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Review Article
OXIDATIVE STRESS: THE ROLE OF REACTIVE OXYGEN SPECIES (ROS) AND ANTIOXIDANTS IN HUMAN DISEASES

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Abstract

Oxidative stress has new but solid route *in vivo* studies. Free radicals characterized by comprising an unpaired electron(s), which enable them from behaving as oxidant agents. Reactive oxygen and nitrogen species are reactive species generated locally in living systems to perform specific functions, and also could be gained from outside environment. The elevated levels of ROS and RNS cause problems to tissue's and organ's cells through the harmful effects of oxidative properties. The neutralize agents of these reactive species are the antioxidant substances which generated *in vivo* as enzymes, metalloproteins, or small metabolites. Antioxidants also provided from external sources such as diet and drugs. Both, reactive species and antioxidants are involving in the development of oxidative stress. It has been proved that oxidative stress associate with certain pathologies, such as Alzheimer's disease, ischemia-reperfusion injury, skin diseases, renal disorders, and more. The oxidative stress associated with diseases increases the outcome risks, in this article we demonstrate how oxidative stress developed as well as certain methodologies for examining the oxidative stress in human and animal diseases.
***Keywords*:** free radicals, ROS, oxidative stress, antioxidant, diseases

Introduction

Free radical in the terms of biology and medicine, is used to describe any chemical species has the ability of independent existence and comprises one or more unpaired electrons in atomic or molecular orbitals (Kunwar & Priyadarsini, 2011). Both anionic and cationic free radicals exist in biological systems. In general, free radicals are reactive species. However, as described below, reactive species are not necessarily free radicals (Rani & Yadav, 2014).

1. Reactive oxygen species

Reactive oxygen species (ROS) is a term used to define oxygen-containing reactive species (Nosaka & Nosaka, 2017). ROS include superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), peroxyl radical ($LOO^{\bullet}$), alkoxyl radical ($LO^{\bullet}$), lipid hydroperoxide (LOOH), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and ozone (O_3). Similarly, the term reactive nitrogen species (RNS) has been used to include nitric oxide ($^{\bullet}NO$), peroxynitrite, nitrogen dioxide ($^{\bullet}NO2$), and other oxides of nitrogen or nitrogen-containing reactive species (de Lucca Camargo & Touyz, 2019).

Table 1: Reactive oxygen and nitrogen species of biological interest (Mohammed, Kadhim, Jassimand, & Abbas, 2015).

Reactive species	Symbol	Half-life (in sec)	Reactivity / Remarks
Reactive Oxygen Species:			
Superoxide	$O_2^{\bullet-}$	10^{-6} s	Generated in mitochondria, in cardiovascular system and others.
Hydroxyl radical	$^{\bullet}OH$	10^{-9} s	Very highly reactive, generated in Fenton reaction.
Hydrogen peroxide	H_2O_2	Stable	Formed in the body by large number of reactions.
Peroxyl radical	$LOO^{\bullet}$	s	Reactive and formed from lipids, DNA, proteins, etc.
Organic hydroperoxide	ROOH	Stable	Reacts with transit metal ions to produce reactive species.
Singlet oxygen	$^1O_2$	10^{-4} s	Highly reactive formed during photosensitization and chemical reactions.
Ozone	O_3	s	Present in the atmosphere.
Reactive Nitrogen Species:			
Nitric oxide	$^{\bullet}NO$	s	Neurotransmitter and blood pressure regulator.
Peroxynitrite	$ONOO^-$	10^{-3} s	Formed from superoxide and nitric oxide.
Nitrogen dioxide	$^{\bullet}NO2$	s	Formed during atmospheric pollution.

ROS are tiny substances with high reactivity. The formation of ROS occur normally in the living system as a part of signaling pathway. However, elevated production of ROS for any reason cause a stressful action which alter cellular structures. The general harmful effects of reactive oxygen species on the cell are most often like -Damage of DNA, oxidations of polydesaturated fatty acids in lipids, oxidations of amino acids in proteins, oxidatively inactivates specific enzymes by oxidation of co-factors, (Greenberg *et al*., 1994; Guzik, Korbut, & Adamek-Guzik, 2003; Halliwell & Gutteridge, 2015; Heinonen *et al*., 1994; Pignatelli, Pulcinelli, Lenti, Paolo Gazzaniga, & Violi, 1998) see Fig 1.

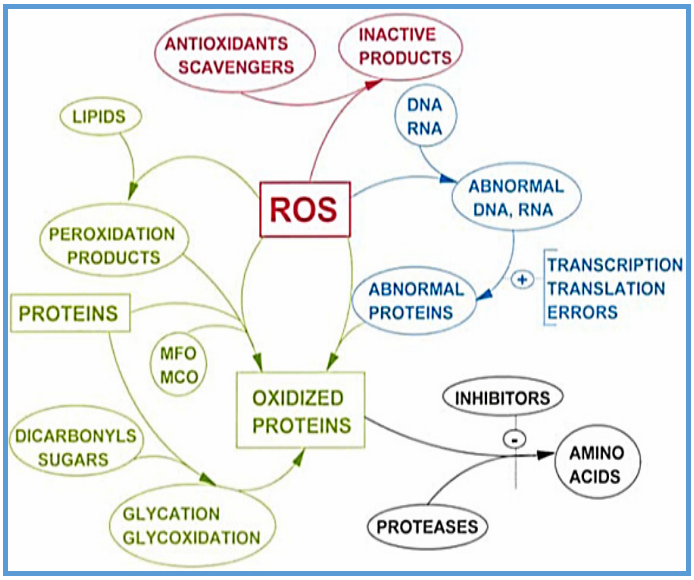

Fig. 1: Effects of ROS (Norris & Lalchandani, 2018).

2. Sources of ROS

The major process of ROS production in aerobic organisms is the oxygen reduction during electronic respiratory chain (Kowaltowski, de Souza-Pinto, Castilho, & Vercesi, 2009; Turrens, 2003). ROS and RNS generation take place in various endogenous, such as NADPH oxidases and mitochondria, and exogenous agents, including physical agents, xenobiotic metabolism, and biologic agents, (Krumova & Cosa, 2016) see Table 2.

Table 2: Sources of Reactive oxygen and nitrogen species in the body (Mohammed *et al*., 2015).

Sources	Description
Endogenous	NADPH oxidases Mitochondria Xanthine oxidoreductase Cytochrome P450 oxidases Nitric oxide synthase Peroxisomes
Exogenous	Physical agents Xenobiotics Biologic agents

2.1. Endogenous sources

Here are some of the endogenous sources in humans:

2.1.1 NADPH oxidases

Phagocytic cells comprises NADPH oxidase which utilize oxygen as a part of defensive system to produce large amounts of $O_2^{\bullet-}$ during respiratory burst. Phagocytic NADPH oxidase is possibly the best well known cellular source of ROS (Lambeth, 2004).

2.1.2 Mitochondria

The respiration of mitochondria accounts for 80-90% from oxygen utilization in the cells of mammalian. In physiological conditions, the mitochondrial complexes I and III involved in the one electron reduction of O_2 to $O_2^{\bullet-}$. Statistics have shown that approximately 0.1% of oxygen is converted into superoxide at physiological respiration (Li, Zhu, & Trush, 1999). The superoxide formed in mitochondria is either spontaneously or catalyzed by manganese superoxide dismutase in the mitochondrial matrix undergoing dismutation to produce hydrogen peroxide. Under various pathophysiological conditions, including tissue ischemia-reperfusion (IR) the development of ROS via the mitochondrial electron transport chain is increased (Ambrosio *et al*., 1993).

2.1.3 Other endogenous sources

Xanthine oxidoreductase (XOR) exists either as xanthine dehydrogenase or xanthine oxidase, both of them catalyze the formation of uric acid from xanthine and hypoxanthine substrates. During the catalytic action of XOR a one- or two-electron reduction to O_2 occurs, yielding $O_2^{\bullet-}$ from the univalent reduction or H_2O_2 from the divalent reduction (Chen, Lü, & Yao, 2016). XOR generated ROS are implicated in pathophysiology of several disorders, such as tissue IR injury. Cytochrome P450 enzymes, particularly P4502E1 can generate significant amounts of ROS when being induced by xenobiotics (Lu & Cederbaum, 2008).

2.2. Exogenous sources

Here are some of the exogenous sources of ROS and RNS:

2.2.1 Physical agents and particulate matter

The formation of hydroxyl radical arises from the homolysis of water as a consequence of exposure of ionization radiations, as well as H_2O_2 homolysis by UV rays. The exposure of biological systems to ionizing radiation involved in the formation of other types of ROS and RNS besides hydroxyl radical. Environmental pollution with transition metals give arise to ROS through Fenton reaction. Various types of nanomaterials, including silicon, gold, and copper nanoparticles as well as CdTe quantum dots have been shown to induce ROS/RNS formation in biological systems though the detailed mechanisms remain to be elucidated. In contrast, cerium oxide nanoparticles and fullerene-derived nanomaterials exert antioxidant effects via scavenging ROS in biological systems (Xia, Li, & Nel, 2009).

2.2.2 Xenobiotics

Xenobiotics, including drugs have the ability to elevate the levels of reactive oxygen and nitrogen species in the body, which ultimately cause oxidative injury. In general, there are four mechanisms explain the increasing of ROS and RNS (El-Demerdash, Tousson, Kurzepa, & Habib, 2018):

- xenobiotics redox amplification, such as quinone compounds.
- Interference with the mitochondrial electron transport chain, which causes increased electron leakage and thus increased superoxide formation
- Induction of ROS/RNS-producing enzymes, such as P4502E
- Inhibition of cellular antioxidants.

2.2.3 Biologic agents

Several biological agents such as bacteria and viruses induce the production of ROS and RNS at the target cells. Four potential mechanisms explain the overproduction of ROS and RNS during bacterial and viral infection, (Abdalla *et al*., 2004; Berger *et al*., 2004):

- Biologic agents induce activation of inflammatory cells, such as phagocytic cells, resulting in ROS formation from NADPH oxidase.

- Biologic agents can cause activation of other ROS/RNS-producing enzymes, such as inducible nitric oxide synthase to generate large amounts of nitric oxide. As described below, nitric oxide reacts with superoxide, generating the highly reactive species peroxynitrite.
- Certain bacteria contain ROS-producing enzymes that may release significant amounts of ROS.
- Some bacteria-derived toxins may downregulate tissue antioxidants. Viral infections may also decrease the expression of certain antioxidants in host cells via modulating cell signal transduction.

3. Free radicals targets

There are three major cellular sites for the attack of free radicals. The first is lipid components, free radicals cause a peroxidation of the cellular lipids, especially to those of cell membrane. Peroxidation of membrane lipids disturbs its fluidity and permeability characteristics (Yin, Xu, & Porter, 2011). The second site is cellular proteins, which cause a damaged proteins through specific oxidation to amino acid sequences, which affect many kinds of proteins and their functions (Stadtman & Levine, 2003). The third site is DNA, in which the attack of free radicals leads to DNA fragmentation (Valko, Izakovic, Mazur, Rhodes, & Telser, 2004; von Sonntag, 2006). The site of tissue damage by free radicals is dependent on the tissue and the reactive species involved. The ultimate result may lead to cell apoptosis and necrosis (cell death) (Lemasters, 2018). The cell own a normal defensive substances against ROS and other free radicals through certain enzymes activity such as superoxide dismutase and catalase, or through small molecules such as uric acid, and glutathione, which collectively known as antioxidants, because they eliminate the oxidant property of ROS and free radicals through several mechanisms (Lawson *et al*., 2017). ROS are involved in cardiovascular disease, hearing impairment via cochlear damage induced by elevated sound levels, ototoxicity of drugs such as cisplatin, and in congenital deafness in both animals and humans (Pacher, Beckman, & Liaudet, 2007; Rhodes, 2000).

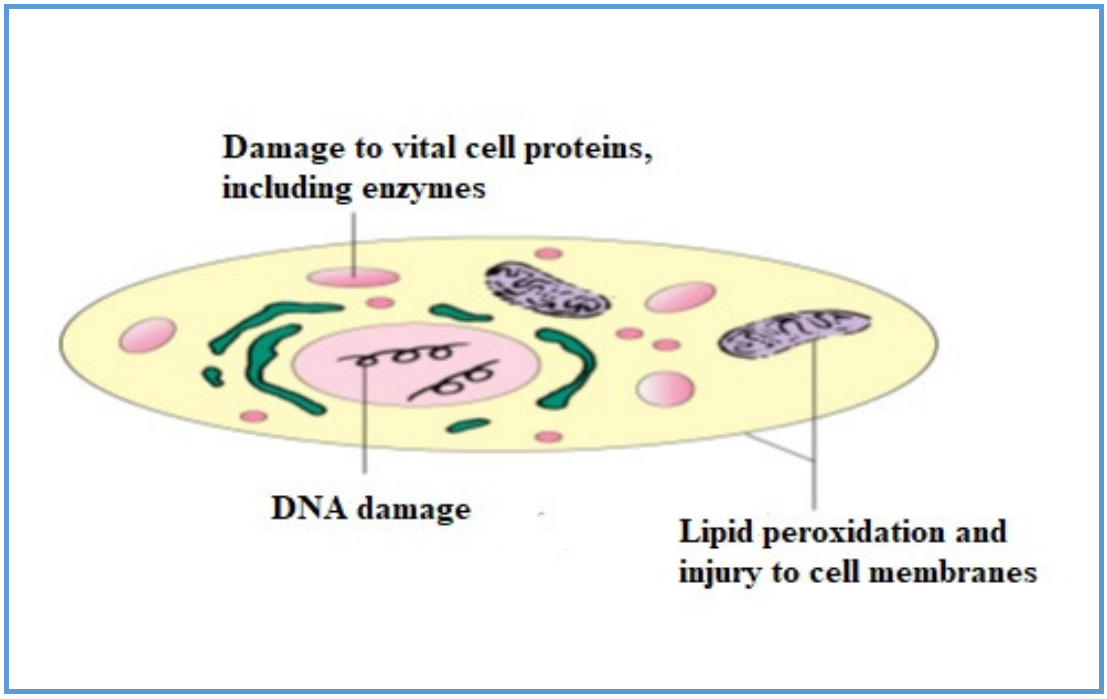

Fig. 2 : Cellular damage due to free radicals (Sen, 2003).

In general, the harmful effects of ROS can be summarized as:

- Damage of DNA
- Oxidations of polyunsaturated fatty acids in lipids
- Oxidations of amino acids in proteins
- Oxidatively inactivate specific enzymes by oxidation of co-factors

4. Oxidative stress in diseases

It has been observed a significant increasing in ROS and RNS levels under several pathological conditions, hence a possible associations may involve between diseases and oxidative stress. The effects of regulating ROS and RNS on disease incidence can be summarized as (Li, 2011):

- ROS/RNS serves as the primary main source of illness. ROS / RNS regulation should inhibit or delay progression of the disease.
- ROS / RNS serves as one of the initial causes of illness. ROS / RNS regulation should help reduce the progression of the disease.
- OS/RNS serve as a contributing factor to the development of diseases. ROS/RNS regulation should delay the progression of the disease.
- ROS / RNS are developed as a result of the disease and contribute to the pathophysiological progression of the disease. ROS / RNS regulation should delay the progression of the disease.
- ROS / RNS is developed as a consequence of the disease and does not play any part in the initiation or development of the disease. The ROS / RNS regulation would have no effect on the mechanism of disease.

4.1. Diseases Involving an Oxidative Stress Mechanism

The establishment in a specific disease of a causal or contributing function for ROS/RNS is the basis for developing strategies to prevent and treat that particular

disease. Based on results from intensive work on animal models of human diseases, as well as individual topic studies over the past few decades, it has been recognized that ROS/RNS play a causal and/or a contributing role in a wide variety of diseases (Valko *et al*., 2007).

Table 3: Disease processes and related conditions in which reactive oxygen and nitrogen species play a causal or contributing role (Li, 2011).

Disease	Description
Cardiovascular diseases	Hypertension, atherosclerosis, myocardial IR injury, heart familiar, and cardiotoxicity.
Diabetes and metabolic syndrome	Diabetes, diabetic complications, obesity, and insulin resistance.
Neurological diseases	Alzheimer's disease, Parkinson's disease, stroke, and amyotrophic lateral sclerosis.
Pulmonary diseases	Chronic obstructive pulmonary disease, asthma, hyperoxia-induced lung injury, and pulmonary toxicity.
Hepatic and gastrointestinal diseases	Alcoholic fatty liver disease, non-alcoholic fatty liver disease, hepatotoxicity, inflammatory bowel disease, and IR injury.
Renal diseases	Diabetic nephropathy, IR injury, and nephrotoxicity.
Eye diseases	Cataract, and age-related macular degeneration.
Skin diseases	UV-induced skin injury, scleroderma, contact dermatitis, and Psoriasis.
Cancer	Chemical carcinogenesis, spontaneous cancer development, angiogenesis, and cancer metastasis.
Aging	Life span, and aging-related organ degeneration.
Arthritic diseases	Rheumatoid arthritis, and other types of arthritis.
Sepsis	Septic shock, and multiple organ dysfunction.
Infections	Viral and bacterial infections.

Ischemia-reperfusion injury have been linked with reactive oxygen species and development of oxidative stress, the relationship between them have well established (Kadhim, Mohammed, & Abbood, 2020; Mohammed, Kadhim, & Abbood, 2020).

5. Antioxidants

Antioxidant materials are chemical substances act to neutralize the free radicals or interfere their action (Halliwell, 1990). Cells comprises an adequate defensive hosts to protect them from the harmful effects made by free radicals. Among these antioxidants are the enzymes; e.g. superoxide dismutases SOD and glutathione peroxidases GPx, the small molecules; e.g. thiols and uric acid, the external antioxidants; e.g. vitamin C and vitamin E (RG, 2005).

5.1. Classification of antioxidants

Antioxidants classified into two main categories, endogenous antioxidants and exogenous antioxidants. The endogenous antioxidants comprise those whom made within the cells of *in vivo* and follow further sub-classification as protein (Elias, Kellerby, & Decker, 2008) antioxidants and non-protein antioxidants. The protein sub-class include enzymes such as SOD, CAT, and GPx, and non-enzymes proteins such as ferritin and metallothionein. The non-protein sub-class include small molecules such as glutathione and bilirubin (Mirończuk-Chodakowska, Witkowska, & Zujko, 2018). The exogenous category refers to antioxidants whom supplied from external sources mainly through diet, and certain synthesized drugs (Mohammed *et al*., 2015; Rizzo *et al*., 2010).

Table 4: Classification of antioxidants in biology and medicine.

Source	Name of antioxidants
Endogenous protein antioxidants	Superoxide dismutase, catalase, glutathione-synthesizing enzymes, glutathione peroxidase, glutathione reductase, glutathione S-transferase, glutaredoxin, thioredoxin, peroxiredoxin, thioredoxin reductase, sulfiredoxin, methionine sulfoxide reductase, hemeoxygenase, NADPH:quinone oxidoreductase, paraoxonase, ferritin, and metallothionein.
Endogenous non-protein antioxidants	Glutathione, bilirubin, coenzyme Q, estrogens, α-lipoic acid, melatonin, pyruvate, and uric acid.
Exogenous dietary antioxidants	Vitamin C, vitamin E, carotenoids, phenolic compounds.
Exogenous laboratory synthesized antioxidants	Antioxidants enzyme mimetics, glutathione precursors, spin traps, and nanoparticles.

6. Antioxidant-based Disease Intervention

The serious involvement of reactive oxygen and nitrogen species in a numerous of pathological conditions force imperative deal to develop ways for controlling these ROS and RNS during pathophysiology processes. Intervention of ROS / RNS-associated disease conditions may theoretically be accomplished through different methods, including the antioxidant-based response.

6.1. Animal Studies on Antioxidant-based Disease Intervention

In order to test the developmental drugs, a studies on animals must applied first for testing their safety, efficiency, and mechanism of actions to treat human diseases. Among these studies, are the studies of antioxidant-based strategies for the interference pathological conditions involving

mediated ROS and RNS as pathophysiology components. There are three approaches used for these studies on animals:

1- Administration of exogenous antioxidant compounds.
2- Transgenic overexpression of antioxidant proteins.
3- Induction of endogenous antioxidants by chemoprotective agents.

Transgenic approach offers the most compelling knowledge concerning the effects of overexpression on a disease condition of a specific antioxidant protein. This also offers the strongest evidence for a specific ROS / RNS being involved in disease pathophysiology (Levonen, Vähäkangas, Koponen, & Ylä-Herttuala, 2008). The use of exogenous antioxidant materials with own a selective ROS and RNS scavenging properties would give a well understanding of the potential role of ROS and RNS in the pathophysiology of disease.

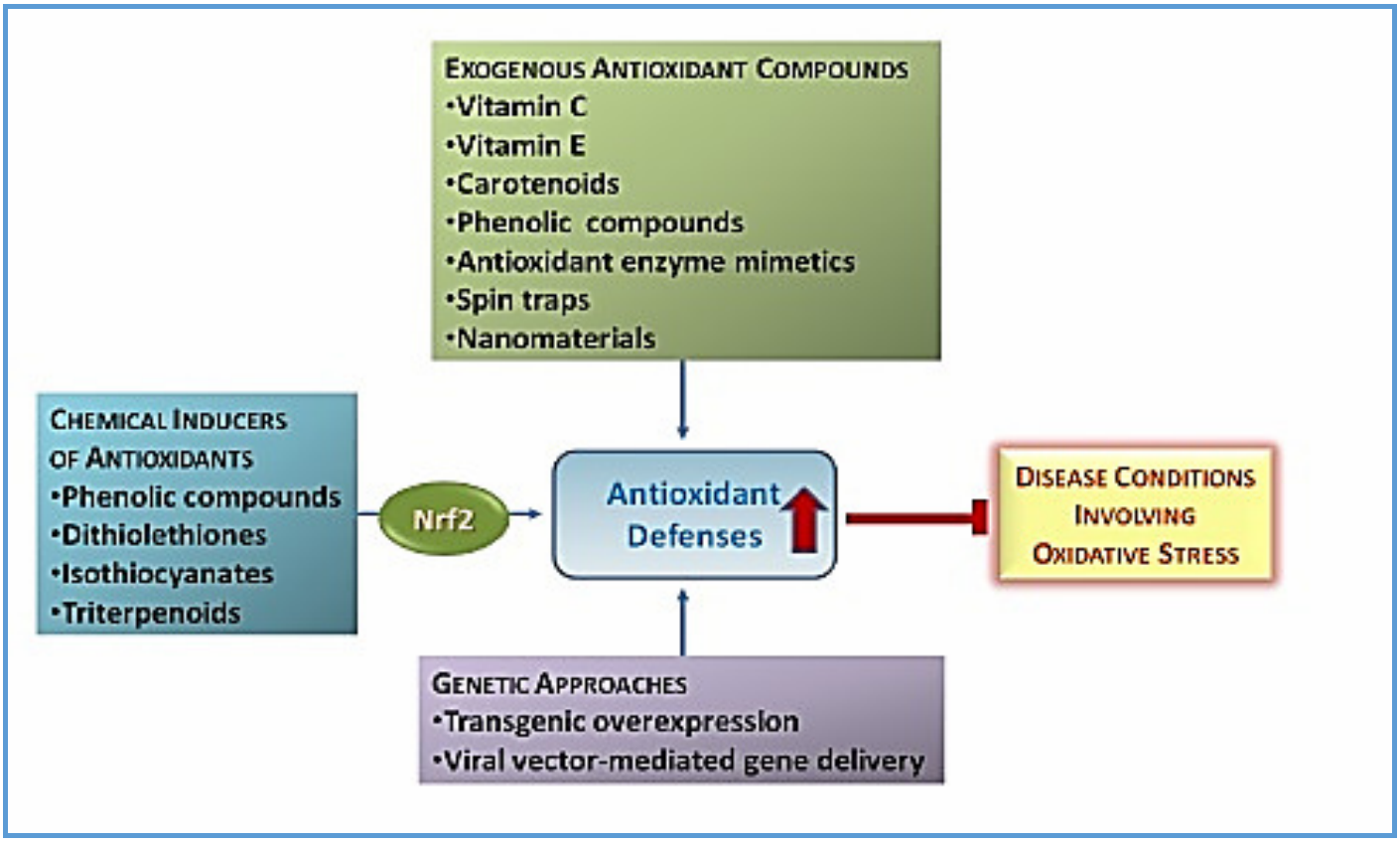

Fig. 3: Major experimental approaches to augmenting tissue antioxidant defenses for the intervention of disease conditions that involve an oxidative stress mechanism (Li, 2011).

In contrast, the efficiency of chemical inducers of antioxidants in preserve against a disease condition may result from the simultaneous induction of multiple endogenous antioxidants. Chemical inducers in fact normally upregulate a variety of specific antioxidant enzymes by activating Nrf2 signals (Zhu *et al*., 2008).

6.2. Human Studies on Antioxidant-based Disease Intervention

The three methods used in experimental animal research could also be extended to human studies, but the use of genetic approach (gene therapy) in humans is currently much limited. In this regard, a more practical antioxidant-based approach in human studies involves the use of exogenous antioxidant compounds or chemoprotective agents capable of inducing endogenous antioxidants. In this context, randomized double-blind, placebo-controlled clinical trials are usually conducted to determine the efficacy of antioxidant-based strategies in the intervention of human diseases that are believed to have an oxidative stress component. The interventional clinical trials can be either preventive or therapeutic (Li, 2011).

Conclusion

The reactive substances radicals and non-radicals which underlie the ROS and RNS have a beneficial functions to the cellular system of humans. By exceeding the permitted limit of endogenous manufacturing of these reactive species, their benefit turn into a curse, and affect the whole cellular system of the organism starting with cell membrane, until the DNA in the core of the cells. The ultimate result of these attacks is cell death. Many diseases have observed to combine an elevation of oxidative stress, either by increasing ROS and RNS levels or by decreasing antioxidants levels. Oxidative stress associated with pathological conditions has the ability of amplification the situation through its harmful effects, hence the future studies of pathogens must involve well designed investigations of oxidative stress markers and their influence in order to reach a proper therapy of diseases.

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