The role of COVID-19 induced oxidative stress and inflammation on multiple organ system damage

By

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A thesis submitted to the Department of Mathematics and Natural Sciences (MNS) in partial fulfillment of the requirements for the degree of
BSc. In Biotechnology

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Abstract

Numerous attempts are being taken globally to comprehend the molecular mechanisms underlying the coronavirus disease 2019 or COVID-19. The majority of deaths among patients might be a direct result of SARS-CoV-2 infection, as many studies suggest a connection between COVID-19-induced oxidative stress and inflammation with multiple organ system damages. To develop treatments for SARS-CoV-2 infected patients, it is currently clinically critical to infer how oxidative stress and molecular inflammatory pathways drive COVID-19 propagation to extreme phenotypes including neurological disorders, cardiac damage, pulmonary dysfunction, etc. This research reviews the molecular pathophysiology of SARS-CoV-2 and how it relates to oxidative stress and inflammation-induced organ damage to the heart, liver, kidney, brain, lungs, and other major organs, as well as the development of cancer. A summary of potential antioxidant treatments that might prevent or minimize the severity of the disease is also discussed.

Keywords: SARS-CoV-2; Oxidative stress; inflammation; multiple organ damage; cancer development; antioxidant therapy.

Dedicated to

My mother and Nasiha Jahan Muna

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List of Acronyms:

Abbreviation	Description
ACE2	Angiotensin-Converting Enzyme 2
AKI	Acute kidney injury
ALT	Alanine transaminase
Ang 2	Angiopoietin-2
ARDS	Acute respiratory distress syndrome
AST	Aspartate transaminase
AT1R	Angiotensin II type I receptor
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular diseases
DAMPs	Damage-associated molecular patterns
DIC	Disseminated intravascular coagulation
HF	Heart Failure
MI	Myocardial infarction
NOX2	NADPH oxidase 2
Nrf2	he nuclear factor erythroid 2–related factor 2
OS	Oxidative stress
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TFN	Tumor necrosis factor
TRPA1	Transient receptor potential ankyrin 1

1.0 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a virus that causes acute respiratory disease-2019 or COVID-19. According to the weekly epidemiological update on COVID-19 by World Health Organization, since, December 12, 2021, the Coronavirus Disease 2019 continues to pose a severe threat to global healthcare systems, with about 269 million patients diagnosed and 5.3 million deaths globally (*Weekly epidemiological update on COVID-19 - 14 December 2021*). Fever, headache, cough, sore throat, shortness of breath, and temporary loss of smell are some of the most typical symptoms (Khamis et al., 2020). Considering the fact that most cases of the disease result in moderate symptoms, few cases develop into pneumonia or even potential organ failure (Lippi et al., 2020). Depending on the age and various health conditions, mortality rates are predicted to be somewhere around 5% and 15% (Amini et al., 2022). When individuals infected with COVID-19 cough and sneeze, tiny respiratory droplets get spread all around and this causes the spread of the disease to other individuals (Lippi et al., 2020). The timeframe of being exposed to the disease and experiencing symptoms ranges from about 2 to 14 days (Amini et al., 2022).

COVID-19 triggers excessive inflammatory reactions as well as the putative direct effects of oxidative stress on body-wide target organs, resulting in disease severity. (Zaim et al., 2020). To illustrate, oxidative stress occurs during COVID-19 infection as a result of excessive ROS generation, which disrupts redox signaling, therefore resulting in molecular damage (Sies et al., 2017 & Baqi et al., 2020). In target organs such as the brain, lung, heart, kidney, and others, oxidative stress causes protein oxidation along with deregulated cell signaling (Baqi et al., 2020). It also impairs several critical processes in such organs, such as vascular function, immune cell activation, and cardiovascular remodeling, etc. thus causing inflammation, apoptosis, proliferation, migration, and fibrosis in those organs (Stanley et al., 2019).

Several studies have suggested that stressors associated with COVID-19 exacerbate the viral disease's consequences by causing oxidative stress (Bakadia et al., 2021; Zaim et al., 2020 & Laforge et al., 2020). Oxidative stress is a situation that occurs when oxidants and antioxidants are out of equilibrium. Extracellular matrix modification, mitochondrial respiration, cell proliferation, and lung defense mechanisms may all be affected by oxidative stress (Pizzino et al., 2017). In addition, oxidative stress causes nucleic acid damage and viral alterations, which could limit the

efficiency of vaccines intended to treat COVID-19 (Bakadia et al., 2021). The repair mechanism and immune control system of the body is one of the major events of the inflammatory response, which is greatly affected by oxidative stress, leading us to believe that oxidative stress is a significant factor in increasing the severity of COVID-19, particularly in chronic diseases involved with the antioxidant system's fragility (Samir, 2020).

The infection of SARS-CoV-2 leads to the death of cells and tissues in target organs which induces a local immunological response, involving the recruitment of macrophages and monocytes, which respond to the infection, produce cytokines, and stimulate adaptive immune responses (Tay et al., 2020). In the vast majority of cases, this procedure is sufficient for eradicating the disease however, sometimes it causes a fatal condition named cytokine storm, which is the increased production of proinflammatory cytokines. COVID-19-induced oxidative stress affects cell signaling proteins as well (Meftahi et al., 2021). Alteration in cell signaling proteins has been associated with cytokine storm (Kellner et al., 2017). Altogether oxidative stress and inflammation in COVID-19 patients cause serious organ damage contributing to disease severity (Tay et al., 2020).

As the structure of COVID-19 has been identified, the researchers are able to learn more about the mechanism of the interacting proteins in comparison to the structure of the severe acute respiratory syndrome or SARS virus 2003, which has 91 percent identity in the domain S2 area but lacks homology in three other locations (Xu et al., 2020). The S1 domain, which is characterized by its target host cell contact enabling cell adhesion and pathogenicity (Zhong et al., 2018), had a significant sequence similarity (55 percent identity). This demonstrates that COVID-19 interacts with several of the previously identified host targets including angiotensin-converting enzyme 2 (ACE2), and cyclophilins, but through slightly different chemical interactions (Vankadari & Wilce, 2020). ACE2 plays a critical role in the pathogenesis of SARS-Cov-2 (Gan et al., 2020). SARS-CoV-2 binds to ACE2 receptors, allowing the virus to gain entry into cells, thus decreasing ACE2 bioavailability. Decreased levels of ACE2 are linked to negative clinical manifestations because of its protective function. Reduced ACE2 bioavailability causes angiotensin II (Ang II) to interact with angiotensin 1 receptor (AT1R). Ang II activates oxidase enzymes (e.g.: NADPH oxidase or NOX) when it interacts with the AT1R (Gan et al., 2020). The generation of reactive oxygen species, including superoxide radical anion and hydrogen peroxide (H_2O_2), is promoted by different oxidase enzyme's activation (Sawalha et al., 2020),

later contributing to the severity of COVID-19 (OUDIT et al., 2007 & Sawalha et al., 2020) (Figures 1 and 2)

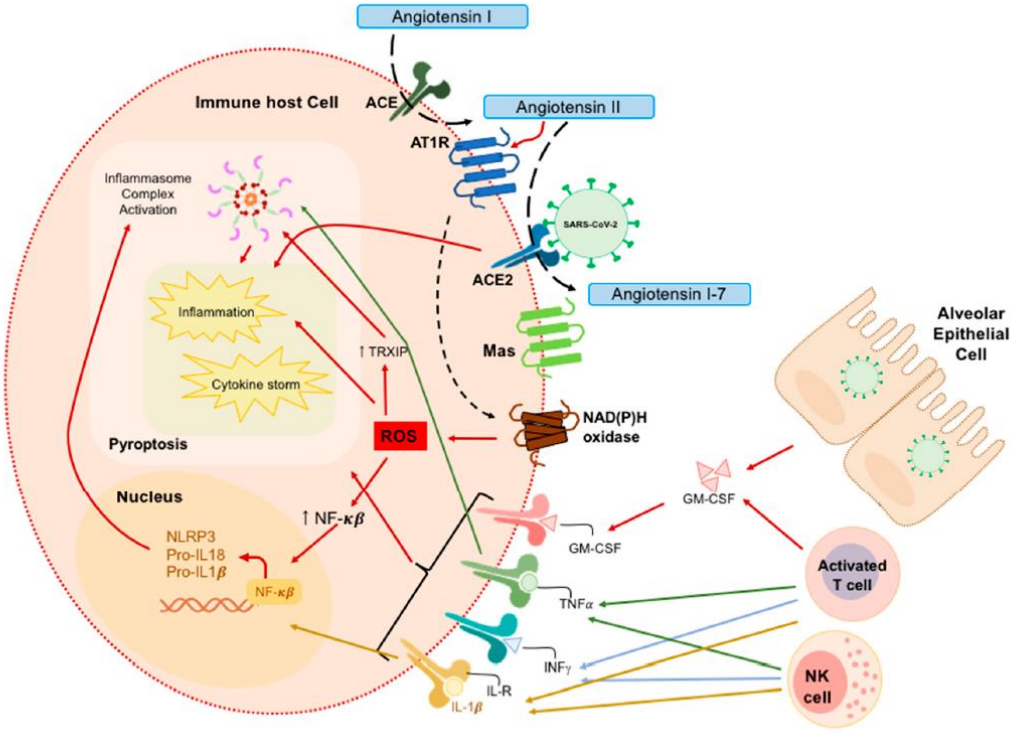

Figure 1: SARS-CoV-2 Molecular Pathogenesis (Beltrán-García et al., 2020).

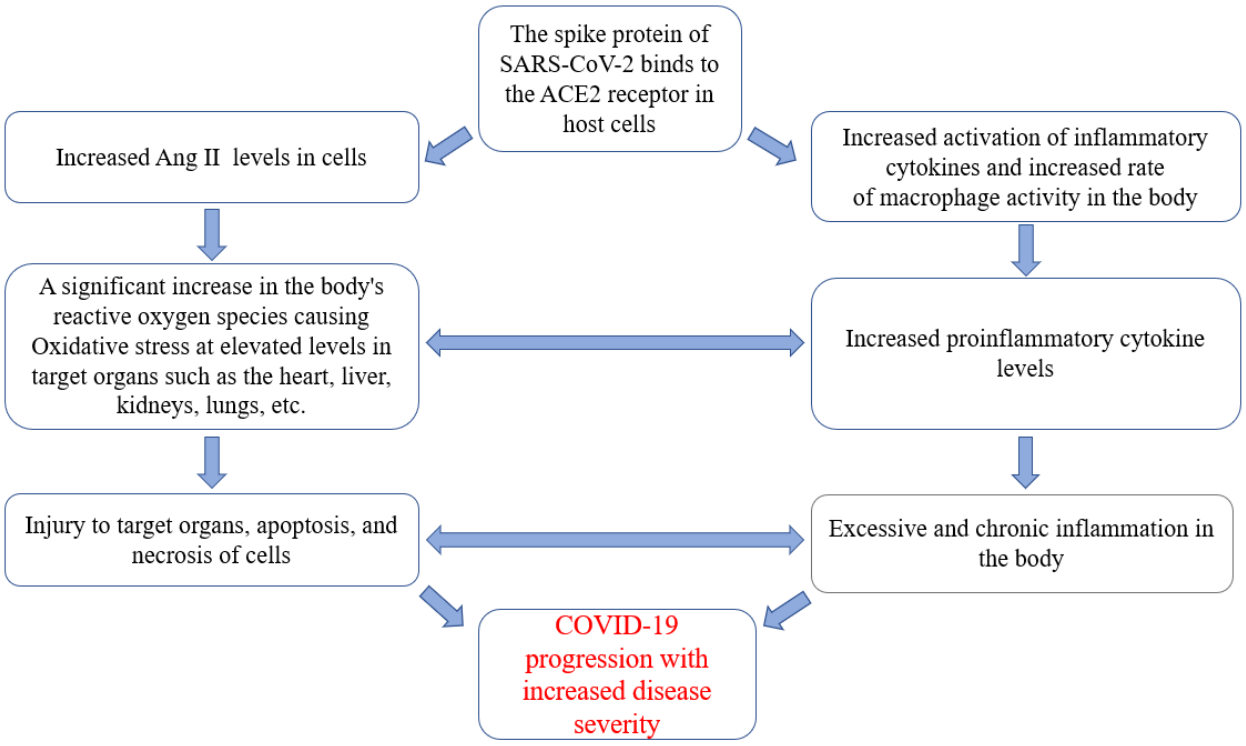

Figure 2: COVID-19 pathophysiology and interaction between oxidative stress and inflammation.

To design an effective treatment strategy for COVID-19 patients, understanding the link between SARS-CoV-2-mediated molecular pathways that induce excessive inflammatory responses, metabolic alterations, and oxidative stress in target organs is necessary (Delgado-Roche & Mesta, 2020).

The proximal tubule cells of the kidney, ileum, bladder, type II alveolar cells (AT2), cardiac cells, lung cells, hepatic cells etc. have high levels of ACE2 expression, making these organs and tissues to be vulnerable to SARS-CoV-2 invasion (Zou et al., 2020). Hence, Covid-19-induced oxidative stress is implicated in a number of clinical pathologies, including neurological disorders, lung injuries, cardiac injuries, liver, and chronic renal disease, as well as cancer development (Ogura & Shimosawa, 2014 & CDC COVID-19 Response Team, 2020). High levels of oxidative stress in target organs including the heart, liver, kidneys, and lungs, among many others, activate numerous intracellular signaling pathways, causing apoptosis or uncontrolled cell proliferation, hence eventually organ malfunction (Mokhtari et al., 2020). Therefore, addressing oxidative stress

is considered a potential therapy for protecting COVID-19 patients from subsequent organ damage (Lapenna, 2021).

The purpose of the review is to study the effects of COVID-19-induced oxidative stress on target organs. In this review, we describe neurological, lung, myocardial, hepatic, and renal injuries, as well as the development of malignancy among COVID-19 patients. Along with that, we discuss potential therapeutic approaches to address oxidative stress-related injuries among COVID-19 patients.

2.0 Effect on target organ systems

2.1 Neurological Disorders

Neurological abnormalities such as compromised consciousness, stroke, and seizure have been documented in COVID-19 individuals, with a greater likelihood in those who have had a more severe course of the disease (Mao et al., 2020). As COVID-19 spread throughout the world, evidence of neurological symptoms accumulated in a variety of locations (Davies et al., 2021). In a case study from France (Helms et al., 2020), encephalopathy, agitation with confusion, and corticospinal symptoms were all linked to severe COVID-19 (Davies et al., 2021). An average of 5.1 percent of COVID-19 patients had disturbance of consciousness (also referred to as "confusion" or "agitation") in nine trials involving 2890 patients (Helms et al., 2020). As suspected, COVID-19 patients with severe COVID-19 had more deteriorated consciousness than those with mild COVID-19. Through 51 trials, 16,446 COVID-19 participants were evaluated for headaches. Headache was reported by 20.1 percent of those surveyed, with rates ranging from 2.0 (C. Sun et al., 2020) to 66.1 percent (Yan et al., 2020). Meningitis, myelitis, and peripheral nerve damage have all been reported in the context of COVID-19 in recent months, implying that SARS-CoV-2 can directly infect the nervous system (Chen et al., 2020). These neurological abnormalities were seen in up to 50% of COVID-19's most severe cases, however, other types of neurological diseases such as seizures, anosmia, ageusia, encephalitis, and Guillain-Barré Syndrome (GBS) have also been linked to COVID-19 (Poyiadji et al., 2020; Zhao et al., 2020).

Several pathways are currently being studied as putative viral (SARS-CoV-2) entry routes to the brain, including the transcribial route (Baig et al., 2020), axonal transport, trans-synaptic transfer (Li et al., 2020), the hematogenous as well as lymphatic route (Cain et al., 2019) (Figure 3).

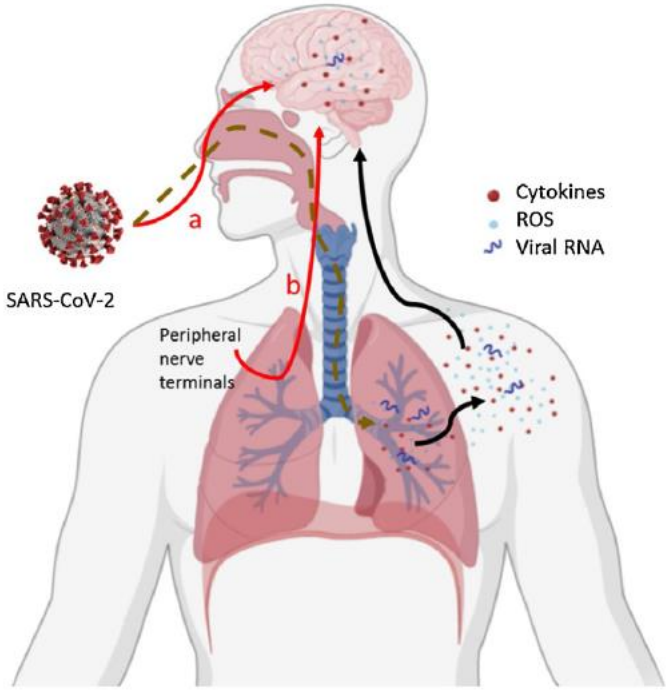

Figure 3: Several pathways by which SARS-CoV-2 potentially enters the brain (Nuzzo & Picone, 2020).

The infection of the olfactory epithelium and subsequent transmission through the cribriform plate to the subarachnoid space by the SARS-CoV-2 is described as a transcribial CNS invasion (Baig et al., 2020). On the other hand, infection of numerous peripheral nerve terminals and spreading along neurons, including the olfactory bulb, and the trigeminal nerve by SARS-CoV-2, would be examples of axonal transport and trans-synaptic transfer (Li et al., 2020). Another possibility is that SARS-CoV-2 enters the CNS through the bloodstream or lymph nodes (Cain et al., 2019). All these routes have the potential to cause neurological disease through CNS infection by SARS-CoV-2.

The presence of coronavirus RNA in human brain samples strongly indicates that these respiratory infections are inherently neuroinvasive in humans and that they can cause a long-term infection in the central nervous system (Nuzzo & Picone, 2020). The ACE-2 receptor has been discovered on

neurons and glial cells in a variety of brain regions (Muus et al., 2020), such as the cerebral cortex, striatum, posterior hypothalamic area, substantia nigra, and brain stem (Chen et al., 2020; Qi et al., 2020). As a result, SARS-CoV-2 can enter and infect the central nervous system (CNS) through ACE2 receptors.

Generation of the excessive inflammatory response by SARS-CoV-2 results in an increase in the high level of reactive oxygen species (ROS) that damages the brain (Nuzzo & Picone, 2020). In their research Cervellati et al., stated that systemic oxidative stress plays a key role in the development of neurodegenerative diseases (Cervellati et al., 2020). Furthermore, inflammatory damage to the surface of the Blood-Brain Barrier (BBB) has been related to a variety of neurological diseases such as multiple sclerosis, stroke, and epilepsy, and infections of the central nervous system (CNS) (Nuzzo & Picone, 2020). An initial phase of pro-inflammatory cytokine release could mediate virus-induced oxidative damage in COVID-19 patients (Zuo et al., 2019; Nuzzo & Picone, 2020). The brain is particularly sensitive to reactive oxygen species (ROS) since it is a significant oxygen metabolizer with comparatively low defensive antioxidant systems (Zuo et al., 2019). In COVID-19 patients, the death of neurons by reactive oxygen species (ROS) is a critical step in the pathogenesis of nervous system disorders (Zuo et al., 2019; Nuzzo & Picone, 2020). Several studies have reported various neurological manifestations caused by COVID-19-induced oxidative stress (Table 1).

Table 1:

Different neurological manifestations due to COVID-19 induced oxidative stress:

Complications of the nervous system	Timing of Onset of symptoms	Comments	Author
Agitation, confusion, diffuse corticospinal tract signs and dysexecutive syndrome	N/A	An experimental program of 58 individuals infected with SARS-CoV-2 was performed.	Helms, J., et al. (2020)
Leukoencephalopathy	16 days	The etiology of COVID-19-induced leukoencephalopathy is yet unknown. Oxidative stress induced by COVID-19 is the most apparent candidate.	Sachs, J. et al. (2020)
Viral Meningitis/Encephalitis	14 days	Patients tested positive for COVID-19 in the Cerebrospinal fluid (CSF). Association of oxidative stress is also a potential candidate.	Efe, I., et al. (2020)
Acute Transverse Myelitis	10 days	There was no conclusive evidence linking COVID-19-induced oxidative stress to a direct influence; nonetheless, the secondary association of oxidative stress is a likely scenario.	Munz, M., et al. (2020)
Acute Cerebrovascular Disease	7 days	Respiratory infections caused by oxidative stress during COVID-19 infection represent a potential risk for acute cerebrovascular impairment.	Valderrama, E.V., et al. (2020)
Encephalopathy	N/A	Encephalopathy was reported in an elderly patient infected with COVID-19. Signs of oxidative stress including hypoxia was also evident	Filatov, A. et al. (2020)
Infectious Toxic Encephalopathy	N/A	Hypoxia and ischemia caused by oxidative stress during COVID-19 infection, suggest a possible association with such incidence	Guo, Y.-R., et al. (2020)

COVID-19's impacts on the brain can be categorized into two types: direct infection and secondary mechanisms such as immune response-induced oxidative stress (Davies et al., 2021). Given many COVID-19 cases with neurological symptoms and the complexity, an initiative should be taken to create an international database that can be shared and used by multispecialty collaborative teams of health care professionals and scientists from around the world to minimize brain damage by COVID-19 (Román et al., 2020).

2.2 Lung injuries

According to Cascella M. (2020), in the lungs, as huge regions are exposed to many types of viruses, COVID-19 prefers to attack this vulnerable organ. This increased susceptibility to inhaled viruses is influenced by the lung's vast capacity and surface area. The lung is also one of the most oxygenated organs in the human body. COVID-19 infection induces an inflammatory response that results in the generation of pro-inflammatory cytokines that are associated with acute lung injury (Li, Geng, Peng, Meng, & Lu, 2020). There is a strong link between pro-inflammatory factors and reactive oxygen species (ROS) in a variety of lung diseases, particularly during Coronavirus infection (Chan, Selemidis, Bozinovski, & Vlahos, 2019). Following research by Chen et al. (2020), in the ICU, almost 30% of patients infected with COVID-19 had significant pulmonary edema, dyspnea, hypoxemia, or possibly acute respiratory distress syndrome or ARDS (Chen et al., 2020). Chen et al. (2020) further concluded that 17% of COVID-19 infected patients had ARDS, with 65% of patients with ARDS dying and 6 patients having a worse prognosis (Chen et al., 2020).

ACE2 has been demonstrated to be the predominant receptor for glycoprotein S of SARS-CoV in the lower respiratory tract, implying that COVID-19 could enter cells in the lower respiratory tract by the same ACE2 receptor (Ou et al., 2020). It has been observed that 83 percent of ACE2 is present in epithelial cells of the alveolar type II, implying that these cells can act as a virus reservoir. Therefore, the presence of ACE2 in these cells aids corona-viral invasion and reproduction, as well as substantial lung injury (Zhang, Penninger, Li, Zhong, & Slutsky, 2020). Lung damage by oxidative stress is also linked to transient receptor potential (TRP) ion channels (Bousquet et al., 2021). The expression of TRPV1 and TRPA1 in the neural system of the lungs

has been linked to morbidity, sickness severity, and basic physiological processes that contribute to worsening health conditions in patients with COVID-19 infection (Nahama et al., 2020). TRPA1 and TRPV1 are transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) that cause inflammation in the body (Bousquet et al., 2021). They enhance sensory or vagal nerve discharges to elicit irritation and a variety of COVID-19 manifestations, such as cough, nasal congestion, nausea, diarrhea, and, at partly, rapid, and severe loss of smell and taste (Bousquet et al., 2021). COVID-19-induced ROS can trigger TRPA1 and TRPV1 expressed in sensory neurons, hence deteriorating a patient's health condition following COVID-19 infection (Andersson et al., 2008). Therefore, the production of ROS is a symptom of oxidative stress, and we can reach the understanding that various lung diseases are greatly associated with COVID-19-induced oxidative stress.

COPD, or chronic obstructive pulmonary disease, is a spectrum of disorders that cause obstruction of the airflow, therefore, breathing difficulties (Singh et al., 2021). Emphysema and chronic bronchitis are examples. In a study by Vogelmeier et al., 2017, it was mentioned that excessive sputum production, cough, and dyspnoea are common symptoms of COPD, and patients may undergo rapid lapse due to respiratory tract infections mediated by COVID-19. As reported by many cohort studies, COPD was a contributing factor to worsening clinical outcomes in hospitalized COVID-19 patients in 2020 (Higham et al., 2020). Nonetheless, most of those studies did not sufficiently account for confounding. Aveyard et al., 2021, took a UK neighborhood-based population sample of more than 8 million people with 14479 hospitalized with COVID-19 to overcome potential sampling error in those cohort studies (Aveyard et al., 2021). After adjusting for age, sex, and comorbidities, COPD was found to be a major risk factor for increased morbidity and mortality in people infected by COVID-19 (Aveyard et al., 2021). The progression of chronic obstructive pulmonary disease (COPD) can be worsened by oxidative stress as patients with COPD are far more prone to viral infection, including infection by SARS-CoV-2 (Vogelmeier et al., 2017). Alveolar oxygen involves maintaining aerobic metabolism in lung tissue and during pulmonary ischemia postponing hypoxia leads to lower levels of ATP production and more severe ATP breakdown, leading to elevated hypoxanthine synthesis (Ferrari & Andrade, 2015 and Johnson, Jinnah, & Kamatani, 2019). These can cause oxidative damage to DNA, lipids, proteins, and carbohydrates that lead to the progression of COPD. Furthermore, ROS activates epithelial cells and alveolar macrophages, causing them to produce chemotactic molecules that

draw neutrophils, monocytes, and lymphocytes into the lungs, leading to chronic inflammation and oxidative stress (Akata & van Eeden, 2020). Such physiological events in the body affect tissue repair mechanisms, accelerates apoptosis, and increase autophagy in lung cells, most of which have been associated with the progression and severity COPD (Hikichi, Mizumura, Maruoka, & Gon, 2019).

Asthma is a long-term inflammatory lung condition that causes narrowing of airways and hyperresponsiveness (Sahiner et al., 2011). COVID-19 infection is responsible for up to 80% of acute asthma exacerbations in children and adults (Liu et al., 2020). Individuals with various respiratory infections, including COVID-19 infection, are more prone to develop asthma, which is accompanied by higher clinical manifestations, reduced lung function, bronchial hyperreactivity as well as inflammation (Message et al., 2008 & Liu et al., 2020). In asthma, there is significant evidence that there is a mismatch between the reducing and oxidizing processes in the body, suggesting the presence of oxidative stress (Sahiner et al., 2011). According to Birben, Sahiner, Sackesen, Erzurum, & Kalayci (2012), the generation of free radicals by inflammatory cells has been linked to many pathophysiological alterations in asthma. Elevated oxidative stress in asthma can cause the production of nitric oxide that reacts with superoxide anions to create peroxynitrite (ONOO-), which has a high oxidative capability (Kurutas, 2015), meaning, it is an endothelial vasodilator that worsens the individual's health condition by narrowing airways (Eisele et al., 2015). The transcription factor nuclear erythroid 2 p45-related factor 2 (Nrf2), which expresses approximately 200 genes (Riedl & Nel, 2008), is activated by low levels of oxidative stress. According to Cho et al. (2002), catalase, superoxide dismutase (SOD)-3, heme oxygenase-1, glutathione-S-transferases, NAD(P)H-quinone oxidoreductase (NQO1), glutathione peroxidase, and glucuronosyltransferase-1a6 (UGT-1a6) are among the enzymes which are encoded by Nrf2 gene, necessary to produce a wide range of antioxidants as well as anti-inflammatory factors (Cho et al., 2002). This shows that oxidative stress induces inflammation in COVID-19-infected people, which later leads to serious health problems including asthma (Chernyak et al., 2020).

COVID-19 has been shown to cause oxidative stress in the lungs in a variety of ways. Increases in pro-inflammatory cytokines are connected to inflammatory reactions and acute lung damage generated by SARS-CoV-2, demonstrating that pulmonary inflammation is caused following

COVID-19 infection (Yi, Lagniton, Ye, Li, & Xu, 2020). Preventative measures should be followed to reduce the consequences of oxidative stress in lung-related injuries.

2.3 Myocardial injuries

Various cardiovascular diseases, including cardiac arrest, myocarditis, acute myocardial infarction, stress-induced cardiomyopathy, cardiogenic shock, arrhythmias, or heart failure (HF) are led by COVID-19 infection (Magadum & Kishore, 2020). Myocardial injury can be caused by a variety of factors, including direct viral entry and heart damage, systemic inflammation, hypoxia, cytokine storm, and an interferon-mediated immune response (Magadum & Kishore, 2020). The ACE2 receptor, which is essential for the corona virus's pathogenicity, is found in abundance in cardiac tissues and aids in the development of cardiac damage caused by the infection by SARS-CoV-2 (Donoghue et al., 2000). COVID-19-infected individuals with underlying CVD (cardiovascular diseases) have a greater severity and death rate (Zeng et al., 2020). Many clinical studies suggest that individuals with CVD, hypertension, coagulation abnormalities, and diabetes experience severe symptoms and greater mortality risk when infected with COVID-19 (Murthy et al., 2020). In a study of 1527 COVID-19-infected patients, Li et al. observed that individuals with CVD, diabetes, or hypertension seem to be more likely to get ICU admissions, therefore, confirming the association between COVID-19 and CVD (Li et al., 2020).

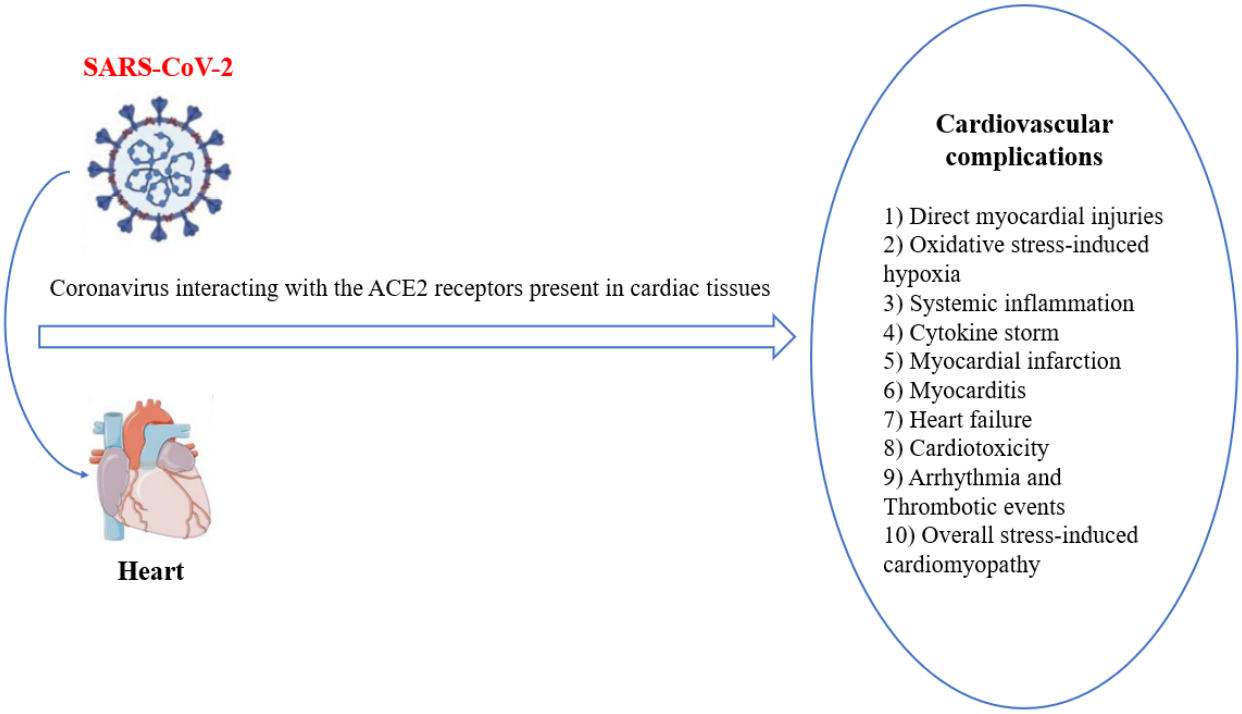

Figure 4: Potential myocardial injuries related to coronavirus infection.

According to many studies, during viral infection, oxidative stress plays a key role in developing cardiac diseases. According to Raedschelders et al., an imbalance between free radical formation and removal, caused by excessive reactive oxygen and nitrogen species (RONS) generation as well as insufficient antioxidant defense, causes oxidative stress-mediated cardiac injuries (Raedschelders et al., 2012). The superoxide anion, hydroxyl radical, hydrogen peroxide (H2O2), peroxynitrite (ONOO–), nitric oxide, and nitrogen dioxide radicals are some of the most prevalent types of free radicals found in the human heart (Chen et al., 2012). During normal conditions, the production of free radicals in the heart is minimal, however, during viral infection, free radical generation is caused by electron leakage from the mitochondrial electron transport chain (Ansley & Wang, 2012).

The conversion of superoxide anion to less harmful H2O2 by the enzyme superoxide dismutase (SOD) in the cytoplasm or mitochondria is part of the cardiomyocyte response to low-level superoxide anion production (Ansley & Wang, 2012). Either the catalase (CAT) or glutathione peroxidase (GPx) systems then convert the hydrogen peroxide to water (Raedschelders et al.,

2012). According to Ansley & Wang, during myocardial injury mediated by viral infection, superoxide anion production is significantly boosted and comes from a variety of cellular sources including, impairment and uncoupling of the mitochondrial electron transport system, uncoupled nitric oxide synthase (NOS), xanthine oxidase, cytochrome P450 monooxygenase, and cyclooxygenase (Ansley & Wang, 2012). Therefore, because viral infections are known to induce cardiac damage, COVID-19 infection is likely to cause damage to the heart, furthermore, the cellular antioxidant defense mechanism is significantly impaired during COVID-19 infection, resulting in an increase in oxidative stress, which may possibly lead to severe cardiac damage (Baqi et al., 2020).

The superoxide anion-producing enzyme NADPH oxidase-2 (NOX-2) is involved in systemic inflammation and the pathogenesis of several RNA viruses, including the coronavirus (To et al., 2017). Furthermore, NOX-2 levels are higher in COVID-19-infected patients and are associated to increase troponin (cTnT) levels in the body, implying that NOX-2 activation may induce myocardial damage (Violi et al., 2015).

SARS-CoV-2 can cause direct cardiotoxicity by developing myocarditis through infecting cells like cardiomyocytes (Yao et al., 2020). Excessive cytokine release after COVID-19 infection can cause vascular inflammation, plaque instability, as well as myocardial inflammation, which can lead to myocardial infarction (MI), cardiomyopathy, and heart failure (Prabhu, 2004). COVID-19 infection causes severe health issues such as sepsis and disseminated intravascular coagulation (DIC), which can lead to a variety of cardiovascular problems including inflammation, cytokine storm, myocyte necrosis, myocarditis, myocardial infarction, and heart failure (Magadum & Kishore, 2020).

Endothelial cells and megakaryocytes produce Von Willebrand factor (VWF), which is either released into the plasma or retained inside intracellular organelles (Magadum & Kishore, 2020). Recent studies suggest that VWF levels are increased (more than 565 percent) in COVID-19 patients (O'Donghaile et al., 2020). By interacting with platelet receptors, high VWF concentrations were found to influence platelet adhesion as well as aggregation (Goshua et al., 2020). Thrombotic microangiopathy, the defining characteristic of thrombotic thrombocytopenic purpura (a severe blood clot-causing condition), is caused by this pathological VWF. This indicates that patient with COVID-19 is likely to undergo such myocardial injuries (Klok et al., 2020).

Individuals with COVID-19 had higher levels of pro-inflammatory cytokines and chemokines, which could impair endothelial function and integrity (Huang et al., 2020). Overexpression of cell adhesion molecules (ICAM-1, integrin v3, P- and E-selectin), secretion of VWF, and endothelial production of cytokines and chemokines are all results of such impairment (Kayal et al., 1998).

2.4 Liver injuries

Severe liver illnesses are one of the leading causes of COVID-19 induced hepatic disorders, and these diseases are frequently associated with elevated oxidative stress (Grattagliano et al., 2012). In various liver disorders, oxidative stress induced by COVID-19 is a major factor (Ristic-Medic et al., 2021). However, both ROS and reactive nitrogen species (RNS) play a role in normal physiological processes, too much of either can damage cellular components such as proteins, lipids, and DNA in the liver (Ristic-Medic et al., 2021). The frequency of liver injury associated with COVID-19 cases can be as high as 58.06 to 78 percent (Huang et al., 2020 & Zhang et al., 2020). The post-mortem investigation of COVID-19 patients' hepatic tissue revealed a connection between histological changes and decreased blood flow. Intrahepatic blood vessel abnormalities have been reported, including portal vein fibrosis and wall inflammation, herniated portal vein with hyperactive Kupffer cells harboring massive necrotic debris, and vascular thrombosis with high D-dimer (500 ng/dL) as well as high platelet count (Zhang et al., 2020).

The expression of ACE2 receptors in biliary epithelial cells (hepatic cholangiocytes) suggests that SARS-CoV-2 can directly infect and replicate itself in the liver (Nardo et al., 2020). Among COVID-19 infected individuals who are critically ill, there is a higher prevalence of liver dysfunction (Morgan et al., 2020). COVID-19-related liver damage has been reported to be caused and aggravated by proinflammatory factors, endothelial alterations, hypoxia, and coagulopathy (Soldo et al., 2020). Hepatic ischemia and hypoxia-reperfusion dysfunction may be mediated by hypoxia which is caused by COVID-19-induced oxidative stress (Yang et al., 2019). The levels of alanine aminotransferase (ALT)/ aspartate aminotransferase (AST), serum albumin, and serum bilirubin in the body change as a result of this phenomenon (Yang et al., 2019; Amin, 2020). Many investigations have found that individuals with SARS-CoV-2 experienced liver injury, which was primarily expressed as mild to moderate elevations of ALT and AST (Amin, 2020).

Serum albumin levels were significantly lower in some patients while serum bilirubin levels were higher (Amin, 2020). To illustrate, as per contemporary COVID-19 research, the prevalence of liver injury varied from 14.8 to 53 percent, with aberrant ALT/AST levels and slightly raised bilirubin levels (Fan et al., 2020). In extreme cases, albumin levels drop to between 26.3 to 30.9 g/L (Chen et al., 2020). In COVID-19 patients, this metabolic discrepancy causes significant liver damage.

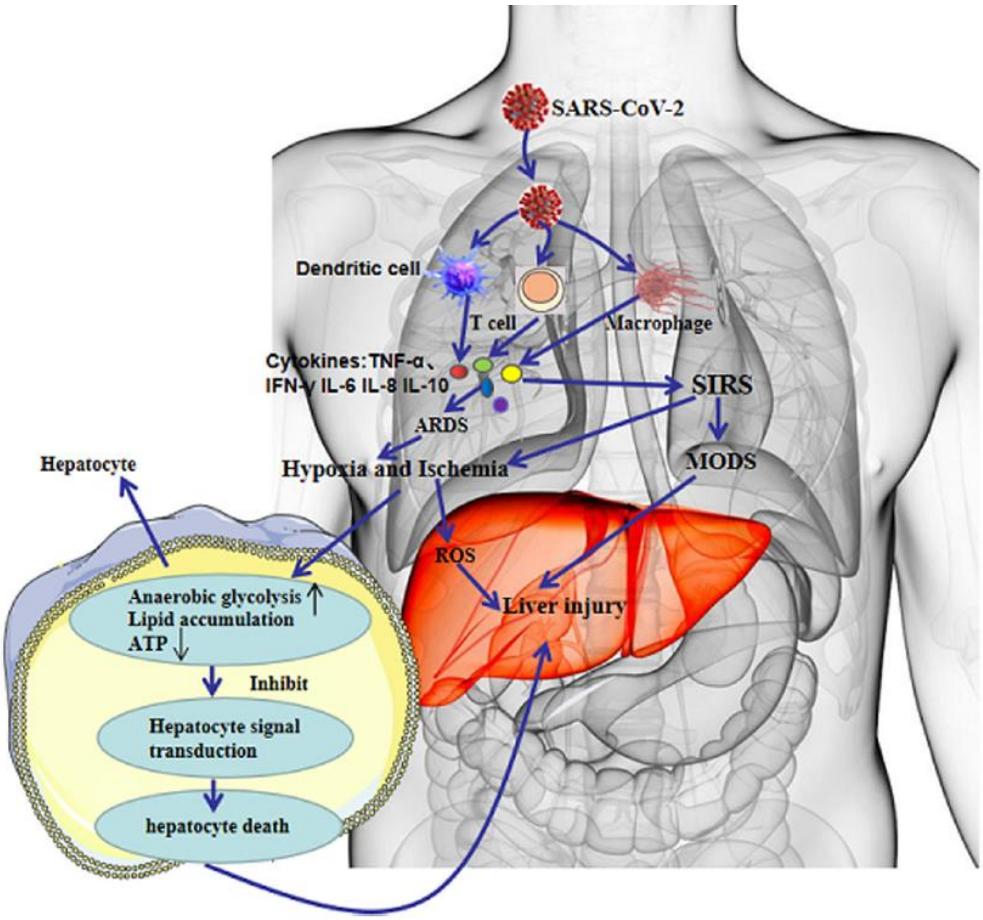

Figure 5: The possible mode of action of SARS-CoV-2 in liver injury (Tian & Ye, 2020)

Hepatic cells that are infected with SARS-CoV-2 produce interleukin (IL)-18 and IL-1 along with ROS (O_2 and H_2O_2) (Beltrán-García et al., 2020). Subsequently, T lymphocytes and natural killer (NK) cells also produce tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-1, stimulating

the generation of many other proinflammatory cytokines, such as IL-6, that leads to the occurrence of hepatic cytokine storm (Libby & Lüscher, 2020). Moreover, IL-6 causes the liver cells to produce more fibrinogen, plasminogen activator inhibitor-1, as well as C-reactive protein (CRP) (Wright et al., 2020). Among COVID-19 patients, the amounts of such components continuously rise resulting in deterioration of health conditions (Wright et al., 2020). Hepatic cytokine storm can also be induced indirectly by COVID-19. To illustrate, SARS-CoV-2 respiratory infection activates alveolar macrophages as well as lung epithelial cells, causing a significant production of proinflammatory cytokines such as IL-6, and TNF, as well as IL-1 (Ye et al., 2021). Proinflammatory cytokines subsequently hyperactivate monocytes, macrophages, and T lymphocytes, resulting in a rapidly self-producing loop in which cytokines overload the system, such incidence is also known as cytokine storm syndrome (CSS) (Beltrán-García et al., 2020). Consequently, the cytokine storm severely damages multiple organs, such as the liver (Beltrán-García et al., 2020).

Hypoxia, which occurs because of pulmonary failure, is one of the most frequent causes of secondary liver injury among individuals infected by SARS-CoV-2 (Zhong et al., 2020). Almost no circulation, decreased oxygen delivery, and hepatic steatosis as well as the hypoxic condition dramatically increase ROS in the liver (Feng et al., 2020). These ROS are directly engaged in hepatic cell death and injury (Feng et al., 2020). They also trigger hepatocyte apoptosis, which is followed by additional infiltration of inflammatory cells into hepatic tissue, resulting in liver damage, sometimes even liver failure (Huang et al., 2020).

SARS-CoV-2 infection can induce severe symptoms and mortality in COVID-19 patients as liver diseases are associated with redox disequilibrium and inflammation, which is significantly induced by oxidative stress (Ristic-Medic et al., 2021). Among individuals diagnosed with severe acute respiratory syndrome-coronavirus-2, varying degrees of liver damage have been observed (Ristic-Medic et al., 2021). Oxidative stress is linked to the onset and progression of hepatic injury in patients with COVID-19 (Ristic-Medic et al., 2021). To counter oxidative stress and prevent possible liver damage, proper dietary planning and antioxidant supplements must be maintained.

2.5 Renal injuries

The COVID-19 infection creates an inflammatory cytokine storm in the patients, which leads to a considerable increase in cytokine levels in the blood circulation system, resulting in severe inflammatory reactions and varying degrees of organ damage, including significant renal injuries (Hu et al., 2020). Inflammatory cytokines enter the kidneys and produce renal tubular injury, which impairs kidney filtration, leads to the aggregation of metabolites in the body, and worsens clinical symptoms thus threatening life (Doi et al., 2018). The incidence of acute kidney damage (AKI) among COVID-19 patients was assumed to be minor at first. For instance, Guan et al. (2020), did a survey of 1099 COVID-19 patients, among which 93.6 % were admitted to the hospital. Among those admitted patients, 91.1% had pneumonia, 5.3% were admitted to the ICU, 3.4% had acute respiratory distress syndrome, and only 0.5% had AKI (Guan et al., 2020). However, according to a new analysis, performed by Diao et al. (2021), the prevalence of AKI among 85 COVID-19 patients was shown to be around 27.6% (Diao et al., 2021).

Direct viral tropism of the kidney was first identified in an early research by Miller & Brealey (2020). Furthermore, Braun et al. (2020), found and isolated SARS-CoV-2 from post-mortem kidney tissue, it was also demonstrated that the virus multiplies in non-human primate kidney tubular epithelial cells, confirming its ability to infect kidney cells (Braun et al., 2020). Another postmortem analysis that attempted microdissection of kidneys from 6 individuals with COVID-19 identified SARS-CoV-2 in several regions in the kidney, predominantly in the glomerulus (Puelles et al., 2020). In situ hybridization with confocal microscopy was also utilized to locate viral RNA and protein in the kidney (Wölfel et al., 2020). Moreover, SARS-CoV-2 particles have been found in urine samples (Sun et al., 2020), which could indicate either virus release from infected, compromised tubule epithelial cells or viral fragment filtration, as SARS-CoV-2's molecular weight, which is 600 kDa, should prevent it from passing through the glomerular filtration barrier (Su et al., 2020). Altogether, there is now considerable evidence suggesting SARS-CoV-2 can infect kidney tissue, thus it is likely that the virus appears to play a direct role in the development of AKI (Legrand et al., 2021).

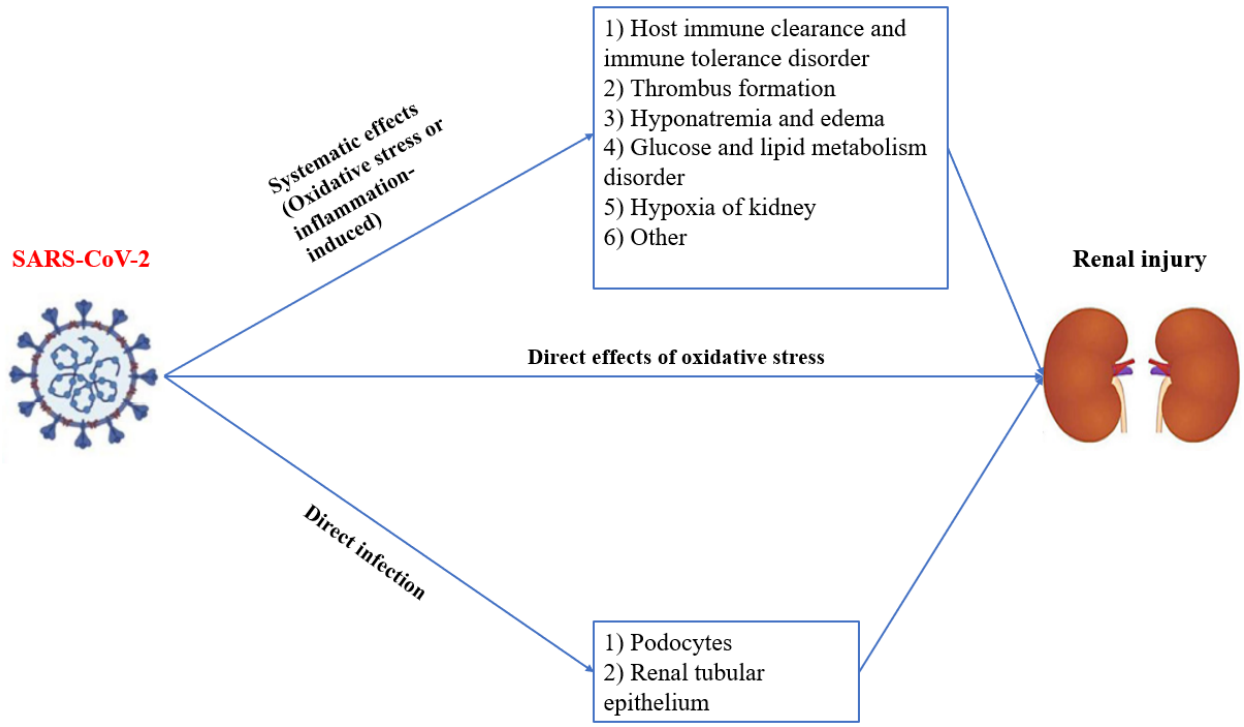

Figure 6: Mechanisms of renal damage in individuals infected with COVID-19.

Though various diseases are linked with renal microvascular and endothelial damage, SARS-CoV-2 is likely to attack the renal endothelium particularly (Ackermann et al., 2020). In a study by Varga et al. (2020) the kidney endothelial cells were found to be infected with coronavirus (Varga et al., 2020). Individuals with COVID-19 have been found to have vascular endothelitis in post-mortem investigations (Ackermann et al., 2020). Among Covid-19 patients, endothelial activation can be triggered by microvascular inflammation, resulting in vasodilation and elevated vascular permeability (Escher et al., 2020 & Connors & Levy, 2020). This results in increased circulation of soluble complement components C5b–9 and C5a, as well as buildup of C5b–9 and C4d in renal tissues, suggesting that complement activation may drive inflammation and coagulation pathways in COVID-19 patients (Pfister et al., 2021 & Cugno et al., 2020).

The generation of DAMPs (Damage Associated Molecular Patterns) from cells as a result of COVID-19-mediated oxidative stress contributes to renal endothelial damage in COVID-19 patients (Fodor et al., 2021 & Ince, 2014). Furthermore, SARS-CoV-2 has been demonstrated to bind with platelets by ACE2 receptors, resulting in platelet activation and immunothrombosis,

later, among those COVID-19 patients platelet activation plays a key role in the pathogenesis of AKI (Taha et al., 2020). The increased release of inflammatory mediators which are generated by oxidative stress in the kidney cells is believed to be a key mechanism of renal tissue injury among COVID-19 patients (Fodor et al., 2021). An abundance of such inflammatory mediators, including tumor necrosis factor (TNF) and Apoptosis antigen 1 or FAS, can bind to particular receptors expressed by renal endothelium and tubule epithelial cells, resulting in direct renal injury (Legrand et al., 2021).

In COVID-19 patients, nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream signaling components are substantially reduced (Olagnier et al., 2020). Nrf2 is a transcription factor that controls antioxidant responses in cells (Olagnier et al., 2020). It is typically kept in an inactive state in the cytosol by its suppressor, Kelch-like ECH-associated protein 1 (KEAP1). However, in response to oxidative stress, which is seen among patients infected by coronavirus (Fodor et al., 2021), KEAP1 is neutralized and Nrf2 is released, thus leading to stress-induced renal cell death (Olagnier et al., 2020).

Since the kidneys are crucial in the control of whole-body metabolism and homeostasis, COVID-19-induced impairment of renal functions will have a detrimental impact on the whole-body metabolism, thus worsening the patient's condition (Xu et al., 2021). Therefore, early diagnosis and preservation of renal functions in COVID-19 patients should be taken seriously during COVID-19 treatment (Xu et al., 2021).

2.6 Cancer development

The link between infections by viruses and a variety of malignancies is well established, and persistent inflammation is one of the pathways that induce oncogenesis (Smith & Khanna, 2018). Prolonged infection by COVID-19 could be the result of a low-titer residual virus being lodged in certain organs (e.g.: the liver, the lung, the brain, etc.), avoiding detection by existing diagnostic procedures (Marshall, 2020). These residual viruses (SARS-CoV-2) have long-lasting immune-modulatory effects and induce chronic inflammation (Marshall, 2020). Chronic inflammation has long been known to be a favorable condition for oncogenesis, therefore cancer development is one

such expected COVID-19 consequence (Saini & Aneja, 2021). Liang et al. examined a group of COVID-19 patients, among whom there was a sizable portion of cancer patients (1%) (Liang et al., 2020). Among them, lung cancer was the most common kind (5 of 18 patients or 28%), which is unsurprising considering the intrinsic pulmonary fragility towards COVID-19 infection (Liang et al., 2020). Fabrice et al. published data on 137 COVID-19 cancer patients, the most common of which were hematological malignancies and breast cancer (Fabrice et al., 2020). About 60% of those surveyed had active advanced disease, whereas 40% were in recovery or receiving potentially curative treatment. 25% of the cohort's overall health was deteriorating (Fabrice et al., 2020). After being infected by COVID-19, 11% were admitted to the ICU and 15% died. Patients with hematological cancer had a higher risk of poor outcomes (Fabrice et al., 2020). Chemotherapy was found to double the risk of illness deteriorating in the previous three months (Fabrice et al., 2020). All these findings imply that COVID-19 infection not only leads to cancer development but also worsens the condition of cancer patients.

Proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, which are well known to induce carcinogenesis, induce immune responses among COVID-19 patients (Del Valle et al., 2020). Moreover, COVID-19 has been linked to T-cell depletion along with oncogenic pathway activation, such as JAK-STAT, MAPK, and NF-κB, which increases the risk of malignant transformation (Li et al., 2020). Oxidative stress, which is directly caused by COVID-19, can also lead to malignant transformation. Hypoxia due to virus-induced ACE-2 depletion can induce oxidative stress and later excessive oxidative stress leads to cancer development (HOCKEL, 2001). Furthermore, as per Alpalhão et al. (2020), through the direct carcinogenic impacts of ROS, DNA single and double-strand breaks, DNA cross-linking, and DNA mismatch repair processes get impaired. Therefore, oxidative stress is acknowledged as both an activator and a promoter of cancer development (Alpalhão et al., 2020). Consequently, ROS can increase cell proliferation, tissue invasion, angiogenesis, cancer cell survivability, and even chemoresistance via interactions with cellular signaling pathways (Reuter et al. 2010). All these findings point to a link between COVID-19-induced oxidative stress and the development of cancer.

COVID-19 has been shown to injure multiple organs, and significant tissue damage promotes the stimulation of oncogenes (Greten & Grivennikov, 2019). DNA damage and consequent carcinogenesis can be caused by prolonged inflammation and oxidative stress (Mokhtari et al.,

2020). The tumor suppressor protein p53 is thought to be degraded by the SARS-CoV-2 non-structural protein 3 (Nsp3) (Saini & Aneja, 2021). Additionally, Nsp15, a SARS-CoV-2 endoribonuclease, binds with the retinoblastoma tumor suppressor protein (pRb), causing it to be degraded by the proteasome pathway (Saini & Aneja, 2021). Through in silico experiments, a linkage between the S2 subunit of SARS-CoV-2 and the proteins p53 and BRCA1/2 has been established (Singh & Bharara Singh, 2020). The absence of these cellular gatekeepers can result in genetic instability and abnormal cell proliferation suggesting that COVID-19 can lead to oncogenesis.

Cancer is typically not the outcome of a single mutagenic event, rather, it is the sequela of a series of mutagenic events over time (Saini & Aneja, 2021). When paired with other mutagenesis events, COVID-19-induced oxidative stress makes the body prone to oncogenesis and accelerates cancer progression (Saini & Aneja, 2021).

3.0 Potential treatment strategies

In COVID-19, antioxidants have been suggested as a complementary treatment method (Li et al., 2020). To treat Covid-19, various antioxidants are now being examined in various clinical studies. Antioxidants such as vitamins A, C, and D, melatonin, resveratrol, reduced glutathione, N-acetylcysteine, silymarin, quercetin, colchicine, amiodarone, etc. have been considered as medicines for treating as well as minimizing COVID-19 symptoms and complications (Deftereos et al., 2020, Sanchis-Gomar et al., 2020).

Regulating nuclear erythroid-related factor 2 (Nrf2) and antioxidant-related elements (ARE), which are the major transcription factor linked to boosting enzymatic antioxidant defense (Beltrán-García et al., 2020), could be a potential way to treat COVID-19. In this context, antioxidants that can activate Nrf2, such as resveratrol, sulforaphane, melatonin, and vitamin D can be applied for treating patients with severe COVID-19 infection (Ahmadi & Ashrafizadeh, 2019 & Marinella, 2020).

Vitamin D regulates cell signaling mediated by Ca^{2+} and reactive oxygen species and plays a key role in phosphorus homeostasis (KUTUZOVA & DELUCA, 2007). Furthermore, vitamin D's

function in balancing oxidative stress and mitochondrial respiratory activity has been postulated as one of the major regulators of systemic inflammation (Wimalawansa, 2019). Vitamin D controls the adaptive immune system; therefore, it also has an anti-inflammatory effect (Chambers & Hawrylowicz, 2010). Vitamin D induces the expression of various molecules involved in the antioxidant defense system, such as catalase, glutathione peroxidase, glutathione-disulfide reductase, and superoxide dismutase, as well as increasing the levels of reduced glutathione and suppressing the expression of NADPH oxidase (Wimalawansa, 2019). Low levels of vitamin D were linked with an elevated risk of mortality, as per a recent retrospective analysis of 780 older male COVID-19 patients (Raharusun et al., 2020), therefore indicating that vitamin D treatment might lower the severity of COVID-19 (Grant et al., 2020). Vitamin D is now being tested as a COVID-19 treatment in 48 research studies, according to ClinicalTrials.gov which is a database made by the U.S. National Library of Medicine. Vitamin D, in addition to countering the negative effects of oxidative stress, also helps to ensure the proper functioning of T-cells (von Essen et al., 2010 & Sigmundsdottir et al., 2007), thereby aiding immunological response. Table 2 includes some of the advanced current clinical trials for patients with COVID-19 utilizing vitamin D as therapeutic supplementation.

Table 2:

The following clinical trials involving vitamin D as a treatment for COVID-19 have been registered on **ClinicalTrials.gov.**

Clinical Trial ID	Development Phase	Goal
NCT04411446	Phase 4	The purpose of the study is to observe if an oral dosage of vitamin D can minimize respiratory impairment and certain other negative clinical outcomes in patients with COVID-19
NCT04386850	Phase 2–3	The therapeutic effectiveness of immediately treating vitamin D deficit in individuals (adults) to lower the risk of SARS-CoV-2 infection thus, minimizing the death rates related to COVID-19, is being evaluated in this clinical investigation.
NCT04535791	Phase 3	The objective of this research is to see how effective vitamin D supplementation is at protecting COVID-19 healthcare personnel from viral infection.
NCT04483635	Phase 3	The objective of this 16 weeks trial is to establish that individuals infected with SARS-CoV-2 who take a high-dose vitamin D supplementation experienced a reduced risk of infection severity and a shorter period of their illness.

Among other medicines, melatonin-based medications are distinct ones. Melatonin (N-acetyl-5-methoxy-tryptamine) is produced in the pineal gland from the amino acid tryptophan, then released into the cerebrospinal fluid (Farez et al., 2016). Melatonin's effective free radical scavenging activity has been very well known for nearly 30 years (Tan et al., 2015). Melatonin is a naturally occurring hormone that has a remarkable ability to lessen oxidative stress in patients with COVID-19 (Reiter et al., 2016 & Beltrán-García et al., 2020). It has been postulated that, as per its antioxidant properties against ROS (including (OH), H_2O_2, singlet oxygen, and RNS), it plays an important part in activating distinct antioxidant enzymes by Nrf2 and blocking the pro-oxidant function of certain enzymes (Beltrán-García et al., 2020). Melatonin has also been shown to have anti-inflammatory properties in both acute and chronic inflammatory diseases including COVID-19 (Nabavi et al., 2019 & Chitimus et al., 2020). Therefore, melatonin might be a viable candidate as a COVID-19 co-adjuvant medication because of its anti-inflammatory, antioxidant, and immunomodulatory effects (Acuña-Castroviejo et al., 2020). In fact, five clinical trials are already being established to assess the safety and efficacy of melatonin among COVID-19 patients (**ClinicalTrials.gov**) (Table 3).

Table 3:

The following clinical trials involving melatonin as a treatment for COVID-19 have been registered on **ClinicalTrials.gov.**

Clinical Trial ID	Development Phase	Goal
NCT04470297	Phase 2	This research examines the therapeutic efficacy of ramelteon 8mg which is a melatonin agonist, in individuals with COVID-19
NCT04530539	N/A	The objective of this trial is to observe how supplementation of vitamin C and melatonin affects the overall health condition of patients with COVID-19
NCT04474483	Phase 2	This clinical trial's goal is to establish melatonin's effect as an anti-inflammatory and antioxidant agent in patients with COVID-19. This trial also covers melatonin’s impact on further disease severity and development mitigation in SARS-CoV-2 patients.
NCT04409522	N/A	The purpose of this research is to establish the effectiveness of melatonin as an adjuvant to standard antiviral therapies in individuals with severe viral infections with COVID-19
NCT04531748	Phase 2	This clinical trial will assess the effects of melatonin alone and in combination with another medicine named Toremifene with a view to minimizing the signs and symptoms of COVID-19 patients. To determine the best treatment, the study includes comparing the medicine-taking group against a placebo group.

Since oxidative stress is a crucial component in the underlying pathophysiology of COVID-19, antioxidants could be a promising co-adjuvant treatment to treat patients with COVID-19 infection.

4.0 Conclusion

The specific molecular pathways underlying SARS-CoV-2-induced pathological inflammation, vascular dysregulation, and many other complications in different target organs (brain, lung, liver, kidney, etc.) are still being explored. It's vital to understand the pathways involved in the various stages of the inflammatory response throughout coronavirus infection, as well as how they affect the patient's overall health condition.

Many researchers believe that COVID-19's excessive generation of ROS causes increased oxidative stress, which leads to local and systemic tissue damage and inflammation in certain organs, thus contributing to COVID-19's severe clinical manifestations. Based on the research and the experience of practicing clinicians, we can conclude that COVID-19 infection is linked with oxidative stress, which causes substantial structural alterations in the tissues of many target organs, mainly in severe instances.

Antioxidant therapy based on vitamin D and melatonin is now being tested in several clinical studies. Because of its antioxidant, immunomodulatory, and vascular homeostasis properties, vitamin D supplementation offers great potential, however, strong clinical evidence is required to establish its effectiveness in COVID-19. Meanwhile, melatonin is another potential therapeutic option as a COVID-19 co-adjuvant therapy due to its anti-inflammatory, antioxidant, and immunomodulatory effects. Nevertheless, we must wait for the release of the findings of existing clinical trials to ensure its efficacy in treating patients with COVID-19.

The underlying causes and effects of COVID-19-induced oxidative stress on target organs must be further studied. It is also necessary to identify the relationships between COVID-19-induced oxidative stress and neurological, lung, myocardial, hepatic, and renal injuries, as well as the development of malignancy in COVID-19 patients. Furthermore, potential therapeutic approaches,

particularly antioxidant therapies, to minimize oxidative stress-related injuries in COVID-19 patients must be examined further to treat patients with COVID-19.

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