Mini review

Impact of reactive oxygen species on the progression of human diseases by damaging biomolecules

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(Received: January 2023 Revised: May 2023 Accepted: June 2023)

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ABSTRACT

Reactive oxygen species (ROS) are the molecules which have oxygen an atom in its highly reactive form. ROS are formed as a byproduct of normal metabolism and are removed by the antioxidants and enzymes present in the system. But, uncontrolled formation of ROS due to various factors like diseases or stress causes damage to the biomolecules. This oxidation of biomolecules by ROS might help in the progression of human diseases. Understanding the mechanism of development of different human diseases caused due to ROS will help to control the severity of the diseases. Also, on the basis of types of ROS involved, an antioxidant supplement can be selected to mitigate the effect of ROS and ultimately lower the severity of the disease. In this review article, we have tried to summarize the literature available from different sources on ROS formation, biomolecule oxidation and their impact on the progression of various diseases in humans.

Keywords: Reactive oxygen species; oxidative stress; biomolecule oxidation; antioxidants.

INTRODUCTION

The name, reactive oxygen species (ROS), denotes a group of compounds which have oxygen as a component in an extremely reactive form. The generation of the ROS results from the stepwise reduction of molecular oxygen (O_2) by high-energy exposure or electron-transfer processes (1). Singlet oxygen ($^1O_2$), superoxide anion radical ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$) etc. are the examples of ROS. ROS form as the byproduct of normal oxidative metabolism and multiple biological functions, including cell proliferation, migration, and differentiation, are regulated by them (2). In normal condition, the antioxidants and enzymes present in the living system scavenge ROS but under circumstances like stress or diseases, they start producing uncontrollably and become beyond the capability of antioxidants and enzymes to control them (3). Exogenous factors such as tobacco, pollution, smoking, pharmaceuticals, ionizing radiation, etc. can induce ROS formation which can have irreversible effects on cellular physiology. Uncontrolled formation of ROS would cause oxidative stress (OS) leading to numerous cellular processes, including apoptosis, necrosis, and autophagy. ROS may be essential signaling molecules across the entire cell death pathway, according to recent studies (4).

Endoplasmic reticulum and mitochondria are the two major cellular compartments which provide the site for formation of ROS. The extent of damage to the biomacromolecules by ROS depends on the life span of the reactive species and the distance it could travel in the cellular environment from the site of its formation. Normally, the life span of such species inside a cell range between ns to µs (5). Overproduction of ROS can damage biomolecules triggering an inflammatory reaction causing several diseases in humans such as neurological diseases, pulmonary diseases, ocular diseases *etc.*, (6). Therefore, strategies for lowering ROS levels should theoretically have beneficial properties and provide a means of alleviating the symptoms of these conditions (7). There is much research which has documented the role of ROS in human diseases but the mechanism is not well understood. In this review, we have tried to summarize the understanding of how ROS affects the progression of human diseases available in the literature.

Role of ROS in progression of neurological diseases

Although the complex pathophysiology of neurological disorders is still poorly understood, evidence points to ROS generation, inflammation, protein misfolding, and cell death as its main causative factors. Numerous brain disorders and traumas are mostly the result of oxidative damage induced by free radicals. ROS, which are chemically reactive molecules and play a vital part in the progression of neurodegenerative illnesses, have been linked to the etiology of such illnesses (8). The therapy of Huntington illness now has a new therapeutic target in free radical involvement. However, it won't take place unless the free radical's mode of action can be adequately comprehended. To counteract free radical generation and precisely target the radicals that cause neurodegeneration, antioxidant treatment can be employed (9).

Role of ROS in progression of pulmonary diseases

The endoplasmic reticulum (ER) stress and ROS have been linked to lung disorders, such as pulmonary infections, pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), asthma, and lung malignancies (10). ROS initiates harmful processes

such as mitochondrial malfunction and epigenetic alterations which lead to lung illnesses (11). Excessive ROS production might stimulate inflammatory cells, which in turn cause the lungs to produce more ROS leading to a ferocious cycle of inflammation and oxidative stress. Oxidative stress (OS) changes gene transcription, causes hypersecretion and hyperplasia of the mucous glands, and speeds up cell death, all of which contribute to COPD (12). Oxidative stress damages essential biological components through the processes of lipid peroxidation, protein oxidation, and DNA oxidation. The generation of ROS is further increased by inflammation, which alters the transcriptional factors that control the pathways that cells use to respond to stress. The negative pathogenic characteristics frequently observed in lung illnesses are a result of this divergence from normal cell activity. By starting signal transduction pathways, increased ROS generation during inflammation may cause recurrent DNA damage, block apoptosis, and activate protooncogenes. It is therefore possible that prolonged inflammation-related ROS generation in the lung predisposes people to lung illnesses (13).

Antioxidants taken up through dietary sources or medicinal supplements can help asthmatic patients better regulate their asthma and maintain healthy lung function. It is still unclear if oxidative stress causes some lung disorders or is merely one of their consequences. Antioxidant therapy may therefore be ineffective for modifying the course of the disease, despite its potential to reduce oxidative stress-related symptoms (14). Oxidative stress in the patients suffering from COPD is a significant factor for chronic inflammation, disease progression, and worsening of the condition of the patient. Therefore, using antioxidants to target oxidative stress makes sense for a common condition for which there are no efficient disease-modifying medications (15).

Role of ROS in progression of COVID-19 disease

The neutrophil extracellular traps (NETs) can be used as therapeutic targets as they kill viruses by releasing ROS. Numerous physiological processes, such as the production of oxygen radicals, prostanoids and lysosomal enzymes can be triggered by neutrophil activation (16). By taking part in the formation of HOCl, myeloperoxidase released by neutrophil azurophilic granules play a particularly significant role. HOCl is very reactive and affects membrane permeability by oxidizing membrane lipids. It also alters functioning of proteins by oxidizing free functional groups (17). This could contribute to the rapid progression of respiratory failure and mortality in COVID-19 patients who are in the serious phases of the disease (18). The E-protein of the COVID-19 virus contains preserved domains of several enzymes e.g., catalase, peroxidase, cytochrome-c oxidase, and Fe-superoxide dismutase. The E-protein showed Fe-superoxide dismutase activity when bound to iron and catalase, peroxidase, and cytochrome-c oxidase activities when bound to hemoglobin. After E protein's heme binding, oxygen and water were chosen as the building blocks for the ROS synthesis process (19). Antioxidants can be used as therapeutic strategies against COVID-19 disease because the release of ROS generates a state of OS leading to progression of the disease (20).

Role of ROS in progression of aging

The cellular system of humans benefits from the reactive chemicals, radicals and non-radicals that constitute ROS. Excess formation of these reactive compounds become a curse and harms every component of the organism's cellular structure, from the cell membrane to the DNA inside the cells. Cell death is the inevitable consequence of these assaults (21). Environmental and metabolic ROS levels are strictly controlled in physiological processes and are crucial signaling molecules that support cell and tissue homeostasis. On the other hand, during acute and chronic oxidative stress, excessive ROS formation and decreased antioxidant activity are linked to inflammation, tissue damage, and toxicity, which can result in senescence or death (22). Cells, organs, and organisms lead to aging because of their damage due to ROS formation and mitochondria, being the major source of intracellular ROS, has the main role in this process (23). In situations of oxidative stress, 4-hydroxy-2-nonenal, a byproduct of lipid damage, can interfere with signal transduction and protein activity, cause inflammation, and start cellular death (24).

Oxidative stress, the main factor causing chronic inflammation, can also be brought on by ROS causing higher content of oxidized DNA in aged cells. Additionally, oxidative stress can activate pro-inflammatory pathways in the body, which aid in the pathogenesis of a number of age-related disorders (25). The accumulation of unfolded or wrongly folded proteins in the endoplasmic reticulum is mainly due to oxidative stress. The unfolded protein response (UPR) is the name of the group of actions taken by the cell under these circumstances. UPR seeks to improve survival and lessen the burden of protein aggregates. However, unrestrained and prolonged ER stress (ERS) can accelerate apoptosis and inflammation (26). There are several functional foods containing natural antioxidants that have been identified as free radical scavengers. Antioxidant-rich functional foods and nutraceuticals may be crucial in slowing down the aging process (27).

Role of ROS in progression of cardiovascular diseases

ROS, highly reactive forms of molecular oxygen, serve as messengers inside a cell. Endothelial dysfunction, which results in vascular damage in both metabolic and atherosclerotic illnesses, is primarily caused by an imbalance between ROS formation and

cellular defense mechanisms involving antioxidants (28). Vascular disorders have a complicated and poorly known exact process. The regulation of vessel hemostasis, angiogenesis, vascular permeability, and the onset and progression of numerous vascular disorders are significantly influenced by ROS and oxidative stress (29). Cardiac hypertrophy, ischemic-reperfusion damage, and myocyte death have been associated with oxidative damage and may lead to heart failure (30). The deterioration of lipids, proteins, nucleic acids, and other biological elements is the major effect of a disproportionate concentration of free radicals resulting into cardiovascular illnesses (31).

Due to their ability to inhibit spinal cord astrogliosis, maintain neuromuscular junction integrity, and preserve muscle function, anthocyanins are demonstrated to have significant therapeutic potential in a preclinical model of Amylotrophic Lateral Sclerosis (32). ROS and mitochondrial metabolism serve as two fundamental nodes in the convoluted pathway connecting sirtuins to the upkeep of cardiovascular homeostasis. It has been shown that dietary therapies such as fasting and calorie restriction (CR) can regulate sirtuins and improve cardiovascular health (33). Some natural phenolic compounds (like ferulic acid, pterostilbene, tyrosol, *etc*.,) defend the heart against the harmful effects of oxidative stress by controlling the PERK pathway. The deacetylation of the translation initiation factor eIF2 by SIRT1 results in the unfolded protein response (UPR). Consequently, making these molecules stronger or more stable will increase SIRT1 deacetylase activity. Perhaps chemically altered versions of these phytonutrients could be a successful approach to the care of cardiomyopathies brought on by oxidative stress (34).

Role of ROS in progression of ocular diseases

ROS can serve as intermediates in a variety of pathways, and they are also causative factors for conditions like inflammation, and damage in the eyes. Scavenging ROS in pathological conditions may prevent cell damage and regulate the pathogenic process (35). Numerous acute and chronic illnesses, as well as natural aging, can cause an overexpression of ROS in the ocular surface. Recent researches have shown that oxidative stress harms the ocular surface resulting in dry eye disease (36).

CONCLUSION

In almost all the articles we reviewed above, the researchers and scientists have emphasized that ROS is the key factor in the progression of several illnesses like, neurological disorders, lung diseases, heart diseases, and many more. On the way to increasing severity of these diseases, ROS oxidizes biomolecules (e.g., lipids, proteins, DNA, etc.,). Understanding the function of ROS in the progression of various human illnesses can provide us a way to prevent severe mortality among the patients infected with such diseases. The inflammatory responses induced by liberation of ROS create a condition of oxidative stress and using antioxidants as remedial strategies is recommended. Although the functions of ROS in the causation of different diseases are not yet fully understood, yet an active lifestyle and a healthy diet have been shown to be effective in lowering disease risk. Antioxidant supplements should be thought of as health maintenance assistance, however, changing one's lifestyle and eating habits is a crucial part of lowering the oxidative stress caused by ROS. Wine, tea, coffee, and other alcoholic and non-alcoholic beverages can help balance ROS in the body. Antioxidant supplements should ultimately be regarded as a suitable food supplement as they are related to human life extension.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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