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Review

Role of free radicals in human inflammatory diseases

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Abstract: The role of free radicals can be found in the inflammatory process which is a complex process resulting many human diseases. Inflammations are mainly divided into acute and chronic inflammation depending on various inflammatory processes and cellular mechanisms. In recent years, there has been a great deal of attention to the field of free radical chemistry. Free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated by our body by various endogenous systems, exposure to different physiochemical conditions or pathological states. The purpose of the present review is to mention the role of free radical formation in the most common inflammatory processes in animals. Continued oxidative stress can lead to chronic inflammation, which in turn could mediate the most chronic diseases including cancer, diabetes, cardiovascular, neurological, and pulmonary diseases. ROS and RNS are well recognized for playing role as deleterious species. ROS and RNS are normally generated by tightly regulated enzymes, such as NO synthase (NOS) and NAD(P)H oxidase isoforms, respectively. The detrimental effect of free radicals causing health damages is termed oxidative stress and nitrosative stress. Overproduction of ROS results in oxidative stress, a deleterious process that can damage cell structures, including lipids, proteins, and DNA.

Keywords: inflammation; human health; reactive oxygen species; oxidative stress; reactive nitrogen species

1. Introduction

The recent knowledge of free radicals and reactive oxygen species (ROS) and its role in human diseases became an important aspect of health and disease management. Oxygen, which is an

indispensable element for life, has deleterious effects on the human body under certain situations. The harmful effects of oxygen are due to the formation and activity of a number of chemical compounds, known as ROS. Free radicals are atoms or molecules having one or more unpaired electrons and capable of independent existence. Free radicals have pivotal role in diverse range of degenerative diseases like atherosclerosis, cancer, inflammatory joint disease, asthma, diabetes, kidney diseases, and degenerative eye disease [1–5]. Most ROS is generated in cells by the mitochondrial respiratory chain [6]. Mitochondrial ROS production is modulated largely by the rate of electron flow [7,8] through respiratory chain complexes [9]. In the mammalian cell, the electron transport chain of mitochondria is the main source of ATP which is essential for life. During energy transduction, some electrons prematurely leak to oxygen resulting in formation of oxygen free radical superoxide [7,8]. Superoxide anion, arising from metabolic processes is considered as primary ROS which can generate secondary ROS by further interacting with other molecules directly or through enzyme- or metal-catalysed processes [10,34]. Recently, it has become clear that, under hypoxic conditions, the mitochondrial respiratory chain also produces nitric oxide (NO), which can generate other reactive nitrogen species (RNS). Although excess ROS and RNS can lead to oxidative and nitrosative stress, moderate to low levels of both function in cellular signaling pathways [11,12,13]. Especially important are the roles of these mitochondrially generated free radicals in hypoxic signaling pathways, which have important implications for cancer, inflammation and a variety of other diseases [4,5]. Table 1 shows list of ROS and RNS.

Free radicals are the products of normal cellular metabolism. An atom or molecule having one or more unpaired electrons in valence shell or outer orbit is considered as free radical [11]. Free radicals are unstable, short lived and highly reactive because of its odd number of electron(s). Because of their high reactivity, they can abstract electrons from other compounds. Thus the attacked molecule loses its electron and becomes a free radical itself. Finally, a chain reaction begins which damages the living cell [9,14,15].

Oxygen plays a fundamental role in both organismal survival and death. Its role in survival is linked to its high redox potential, which makes it an excellent oxidizing agent, capable of accepting electrons easily from reduced substrates. These partially reduced reactive oxygen species include superoxide, hydrogen peroxide and the hydroxyl radical. Ironically, the mitochondrial respiratory chain, responsible for most of the oxygen reduction and energy produced in cells, is also responsible for generating the most cellular ROS. Indeed, ROS has often been thought of as toxic byproducts of respiratory metabolism. It has been known for some time that excess ROS can oxidize and damage proteins, nucleic acids, polysaccharides and lipids [12,16].

The present review provides a brief overview of oxidative stress mediated inflammatory diseases. Inflammation includes a long chain of molecular reactions and cellular activity, which are designed to restore a tissue from simple skin cut or to repair tissue after giving birth or to cure several burn injuries. An inflammatory process of cellular and tissue levels includes a series of occasions with dilation of venules and arterioles, enhanced blood vessel permeability, and blood flow with percolation of leukocytes into the tissues. An inflammation cascade contributes to organ disorder and death. Inflammation is one of the major target research areas among biomedical researchers, which includes various cellular processes [17,18].

The aim of this review is to mention the role of free radicals in inflammatory diseases.

2. Classification of Inflammation

Free radicals cause inflammation in human by cellular damages. Chronic inflammation produces lots of free radicals which ultimately create more inflammation. This continuous vicious cycle can damage many systems in the human body.

2.1. Acute inflammation

Acute inflammation is a short procedure, lasting from minutes to a few days. The major features of acute inflammation are leakage of plasma proteins or fluid and movement of leukocytes into an extravascular area. These cellular and vascular reactions are intermediated by chemical factors produced from cells or plasma and are responsible for the classic clinical symptoms of inflammation such as swelling, redness, pain, warmth, and loss of function. Even though an inflammatory response can happen to any injurious stimulus, the characteristic of this process is the reaction of vascularized connective tissue [15,19].

2.2. Chronic inflammation

Inflammation is a vital response to human immune system. The chronic inflammation can have several secondary consequences of biological response associated with enhanced risk of chronic diseases and disorders. Chronic inflammation in tissue usually occurs through infections that are not resolved either within endogenous protection mechanisms or via some other resistance mechanism from host defenses. They can also happen to physical or chemical agents, which cannot be broken down, as well as from some kind of genetic susceptibility. Persistence of foreign bodies, continuous chemical exposures, recurrent acute inflammation, or specific pathogens is all crucial reasons for chronic inflammation. Molecular and cellular process of chronic inflammation depends on the type of inflamed cells and organ [20,21,22].

3. History of Free Radicals

Existence of free radical named triphenyl methyl radical ($Ph_3C^{\bullet}$) in living system was postulated in 1900 by Professor Moses Gomberg, University of Michigan, USA [23]. In 1954, Professor Gershman stated the cause of oxygen toxicity and proposed that, oxygen can form free radicals [24]. In the same year, experiment by Commoner *et al*. showed that, free radicals occur to animal tissues (and in other biological materials), and the report was based on electron spin resonance (ESR) studies of frozen-dried samples [25]. In the year 1956, free radical theory of aging was revealed by Denham Harman. In 1969, superoxide dismutase was discovered by McCord and Fridovich [9,26]. On the other hand, some research groups discovered the involvement of free radicals in combating infection as part of the cellular immune response, where ROS and reactive nitrogen species (RNS) operate in concert with reactive halogen species to fight invading microorganisms [27,28,29]. In 1989, Hallliwell and Gutteridge reported that, ROS include both free radical and non-radical derivatives of oxygen [30].

Table 1. List of ROS and RNS [9,31,32,33].

Reactive Oxygen Species (ROS)	Symbols
Superoxide (very short half-life)	$O_2.^-$
Hydroxyl (approximately 10^{-9} seconds)	$OH^·$
Alkoxyl radical	$RO^·$
Peroxyl radical (about 7 seconds)	$ROO^·$
Hydroperoxyl	$HO_2^·$
Hydrogen peroxide (normally a short-lived substance in the environment but half-lives vary greatly depending on the circumstances)	H_2O_2
Singlet oxygen (exhibits a half-life time in water of ~3.5 μs)	$^1O_2$
Ozone (The half-life of ozone in water is a lot shorter than in air)	O_3
Organic peroxide	ROOH
Hypochlorous acid (less than 1 min)	HOCl
Hypobromous acid (few hours depending on the concentration of the solution)	HOBr
Reactive Nitrogen Species (RNS)	
Nitric Oxide (half-life time depends on the environmental medium)	$^·NO$
Nitrogen Dioxide	$NO_2^·$
Peroxynitrite [The biological half-life of peroxynitrite is low (<0.1 seconds)]	$ONOO^-$
Alkyl peroxynitrites	ROONO
Nitrosyl cation	NO^+
Nitrosyl anion	NO^-
Dinitrogen trioxide	N_2O_3
Dinitrogen tetroxide	N_2O_4
Nitrous acid (the half-life in a typical indoor environment appears to range from 2 to 8 h)	HNO_2
Peroxynitrous acid	ONOOH
Nitryl chloride	NO_2Cl

4. Some Free Radicals

4.1. Reactive oxygen species (ROS)

In living system, among the radical species, oxygen derived radicals are most important and it is called reactive oxygen species (ROS) [9,34,35,36]. The ROS forms as products of normal physiological conditions due to the partial reduction of molecular oxygen [37]. ROS can be produced from several endogenous sources, such as xanthine oxidase, cytochrome oxidase, cyclooxygenase, mediated unsaturated fatty acid oxidation, oxidation of catecholamines, mitochondrial oxidation, inflammation, phagocytosis, ischemic reperfusion injury, exercise activation of leukocyte nicotinamide adenine dinucleotide phosphate oxidase, iron release, and reduction-oxidation reaction cycling [38–43]. In eukaryotic cell, ROS is generated mostly in electron transport chain of mitochondria [44]. Along with endogenous sources, various exogenous sources like smoking of cigarette, X-ray exposure, industrial chemicals, ozone, and air pollutants also up regulate ROS production [39,45,46,47]. There are two types of ROS, such as oxygen-centered radicals and oxygen-centered non-radicals [9,32]. Oxygen-centered radicals are superoxide anion ($O_2^{·-}$), hydroxyl

radical ($^{\cdot}OH$), alkoxyl radical ($RO^{\cdot}$), and peroxyl radical ($ROO^{\cdot}$). Other reactive species are nitrogen species such as nitric oxide ($^{\cdot}NO$), nitric dioxide ($NO_2^{\cdot}$), and peroxynitrite ($OONO^-$). Oxygen centered non-radicals are hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$), hypochlorous acid and ozone [48–51]. ROS can cause tissue damage in various ways like DNA damage; lipid peroxidation [through activation of cyclooxygenase (COX) and lipoxygenase pathway]; protein damage including gingival hyaluronic acid and proteoglycans; oxidation of important enzymes; stimulate proinflammatory cytokine which are released by monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor kappa beta (NF-κB) [52,53].

4.2. Superoxide

In biological system superoxide ion ($O_2^{\cdot -}$) is the most significant widespread ROS [54]. It is formed by various enzymatic (autoxidation reaction) and non-enzymatic process (an electron is transferred to molecular oxygen) [55]. Superoxide, an anion radical of dioxygen, is the precursor of paramagnetic reactive free radicals (hydroxyl radicals) and reactive diamagnetic molecules (hydrogen peroxide and peroxynitrite) in biological systems. Superoxide is a radical anion as well as a strong nucleophile. It could participate in DNA methylation, histone methylation and acetylation through mechanism of nucleophilic substitution and free radical abstraction [56].

The enzymes which generate superoxide are xanthine oxidase [26,57,58], lipoxygenase, cyclooxygenase [59,60,61] and NADPH dependent oxidase [62,63]. It can be present as $O_2^{\bullet -}$ or hydroperoxyl radical (HO_2) at low pH [64]. It has both reducing and oxidizing properties.

4.3. Peroxyl radical ($ROO^{\cdot}$)

The source of peroxyl radical in living system is oxygen. Perhydroxyl radical ($HOO^{\cdot}$) is the simplest form of peroxyl radical and it is derived by protonation of superoxide [65]. About 0.3% of the total $O_2^{\bullet -}$ in the cytosol of a typical cell is in the protonated form. It initiates fatty acid peroxidation and also can promote tumor development [66].

4.4. Hydrogen peroxide (H_2O_2)

Hydrogen peroxide is the major oxidant product of xanthine oxidase [67]. Hydrogen peroxide is also directly produced by a range of oxidase enzymes including glycollate and monoamine oxidases [68,69]. As low as 10 μM of hydrogen peroxide can damage living cell and it can potentially inactivate the cellular energy producing enzymes (as glyceraldehyde-3-phosphate dehydrogenase are inactivated in higher concentration). It can easily penetrate the biological membranes. In the presence of transition metal ions it can damage DNA by producing hydroxyl radical (OH) [70]. The major antioxidant enzymes that can eliminate the H_2O_2 include catalase, glutathione peroxidase and peroxiredoxins are important antioxidant enzyme which can protect cell from the deleterious effect of hydrogen peroxide [71,72].

5. Mitochondrial ROS Targets-Oxidative Damages to DNA, Lipids and Proteins

5.1. DNA

Mitochondrial DNA (mtDNA) is more susceptible to oxidative damage than nuclear DNA (nDNA), most probably because it is closer to the site of ROS generation [11]. The hydroxyl radical is known to react with all components of the DNA molecule, damaging both the purine and pyrimidine bases and also the deoxyribose backbone [73].

5.2. Proteins

A useful measure of protein oxidation caused by ROS is protein carbonylation. Carbonylated proteins are easily identified after derivatization with 2,4-dinitrophenylhydrazine. This approach demonstrated that, oxidative stress increases transiently in cells exposed to hypoxia/anoxia and protein carbonylation levels increased. Some of the carbonylated proteins reside in the mitochondrion, whereas others are cytosolic proteins. A shift to anoxia allows a burst of mitochondrially generated ROS, which distribute themselves among both mitochondrial and cytosolic compartments and carbonylation in response to hypoxia-induced oxidative stress affects specific proteins [74]. The side chains of all amino acid residues of proteins, in particular cysteine and methionine residues of proteins are susceptible to oxidation by the action of ROS/RNS [75].

5.3. Lipids

Membrane lipids are the third major target of mitochondrial ROS. The OH radical interacts with unsaturated bonds in a membrane lipid and starts the process of lipid peroxidation. The end product of this reaction is 4-hydroxynonenal, a compound that affects the activity of various membrane proteins. 4-Hydroxynonenal is a major inducer of oxidative stress and has been associated with a variety of pathophysiological states [76].

6. Involvement of Free Radicals in Various Diseases

6.1. Cardiovascular disease

One of the leading causes of mortality and morbidity worldwide is cardiovascular disease (affecting the heart and blood vessels) for men and women [39,77–83]. In the blood vessel wall, each layer can produce ROS in pathological conditions [84]. ROS-induced oxidative stress plays a role in various cardiovascular diseases such as, ischemic heart disease, atherosclerosis, cardiomyopathies hypertension, congestive heart failure and cardiac hypertrophy [3,85,86]. Several research groups reported development of cardiac hypertrophy caused by mitochondrial ROS [87–90]. Recent research stated that, fructose induced cardiac hypertrophy caused by total ROS and mitochondrial H_2O_2. [91,92,93]. Other studies demonstrated that, ROS generated by smoking plays an important role to develop cardiovascular injury [94–97]. ROS causes remodeling through proliferation of smooth muscle cell and increased inflammation [98].

6.2. Diabetes

Diabetes mellitus is a chronic metabolic disorder, characterized by hyperglycemia, dyslipidemia and insufficient production of insulin [99–102]. ROS production increases in chronic hyperglycemia of uncontrolled diabetes as well as decreases enzymatic antioxidant defenses leads to retinopathy and cataract formation [103]. Oxidative stress is one of the major causes of diabetes mellitus [99,104–107]. In hyperglycemic condition both mitochondrial and non-mitochondrial ROS production increases significantly to induce oxidative tissue damage. Superoxide radicals and NO both play major role to induce complication under hyperglycemic condition [108,109]. A serious complication of diabetes mellitus is diabetic nephropathy which is caused by oxidative stress and inflammation. Oxidative stress changes the structure and function of proteins and lipids, and induces glycoxidation and peroxidation in chronic hyperglycemia [110,111,112]. Previous studies also reported the link between oxidative stress and diabetes [113,114].

6.3. Inflammatory bowel diseases

Inflammatory Bowel Diseases (IBD) is a chronic disorder of the gastrointestinal (GI) tract. It is characterized by body weight loss, hemorrhage, lower abdominal pain and diarrhea [115,116]. Ulcerative colitis (UC) and Crohn's Disease (CD) are two forms of IBD. In IBD, granulocytes and monocytes/macrophages are accumulated at site of the inflammation and produce reactive oxygen [117]. Recent research revealed that, ROS related diseases like IBD might be ameliorated by inhibiting xanthine oxidase [118]. Oxidative stress (major etiological factors in Crohn's disease) resulted due to imbalance between ROS production and antioxidant elements [119–122]. Concentration of nitric oxide also plays a vital role in IBD [116,123]. Several clinical studies also supported the deleterious role of NO in IBD patients [124–128]. Recent studies demonstrated that, anti-oxidative therapy might be a good approach to ameliorate IBD by scavenging free radicals [116,129,130].

6.4. Asthma

Free radicals are responsible for several various respiratory diseases such as chronic bronchitis, respiratory distress syndrome, chronic obstructive pulmonary diseases (COPD), asthma [131,132]. Asthma is one of the important global health problems [133] and is characterized by chronic disorder of the airways, airway inflammation, hyper responsiveness, variable airflow obstruction and airway remodeling [134,135,136]. Free radicals and oxidative stress play significant role in airways inflammation [136,137,138]. In lung, reactive oxygen species are produced by lung parenchymal cell and lung macrophages and this ROS provoked airway inflammation by inducing diverse proinflammatory mediators [139]. ROS helps in overexpression of oxidative stress sensitive transcription of NFκB by various chemokine and cytokine over production in bronchial epithelial cells [140]. Several research works demonstrated that, oxygen free radicals, superoxide radical (O_2^-) production significantly increased in asthma patients [141,142,143]. Recent work reported that, oxidative stress induced by free radical generation is linked with asthma [144,145,146]. Among the nitrogen free radicals, nitric oxide is the principle free radical produce in lung [147]. NO is endogenously produced in mammalian airways by Nitric oxide synthase (NOS). NO modulates

airway and vascular smooth muscle and regulate various aspects of asthma in human. Increased production of airway NO is the key factor in the development of airway hyper responsiveness [148]. Various studies reported that, higher NO levels are directly associated with higher risk factor of asthma and its severity [147,149,150].

6.5. Arthritis

Rheumatoid arthritis (RA) is a systemic disease characterized by progressive, erosive, and chronic polyarthritis. Cellular proliferation of the synoviocytes and neo-angiogenesis leads to formation of pannus which destroys the articular cartilage and the bone [151]. RA is a systemic autoimmune disorder resulting in an unchecked synovial inflammation [152,153,154]. It has been found that, isoprostanes and prostaglandins level increased in serum and synovial fluid due to free radical injury in various RA [34]. ROS as well as RNS can directly or indirectly damage basic articular constituents and lead to the clinical expression of the inflammatory arthritis. Chronic inflammation exerts its cellular side effects mainly through excessive production of free radicals and depletion of antioxidant defense in the body.

6.6. Burn

Burn injuries are the major cause for human suffering and a major global public health crisis. Along with high mortality and morbidity, it also deprives the quality of life [155,156]. It is a traumatic injury which damages local tissue as well as systemic mediator-induced response. Upregulation of free radical activity and lipid peroxidation are manifested as a result [156]. Pathophysiology of burn injury is very complex. Severe burn injury develops hypovolemic shock and very rapid increase of various chemokines and cytokines which initiates inflammatory cascade [157]. Thermal injury leads to hyper metabolism which in turn increases the production of proinflammatory cytokines and various ROS and RNS [158]. Burn injury activates intravascular neutrophil granulocyte, which leads to increased ROS production [159]. Lipid peroxidation plays vital role in burn injury [160–164]. Severe lipid peroxidation in burn injury leads to burn related organ failure and burn shock [165,166,167]. After thermal injury, tissue ATP level falls down slowly and increased AMP is converted to hypoxanthine which supplies substrate for xanthine oxidase [168]. These complex events help to produce deleterious free radicals, superoxide and hydrogen peroxide [168,169]. Same explanation also stated previously that, in case of skin burn, xanthine oxidase activity increases which is an important source of free radicals in serum of burn patients [170]. Thermal injury also results in prolonged and profound hyper metabolism that involves increased production of proinflammatory cytokines, as well as the formation of ROS and RNS [158,169].

6.7. Cancer

Cellular DNA can be damaged by reactive oxygen species lead to genetic changes and as a result, uncontrolled regulation of oncogenes and tumour suppressor genes finally contributes to carcinogenesis [171,172,173]. Various oxygen free radicals generated from activated leucocytes and these activated neutrophils can stimulate mutagenesis *in vitro*. Oxidative stress from chronic

inflammation upregulates cancer development in various organs and it has been postulated that, one third of the World's cancer come from chronic inflammation. Oxygen free radicals also responsible for cancer caused by tobacco smoking [174,175]. Carcinogens present in tobacco smoke induces tumour by OFR stimulate the metabolism of benzo(a)pyrene (aromatic hydrocarbon present in tobacco) to diol-epoxides that initiate tumours through the formation of DNA adducts.

6.8. β-thalassemia and sickle cell disease

Sickle cell disease and β-thalassemia are inherited autosomal recessive red cell disorders. It is one of the major causes of morbidity and mortality worldwide [176]. In Sickle cell disease, glutamic acid is replaced by valine at position 6 of the β-globin protein of haemoglobin and as a result, sickle haemoglobin (HbS) forms. In micro environment, HbS tends to polymerize under low oxygen and this in turn lead to erythrocytes deformation and impairment of oxygen delivery capacity of erythrocytes to tissues occurs which in turn impact the oxidative environment both intracellularly and extracellularly. A subsequent series of complications, such as pain crises, pulmonary hypertension and heart failure, comprise the characteristic symptoms of the disease.

6.9. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative condition characterized by the formation of amyloid-β plaques, aggregated and hyperphosphorylated tau protein, activated microglia and neuronal cell death, ultimately leading to progressive dementia [177,178]. Reactive oxygen species are very important factor of early behavioural changes in Alzheimer's diseases. Evidences suggest, ROS play an early role in the behavioural deficits observed in AD [179]. Recent research also supported that, oxidative stress is an important factor of AD and ascorbic acid reduced neurodegenerative processes and behavioural alterations in AD patients [180].

7. Discussion

The harmful effect of free radicals causing potential biological damage is termed oxidative stress and nitrosative stress [181,182,183]. In biological systems this detrimental effects occurs due to the overproduction of ROS and RNS. The oxidative stress result from the metabolic reactions represents a disturbance in the biological equilibrium status in living organisms. The excess ROS can fully destroy lipids, proteins, or DNA inside the cell and inhibit their normal function ultimately causing a number of human diseases [2,184].

Exposure to free radicals from a variety of sources has led organisms to develop a series of defense mechanisms [185]. Such defense mechanisms against oxidative stress are repairing mechanisms, preventative mechanisms, and antioxidant defenses. Enzymatic antioxidant defenses include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Non-enzymatic antioxidants are represented by ascorbic acid, vitamin E, glutathione, carotenoids, and flavonoids. Under normal conditions, there is a balance between enzymatic antioxidant defense and non-enzymatic antioxidant defense. This balance is essential for the survival of organisms and their health.

Reactive oxygen species and free radicals are thought to act indirectly as cellular messengers and elicit an inflammatory response. ROS and free radicals also activate a series of enzyme systems,

including protein kinases, protein phosphatases, transcription factors and heat shock proteins. ROS are also critical for gene expression which encodes inflammatory proteins e.g. proteinases involved in tissue destruction such as collagenases and gelatinases. In the case of rheumatoid arthritis, rheumatoid factor binds IgG when it is exposed to free radicals and ultimately stimulates the production of more free radicals and then attacks the cartilage matrix.

ROS and RNS are products of normal cellular metabolism and are known to act as secondary messengers controlling different normal physiological functions of the organism. Overproduction of ROS, either by excessive stimulation of NAD(P)H by cytokines, or by the mitochondrial electron transport chain and xanthine oxidase result in oxidative stress which ultimately destroy the cell structures.

8. Conclusion

A balance between free radicals and antioxidants is necessary for proper physiological function in the body. Cellular damage by free radicals contributes to the etiology of many chronic health problems. Antioxidant prevents free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition. Many factors regulate the production of free radicals by the mitochondrial respiratory chain. In general, these factors alter the inner mitochondrial membrane potential and the rate of electron transport. Oxygen concentration plays an important role in determining which free radicals are generated. Although evidence points to a role in these mitochondrial free radicals in intracellular signaling pathways, the challenge is to determine which free radicals are involved and the precise mechanisms by which they alter the activity of components of these signaling pathways. ROS and RNS are known to act as secondary messengers controlling various normal physiological functions of the organism. Oxidative stress is a harmful process and can damage cell structures which ultimately can develop inflammatory diseases. In the near future, development of effective and economical nonsteroidal anti-inflammatory drugs with minimal or no gastrointestinal side effects will be an area of importance of drug discovery pharmaceutical industry.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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