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Review

Oxidative Stress and Propagation of COVID-19 Virus Pandemic

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Abstract

It was in China, on December 31, 2019, that the infection with a new Coronavirus appeared, now well-identified: COVID-19. The epidemic is in full swing in China and the number of cases continues to expand across the world causing concern among health specialists and all populations. Oxidative stress is a main issue augmenting the gravity of COVID-19, particularly throughout chronic diseases coupled with the instability of the antioxidant system.

In the present systematic review, a literature search was performed using PubMed and Science Direct databases to search for appropriate keywords such as Covid-19 and oxidative stress, for pertinent publications up to 06.10.2021. Data extraction and quality evaluation of articles were performed by three reviewers. The results of the search are based on the inclusions and exclusions criteria based on the PRISMA protocol. This review focuses on the relationship between oxidative stress and COVID-19 in the final 05 articles were comprised.

The result of this study showed that there is a countless relationship between oxidative stress, the propagation, and gravity of COVID-19 disease.

Keywords:

Covid-19; Oxidative Stress; Antioxidant; Enzymes; Docking.

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1. Introduction

COVID-19, a viral epidemic that broke out in China in 2019, has become a global health crisis. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is to blame for this zoonotic epidemic.

The virus is referred to as SARS-CoV-2, and the associated disease is COVID-19. Coronaviruses are a family of viruses that can cause respiratory or gastrointestinal illnesses. Respiratory illnesses can range from the common cold to more severe illnesses, such as Middle East Respiratory Syndrome (MERS). Coronaviruses are grouped into four Genus: Alphacoronavirus, Beta-coronavirus, which are the only genera that can infect humans, Gamma-coronavirus and Delta-coronavirus, there are 14 main species, but only six are known in humans, four of which are benign; Hcov-229E, Hcov-oc43, Hcov-NL63, Hcov-HKU1 and other pathogens; SARS-Cov, MERS-Cov, and SARS-Cov2 which are part of the genus Beta-coronavirus [1]**.**

SARS-CoV-2 continues to be a major threat to humans. Its viral transmission from human to human happens through direct contact or by contact with expelled small liquid particles through the mouth or nose when an infected person coughs, sneezes, speaks, sings, or breathes deeply [2]**.** Researchers reported the possibility of the incessant comeback of SARS and focused their research on this ongoing pandemic to better understand its involved mechanisms and highlight the achievable therapeutic strategies.

SARS-CoV-2 is an enveloped virus with a positive-stranded RNA genome. The coronaviruses are a large group of several viruses comprising and prearranged four structural proteins: the spike protein, the nucleocapsid protein, the membrane protein, and the envelope protein [3]. A viral envelope union with the cell membrane occurs after the virus binds to the angiotensin-converting enzyme (ACE-2) receptor on the surface of the host cell [4]**.**

Redox status contributes to the stability of proteins and interactions on the cell membrane. Oxidation is part of a redox reaction that transfers electrons from a substance to an oxidizing agent. This reaction can produce radicals that lead to destructive chain reactions. The conformational cell surface change inducts a disequilibrium in the balance of oxidants and antioxidants contributed by the production of reactive oxygen and nitrogen radicals at high levels, which is an important factor in viral entry [5]. A successful viral entry into the host will trigger the native immunity system to identify the external genome and respond through activating macrophages and dendritic cells, which contribute to inflammation and aggravate the host system response in favor of COVID-19 evolution [4]. COVID-19 is reported as a multiorgan disease because of the oxidative stress that causes several cellular and tissular alterations. Complications of severe COVID-19 include acute respiratory distress syndrome (ARDS), septic shock, coagulation dysfunction, metabolic acidosis, cardiac arrhythmia, kidney damage, liver dysfunction, heart failure, or secondary infections [6].

Oxidative stress arises from the imbalance of reactive oxygen (ROS) and nitrogen species (RNS), including singlet oxygen, lipid peroxides, and nitric oxide, counteracted by reduced antioxidant activity or compounds. Endogenous antioxidants like albumin, urea, and reduced glutathione, along with exogenous antioxidants such as vitamin E, vitamin C, polyphenols, carotenoids, and endogenous enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), play a crucial role [7]. Previous investigations have previously discussed the injury caused by oxidative stress in respiratory diseases and the consequences that advance in SARS-CoV-2 infection, showing the importance of this topic with COVID-19, as well as apoptosis and autophagy in the same background [8].

Respiratory viruses cause enzymes like nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidases, Nox) and xanthine oxidase (XO) to make ROS, which throws off the levels of antioxidants. When IV is added to mouse cells grown in a lab, the production of ROS goes down after NOx is blocked [9].

The present systematic review was achieved based on the PRISMA procedure. Three reviewers performed the data concept and quality abstraction of the articles. 26 articles were the results of the search, and based on the inclusions and exclusions criteria, 05 articles were included in this systematic review.

2. Methods

The current systematic review is arranged and stated according to PRISMA and meta-analysis guidelines [10], as represented in Fig. 1.

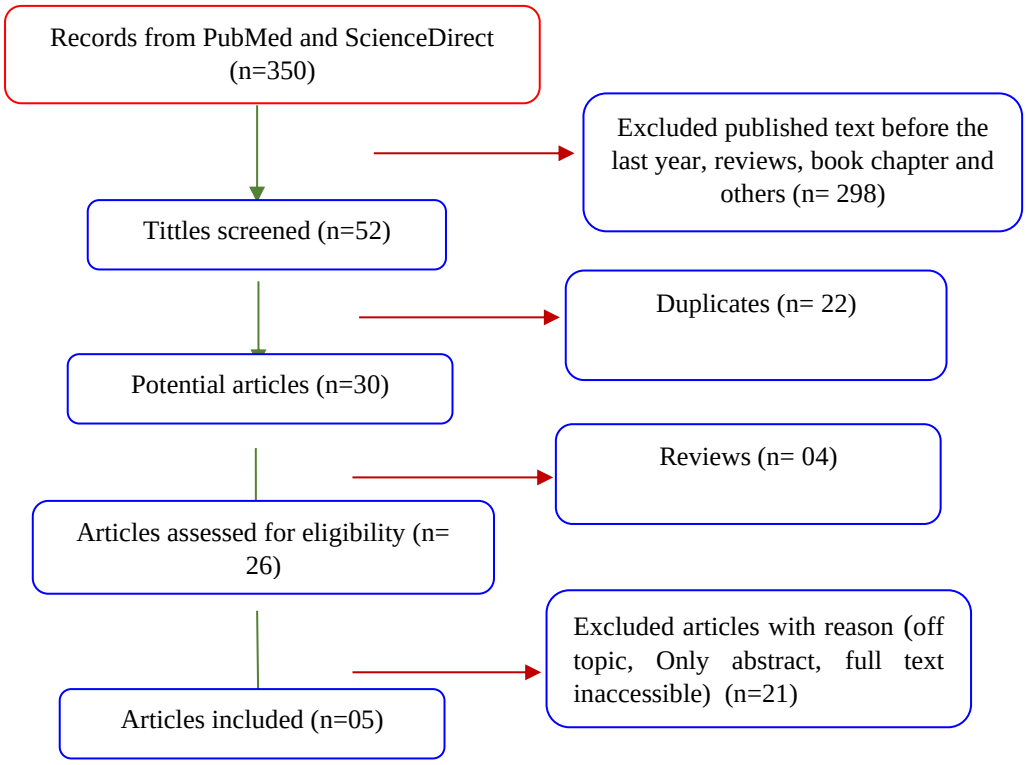

Fig. 1. Flowchart of the studies selection

2.1. Search strategy and selection criteria

A total of 350 records were identified through electronic search using PubMed and Science Direct databases to search for the proper keywords, such as COVID-19 and oxidative stress, for publications published until 06.10.2021. Based on predetermined eligibility criteria, three authors evaluated the titles and abstracts of records from selected investigations.

2.2. Data extraction

Articles data were analyzed autonomously by three assessors.

2.3. Included studies

In this review, we selected only the full research articles published in 2021. Only articles in the English language. The selection was done in particular areas such as pharmacology, toxicology, pharmaceutical science, biochemistry, genetics, molecular biology, and biological sciences.

2.4. Excluded studies

Articles with only abstracts, review articles, book chapters, encyclopedias, conference abstracts, conference info, and editorials were discarded throughout the data assortment. Articles off-topic are also rejected.

2.5. Statistical analysis

There were not enough selected research articles on our topic, so this review could not achieve a meta-analysis study.

3. Results

3.1. Study selection

A total of 350 articles were obtained from initial database searches; 298 articles were excluded (book chapters and others), and 22 articles were excluded because they were duplicates. 21 articles were also excluded because their full text was not accessible or off-topic, and some of them had only abstracts. Therefore, a total of 5 articles were included in the final analysis as mentioned in the flowchart illustrated in Fig. 1.

Table 1. Prooxidative and antioxidative parameters in groups with coronavirus disease

Oxidative stress and antioxidant parameters														
	Pro-oxidant			Lipid peroxidation		Proteins oxidation		Antioxidant enzymes and thiols						**REF**
COV-19	O_2^-	H_2O_2	NO^-	TBAR-S (μmol/ml)	MDA (µmol)	IMA (ABSU)	AOPP µmol/L of chloramine T eq	GSH	NOX4 (µmol/L)	CoQ10 (µmol)	GST	CAT	SOD	
	(nmol/ml)										(U/Hb × 10^3)			
Moderate and Healthy	4.84 ± 3.29	2.18 ± 0.65	3.20 ± 0.68	1.28 ±0.64		ND		96202.84±21664.02 (µmol/l)		ND		0.68±0.36	19.76±9.53	[11]
	ND	2 µmol	ND		0.16 (nmol/ml)	ND		240 µmol	ND		22 (U/L)	ND		[12]
			ND			0.11	80	272			ND			[13]
		ND			4.46 ± 0.81	2.02 ± 0.73		ND	5.71 ± 1.29	2.63 ±0.63		ND		[14]
	ND							+			ND			[15]
Severe	11.30±5.66	2.07±0.44	2.66±0.45	1.20±0.71		ND		95272.71±21315.30		ND		1.15±0.90	22.39±11.19	[11]
	ND	2.4µmol	ND		0.17 (nmol/ml)	ND		200 µmol	ND		21 (U/L)	ND		[12]
			ND			0.21	140	112			ND			[13]
		ND			7.91 ± 1.88	3.79 ± 0.86		ND	16.9 ± 5.54	4.45 ±1.24		ND		[14]
			ND					++			ND			[15]

H_2O_2: Superoxide; **TBAR-S :** thiobarbituric acid reactive substances ; **MDA :** Malondialdehyyde ; **IMA :** Ischemia modified albumin ; **ABSU** : absorbance unit ; **AOPP**: advanced oxidation protein products; **GSH** : gluthatione disulfide ; **NOX4** : nicotinamide adenine dinucleotide phosphate oxidase 4 ; **CoQ10** : Coenzyme Q10 ; **GST** : gluthatione transferase; **CAT** : catalase ; **SOD** : Sulfoxyde dismutase ; **ND** : not determined ; **++:** Increased

Table 2. Different conditions adopted in several studies to explain the relationship between COVID-19 and oxidative stress

	Region	Patients N°	Age	Comorbidities	Period	Symptoms	Specimens/Sample	Diagnosis	References
Patients with COVID-19	Serbia	127	>18	Hypertension	April-August, 2020	Cough, Anosmia, Ageusia	Blood	RT-PCR	[11]
	Brazil	77		Hypertension diabetes mellitus	June-July, 2020	fever, cough, and dyspnea			[12]
	India (Cochin)	160	> 60	Hypertension, diabetes mellitus, Chronic kidney disease	April-May, 2020	Fatigue, Cough, Dyspnea	Plasma		[13]
	Turkey	58	>18	NM	April-November, 2020	NM	Nasal swab and blood		[14]
	Iran	6	45 to 58	Hypertension diabetes mellitus	NM		Lung and testes		[15]

RT-PCR: Real Time-Polymerase Chain Reaction; **NM**: Not Mentioned

4. Discussion

Oxidative stress is defined as an imbalance between the production of reactive oxygen species and the ability of the body to neutralize them [16]. Free radicals play a crucial role in physiological functions in the human body as signaling regulators [17]. However, the presence of these reactive molecules in high amounts causes chronic diseases such as inflammation, cancer, and infections [18]**.** The body's defense mechanism against viruses' invasive actions, which white blood cells have adopted, or electron chain transfer could be to blame for the excessive production of free radicals.

One specific molecule, superoxide (O_2^-), is generated either during incomplete electron transfer or by activating white blood cells to destroy a pathogen during immune defense [19]. Upon production, O_2^- molecules are speedily transformed into hydrogen peroxide (H_2O_2), which further promotes the growth of pathogens. When there are moderate amounts of some other ROS, they activate nuclear factor κB (NF-κB) and activating protein-1 (AP-1), which are transcription factors that boost several antioxidant pathways [20].

There is currently very little information available about the role of oxidative stress in various forms of SARS-CoV-2-caused viral pneumonia. In the present day, there are just a few studies that have evaluated the redox status in COVID-19 patients.

The results in Table 2 disclosed that there was a significant increase in the concentration of O_2^- from 4.84 ± 3.29 nmol/ml in patients with moderate disease to 11.30 ± 5.66 nmol/ml in patients with severe COVID-19 disease. There was a remarkable decrease in NO; however, the data showed a mild decrease in H_2O_2 in patients with severe pathology. On the other hand, for the antioxidant system, there was a significant increase in catalase and SOD in patients with severe COVID-19, while no change was observed in the level of GSH in both patient types [11].

Gadotti et al. reported that there was a significant change in H_2O_2 and GSH concentrations, while no modification occurred in the enzyme GST amounts [12]. Several studies have reported the inverse relationship between H_2O_2 and GSH [20]. Ducastel et al.'s findings also reported that there is a diminution in the GSH amounts in patients with severe COVID-19 [13]. These data are those described by de las Heras and his team [21], who demonstrated that during a respiratory syncytial virus (RSV) infection, there is a decrease in GSH amounts. These results are in line with the report of Butnariu [22]**,** which disclosed that GST are intracellular enzymes, and the radical attack is in extra cells, especially the peroxidation of lipids. The reduction of redox status may occur in the pathophysiological process in COVID-19 patients. Less availability of reduced thiol may play a vital role in the interaction of the SARS-CoV-2 viral spike protein and the functional receptor for the SARS coronaviruses, the angiotensin-converting enzyme 2 (ACE2). Molecular dynamic simulations showed that the binding affinity was significantly impaired when all the disulfide bonds of both ACE2 and viral spike proteins were reduced to thiol groups, which provided a molecular basis for the severity of COVID-19 infection due to oxidative stress [23].

Ducastel et al.'s results revealed that there was an increase in IMA concentration while the amounts of AOPP decreased significantly [13]. Ischemia-modified albumin (IMA) is a form of human serum albumin in which the N-terminal amino acids have been modified by ischemia as the result of hypoxia, acidosis, free-radical injury, and energy-dependent membrane disruption [24]. It is a biomarker that is elevated in different diseases associated with ischemia and oxidative stress, like myocardial infarction and pulmonary embolism [25]. These findings are those reported by [26] Yavuz et al., who disclosed that the concentration of IMA elevated in patients attended Hepatitis B.

Malondialdehyde (MDA) is one of the end products of the peroxidation of unsaturated fatty acids in phospholipids and is responsible for cell membrane damage. The results obtained by Yildiz et al. concluded that there is a noticeable increase in the concentrations of MDA with the severity of the pathology [14]. These data are similar to those reported by Sharma et al. [27], which demonstrated that MDA amounts increased with oxidative stress. While Gadotti and his colleague's results showed no significant modifications [12]**.**

Several studies looked at how the presence of free radicals (ROS) relates to the severity of COVID-19 disease. They found that ROS causes tissue damage, thrombosis, and red blood cell dysfunction, all of which make COVID-19 disease more severe. Likewise, Ntyonga-Pono et al. established that oxidative stress is a strong contributor to COVID-19 infections and their complications [28].

Several parameters of oxidative stress were tested, and from the collected data, we concluded that SARS-CoV2, probably like other RNA viruses, can trigger oxidative stress by disturbing the chief reactive oxygen and nitrogen species, such as superoxide anion radical and nitric oxide.

5. Conclusion

The results showed that there was a strong correlation between oxidative stress, propagation, and the severity of COVID-19 disease. The latest data about the role of oxidative stress in COVID-19 infection support the recommendation of antioxidant supplementation as a valuable strategy against COVID-19. Numerous bioactive molecules have a confirmed aptitude for immune-boosting, antiviral, antioxidant, and anti-inflammatory effects. These comprise Zn, vitamins (D, and C), curcumin, selenium, lactoferrin, and quercetin.

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