REVIEW

# The Role of Oxidative Stress and Cytokine Storm in the Pathogenesis, Oral Manifestation, Progression and Adverse Effects Related to SARS-Cov2 Infection- A Review.

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## Abstract

**Introduction:** COVID-19 pandemic has been the most challenging global health concern that the world has ever seen and is the focus of active research around the world. The interaction of the SARS CoV2 virus with the target cells, their action on the immune system and the subsequent reaction has all been linked to the inflammatory processes that are taking place in the human body mainly the oxidative stress.

**Objective:** Through this article we aim to analyse the effect of oxidative stress in the pathogenesis of COVID-19, highlighting the role of the same in the oral manifestations that are being reported in literature and its subsequent impact in the transmission and propagation of SARS-CoV2. The role of antioxidants in the control of the SARS-CoV2 infection has also been explored.

**Materials and Methods:** Four reviewers independently collected the data pertaining to the topic from case reports and review articles published in electronic databases like PubMed, Scopus, Science Direct and Research gate.

**Conclusion:** Increased release of cytokines known as cytokine storm has been associated with disease progression, oral manifestation as well as adverse effects in patients with COVID 19. However, as this is an ongoing pandemic with new mutations occurring frequently, further clinical trials are required to evaluate the exact mechanisms that may be at play in the pathogenesis of SARS-CoV2 infection.


**Keywords:** SARS-CoV2, COVID-19, oxidative stress, cytokine storm

Oral and Maxillofacial Pathology Journal (2023): ***https://www.ompj.org/archives***

## Introduction

COVID-19 is a multi-organ disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which was first detected in Wuhan, China in December 2019. SARS-CoV-2 is a zoonotic, single-stranded, enveloped, ribonucleic acid (RNA) beta-coronavirus. The family of corona viruses includes the Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV) and Middle East Respiratory Syndrome CoronaVirus (MERS-CoV), which bear a phylogenetic similarity of 79% and 50%, respectively with SARS-CoV-2 strain.

Free radicals are highly reactive, unstable molecules which are produced as a result of normal physiological process in the human body. Oxidative stress is the result of an imbalance between the production of free radicals such as Reactive Oxygen Species (ROS) or Reactive Nitrogen Species (RNS) and the antioxidant system. The commonly present ROS are Superoxide radicals (O2•−), hydrogen peroxide (H2O2), hydroxyl radicals (•OH), and singlet oxygen (1O2) and RNS are nitric oxide (NO•), nitrogen dioxide (NO2•), nitrous acid (HNO2) and peroxynitrite (ONOO-).

These free radicals have a dual role as a physiological necessity and in excess as a detrimental factor. The beneficial effects occur at low/moderate concentrations and is a necessary factor in cellular signaling systems, maturation process of cellular structures, regulation of cytokines, induction of a mitogenic response, transcription and immunomodulation.[1]

When produced in excess, free radicals lead to deleterious

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**How to cite this article:** Thampy LM, Niveditha, Athira CP, Sadasivan S, Deepthy PM. The role of oxidative stress and cytokine storm in the pathogenesis, oral manifestation, progression and adverse effects related to SARS-Cov2 infection- a review. Oral Maxillofac Pathol J 2023;14(1): page number. 66-69

**Source of Support:** Nil

**Conflict of Interest:** None

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effects that can damage cellular lipids, proteins, or DNA inhibiting their normal function. Because of this, oxidative stress has been implicated in a number of human diseases as well as in the ageing process, cancer, diabetes mellitus, ischemia/reperfusion injury, inflammatory diseases, neurodegenerative disorders and ageing.

This review aims to explore the effect of oxidative stress in the pathogenesis and outcome of Covid-19 infection, highlighting the orofacial manifestations associated with the disease, with a brief note on the use of antioxidants as a potential preventive as well as therapeutic tool in the fight against Corona virus.

**Oxidative Stress in Covid 19**

**1. Pathogenesis of SARS CoV-2**

SARS- CoV-2 enters the cells using the host receptor, Angiotensin Converting Enzyme II (ACE2) which is also the known receptor for SARS-CoV.[2] ACE2 expression was recognized in alveolar cells (AT2) of lung, esophagus, enterocytes from ileum and colon, cholangiocytes, proximal tubule cells of the kidney, myocardial cells, and bladder urothelial cells. Organs showing such high ACE2 expression should be considered as potential high risk for SARS- CoV2 infection.[3]

The virus once it enters the host, passes through the mucous membrane of particularly nasal and laryngeal mucosa and enters the lungs through respiratory tract, where it would attack the target organs that express ACE2. After entering into the host cell, SARS CoV2 encounters the innate immune response causing an immune reaction in the host, which can help in defending the body against the invading virus. However, over activation of the immune response induced by the viral infection and its pathological process are always accompanied by oxidative stress. The innate immune system of the host recognizes and responds to the foreign genome of the SARS-CoV2 by activating macrophage and dendritic cells whichgenerates the reactive oxygen/nitrogen radicals and cytokines, causing inflammation and which further exacerbate the hostsystem response in favor of COVID-19 progression. Proinflammatory cytokines like IL-6, IL-8, IL-12 and TNF as well as anti-inflammatory cytokines like IL-10 have been implicated in the process. This phenomenon characterized by a rapid release of proinflammatory cytokines known as cytokine storm or cytokine release syndrome is considered to be the main cause of ARDS (Acute Respiratory Distress Syndrome) and multiple organ failure in COVID-19 patients.

**2. SARS-CoV2 and the Oral Cavity:**

Studies have indicated that the oral mucosa may be a potentially high risk route for Covid 19 infection. The distribution of ACE2 receptors in the oral cavity will help in shedding light on the potential pathogenesis of the SARS-CoV2. Xu et al have explored the ACE2 expression in the oral mucosa and have found that the mean ACE2 expression was highest in the tongue when compared to other sites in the oral cavity. Moreover, ACE2 expression was seen to be highly enriched in the epithelial cells of the oral cavity when compared to T cell and fibroblasts. ACE2 receptors have also been identified in oral sites such as tongue, salivary gland ductal epithelial cells and periodontal tissue.[3]

Saliva has been considered widely as a potential route for the transmission and propagation of SARS-CoV2. This puts the focus on the major and minor salivary glands in the oral cavity as a site for possible early infection which could then be passing on the virus to the gastrointestinal tract via the salivary secretion.[4] As quoted by Matuck et al in their study, saliva and GCF are considered to be the sources of human viruses in the oral cavity. Furthermore, co-infection of the SARS-CoV-2 virus and the pathobionts of the oral cavity plays a critical role in increasing the inflammatory response and cytokine storm.[5]

Oral manifestations associated with SARS- CoV2 infection has been widely reported in the literature. The high viral load in the saliva apart from the nasal secretions could be the factor responsible for the oral changes associated with Covid-19.6Anosmia and dysgeusia have been regarded as the two most important manifestations associated with COVID 19. The orofacial manifestations reported were variable. The most common reported manifestations were multiple oral ulcers, vesiculobullous lesions, erythematous lesions, candidiasis, dry lips, depapillated tongue, halitosis, Kawasaki like angular cheilitis and Sweet syndrome. Several predisposing factors have been considered for the onset of oral lesions in COVID-19 like lack of oral hygiene, stress, immunosuppression as well as opportunistic infections.

Sampson et al has postulated that poor oral hygiene may increase the potential risk for complications of COVID-19, such as bacterial superinfection, particularly in patients with diabetes and other lifestyle diseases.[7]

Periodontitis is a chronic, multifactorial, infectious disease leading to destruction of the supporting structures of the tooth. Chronic periodontitis has been considered as a distinct risk factor for several systemic diseases with a moderate to strong association with respiratory diseases especially COPD (Chronic Obstructive Pulmonary Disease) and pneumonia. The role of periodontal pockets as a possible favourable anatomical niche for the SARS- CoV2 has been hypothesised by Badran et al.[8] Periodontal pockets are a biologically dynamic environment with a constant interaction of the subgingival biofilm with the oral cavity as well as the peripheral circulatory system. The migration of microorganisms from the periodontal pocket can either be through the GCF fluid to the oral cavity, or to the systemic circulation via the periodontal capillary system. It has become more widely accepted that apart from the bacteriae present in the periodontal pockets, viruses could also infect distant organs and generate focal infections.[8]

Worsened prognosis in SARS-CoV2 infection is primarily due to the cytokine storm leading to oxidative stress. It mostly manifests either as Acute Respiratory Distress or Multi Organ Failure. A similar mechanism occurs in periodontal infection, where cytokine storm plays a major role in its pathogenesis. Since patients with existing periodontal diseases prior to SARS CoV 2 infection are likely to have elevated cytokine level, they may be susceptible to more severe, and fatal, outcomes. The aspiration of oral pathogens into the lower respiratory tract especially in hospitalised Covid Patients with periodontal infection could potentially be considered as a reason for hospital acquired pneumonia.[9] Periodontitis has hence been regarded as a preexisting condition that can worsen the COVID-19 infection.

The role of Diabetes mellitus in the progression of

periodontal disease has been well studied in literature. The role of F. nucleatum, P. intermedia and P. gingivalis have been associated not only with the progression of periodontitis, but is also a significant finding in diabetes, hypertension and heart disease. This can be considered as a double edged sword as hyperglycemia facilitates the SARS- COV2 virus entry into the cells since ACE2 and virus both need glucose for their function. This hyperglycemia in turn impairs the phagocytic activity of the defense system causing an increase in the oral microflora. Pathogenic oral microrganisms as a result increase the severity of a periodontal infections by releasing cytokines and metalloproteinases into the circulatory system causing tissue destruction and further exacerbating insulin resistance. This results in increased Reactive Oxygen Species (ROS) thereby leading to oxidative stress which is further detrimental for a SAR-CoV2 infected patient.

**3. Antioxidants as a potential therapeutic tool for Covid 19:**

The role of antioxidants as a therapeutic and preventive means for COVID-19 has been widely discussed in the literature. Zinc is an essential metal biologically indispensable for normal cellular processes including DNA synthesis and RNA transcription. It is also vital for the normal development, differentiation and function of immune cells. Several studies have explored the efficacy of zinc as an antiviral agent to several viruses including SARS-CoV2 by mounting both an innate as well as humoral immune response which suggests that supplementation of zinc may be beneficial both as a prophylactic as well as a therapeutic means against COVID 19.[10]

Vitamin D is a fat soluble vitamin which acts as a modulator of innate and adaptive immune system and has been shown to have antioxidant effects. It has been shown to prevent protein oxidation, lipid peroxidation and DNA damage.[11] Lower levels of Vitamin D have been linked with an increased risk of pneumonia and upper respiratory tract infections. This is of particular importance in COVID 19 as pneumonia is considered to be a factor associated with increased risk of mortality. Vitamin D has also been shown to downregulate inflammatory cytokines like TNF-$\alpha$ and IL6 which opens up the possibility that supplementation of patients with Vitamin D may reduce the incidence of cytokine storm.[12]

Curcumin and Echinacea are active components of medicinal plants which have been shown to have antioxidant as[7] well as immunomodulatory effects. Curcumin which is the bioactive ingredient of turmeric has been well studied in literature and has been shown to have antioxidant, antibacterial, antiviral as well as anti-inflammatory effects. It has been shown to block the entry of virus and prevent budding by modifying the structure of surface protein. This prevents viral attachment and penetration as well as replication.[13] Echinacea supplementation has been shown to reduce the severity and duration of Acute Respiratory Infection when taken at the onset of symptoms. It has also been shown to decrease the proinflammatory cytokines like IL-6, IL-8 and TNF, which in turn will reduce the risk of developing cytokine storm and ARDS.[14]

Vitamin C has been shown to have antioxidant, anti-inflammatory, antithrombotic, and immuno-modulatory functions.[15] Studies have shown that Vitamin C supplementation can generally increase the host immunity and reduce the oxidative stress. Decreased cytokine storm in COVID 19 patients administered with high dose Vitamin C has been associated with improved outcomes especially in severely ill patients.[16] This makes it a potential therapeutic candidate but one which warrants more clinical trials before it can be considered as a reliable adjunct to treating severely infected COVID 19 patients.

Quercetin is a plant flavonoid which has been studied in various viral infection models as it has antioxidant, antiviral as well as anti-inflammatory effects. Inhibition of proinflammatory cytokines by Quercetin has shown to decrease cytokine storm which is considered to be directly related to the patient outcome.[17] Studies have also shown that it may disrupt viral entry, replication as well as protein assembly.[18]

A variety of other antioxidants like N-acetylcysteine, Melatonin, Glutathione, Astaxanthin, Polyphenols, BEN815 etc have also been studied to act as an adjunct in the prevention and treatment of COVID 19. As it is an ongoing dynamic pandemic, with researchers focusing more on the "magic pill" to curb the SARS-CoV2 virus, more and more antioxidants are being widely explored to help reduce the incidence as well as the mortality rate associated with Covid.

## Conclusion

The COVID 19 pandemic has opened the venue for more researches in the field of virology. Viruses have never before been studied in such a spotlight as it is being done now. The presence of oral manifestations in COVID patients opens up an entirely new field of research and this can also help in better understanding the pathogenesis of the SARS-CoV2 virus. Whether oral lesions are a direct manifestation of the virus, an opportunistic infection considering the hit on the immune system or an adverse effect of the treatment administered is yet to be extensively explored. Nevertheless, the role of a dentist in the multidisciplinary team treating COVID 19 cannot be ignored.

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