REVIEW ARTICLE

OXIDATIVE STRESS: A KEY PLAYER FOR THE PATHOGENESIS OF COVID 19.

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Keywords:

Oxidative stress, Covid 19, redox imbalance, reactive oxygen species

Introduction:-

Coronavirus (COVID 19) is a zoonotic infection affecting numerous organs brought about by Severe Acute Respiratory Syndrome Covid 2 (SARS-Cov-2). In December 2019, Pneumonia of unknown originwas identified in Wuhan,Hubei Area,China. By 5 January2020, the virus has been confirmed to have infected 59 individuals in the city of Wuhan. By the end of January, the WHO declared a General Health Crisis of Global Concern, which recommended guidance for nations for carrying out open - wellbeing measures,testing strategies, and isolating their contacts. Most of the nations are facing a second influx of the disease with a mutant form of the virus with a high pace of transmission and increased mortality rates.[1]

The mode of entry of the SARS-Cov-2, similar to that of SARS-CoV, is with the help of the receptor angiotensin-changing over protein II (ACE2).Although the primary route of infection is through the lungs,the presence of ACE2 receptors in other parts of the human body, particularly in the heart,gastrointestinal framework and kidney makes these organs also vulnerable to the harmful effects of the infection. Once the virus enters inside the host organism, the host immune system will be activated to react against the foreign organism with the help of macrophage and dendritic cells that uses reactive oxygen/nitrogen and cytokines. This leads to the creation of an inflammatory environment in the host further aggravating the body's response to covid19 infection. The overt oxidative stress thus created due to the different cytokines released is of a higher magnitude so that the normal defense mechanisms against oxidative injury prevailing in the host cell are not capable to prevent this onslaught of COVID-19 induced oxidative injury.The current review provides insight into the role of oxidative stress in the aggravation of covid19 and the inherent defense mechanisms employed by the host cell to prevent oxidative damage. [2,3].

Oxidative stress (OS):

Reactive oxygen species [ROS] are highly reactive molecules that are generated in different subcellular sites or compartments and it serves as a body defense during any viral or bacterial infection [4].Thelungs, being one of the most oxygenated organs in the human body and having an enormous surface exposed, are the primary target of the COVID 19 virus [5].Various lung diseases have been demonstrated to cause an increase in levels of reactive oxygen species [ROS] as a result of apnoea and subsequent alveolar hyperventilation, pulmonary artery vasoconstriction, and cyclic changes in hypoxemia. Hypoxia culminates in tissue edema, inflammatory cell infiltration, elevated levels of cytokine, and oxidative stress.The proinflammatory cytokines such as interleukin-6 (IL-6),tumornecrosis factor (TNF-α), and IL-8released during lung injury act as additional stress over the injured lungs[6]. Oxidative stress contributes to various metabolic and physiological changes andalso acts as a significant etiology in a variety of diseases in the body [7]. COVID 19 infection leads to an inflammatory response resulting in the release of pro-inflammatory cytokines that are known to cause acute lung injury [8]. The strong link between pro-inflammatory components and reactive oxygen species [ROS] has been documented in various lung diseases [9]. The oxidative stress leads to an imbalance between prooxidants and antioxidantsleading to the accumulation of pro-oxidants culminating in cell death[10]. Reactive oxygen species (ROS) are essential for the normalphysiological functions of a cell; however, the role of ROS is tightly regulated via redox regulation, redox sensing, and redox signaling [11]. ROS can be produced by a variety of cell types in the lungs, including monocytes and macrophages, neutrophils, and pulmonary endothelial and epithelial cells [12]. The expression of enzymes NADPH and xanthine oxidase [XO] in the aforementioned cells help these cells to generate ROS [12-13]. Endogenous antioxidants, such as SOD [Superoxide Dismutase], neutralize free radicals and play a crucial role in protecting cells from free radical damage[14]. However, in certain disease states, these antioxidants are quickly depleted, resulting in an excess of ROS. This increased ROS leads to cell injury by inciting direct damage of membranes by lipid peroxidation,oxidation of proteins leading to protease release, and inactivation of antioxidants and antiprotease enzymes. Further, these

alterations can lead to changes in transcription factors such as activator protein 1[AP1] and nuclear factor [NF] -KB leading to increased expression of pro-inflammatory cytokines[15-16]. The development of cytokine storm by these proinflammatory cytokines have been linked to the pathogenesis of ARDS during respiratory viral infections. Interleukin-1beta [IL-1BETA] and tumor necrosis factor-alpha [TNF-ALPHA] are also pro-inflammatory cytokines that can induce the generation of reactive oxygen species (ROS), exacerbating ARDS and lung damage [17]. Hence, the pathophysiology of ARDS is characterized by a vicious spiral of oxidative stress and cytokine storm. Thus, any factor leading to excessive production of ROS in its pathological state can lead to the initiation of this vicious spiral which would manifest as a severe phenotype of the disease and result in heightened morbidity and mortality.

The OS is caused by an unregulated generation of ROS disrupting the redox circuits and causing molecular damage [18]. In addition, the OS also results in irregular cell signaling [19,20]. As a result, OS impairsvarious processes such as inflammation, apoptosis, immune cell activation, cardiovascular remodeling, renal dysfunction, and excitation of the sympathetic nervous system [21]. The production of high ROS levels and the subsequent OS has been associated with various chemicals, pollutants, and respiratory viral infections. Respiratory viral infections have been associated with cytokine production, cellular damage, and inflammation; all of which have been linked to OS or redox imbalance. The increased ROS and concurrently weakened antioxidant systems provide a facilitatory environment for the viruses to replicate and lead to the progression of the disease [22].Acutelung injury (ALI) and Acute respiratory distress syndrome (ARDS) are the severe manifestations of respiratory viral infectionsthat can cause high morbidity and mortality[23].Followinga viralinfection, pulmonary macrophages and endothelium get sensitized and regulate thesurface expression of adhesion molecules [24]. Theadhesion of neutrophils to microvascular endothelium activates the neutrophils and culminates in endothelial hyperpermeability during inflammation [25].As a result, an excessive secretion of inflammatory mediators, including reactive oxygen species (ROS) such the hydroxyl radical and nitric oxide (NO), as well as cytokines and chemokines, are released leading to oxidative stress and subsequent acute lung damage [26].

Oxidative stress and inflammatory response

Inflammation of the upper and lower respiratory tract and the subsequent oxidative stresshas been demonstrated to play a crucial role inthe pathogenesis of Chronic Obstructive Pulmonary Disease [27]. An increased number of neutrophils, macrophages, and lymphocytes were observed in the alveolar lavage fluid during the inflammatory reactions. In addition,increased levels of TNFα and IL8 were also detected in the plasma of patientswith COPD.IL8, being a potent chemoattractant for neutrophils, initiates the production of reactive oxygen species leading to both oxidative stress and inflammatory response[28]. Extracellular matrix, mitochondrial respiration, cell proliferation, and defense mechanisms in the lungs can be affected by oxidative stress[29]. Polymorph neutrophils and macrophages have been identified as the major inflammatory cells responsible for the oxidant production inthe lungs of patients suffering from COPD[30]. In addition, oxidative stress also affects the

regenerating mechanism and immune system, affecting the ability of the host to respond and mitigate the damage caused by the viral infection.[31]

Antioxidants Approach: improve oxidative stress in COVID 19

GSH and its precursor N-acetylcysteine (NAC) are some of the most promising molecules for tackling OS. NAC is a plant-derived antioxidant whose thiol group directly scavenges ROS and aids GSH production [32].Based on NAC's protective role inthe various models of influenza and other viral infection [33,34], it has been hypothesized that the NAC could be effective intreating as well as preventing COVID-19 infection [35]. In addition, NAC canalso stimulate the Nuclear factor erythroid 2 p45-related factor2 (NRF2), which increases thetranscription of enzymes involved in phase II detoxification reactions and reduces inflammatory changes [36].NAC also prevented the OS-mediated NF-ƙB activation that upregulated the pro-inflammatory genes[37]. The translocation of NF-ƙBto the cellular nucleus and activation of p38 mitogen-activated protein kinase lowers the intracellular hydrogen peroxide and restores the intracellular total thiol levels [38]. Hence, NRF2 inducers may protect COVID-19 patients from an excessive inflammatory response through the activation of an anti-inflammatory milieu and by preventing the production of excessive proinflammatory cytokines.

The other strategic methods to improve the anti-oxidant defense against COVID-19 can be by limiting the generation of NO [39], supplementing deficient antioxidants such as GSH, vitamins, and trace elements, or directly by trapping ROS [40].Contrastingly,the majority of the aforementioned techniques hada little or negligible effect in the treatment of respiratory illness [41]. However, effective therapeutic use of antioxidants requiresthe right dose, appropriate timing based on the half-life of the antioxidants supplemented, targeting of the appropriate tissue, organ, or cells; and identification of the right type of patient and disease for the therapy [42, 43].

Apart from the above-mentioned methodologies, several laboratory studies have also shown that suppressing ROS generation can have a protective effect in pulmonary vascular disorders [44].Dietary phytochemicals have been demonstrated to have beneficial effects by reducing oxidative damage, epigenetic alterations, and chronic inflammation [45]. Curcumin, an active component in the perennial herb Curcuma longa, is a good example of polyphenol with antioxidant action[46]. In the lungs, it suppresses the expression of NF-ƙB, COX 2, andhemeoxygenase 1 as well as the release of IL8, cytokines, and recruitment of neutrophils[47].It also functions as a scavenger for oxygen and hydroxyl radicals, as well as increasing glutathione levels [48]. Another flavonoid, resveratrol, has been demonstrated to inhibit macrophages that produce inflammatory cytokines in the infected lung. Polyphenols can also induce phase II detoxification genes by a mechanism dependent on Nrf2 [49].Further, the catechins present in green tea (epigallocatechin-3-gallate) as well as theophylline have antioxidant and anti-inflammatory properties and may be effective in increasing glucocorticoids inlungs diseases [50]. The diet comprising of the abovementioned natural anti-oxidants has to be tested in patients with COVID-19 for their efficacy in controlling inflammation and preventing severe phenotype. Well-designed RCTs with anti-

oxidants will provide the necessary scientific evidence to assess the efficacy and calibrate the dose and route for the above-mentioned therapies.

CONCLUSION:

Multiple treatment modalities have been practiced worldwide in the treatment of COVID-19.The emergence of vaccines has helped a lot in combating COVID-19 infection.COVID-19 has a wide range of clinical manifestations, ranging from asymptomatic to severe disease. Various vitamins and trace elements have been found to play different roles in COVID-19 infection and progression.Vitamins such as A, C, E, thiamine (B1), riboflavin (B2) niacin (B3), folic acid (B9), and cobalamin (B12) act as potent anti-oxidant vitamins to counteract the oxidative stress in COVID-19.However, the various antioxidant therapies, which have been used for various respiratory illnesses, have to be validated for the treatment of COVID-19 before being used in the management of the disease.

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