Review Article

When oxygen can be toxic? A review

Abstract

No one in the previous recent years had in mind that the oxygen we breathe that contributes to saving the lives of millions of patients and the main element of life has no harmful or toxic effects on the body. Oxygen and water are the lifeblood of living organisms in general, but under certain conditions such as weak immune status and lack of the body's ability to excrete natural antioxidants occurs that the oxygen molecule reacts as a receptor for electrons, since its structure in the case of electronic stability contains two electrons that are not bound and as a result of successive reactions that produce some intermediate compounds (such as hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2) and anion superoxide anion radical ($^{\bullet}O^{-}_{2}$) that are not desirable and that affect for great extent the degree of cell division process and physiological activities that it performs because it is a powerful oxidizer. For this reason, the role of natural antioxidants has become necessary and important to get rid of the toxicity of these compounds (Reactive Oxygen Species, ROS), and among the well-known antioxidants are Vitamin C (ascorbic acid) and Vitamin D and glutathione. Some body-secreting enzymes such as catalase, peroxidase and superoxide dismutase make an effective contribution to the elimination of these oxidizing substances.

Keywords: Interaction of oxygen, Oxygen Reactive Species (ROS), Oxidative damage, Anti-oxidative defense.

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1. Introduction

There are indications that oxygen was not present in the atmosphere of the earth at the time of its formation, that is, from about 4.5 to 4.8 billion years ago, and there was much controversy that oxygen existed in the atmosphere about 2 billion years ago as a result of the development of the activity of photosynthetic organisms, the first of which was blue-green algae. Since then, the organisms present at that time were anaerobic microorganisms, and the evolution of photosynthetic organisms was accompanied by a gradual accumulation of oxygen that had a great impact on the emergence of aerobic organisms about 1.5 billion years ago [1,2]. By using oxygen as a final oxidizing agent, air cells can extract more energy from non-oxidizing nutrients such as glucose, because it can be fully oxidized to carbon dioxide (CO_2). Thus, aerobic life images flourished and compared to those in anaerobic organisms, and on the other hand oxygen was defined as deadly or toxic to some forms of life, for example some obligatory anaerobic organisms such as those that live in the soil thrive only in the absence of oxygen and die in its presence, like Clostridium [3]. Many questions come to mind, for example, why is oxygen toxic to some organisms? How can anaerobic organisms survive and thrive in the presence of this toxic substance (oxygen)? It can be answered by these two questions that the oxygen in the case of electronic stability is not toxic or harmful to the organism, but because its electronic structure contains two electrons that are not bound, there are restrictions on the possibility of the oxygen molecule interacting as a receptor for the electrons, for example when the oxygen molecule is converted into a union of hydrogen atoms to form water, it occurs in four consecutive steps, each step in which one electron transfer takes place [4]. If the oxygen reacts in such a way, and it often happens, this results in the appearance of intermediate compounds that lead to many problems of life, because it is one of the strong oxidizing materials. Examples of these oxidizing materials or reactive oxygen species (ROS) are the superoxide anion radical ($^{\bullet}O^{-}_{2}$), hydroxyl radical ($^{\bullet}OH$) and hydrogen peroxide (H_2O_2) [5]. The present review deals with different types of ROS, their production, and their role as messenger and inducer of oxidative stress and to focus on the anti-oxidative defense system against ROS.

2. Interaction of oxygen molecule as an electron receiver

There is no doubt that the oxygen we breathe represents the element of life for humans and all living things except for anaerobic bacteria. In case of patients

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who have difficulty in breathing, they are given oxygen in balanced quantities through oxygen mask (Fig 1). The nutrient compounds, inside of the cell, are oxidized through complex enzymatic processes and reactive oxygen species (ROS) are formed in small amounts as natural byproducts of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis [6], however, during times of environmental stress such as heat or Ultraviolet (UV) exposure, ROS levels can increase dramatically. This may result in significant damage to cell structures and this is well known as oxidative stress. In plants the production of ROS is mainly influenced by stress factor responses including nutrient deficiency, drought, salinity, chilling, UV radiation and metal toxicity [7]. During a variety of biochemical reaction within the cell, ROS are produced especially within mitochondria, endoplasmic reticulum and perisomes [8,9]. Through the process of oxidative phosphorylation mitochondria convert energy into adenosine triphophate (ATP). In this process, protons are transported across the inner mitochondrial membrane by electron transport chain, which pass through a series of proteins via oxidation/reduction reactions in which each acceptor protein along the chain having a greater reduction potential than the previous. The last destination of an electron in this chain is an oxygen molecule. Normally, the oxygen is reduced to produce water; however, in about 0.1–2% of electrons passing through the chain and oxygen is incompletely reduced to give the superoxide anion radical ($^{\bullet}O^{-}_{2}$) [10]. The reduction of molecular oxygen (O_2) produces superoxide anion radical ($^{\bullet}O^{-}_{2}$), which is the precursor of most other reactive oxygen species [equation 1]. Dismutation of $^{\bullet}O^{-}_{2}$ produces hydrogen peroxide (H_2O_2) [equation 2]. Hydrogen peroxide in turn may be partially reduced, thus forming hydroxide ion and hydroxyl radical ($^{\bullet}OH$), or fully reduced to water [equation 3 & 4] [11]. The formation of ROS can also be stimulated by a variety of agents such as xenobiotics, pollutants, radiation and heavy metals [12]. Another type of reactive oxygen species is singlet oxygen ($^1O_2$) which is produced for example as a byproduct of photosynthesis in plants. In the presence of light and oxygen, photo-sensitizers (chlorophyll) may convert triplet oxygen ($^3O_2$) to singlet oxygen ($^1O_2$) [13].

$$O_2 + 1e \longrightarrow {}^{\bullet}O^{-}_{2}\ \text{[Superoxide anion radical]}\ldots\ldots\ldots\ \text{equation 1}$$

$$^{\bullet}O^{-}_{2} + 1e + 2H^{+} \longrightarrow H_2O_2\ \text{[Hydrogen peroxide]}\ \ldots\ldots\ldots\ldots\ \text{equation 2}$$

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$H_2O_2 + 1e + H^+ \longrightarrow H_3O_2 \longrightarrow H_2O + {}^{\bullet}OH$ [radical] …. equation 3

${}^{\bullet}OH + 1e + H^+ \longrightarrow H_2O$ ..... equation 4

$O_2 + 1e + H^+ \longrightarrow 2H_2O$

In the first step, an electron is transferred to the oxygen molecule, leading to the formation of the superoxide anion radical (${}^{\bullet}O^-_2$). In the second step, the electron moves from the superoxide anion radical (${}^{\bullet}O^-_2$) in the previous step in the presence of a pair of protons ($2H^+$) leading to the formation of a molecule of hydrogen peroxide (H_2O_2), and in the third step, hydrogen peroxide is converted in the presence of a proton and an electron to give a molecule of water (H_2O) and a hydroxyl radical (${}^{\bullet}OH$) through the central compound H_3O_2 and finally the hydroxyl radical is combined with a proton (H^+) and an electron (1e) to give a molecule of water (H_2O) . The result of the previous steps is the interaction of a molecule of oxygen (O_2) with four electrons and four protons to give two molecules of water ($2H_2O$). Fig.2 represents the structures of oxygen molecule and reactive oxygen species (ROS).

Harber-Weiss reaction generates the highly reactive hydroxyl radical (${}^{\bullet}OH$) from an interaction between superoxide (${}^{\bullet}O^-_2$) and hydrogen peroxide (H_2O_2) as follows [14]:-

$H_2O_2 + {}^{\bullet}O^-_2 \longrightarrow O_2 + OH^- + {}^{\bullet}OH$ [Hydroxy radical]

Metal catalysis is necessary for this reaction. In the first step First, ferric ions (Fe(III)) is reduced by ${}^{\bullet}O^-_2$ to ferrous ions followed by oxidation by dihydrogen peroxide (Fenton reaction).

$Fe^{3+} + {}^{\bullet}O^-_2 \longrightarrow Fe^{2+} + O_2$

$Fe^{2+} + H_2O_2 \longrightarrow Fe^{2+} + OH^- + {}^{\bullet}OH$ [Hydroxy radical].

3. Oxidative damage of ROS

The formed reactive oxygen species (ROS) are extremely harmful to organism at high concentrations and this state of oxidative stress can occur when the level

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of ROS exceeds the defense mechanisms. These species pose their damage effects previously by lipid peroxidation, nucleic acid damage, proteins oxidation and enzyme inhibition followed by causing activation of programmed cell death (PCD) pathway which ultimately leading to death of the cells [15,16]. ROS can also serve as second messengers in different cellular processes including tolerance to environmental stresses [17,18]. The fact that ROS can act as damaging or signaling molecule depends on the delicate equilibrium between ROS production and scavenging activities of cells. The excess of ROS is achieved by antioxidative system including enzymatic and non-enzymatic antioxidants. Examples of enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), guaiacol peroxidase (GPX), glutathione reductase (GR) and mono-dehydroascorbate reductase (MDHAR) [19]. However glutathione (GSH), carotenoides, tocopherols ascorbate and phenolics serve as non-enzymatic antioxidants inside the cell. Studies indicated that $^{\bullet}OH$ represents the most reactive among all ROS because it has a single unpaired electron, capable to react with oxygen in triplet ground state. As cells have no enzymatic mechanisms, the elimination of the excess of hydroxyl radical eventually lead to cell death [20]. The oxidation of organic substrates in the cell by hydroxyl radical may proceed either by addition of $^{\bullet}OH$ to organic molecules or by the abstraction of a hydrogen atom from it. Hydroxyl radical ($^{\bullet}OH$) causes subsequent cellular damages and interacts with all biological molecules resulting to protein damage, lipid peroxidation, and membrane destruction [21]. However superoxide anion radical ($^{\bullet}O^{-}_{2}$) and H_2O_2 are only moderately reactive and can be inhibited by both SOD and CAT. Under normal and stress conditions H_2O_2 can be generated in the cells. Photorespiration, photooxidation, NADPH oxidase, xanthine oxidase and *β*-oxidation of fatty acid are the major sources of H_2O_2 in plant cells [22]. Fig.3 shows the stepwise oxidative damage of cells by overproduction of ROS.

4. Site of ROS production

Reactive oxygen species (ROS) are produced either in stressed and unstressed cells at several locations in mitochondria, plasma membrane, chloroplasts, peroxisomes, endoplasmic reticulum and cell walls. ROs are formed by the leakage of electrons onto oxygen from mitochondria, plasma membranes, chloroplasts or as by-products of some metabolic pathways localized in different cellular compartments. Fig.4, demonstrates the different sites of ROS production in plants.

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5. Antioxidative defense system against ROS

In normal conditions, there is a proper balance between productions and quenching of ROS, however this balance may be perturbed due many adverse environmental factors giving rise to an increase of intracellular ROS levels and consequently can induce oxidative damage proteins, lipids and nucleic acids [23]. In order to avoid such oxidative damage non-enzymatic and enzymatic components of anti-oxidative defense system have been manipulated. The non-enzymatic oxidative components include glutathione (*γ*-glutamyl-cysteinyl-glycine (GSH) [24], ascorbate [25], tocopherol [26], carotenoids [27], and phenolic compounds [28]. On the other hand, the enzymatic components of the anti-oxidative defense system operate in different sub-cellular compartments and respond in concert when cells are exposed to oxidative stress conditions. These enzymes include glutathione reductase, superoxide dismutase [29], catalase [30], enzymes of ascorbate-glutathione [15], guaiacol peroxidase [31], mono-dehydroascorbate reductase [32] and dehydroascorbate reductase [19].

6. Conclusion

Under various environmental stress conditions (such as salinity, chilling, drought, metal toxicity, and Ultraviolet) if prolonged over to a certain extent, disrupt the cellular homeostasis and enhance the production of ROS. However, under normal growth condition, ROS production in various cell compartments is low. In low concentrations ROS act as signaling molecules that mediate several responses in cells. High level of ROS production causes oxidative damage to protein, lipid and DNA, these effects lead to altered membrane properties such as fluidity, loss of enzyme activity, protein inhibition and cross-linking and ion transport resulting in cell death. These detrimental oxidative damage can be avoid by implementation of the anti-oxidative defense system comprising of enzymatic and non-enzymatic components. Recently, the future progress in proteomics, genomics and metabolomics, will help in clear understanding new pathways by which cellular cell responses to oxidative stress damage.

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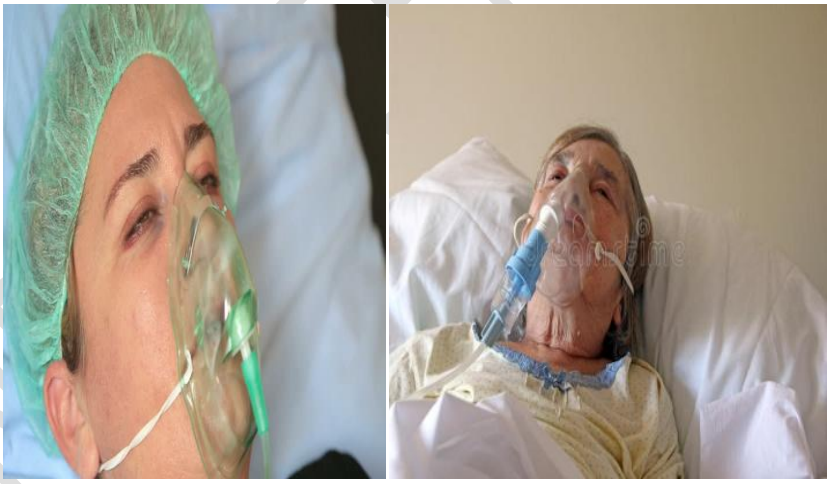

Fig. 1: Oxygen masks deliver higher concentrations of oxygen for patients with serious respiratory conditions

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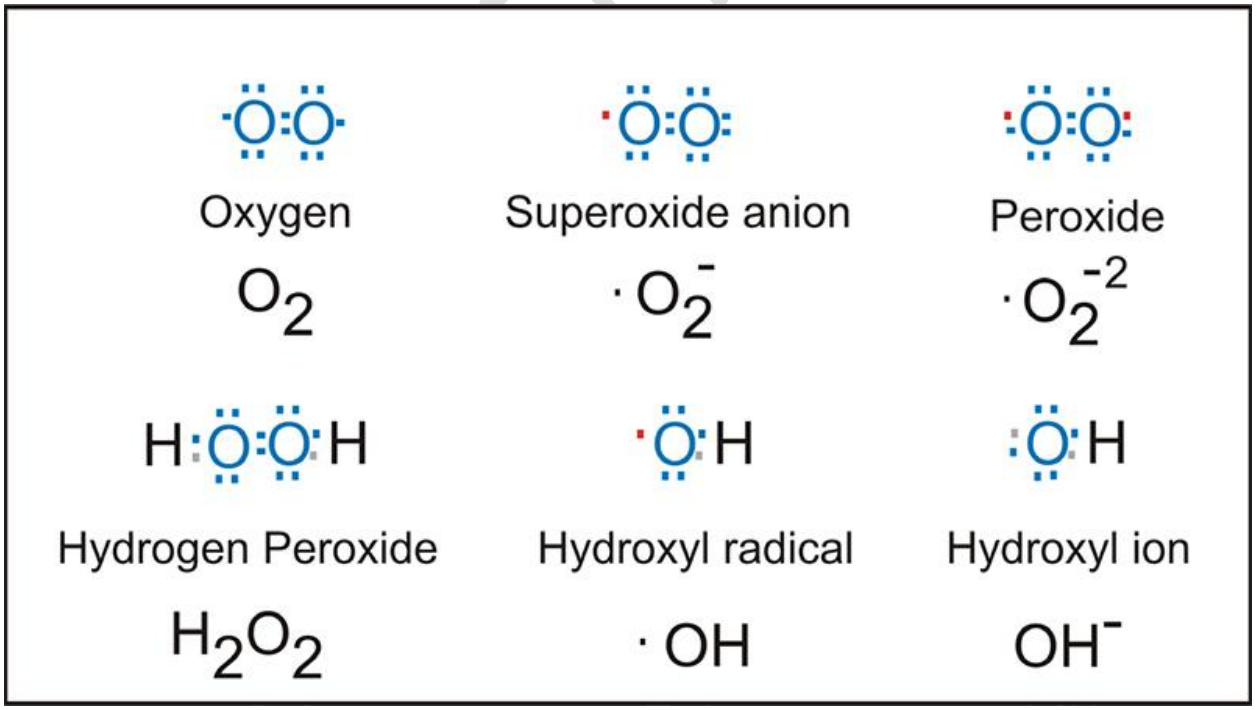

Fig 2: Structures of oxygen molecule and reactive oxygen species (ROS).

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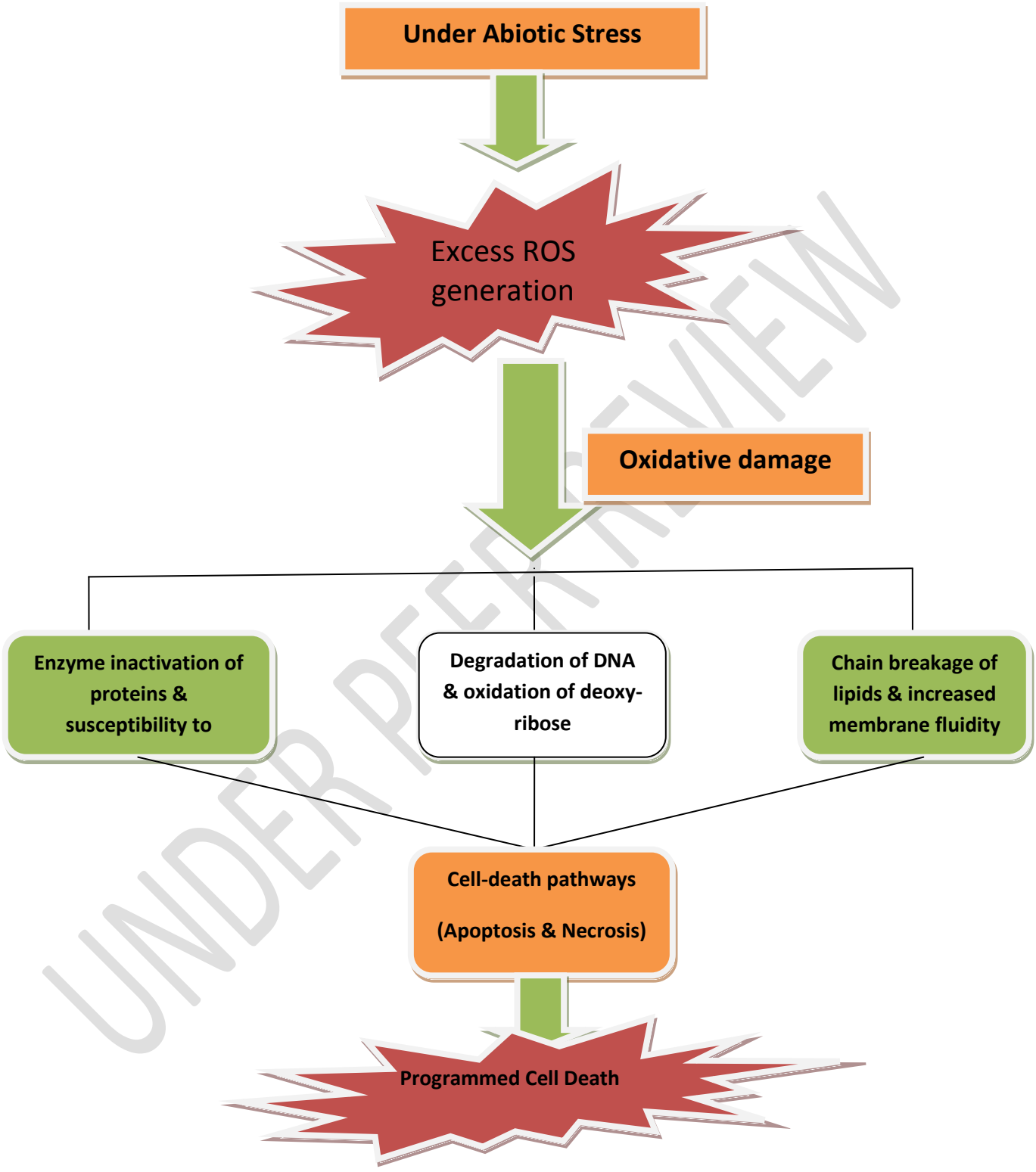

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Fig.3: Stepwise oxidative damage of cells by overproduction of ROS.

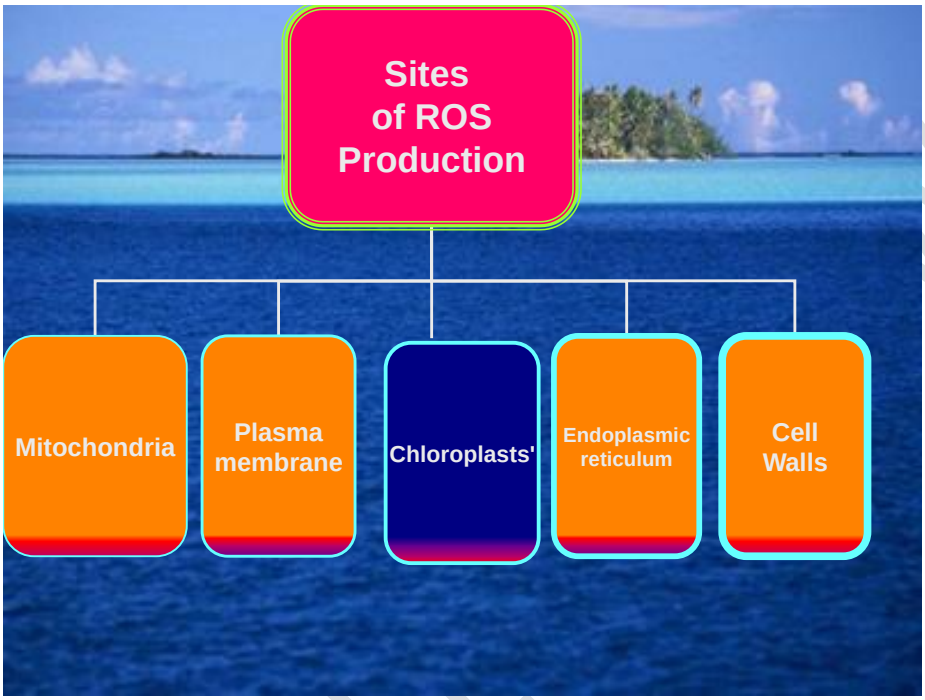

Fig.4: Sites of reactive oxygen species (ROS) production in plants.

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Figure Legends:

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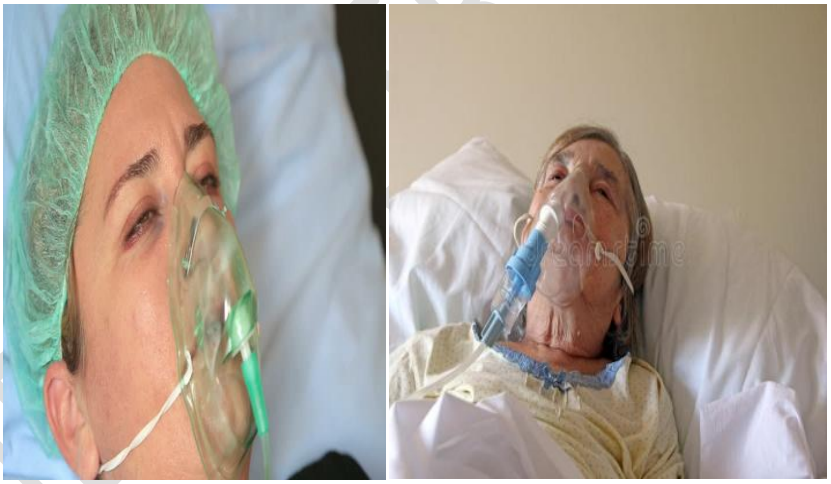

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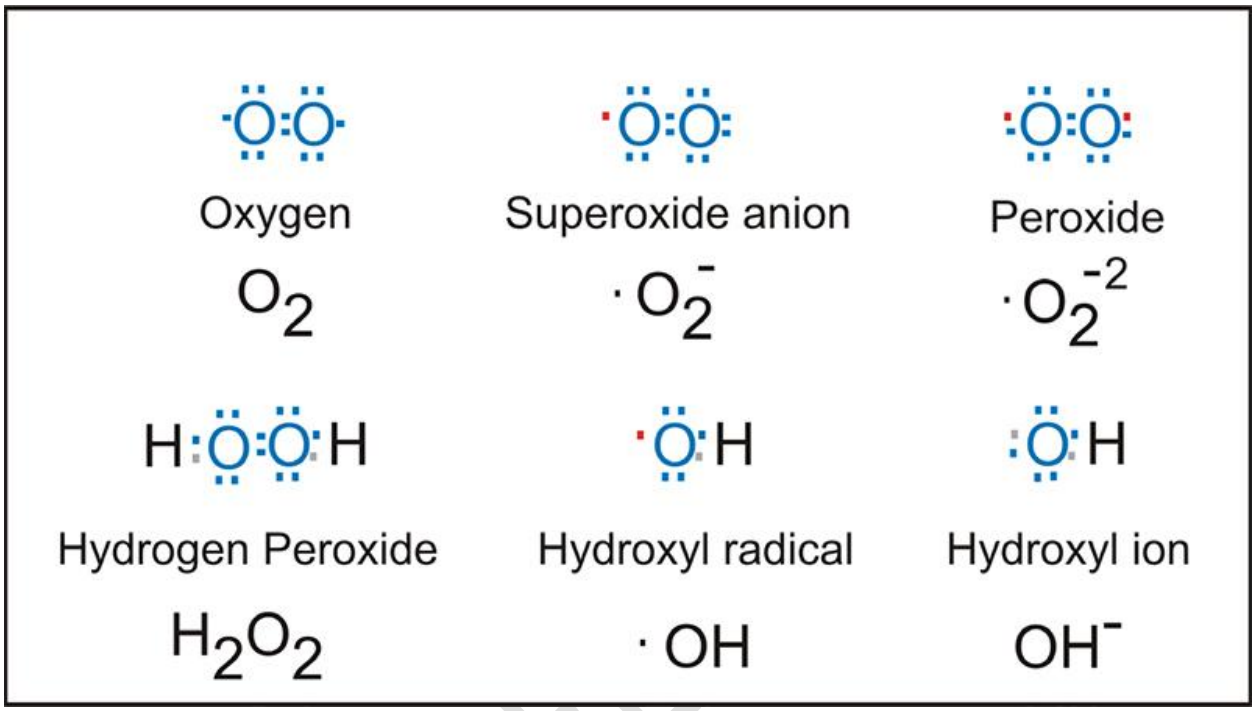

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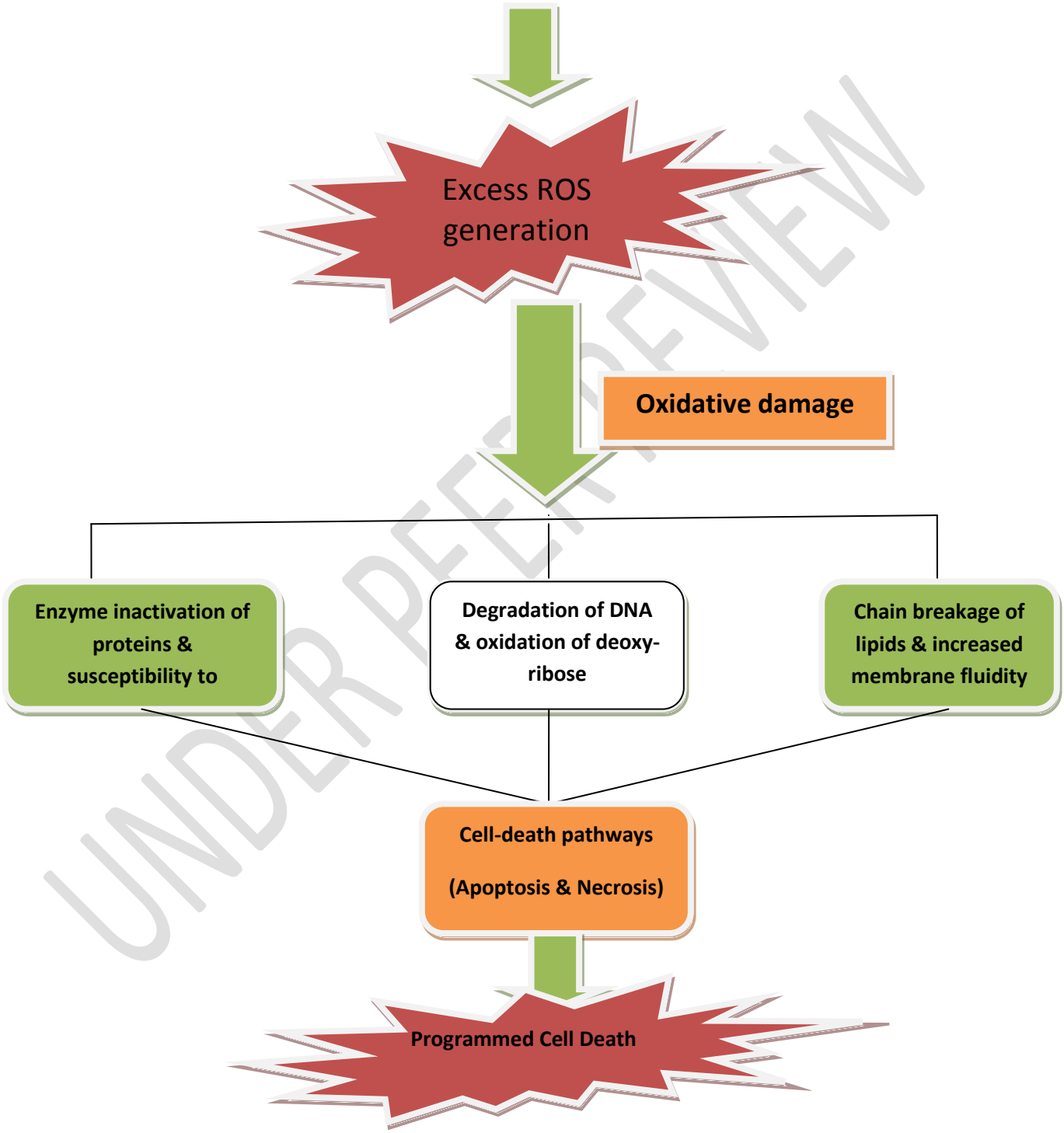

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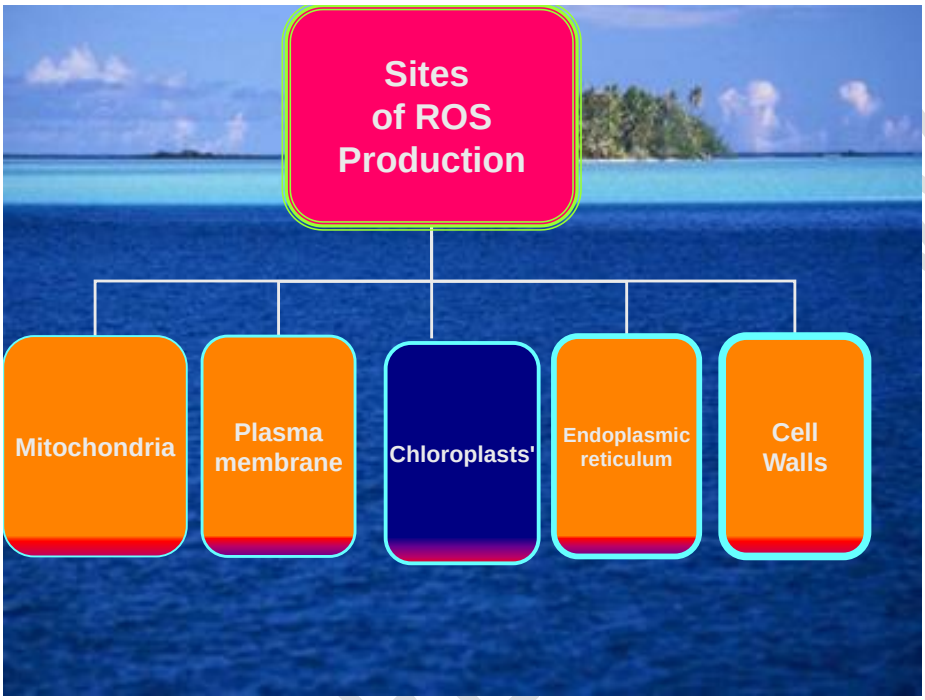

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