on the body may affect immunity along with any epidemic, especially during the covid-19 crisis.

Nevertheless, the evidence obtained in this review highlights Antioxidants seem to play an important role in the immune system and it's related to the COVID-19 crisis.

CONCLUSION

According to all the selected studies, antioxidants plays an important role in the improvement of the immune system by eliminating oxidative stress, which can cause harmful effect on immunity. Coronavirus infections are most probable to happen in people who have a compromised immune system. COVID-19 infection inhibits the conversion of angiotensin 2 (AT-II) to angiotensin 1, 7 by blocking the angiotensin-converting enzyme 2 (ACE2) which results to increase superoxide production (O_2), the superoxide leads to oxidative modification of lipids, protein, and DNA, which leads to inflammation in the lungs. So, as we recognize from the articles, antioxidants may help in preventing this mechanism and lead to reducing the free radicals and enhancing the functioning of immune cells to fight the virus.

LIMITATION

The limitations of this review are we found very few articles about the association between antioxidants, especially selenium and glutathione reductase, and coronavirus infection.

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Ethics declarations

Conflict of interest: The authors declare no conflict of interest

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