2023
3(2), 587

Journal of
Molecular Chemistry

Molecular mechanism facets of Oxidative stress mediated pathogenesis

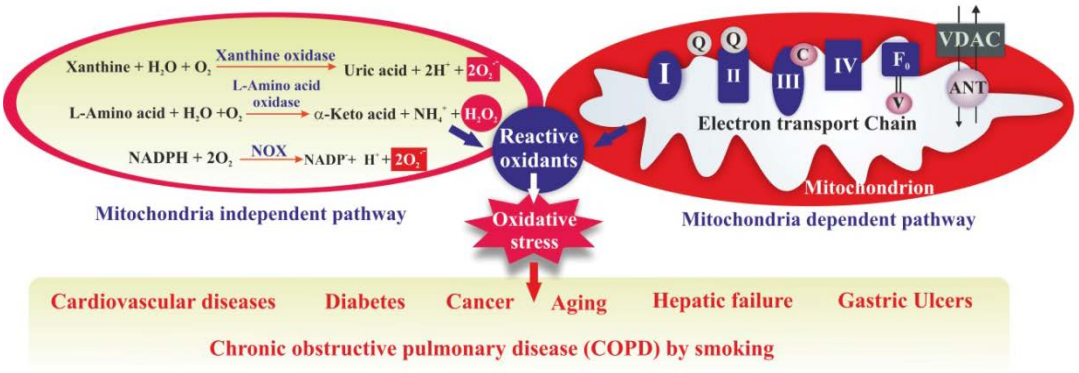
Chinmay Pal

Department of Chemistry, Gobardanga Hindu College; North 24 Parganas, West Bengal 743273, INDIA

Submitted on: 26-May-2023, Accepted and Published on: 17-Jul-2023

Review

ABSTRACT



Oxidative stress arises from an imbalance between reactive oxidants and the antioxidant defense system in cells. This article outlines the mechanisms and effects of oxidative stress on disease onset. Reactive oxidants, like superoxide anion and hydrogen peroxide, are normal byproducts of cellular metabolism. The antioxidant defense system maintains a delicate equilibrium by neutralizing these oxidants through enzymatic and non-enzymatic processes. However, when the production of reactive oxidants exceeds the antioxidant capacity, oxidative stress occurs, causing cellular damage. This damage includes lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction. These processes lead to cellular damage, inflammation, and activation of disease-related signaling pathways. Oxidative stress further worsens tissue damage and promotes chronic diseases by increasing immunological responses and inflammation. The article extensively covers oxidative stress in various diseases such as cardiovascular diseases, COPD from smoking, aging, gastric ulcers, hepatic failure, diabetes complications and cancer. Understanding oxidative stress mechanisms and developing effective therapeutic strategies can provide new options for disease prevention and treatment.

Keywords: Oxidative stress, ulcers, aging, cardiovascular diseases, pulmonary disease, hepatic failure, diabetes complications, cancer

INTRODUCTION

Oxidative stress can be described as an imbalance caused by the inability to effectively eliminate reactive products formed during cellular metabolism, particularly reactive oxidants.[1,2] This imbalance leads to an accumulation of free radicals, which have detrimental effects on intracellular proteins, cellular membranes through polyunsaturated fatty acid peroxidation, nucleic acids with base modifications, and chromosomal alterations. These effects include DNA single-strand and double-strand breaks, DNA and protein cross-links, as well as damage to cellular structures and components like polysaccharides and carbohydrates.[3] Ultimately, oxidative stress can result in cell death and degradation of cellular components.[4]

Another important facet is the activation of signaling pathways in response to oxidative stress. Cells have evolved intricate signaling networks to detect and respond to increased reactive oxidants levels. The nuclear factor-κB (NF-κB) pathway and mitogen-activated protein kinases (MAPKs) are two major signaling pathways that are commonly activated by oxidative stress.[5] These pathways regulate the expression of numerous genes involved in inflammation, cell survival, apoptosis, and other cellular processes.[6]

A fundamental component of aerobic biological activities is oxygen (O_2). However, via univalent reduction of O_2, roughly 5% or more of the breathed O_2 is transformed into reactive oxidants like superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$).[7,8] Therefore, reactive oxidants represent a constant threat to cells operating in an aerobic environment.[9] However, these insults are successfully neutralized by the cell's extremely potent antioxidant mechanisms without causing any negative side effects. When the balance between the production of reactive oxidants and antioxidant defenses is upset, "oxidative stress" results, which through a series of actions deregulates cellular functions and results in a variety of pathological conditions like metabolic dysfunction in almost all vital organs, cancer, and premature aging.[10,11]

Oxidative stress caused by free radicals leads to DNA oxidation, glycoxidation, and oxidation of membrane lipoproteins, all of which cause cell death [12]. Injury to the tissue

*Corresponding Author: Dr.Chinmy Pal
Tel: +91-9874678310, +91-7699042305
Email: chinmaypal2006@gmail.com;

URN:NBN:sciencein.jmc.2023.587.

https://pubs.thesciencein.org/jmc

is eventually the result of several necrotic components, proteases, and reactive oxidants from injured cells attacking the surrounding cells. Additionally, it has been noted that tissue damage itself can result in significant oxidative stress.[13,14] Reactive oxidants are produced as a result of injury brought on by ischemia reperfusion, heat, trauma, cold, intense exercise, toxins, radiation, or infection.[7]

This review article focuses on two main topics: the mechanism of reactive oxidant formation in respiring cells under aerobic conditions and the molecular mechanism of reactive oxidant-mediated diseases, including cardiovascular diseases (chronic heart failure), chronic obstructive pulmonary disease (COPD) brought on by smoking, aging, gastric ulcers, liver failure, diabetes complications, and cancer which have been extensively studied.

CELLULAR SOURCE OF REACTIVE OXIDANTS

Electron transport chain dependent pathway

The electron transfer mechanism in mitochondria's electron transport chain (ETC) is linked to the method by which living things obtain their energy. Reactive oxidants are created during this process in small amounts (approximately 5% of the oxygen inhaled), but they are always handled by the body's natural antioxidant system.[15] $O_2^{\bullet-}$, singlet oxygen ($^1O_2$), H_2O_2, nitric oxide in free radical form ($^{\bullet}NO$), ONOO, and the highly reactive $^{\bullet}OH$ are examples of reactive oxidants. $O_2^{\bullet-}$, a moderately stable intermediate, is created when molecular oxygen undergoes one-electron reduction. The majority of reactive oxidants are thought to have $O_2^{\bullet-}$ as their precursor.[16,17] $O_2^{\bullet-}$ is produced as a result of electron leakage from the mitochondrial ETC to molecular oxygen (Figure 1A). An essential inner membrane multi-protein complex called Complex I (NADH-ubiquinone oxidoreductase, C-I) is exposed to both the matrix and the intermembrane gap. In a reversible reaction accompanied by a proton pump that creates transmembrane potential, it oxidises NADH using coenzyme Q as an electron acceptor.[18] There are conflicting reports on the quantity and location(s) of reactive oxidants produced in Complex I. It might be situated between flavin and the location where rotenone binds. The reactive oxidants generating site in Complex I may also be a complex of half-reduced NAD radical bound to flavin[19,20] or a complex of flavin.[21] Iron-sulfur centres are potential candidates because, according to research by Herrero et al., the complex I oxygen radical generator may be situated between the ferricyanide and the ubiquinone reduction site.[22] However, unstable semiquinones may potentially have a similar function. Complex I generates superoxide, which is mostly found in the mitochondrial matrix. The synthesis of $O_2^{\bullet-}$ is not significantly aided by Complex II and Complex IV. When mitochondrial respiration is inhibited, Complex III (ubiquinol:cytochrome c oxidoreductase) can also produce a sizable amount of $O_2^{\bullet-}$. On both sides of the inner mitochondrial membrane (IMM), which is formed at Complex III, is located $O_2^{\bullet-}$.[23] Following superoxide anion dismutation by Mn-dependent superoxide dismutase (MnSOD), H_2O_2 is produced, which can then result in the creation of $^{\bullet}OH$ (Figure 1). Normal cellular defences against these oxygen radicals include antioxidant enzymes and lipid-soluble antioxidants like vitamin E and reduced CoQ.[24] The mitochondrial outer membrane enzyme monoamine oxidase (MAO) catalyses the oxidative deamination of biogenic amines and is a quantitatively large source of H_2O_2 that contributes to an increase in the steady state concentrations of reactive species within both the mitochondrial

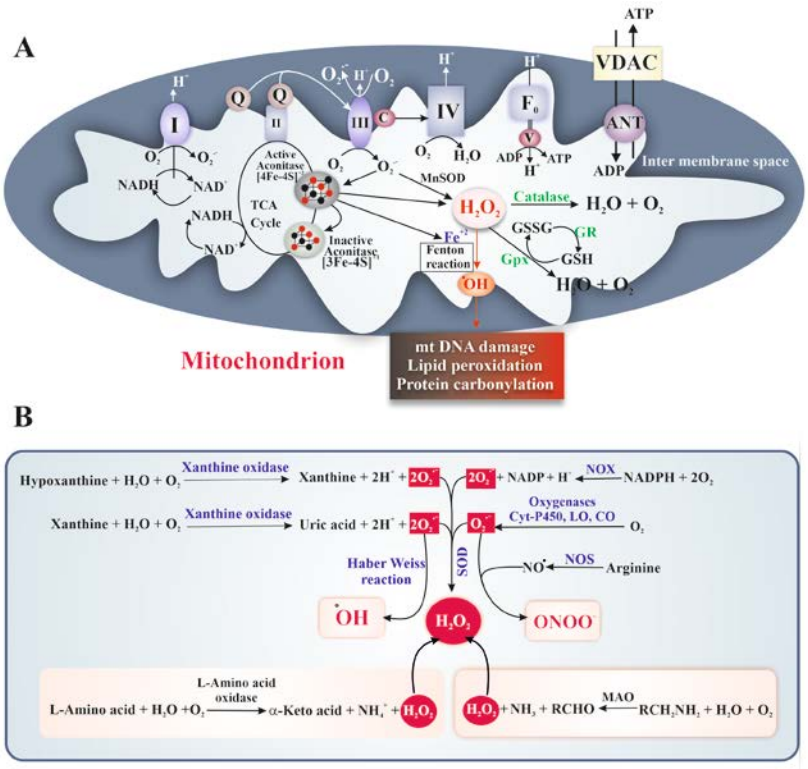


Figure 1. A **Generation of reactive oxidants by ETC dependent pathways** Superoxide ($O_2^{\bullet-}$) is produced in the mitochondria when molecular oxygen captures electrons that have escaped the electron transport chain. The majority of reactive oxidants are formed from superoxide, which superoxide dismutases (SOD) can quickly convert to H_2O_2. H_2O_2 can be changed into hydroxyl radicals ($HO^{\bullet}$) in the presence of transition metals (like Fe^{2+}), which are produced by aconitase or cytochrome c. In the presence of GSH, glutathione peroxidase (GPx) can scavenge H_2O_2. In the presence of NADPH, glutathione reductase (GR) converts the oxidised glutathione (GSSG) back to GSH. **B. Generation of reactive oxidants by ETC independent pathway**. Reactive oxidants is also generated by other than ETC. $O_2^{\bullet-}$ is formed by NAD(P)H oxidases (NOX), xanthine oxidase and oxygenase like cytochrome P450, lipoxygenases (LO) and cycloxygenases (CO). L-amino acid oxidase and monoamine oxidase (MAO) generates H_2O_2 by reducing O_2 while catalyzing their respective reactions.

matrix and cytosol in addition to these toxic electron transport chain reactions of the inner mitochondrial membrane.[25] The Fenton reaction allows $O_2^{\bullet-}$ and Fe^{2+} to further interact, creating the extremely reactive and cytotoxic $^{\bullet}OH$.[15] Aconitase is extremely vulnerable to $O_2^{\bullet-}$. As a result of $O_2^{\bullet-}$ attacking the aconitase, iron is released from its Fe-S cluster, serving as the cell's source of Fe^{2+} [26] (Figure 1A). Cytochrome C, which releases its iron from its heme moiety in the presence of H_2O_2, may be a further reliable source of iron.[27]

Electron transport chain independent pathway

Alternative than ETC, there are a number of alternative mechanisms for cells to produce reactive oxidants (Figure 1B). A combination of enzymes known as phagocyte NADPH oxidase (Phox) causes phagocytes like neutrophils and macrophages to purposefully produce reactive oxidants. The oxidase is made up of the small GTPase RAC, the catalytic component gp91phox (also known as Nox2), the regulatory subunits p22phox, p47phox, p40phox, and p67phox, and the regulatory subunit p47phox.[28] The combination of these regulatory subunits and gp91phox to produce an active complex controls the enzyme's activity.[28] Some Nox2-like flavoproteins are the non-mitochondrial source of reactive oxidants in non-phagocytes. Six novel NADPH oxidase enzymes were found by homology searches in human genome databases: Nox1, Nox3, Nox4, Nox5, Duox1, and Duox2.[29-31] This enzyme complex produces superoxide anion by using electrons from intracellular NADPH, which is then converted into H_2O_2 and other reactive oxidants.[32] Xanthine oxidase,[33] which catalyses the oxidation of hypoxanthine to xanthine and eventually to uric acid, is another source of reactive oxidants. The oxidant is molecular oxygen, and the products are superoxide and H_2O_2. This enzyme has a dual function in cell signalling because it can also generate $^{\bullet}NO$. Cytochrome P450, a component of the five-electron oxidation of nitrogen, is known to decouple from substrate oxidation under specific circumstances, resulting in the production of reactive oxidants. Cytochrome P450 2E1 (CYP2E1), a component of the cytochrome P450 mixed-function oxidase system, is present in higher amounts under a number of physiological and pathological circumstances, as well as during acute and long-term alcohol use. Additionally, CYP2E1 generates potent oxidants such $^{\bullet}OH$ when iron catalysts are present, in addition to producing reactive oxidants like $O_2^{\bullet-}$ and H_2O_2.[34] The mitochondrial enzymes known as monoamine oxidases (MAOs) catabolize prohypertrophic neurotransmitters like norepinephrine and serotonin to produce hydrogen peroxide. MAOs may be crucial in this process since too much reactive oxidants and catecholamines are critical factors in the pathophysiology of congestive heart failure.[35]

Role of Oxidative Stress in the Pathogenesis

Cardiovascular diseases

The high prevalence of cardiovascular disease (CVD) seems to correspond with a widespread global issue of physical inactivity 37005351. The tidal wave of CVDs is about to hit the planet. In low- and middle-income nations, it accounts for 10% of lost DALYs, whereas in high-income countries, it accounts for 18%.[36] Although the etiology and pathophysiology of CVDs are complex, unhealthy lifestyles and behaviors along with a multifactorial complex interaction between environment and genetic variables are the key risk factors. Increasing evidence points to the involvement of highly reactive oxygen-derived free radicals, whether they are endogenous or environmental, in the development and progression of various CVDs.[37,38] Normally, the various levels of antioxidant defenses are capable of efficiently containing these free radicals. Oxidative stress is caused when this process is out of balance, either because too many free

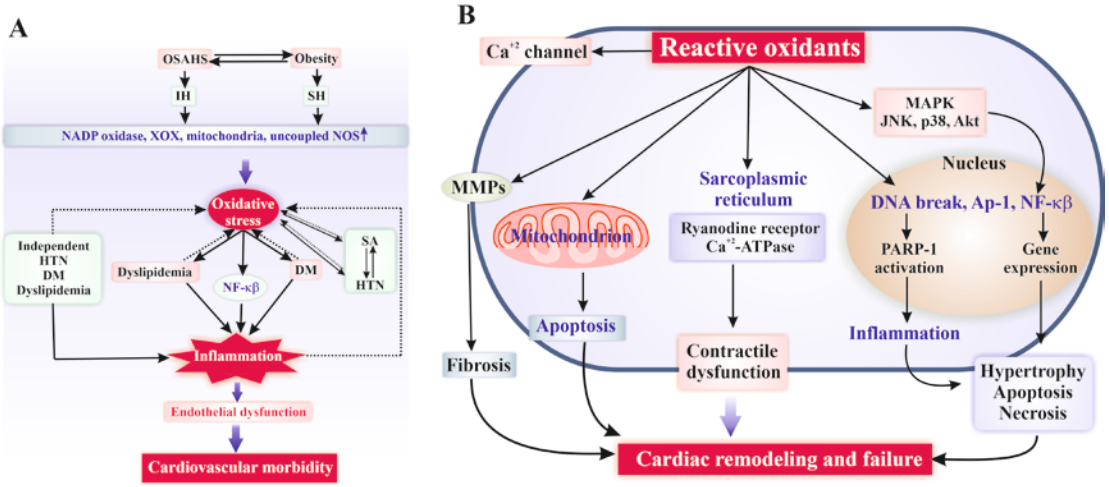


Figure 2. A. Obstructive sleep apnea/hypopnea syndrome (OSAHS) and the emergence of related diseases and comorbidities are depicted schematically to highlight the central role that inflammation and oxidative stress play in these situations. Comorbidities and related illnesses may arise independently or as a result of oxidative stress. Regardless of the mechanisms that cause these illnesses and comorbidities to arise, once they do, they cause a number of complex interactions with different transduction pathways that encourage oxidative stress and inflammation. An increase in oxidative stress causes inflammation to worsen, which in turn makes oxidative stress worse. This vicious cycle eventually results in cardiovascular morbidity. IH: intermittent hypoxia; SH: sustained hypoxia; NADPH: reduced nicotinamide adenine dinucleotide phosphate; XOX: xanthine oxidase; NOS: nitric oxide synthase; SA: sympathetic activation; HTN: hypertension; DM: type 2 diabetes.[56] **B.** Potential oxidative stress targets in relation to heart failure (HF) at the cellular and subcellular levels. MAPK, mitogen-activated protein kinases; JNK, Jun-nuclear kinase;PARP-1, poly(ADP-ribose) polymerase-1; MMPs, matrix metalloproteinases; AP-1, activator protein-1.[55]

radicals are produced or because not enough are removed by antioxidants.[39] A number of known risk factors, including smoking in particular, drinking, diet, pollution, exercise, and metabolic abnormalities, increase oxidative stress as a result of excessive free radical activity. These reactive oxidants can then stimulate the oxidation of proteins as well as low density lipoprotein (LDL), cholesterol, and species derived from cholesterol, which can result in foam cell formation and atherosclerotic plaques.[40] Therefore, it makes sense to assume that antioxidants will aid in the prevention of CVDs. Although some new reservations have been expressed, there is evidence that vitamin C and E have a preventive impact against CVDs by lowering OS.[41-43] Reactive oxidants and antioxidants therefore have a significant impact on CVDs, including atherosclerosis, hypertension, myocardial infarction, and stroke.[44] Figure 2A illustrates how oxidative stress plays a part in the development of cardiovascular repercussions in the obstructive sleep apnea/hypopnea syndrome (OSAHS).

Heart failure

Heart failure (HF) is a complex clinical illness that may be caused by any anatomical or functional cardiac condition that affects the ventricle's capacity to fill with or expel blood [45]. In cardiac remodeling and failure, oxidative stress may activate crucial signaling molecules due to its direct impact on cellular structure and function (Figure 2B). Myocardial development, matrix remodeling, and cellular dysfunction are induced by oxidative stress and entail the activation of numerous downstream signaling cascades. First, a wide range of hypertrophic signaling kinases and transcription factors are activated by reactive oxidants.[46] Tyrosine kinase Src, GTP-binding protein Ras, protein kinase C, mitogen-activated protein kinases (MAPK), and Jun-nuclear kinase (JNK) are all stimulated by reactive oxidants. High amounts of H_2O_2 stimulate MAPK, JNK, p38, and protein kinase B (Akt) kinases to cause apoptosis, but low levels of H_2O_2 are linked to MAPK activation and protein synthesis.[47] Second, reactive oxidants cause apoptosis, a significant factor in remodeling and dysfunction, which is brought on by reactive oxidants' activation of proapoptotic signaling kinases and damage to DNA and mitochondria. Third, DNA strand breaks brought on by reactive oxidants trigger the nuclear enzyme poly (ADP-ribose) polymerase-1 (PARP-1). The expression of several inflammatory mediators is controlled by PARP-1, which speeds up the process of cardiac remodeling. Fourth, MMPs, a group of proteolytic enzymes, can be activated by reactive oxidants.[48] The majority of the time, MMPs are secreted inert, and they are only activated post-translationally by reactive oxidants through specific interactions with crucial cysteines in the propeptide auto inhibitory domain. Nuclear factor-κB, Ets, and activator protein-1 are further transcription factors that reactive oxidants activate to promote MMP production. MMPs are critical in activities like cell migration, invasion, proliferation, and apoptosis that occur during normal tissue remodeling. It has been demonstrated that failing hearts exhibit higher MMP activity.[48,49] Additionally, after an experimental MI, an MMP inhibitor can reduce left ventricular (LV) dilatation.[50] In MMP-2 knockout mice, Hayashidani et al.[51] found a considerable improvement in survival following MI that was mostly due to the suppression of early myocardial rupture and the subsequent development of LV remodeling and failure. One theory for LV remodeling is the activation of MMPs as a result of increased reactive oxidants.[52] This is because MMP can be activated by reactive oxidants. Through the creation of an aberrant extracellular milieu with which the myocytes interact, persistent MMP activation may have an impact on the structural characteristics of the heart. Dimethylthiourea, an $^{\bullet}OH$ scavenger, prevented MMP-2 from becoming activated in connection with the onset of LV remodeling and failure following MI [53]. These data suggest that increased oxidative stress may serve as a trigger for myocardial MMP activation, which is crucial for the onset and progression of HF. Last but not least, reactive oxidants directly affect the activity of contractile fibers by altering the excitation-contraction coupling proteins.[54] This involves modifying crucial thiol groups (-SH) on the ryanodine receptor to increase its open probability, suppressing the L-type calcium channel, and inhibiting Ca^{2+} absorption through an oxidative interaction with Ca^{2+} ATPase in the sarcoplasmic reticulum. In order to develop effective treatment plans for HF, it may be helpful to regulate oxidative stress in the heart and skeletal muscle.[55]

Cigarette smoke chronic obstructive pulmonary disease (COPD).

COPD is strongly associated with cigarette smoking, which is a significant environmental risk factor. Individuals who smoke cigarettes have a higher prevalence of respiratory symptoms, lung function abnormalities, and experience a more rapid decline in forced expiratory volume in 1 second (FEV1). Moreover, the mortality rate due to COPD is higher among smokers compared to nonsmokers. However, it is important to note that less than half of heavy smokers actually develop COPD.[57]

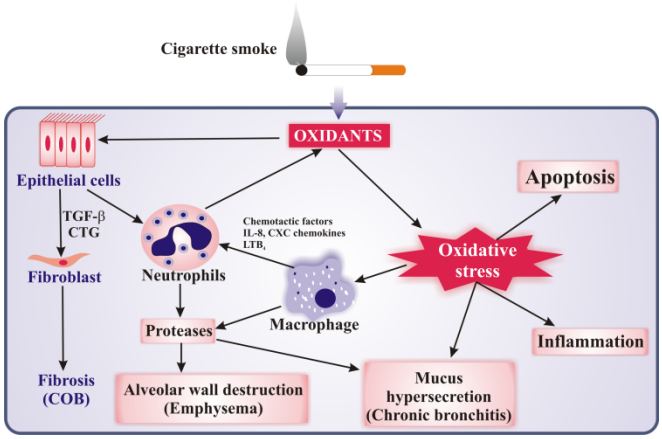


Figure 3. Chronic obstructive pulmonary disease (COPD) caused by smoking. Smoke from cigarettes causes the respiratory tract's macrophages to generate IL-8 and LTB4, which are neutrophil chemotactic factors. The proteases that are then released by these cells cause emphysema by destroying connective tissue in the lung parenchyma and by inducing mucus hypersecretion. Growth factors released by macrophages and epithelial cells may stimulate fibroblasts. CTG, connective tissue growth factor; COB, chronic obstructive bronchiolitis.[60]

Smokers have been found to have lower serum levels of the antioxidant enzymes GPx, glutathione reductase (GR), and ECSOD than non-smokers.[58] Smokers of all levels - heavy, light, and passive - have significantly lower erythrocyte SOD and CAT activities than non-smokers. It has been noted that ambient smoke has the same negative effects on passive smokers as it does on active smokers. Quitting smoking enhances tolerance to oxidative stress and raises plasma levels of certain antioxidant micronutrients. Numerous studies have shown that giving antioxidants such vitamins C and E to smokers reduces the lipid peroxidation markers that are linked to increased smoking.[59] The leading contributor to chronic obstructive pulmonary disease (COPD) in developed nations is tobacco usage.[60] The mechanism of COPD brought on by cigarette smoke is shown in Figure 3.

Aging

Aging is a intricate biological phenomenon characterized by a gradual deterioration in the physical capabilities of an organism, as well as an elevated susceptibility to age-related chronic ailments, including cardiovascular disorders, cancer, and neurodegenerative conditions.[61] The accumulation of mitochondrial DNA (mtDNA) mutations and the net creation of reactive oxidants are assumed to be the mechanisms by which mitochondria accelerate aging.The respiratory chain's 13 polypeptide components are encoded by the circular human mtDNA, which has 16,569 base pairs. It also contains the rRNAs and tRNAs required to enable intramitochondrial protein synthesis.

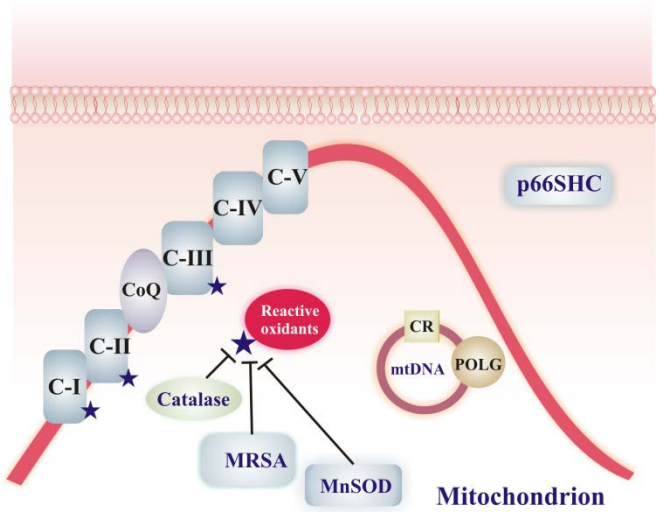


Figure 4. Role of mitochondria in aging. Oxidative stress and mitochondrial DNA (mtDNA) mutations may speed up aging. Age-related somatic mutation accumulation in mtDNA. Age-related disease is accelerated in transgenic mice by inducing mtDNA mutations by inhibiting mtDNA POLG's proofreading function. By lowering membrane potential and reducing the production of reactive oxygen species (reactive oxidants, red stars), certain mtDNA mutations may contribute to improved longevity. Increased expression of the reactive oxidants-scavenging enzymes catalase, methionine sulfoxide reductase A, or manganese superoxide dismutase (MnSOD), in mitochondria extends life. The lifetime is also extended by p66SHC knockout, a protein that encourages the production of reactive oxidants and mitochondrial death. A protein called p66SHC, which encourages the production of reactive oxidants and mitochondrial apoptosis, is likewise life-extending when knocked out. With aging, complex IV (C-IV) and complex V activities diminish, and complex V activity suppression resulting in oxidative damage to nuclear DNA, which most likely causes a fall in gene expression. Inner mitochondrial membrane, or IMM.[10]

The majority of the disorders that are known to be brought on by inherited mtDNA abnormalities affect the brain and muscles, two areas with high energy needs. One theory is that age-related somatic mtDNA mutations have a role in the physiological changes associated with aging and age-related neurodegeneration.[10] Another significant method by which mitochondria are thought to contribute to aging is the net generation of reactive oxidants. Both a vast network of antioxidant defenses and numerous electron carriers with the capacity to produce reactive oxidants are present in mitochondria (Figure 4). Reactive oxidants can be produced more than they are removed from the body as a result of mitochondrial insults, including oxidative damage itself.[62] The fact that improving mitochondrial antioxidant defenses can lengthen life is evidence for the significance of net mitochondrial reactive oxidants production to aging. The lifetime of Drosophila is increased by overexpressing the mitochondrial antioxidant enzymes methionine sulfoxide reductase and manganese superoxide dismutase (MnSOD).[63,64] The *Drosophila* strains with the shortest lifespans benefit the most from this tactic, while strains with lengthy lifespans are unaffected. However, it has recently been demonstrated that overexpression of CAT that was experimentally targeted to mitochondria lengthened the lifetime of a mouse strain that was already long-lived.[65] To overexpress CAT in peroxisomes, nuclei, or mitochondria, the authors of this study created transgenic mice. With a 20% increase in median and maximum lifetime, the mitochondrially targeted design offered the greatest advantage. In isolated cardiac mitochondria, H_2O_2 production and the oxidative inactivation of aconitase were decreased. In skeletal muscle, DNA oxidation and the quantity of mitochondrial deletions were also reduced, and the development of cataracts, arteriosclerosis, and heart disease was postponed.

Gastric ulcer

Peptic ulcer disease is a prevalent condition, impacting around 1 in 12 individuals in the United States. Roughly 1 in 5 cases of peptic ulcers are linked to an infection caused by Helicobacter pylori, while the majority of other cases are attributed to the use

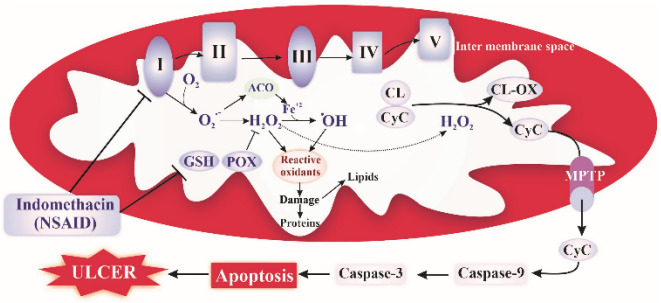


Figure 5. Schematic representation of the proposed mechanism of indomethacin (NSAID)-induced gastric ulcer.

of nonsteroidal anti-inflammatory drugs (NSAIDs).[66] Reactive oxidants have long been understood to have a part in oxidative stress and the pathophysiology that follows.[67,68] Although it has been demonstrated that reactive oxidants play a role in the etiology of gastroduodenal ulcers,[69-72] much more research needs to be done.[71] The components of the gastroduodenal mucosa suffer oxidative damage as a result of reactive oxidants.

In addition, the mucosa becomes more vulnerable to oxidative damage when endogenous antioxidant levels decline.[72,73] Reactive oxidant generation is increased in biopsy samples taken by endoscopy from patients with *H. pylori* infection. Gerbils with *H. pylori* infections also show signs of lipid oxidation in their stomachs, suggesting that this bacterial infection causes oxidative damage.[74] By scavenging reactive oxidants, endogenous antioxidants such catalase (CAT), SOD, peroxidases, and sulphydryls (glutathione, cysteine, and methionine) shield the mucosa from oxidative damage.[70,73,75,76] In WRS stress and ethanol-induced ulcers, mucosal SOD activity decreases.[71] Additionally, human ulcerated tissues have decreased total SOD activity (combined Cu-Zn SOD and MnSOD activity). It has previously been established that *H. pylori* infection causes the formation of reactive oxidants in human antral mucosa.[77] Both *H. pylori*-mediated and non-mediated human stomach ulcers have demonstrated the critical roles of antioxidant enzymes, neutrophil infiltration, and reactive oxidants-mediated oxidative damage.[78] Reactive oxidants are also produced by cellular ischemia, which is caused by decreased stomach mucosal blood flow,[79,80] in addition to the dysfunction of antioxidant mechanisms. Nonsteroidal anti-inflammatory medications (NSAID)-induced stomach ulcers are significantly influenced by mitochondrial oxidative stress.[13,81] Indomethacin (NSAID)-induced mitochondrial oxidative stress, activation of the mitochondrial route for apoptosis, and the onset of gastropathy are schematically summarized in Figure 5. The NSAID indomethacin interacts with the complex I of the electron transport chain[82] and causes an electron leakage in the mitochondria, which produces $O_2^{\bullet-}$ and reactive oxidants. Through the oxidation of proteins and lipids such cardiolipin and protein thiol, elevated reactive oxidants cause mitochondrial oxidative stress (MOS).[13,81] Due to damage caused by reactive oxidants, iron (Fe^{++}) is liberated from the Fe-S cluster of aconitase and worsens oxidative stress by generating $^{\bullet}OH$.[13] Figure 5 depicts the schematic summary of all the pathogenic mechanisms underlying indomethacin (NSAID)-induced mitochondrial oxidative stress, activation of mitochondrial pathway of apoptosis and development of gastropathy. Indomethacin (NSAID) interacts with the complex I of electron transport chain [82] and results in the leakage of electron in mitochondria leads to the formation of $O_2^{\bullet-}$, which leads to the generation of reactive oxidants. Increased reactive oxidants develop mitochondrial oxidative stress (MOS) by oxidizing protein and lipid including cardiolipin and protein thiol.[13,81] Iron (Fe^{+2}) is released from Fe-S cluster of aconitase due to reactive oxidants-mediated damage and further aggravates oxidative stress by producing $^{\bullet}OH$.[13] The MOS causes mitochondrial disease or dysfunction and activates the pathway in the mitochondria that leads to apoptosis, which is hazardous for ulcers.

Hepatic failure

Hepatic failure causes around two million deaths each year, accounting for 4% of all global deaths, which means that approximately 1 in 25 deaths worldwide, is attributed to this condition. Among all liver-related deaths, about two-thirds occur in men.[83] The oxidant-induced apoptosis of hepatocytes is thought to be mediated by a number of general mechanisms. The most straightforward explanation is that excessive oxidant-induced chemical damage to cellular macromolecules causes apoptosis to occur. Reactive oxidants may interact with lipids, proteins, and DNA in oxidative stress, which happens when cellular oxidant levels are higher than the antioxidant defenses can handle them. An apoptotic cell death pathway may be activated by the hepatocyte when it detects a critical level of cellular damage. Antioxidants' crucial role in hepatocellular defense against cell death lends credence to this theory. Rat hepatocytes grown in culture were made sensitive to H_2O_2 mortality by CAT and glutathione peroxidase inhibition.[84] Galactosamine and lipopolysaccharide-induced liver injury resulted in neutrophil-generated reactive oxidants that similarly predisposed mice lacking glutathione peroxidase to hepatic cell death.[85] Hepatocyte iron, which accelerates the conversion of H_2O_2 to the more lethal $^{\bullet}OH$, is one factor other than antioxidant levels that may further influence the development of oxidative

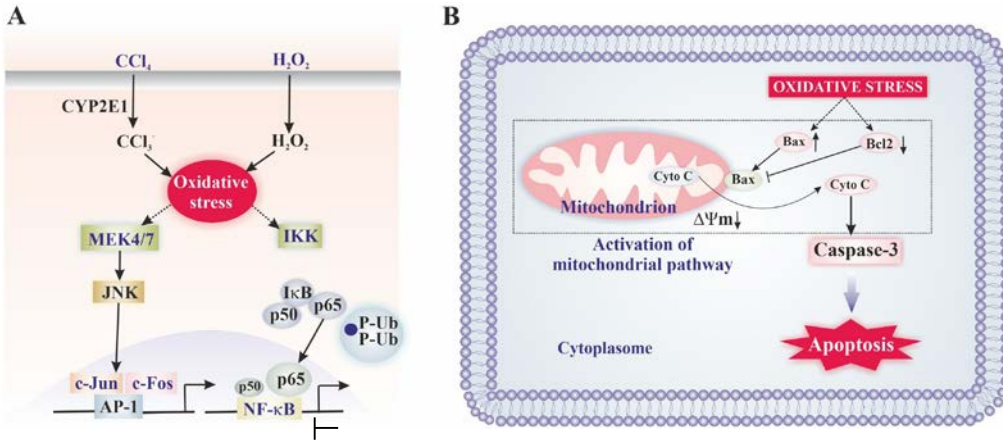


Figure 6. A. Oxidant-induced signaling cascades cause transcriptional activation in hepatocytes **B.** Schematic presentation of oxidative stress induced mitochondrial pathway of apoptosis in liver of malaria infected mice. Scavenging of $^{\bullet}OH$ by scavengers and spin trap inhibited the mitochondrial pathway of apoptosis (◄┈┈unknown pathway, ⊣ inhibition).[14]

stress.[86] Antioxidant supplementation can be interpreted as proof that apoptosis is oxidant driven and that death results from direct cellular injury by reactive oxidants by inhibiting apoptosis from activator protein-1(APAP)[87] and bile acids.[88] Antioxidants may, however, change redox-sensitive pro- or antiapoptotic signaling cascades that control death, which may have an impact on cell survival. The effects on cell signaling may prevent cell death without causing direct cellular damage from procedures like lipid peroxidation, which are actually secondary consequences.

It is believed that the transcriptional control of particular cellular genes is crucial for the cell to respond to external stimuli like oxidants. When signaling cascades like the MAPK pathways are involved, transcriptional activation is typically the result (Figure 6A). Exogenous H_2O_2 produced by inflammatory cells or hepatotoxin metabolism, such as the conversion of carbon tetrachloride (CCl_4) by the cytochrome P450 isoform 2E1 (CYP2E1) to the trichloromethyl (-CCl_3) free radical, induce oxidative stress in the hepatocyte. The JNK/AP-1 and NF-kB pathways are two signaling cascades that are activated by the resulting oxidative stress in the cell and result in transcriptional activation. The upstream kinases MEK4/7 commonly phosphorylate JNK, which activates it. The transcriptional activity of c-Jun is increased when activated JNK phosphorylates it. Specific genes' AP-1 sites are bound by c-Jun hetero, which dimerizes with other AP-1 family members like c-Fos to activate transcription. The IkB kinase (IKK) phosphorylation of IkB is the traditional activation mechanism for NF-kB. This phosphorylation sets off IkB ubiquitination, which is followed by 26S proteosome destruction. The nuclear translocation signals of NF-kB are revealed by IkB degradation, enabling it to go there and activate the transcription of target genes. It is yet unknown how hepatic oxidative stress triggers the JNK and NF-kB pathways, as indicated. However, it has been shown that hepatocyte death brought on by oxidative stress is modulated by both AP-1 and NF-kB-dependent gene products.[89] Hepatic dysfunction during malaria infection is significantly impacted by the mitochondrial mechanism of apoptosis generated by oxidative stress.[14,90] One of the most significant organs to be impacted by malaria infection is the liver, and free radicals have been suggested to play a significant role in the pathophysiology of the liver.[91,92] Hepatic xanthine oxidase and lipid peroxidation levels rise during *P. berghei* infection, suggesting that the liver produces more oxidative stress.[93] Reduced GSH and GR, an antioxidant defense system, guard cells against free radical damage. Oxidized glutathione is converted to reduced glutathione as a result of GR. GSH acts as a sulfhydryl buffer to shield proteins' -SH groups from reactive oxidants' harmful effects.[94] SOD and CAT stand in for the other antioxidant system. While CAT catalyzes the dissipation of H_2O_2 to water and oxygen, SOD catalyzes the dismutation of $O_2^{\bullet-}$ to H_2O_2. The signaling mechanism of liver apoptosis during malaria infection is summarized in Figure 6B. Malaria infection increases oxidative stress in the liver, and oxidative stress causes liver damage by activating the mitochondrial pathway and inducing apoptosis (Figure 6B).

Diabetes complications

Diabetes is a significant global health crisis, and its management aims to prevent complications resulting from inadequate control of blood sugar levels. Understanding the factors that contribute to poor glycemic control is crucial for implementing appropriate interventions to regulate blood sugar levels effectively and prevent the development of chronic complications.[95] Various metabolic processes, such as the polyol pathway, prostanoid synthesis, and protein glycation, can lead to an increased production of free radicals when there is high blood sugar (hyperglycemia). Moreover, when endothelial cells are exposed to elevated glucose levels, they generate more $O_2^{\bullet-}$.[96] The detrimental effects of high glucose on endothelial function, such as impaired relaxation of blood vessels and delayed cell proliferation, can be reversed by antioxidants in living organisms, providing further evidence of the involvement of oxidative stress in the development of these complications. It is proposed that the varying susceptibility of individuals with diabetes to microvascular and macrovascular problems may be related to their endogenous antioxidant levels, thus highlighting the importance of oxidative stress in diabetic complications [97]. Figure 7 illustrates the role of reactive oxidants and oxidative stress in the context of diabetic complications.

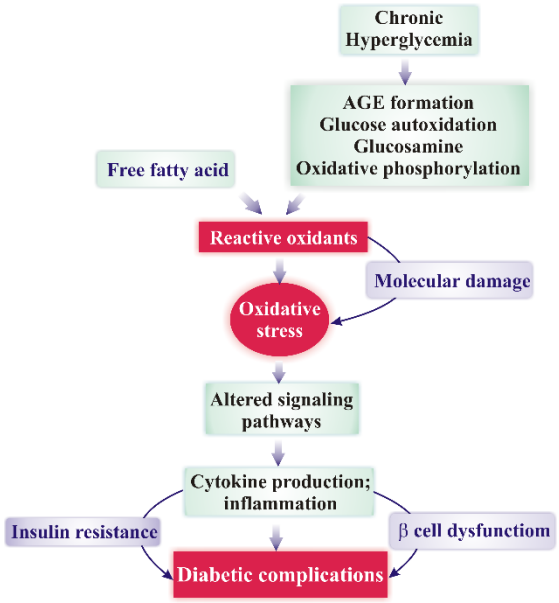


Figure 7. Schematic illustration suggestive of the central role played by reactive oxidants and oxidative stress in diabetic complications

Cancer

Cancer is a significant global public health issue and the second leading cause of death in the United States.[98] Research suggests that chronic inflammation, which involves communication between myeloid cell-derived reactive oxidants and tumor necrosis factor alpha (TNF-α)-mediated signaling, can contribute to the development of cancer.[99] It is also known that prolonged exposure to high levels of reactive oxidants can cause

DNA damage, and there is a specific mutation signature associated with oxidative DNA damage known as COSMIC (Catalogue of Somatic Mutations in Cancer) mutation signature.[100] Studies conducted on mice with deficient reactive oxidanats scavenging enzymes provide compelling evidence that reactive oxidants can increase the risk of cancer when antioxidant defenses are insufficient to counteract oxidative stress. For example, mice with a complete lack of cytoplasmic Sod1 or partial lack of mitochondrial Sod2 enzymes experience severe oxidative damage and spontaneously develop cancer.[101] Loss of certain genes encoding H_2O_2-scavenging enzymes, such as Prdx and selenium-dependent Gpx enzymes, also predisposes mice to tumorigenesis. Mice with reduced or absent expression of the Prdx1 gene exhibit increased oxidative DNA damage and a higher incidence of various cancers compared to mice with normal Prdx1 expression as they age.[102] In contrast, mice lacking Prdx2, Prdx4, or Prdx6 genes do not develop cancer spontaneously.[103] Similarly, while Gpx1 and Gpx2 single knockout mice remain healthy, Gpx1/2 double knockout mice are prone to developing ileocolitis and subsequent intestinal tumors dependent on the presence of commensal microflora. Elevated production of $^{\bullet}OH$ also increases susceptibility to tumorigenesis by modifying DNA.[104] This is consistent with the observation that patients with iron overload or hemochromatosis have a higher risk of cancer.[105]

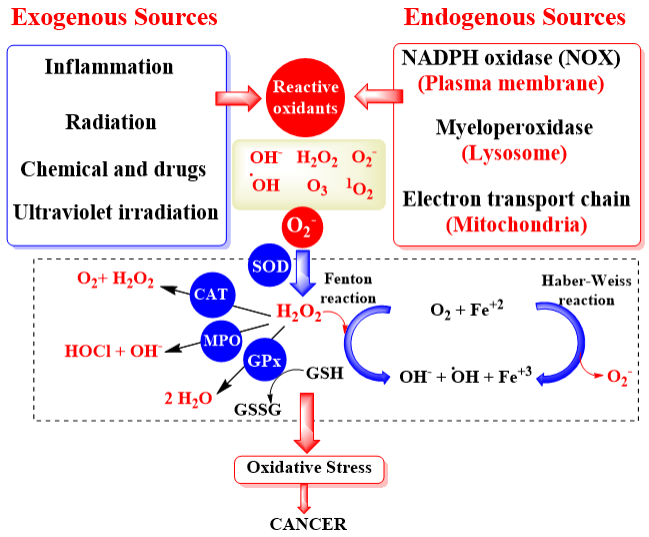


Figure 8. Schematic illustration suggestive of the central role played by reactive oxidants and oxidative stress in cancer [108]. superoxide dismutases (SOD) reduced glutathione (GSH); oxidised glutathione (GSSG); myeloperoxidase (MPO); Catalase (CAT); Glutathione peroxidase (GPx)

However, the susceptibility of mice with ferritin deficiency or iron-replete ferritin knockout to cancer is not yet known. In cases of chronic inflammation, levels of peroxynitrite ($ONOO^-$) may substantially increase. When combined with carbon dioxide (CO_2), $ONOO^-$ can form nitrosoperoxycarbonate, which decomposes into $CO_3^{\bullet-}$ and $^{\bullet}NO_2$, initiating selective oxidation and nitration of guanine in DNA. This process leads to the formation of guanine-thymidine crosslinks, which contribute to DNA damage.[106] Given that an increase in reactive oxidants levels is associated with a higher risk of tumorigenesis, it can be inferred that chronic depletion of antioxidant status is similarly linked to an increased risk. However, fully understanding the role of glutathione (GSH) in modulating the risk of carcinogenesis is complicated by the fact that knockout of genes Gclc or Gss is lethal during embryonic development. On the other hand, knockout of Gclm has a less significant impact on GSH levels, reducing them to approximately 15% of wild-type levels in certain organs and cells.[102] Although fibroblasts derived from Gclm-deficient mice exhibit elevated ROS levels, DNA damage, and upregulation of Tp53 and p21 genes, these mice do not spontaneously develop tumors.[107] Fig 8 illustrates the role of reactive oxidants and oxidative stress in the context of cancer.

Discussion

The article discusses the concept of oxidative stress, which arises when there is an imbalance between reactive oxidants and the antioxidant defense system within cells [1]. It explains that reactive oxidants, such as $O_2^{\bullet-}$ and H_2O_2, are normal byproducts of cellular metabolism.[109] The antioxidant defense system is responsible for maintaining a delicate equilibrium by neutralizing these oxidants through enzymatic and non-enzymatic processes [110]. However, when the production of reactive oxidants exceeds the capacity of the antioxidant defense system, oxidative stress occurs.[111] This oxidative stress leads to cellular damage through various mechanisms, including lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction [112]. These processes have detrimental effects on cellular health and can activate signaling pathways related to disease onset. The article highlights that oxidative stress plays a significant role in the development of various diseases. It discusses its involvement in cardiovascular diseases, chronic obstructive pulmonary disease (COPD) resulting from smoking, aging-related diseases, gastric ulcers, hepatic failure, diabetes complications, and cancer. In each case, oxidative stress contributes to tissue damage, inflammation, and the activation of disease-related pathways.

The perspective presented in the article emphasizes the importance of understanding oxidative stress mechanisms and developing effective therapeutic strategies. By gaining a deeper understanding of the underlying processes and consequences of oxidative stress, researchers can explore new options for disease prevention and treatment. This knowledge can potentially lead to the development of targeted interventions that aim to restore the balance between reactive oxidants and the antioxidant defense system, thereby mitigating cellular damage and preventing the progression of various diseases.

In terms of future applicability, the insights provided in the article can serve as a foundation for further research and the development of therapeutic interventions. By targeting oxidative stress pathways and developing strategies to enhance the antioxidant defense system, it may be possible to mitigate the damaging effects of oxidative stress and improve patient outcomes across a range of diseases. In a relative analysis, the

article demonstrates the widespread impact of oxidative stress on multiple diseases, highlighting its role as a common underlying factor. By examining various conditions and their association with oxidative stress, the article underscores the importance of considering oxidative stress as a potential therapeutic target. The discussion of the mechanisms and consequences of oxidative stress provides a comprehensive overview of its implications, further emphasizing its relevance in disease development and progression.

CONCLUSION

In conclusion, oxidative stress is an important factor in the aetiology of many diseases, such as chronic heart failure, diabetes complications, aging, gastric ulcers, and chronic obstructive pulmonary disease (COPD) brought on by smoking. Cellular damage and malfunction in these circumstances are a result of an imbalance between the generation of reactive oxidants and antioxidant defense mechanisms. Oxidative stress encourages inflammation, endothelial dysfunction, and oxidative alteration of lipids in cardiovascular disorders, which helps to cause and advance chronic heart failure. Smoking-related oxidative stress worsens inflammation and impairs lung function in COPD by causing oxidative damage to lung tissues. Age-related disorders like hepatic failure and stomach ulcers are influenced by increased oxidative stress, which is linked to aging. Stomach ulcers form as a result of oxidative stress damaging the stomach mucosal barrier. Oxidative stress contributes to liver damage and dysfunction in hepatic failure. For the creation of specialized therapeutic approaches, it is essential to comprehend the processes of oxidative stress in various disorders. The pathogenesis and course of these diseases may be slowed down through the use of techniques to lessen oxidative stress and strengthen antioxidant defense mechanisms. To investigate these pathways and find new therapeutic strategies, more study is required.

DISCLOSURE OF INTEREST

Author has no conflict of interest in any part of this article and none of the material has been published or is under consideration elsewhere.

ACKNOWLEDGMENTS

Author thanks The Department of Science and Technology (DST) [Innovation in Science Pursuit for Inspired Research (INSPIRE) Faculty scheme] for providing me fund to carry out the work.

REFERENCES AND NOTES

1. T.R. Kıran, O. Otlu, A.B. Karabulut. Oxidative stress and antioxidants in health and disease. *J. Laboratory Med.* **2023**, 47(1), 1-11.
2. G. Pizzino, N. Irrera, M. Cucinotta et. al. Oxidative Stress: Harms and Benefits for Human Health. *Oxidative medicine and cellular longevity* **2017**, 20178416763.
3. C.A. Juan, J.M. Pérez de la Lastra, F.J. Plou, E. Pérez-Lebeña. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. *Int. J. Mol. Sci.* **2021**, 22(9), 4642.
4. R. Zhang, R. Kang, D. Tang. Reductive cell death: the other side of the coin. *Cancer Gene Therapy* **2023**, 1-3.
5. P. Moustardas, D. Aberdam, N. Lagali. MAPK Pathways in Ocular Pathophysiology: Potential Therapeutic Drugs and Challenges. *Cells* **2023**, 12(4).
6. T. Liu, L. Zhang, D. Joo, S.C. Sun. NF-kB signaling in inflammation. *Signal transduction and targeted therapy* **2017**, 217023.
7. U. Bandyopadhyay, D. Das, R.K. Banerjee. Reactive oxygen species: oxidative damage and pathogenesis. *Current Science* **1999**, 77(5), 658-66.
8. D. Harman. Free radical involvement in aging. Pathophysiology and therapeutic implications. *Drugs Aging* **1993**, 3(1), 60-80.
9. H.J. Shields, A. Traa, J.M. Van Raamsdonk. Beneficial and detrimental effects of reactive oxygen species on lifespan: a comprehensive review of comparative and experimental studies. *Front. Cell Developmental Biol.* **2021**, 9181.
10. M.T. Lin, M.F. Beal. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* **2006**, 443(7113), 787-95.
11. A.V. Kudryavtseva, G.S. Krasnov, A.A. Dmitriev et. al. Mitochondrial dysfunction and oxidative stress in aging and cancer. *Oncotarget* **2016**, 7(29), 44879-905.
12. R. Vona, L. Pallotta, M. Cappelletti et. al. The Impact of Oxidative Stress in Human Pathology: Focus on Gastrointestinal Disorders. *Antioxidants* **2021**, 10(2).
13. P. Maity, S. Bindu, S. Dey et. al. Indomethacin, a non-steroidal anti-inflammatory drug, develops gastropathy by inducing reactive oxygen species-mediated mitochondrial pathology and associated apoptosis in gastric mucosa: a novel role of mitochondrial aconitase oxidation. *J Biol Chem* **2009**, 284(5), 3058-68.
14. M. Guha, S. Kumar, V. Choubey et. al. Apoptosis in liver during malaria: role of oxidative stress and implication of mitochondrial pathway. *FASEB J* **2006**, 20(8), 1224-6.
15. D.D. Bandyopadhyay U, Banerjee R-K. Reactive oxygen species: Oxidative damage and pathogenesis. *Current Science* **1999**, 77658-66.
16. I. Fridovich. Fundamental aspects of reactive oxygen species, or what's the matter with oxygen? *Ann N Y Acad Sci* **1999**, 89313-8.
17. J.F. Turrens. Mitochondrial formation of reactive oxygen species. *J. Physiology* **2003**, 552(Pt 2), 335-44.
18. V.P. Skulachev. Membrane Bioenergetics, Springer-Verlag: New York, **1988**.
19. Y. Liu, G. Fiskum, D. Schubert. Generation of reactive oxygen species by the mitochondrial electron transport chain. *J Neurochem* **2002**, 80(5), 780-7.
20. A.P. Kudin, N.Y. Bimpong-Buta, S. Vielhaber et. al. Characterization of superoxide-producing sites in isolated brain mitochondria. *J. Biol. Chem.* **2004**, 279(6), 4127-35.
21. G. Krishnamoorthy, P.C. Hinkle. Studies on the electron transfer pathway, topography of iron-sulfur centers, and site of coupling in NADH-Q oxidoreductase. *J. Biol. Chem.* **1988**, 263(33), 17566-75.
22. A. Herrero, G. Barja. Localization of the site of oxygen radical generation inside the complex I of heart and nonsynaptic brain mammalian mitochondria. *J Bioenerg Biomembr* **2000**, 32(6), 609-15.
23. F.L. Muller, Y. Liu, H. Van Remmen. Complex III releases superoxide to both sides of the inner mitochondrial membrane. *J. Biol. Chem.* **2004**, 279(47), 49064-73.
24. G. Lenaz. Role of mitochondria in oxidative stress and ageing. *Biochim Biophys Acta* **1998**, 1366(1-2), 53-67.
25. E. Cadenas, K.J. Davies. Mitochondrial free radical generation, oxidative stress, and aging. *Free Radical Biology & Medicine* **2000**, 29(3-4), 222-30.
26. I. Fridovich. Superoxide anion radical (O2-.), superoxide dismutases, and related matters. *J. Biol. Chem.* **1997**, 272(30), 18515-7.
27. S. Harel, M.A. Salan, J. Kanner. Iron release from metmyoglobin, methaemoglobin and cytochrome c by a system generating hydrogen peroxide. *Free Radic Res Commun* **1988**, 5(1), 11-9.
28. P.V. Vignais. The superoxide-generating NADPH oxidase: structural aspects and activation mechanism. *Cellular and Molecular Life Sciences* **2002**, 59(9), 1428-59.
29. J.D. Lambeth. NOX enzymes and the biology of reactive oxygen. *Nat Rev Immunol* **2004**, 4(3), 181-9.

30. M. Geiszt, T.L. Leto. The Nox family of NAD(P)H oxidases: host defense and beyond. *J. Biol. Chem.* **2004**, 279(50), 51715-8.
31. H. Sumimoto, K. Miyano, R. Takeya. Molecular composition and regulation of the Nox family NAD(P)H oxidases. *Biochemical and Biophysical Research Communications* **2005**, 338(1), 677-86.
32. M.T. Quinn, K.A. Gauss. Structure and regulation of the neutrophil respiratory burst oxidase: comparison with nonphagocyte oxidases. *J. Leukocyte Biology* **2004**, 76(4), 760-81.
33. R. Harrison In Free Radicals and Inflammation P. Winyard, Blake, DR., Evans, CH., Ed. Birkha$user, Switzerland, **2000**, pp 65-81.
34. I. Kessova, A.I. Cederbaum. CYP2E1: biochemistry, toxicology, regulation and function in ethanol-induced liver injury. *Curr Mol Med* **2003**, 3(6), 509-18.
35. N. Kaludercic, E. Takimoto, T. Nagayama et. al. Monoamine oxidase A-mediated enhanced catabolism of norepinephrine contributes to adverse remodeling and pump failure in hearts with pressure overload. *Circ Res* **2010**, 106(1), 193-202.
36. WHO publishes definitive atlas on global heart disease and stroke epidemic. *Indian J Med Sci* **2004**, 58(9), 405-6.
37. J.L. Marx. Oxygen free radicals linked to many diseases. *Science* **1987**, 235(4788), 529-31.
38. M.L. Myers, R. Bolli, R.F. Lekich et. al. Enhancement of recovery of myocardial function by oxygen free-radical scavengers after reversible regional ischemia. *Circulation* **1985**, 72(4), 915-21.
39. A.C. Maritim, R.A. Sanders, J.B. Watkins, III. Diabetes, oxidative stress, and antioxidants: A review. *J. Biochem. Mol. Toxicol.* **2003**, 17(1), 24-38.
40. A. Boullier, D.A. Bird, M.K. Chang et. al. Scavenger receptors, oxidized LDL, and atherosclerosis. *Ann N Y Acad Sci* **2001**, 947214-22.
41. B. Van der Loo, R. Labugger, C.P. Aebischer et. al. Cardiovascular aging is associated with vitamin E increase. *Circulation* **2002**, 105(14), 1635-38.
42. R. McKechnie, M. Rubenfire, L. Mosca. Antioxidant nutrient supplementation and brachial reactivity in patients with coronary artery disease. *J Lab Clin Med* **2002**, 139(3), 133-9.
43. C.G. Schnackenberg. Oxygen radicals in cardiovascular-renal disease. *Curr. Opin. Pharmacol.* **2002**, 2(2), 121-25.
44. A.H. Lichtenstein. Nutrients and cardiovascular disease: no easy answers. *Curr. Opin. Lipidol.* **2005**, 16(1), 1-3.
45. S.A. Hunt, W.T. Abraham, M.H. Chin et. al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* **2009**, 119(14), e391-479.
46. A. Sabri, H.H. Hughie, P.A. Lucchesi. Regulation of hypertrophic and apoptotic signaling pathways by reactive oxygen species in cardiac myocytes. *Antioxid Redox Signal* **2003**, 5(6), 731-40.
47. S.H. Kwon, D.R. Pimentel, A. Remondino et. al. H(2)O(2) regulates cardiac myocyte phenotype via concentration-dependent activation of distinct kinase pathways. *J Mol Cell Cardiol* **2003**, 35(6), 615-21.
48. F.G. Spinale, M.L. Coker, C.V. Thomas et. al. Time-dependent changes in matrix metalloproteinase activity and expression during the progression of congestive heart failure: relation to ventricular and myocyte function. *Circ Res* **1998**, 82(4), 482-95.
49. E.E. Creemers, J.P. Cleutjens, J.F. Smits, M.J. Daemen. Matrix metalloproteinase inhibition after myocardial infarction: a new approach to prevent heart failure? *Circ Res* **2001**, 89(3), 201-10.
50. L.E. Rohde, A. Ducharme, L.H. Arroyo et. al. Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. *Circulation* **1999**, 99(23), 3063-70.
51. S. Hayashidani, H. Tsutsui, M. Ikeuchi et. al. Targeted deletion of MMP-2 attenuates early LV rupture and late remodeling after experimental myocardial infarction. *Am J Physiol Heart Circ Physiol* **2003**, 285(3), H1229-35.
52. S. Rajagopalan, X.P. Meng, S. Ramasamy et. al. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. *J Clin Invest* **1996**, 98(11), 2572-9.
53. S. Kinugawa, H. Tsutsui, S. Hayashidani et. al. Treatment with dimethylthiourea prevents left ventricular remodeling and failure after experimental myocardial infarction in mice: role of oxidative stress. *Circ Res* **2000**, 87(5), 392-8.
54. A.V. Zima, L.A. Blatter. Redox regulation of cardiac calcium channels and transporters. *Cardiovasc Res* **2006**, 71(2), 310-21.
55. H. Tsutsui, S. Kinugawa, S. Matsushima. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol* **2011**, 301(6), H2181-90.
56. L. Lavie, P. Lavie. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. *Eur Respir J* **2009**, 33(6), 1467-84.
57. A. Agusti, B.R. Celli, G.J. Criner et. al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Eur Respir J* **2023**, 61(4).
58. S.H. Kim, J.S. Kim, H.O.S. Shin, C.L. Keen. Influence of Smoking on Markers of Oxidative Stress and Serum Mineral Concentrations in Teenage Girls in Korea. *Nutrition* **2003**, 19(3), 240-43.
59. M. Dietrich, G. Block, M. Hudes et. al. Antioxidant supplementation decreases lipid peroxidation biomarker F2-isoprostanes in plasma of smokers. *Cancer Epidemiol., Biomarkers Prev.* **2002**, 11(1), 7-13.
60. P.J. Barnes. Mediators of chronic obstructive pulmonary disease. *Pharmacol Rev* **2004**, 56(4), 515-48.
61. E. Maldonado, S. Morales-Pison, F. Urbina, A. Solari. Aging Hallmarks and the Role of Oxidative Stress. *Antioxidants* **2023**, 12(3), 651.
62. A.Y. Andreyev, Y.E. Kushnareva, A.A. Starkov. Mitochondrial metabolism of reactive oxygen species. *Biochemistry* **2005**, 70(2), 200-14.
63. J. Sun, D. Folk, T.J. Bradley, J. Tower. Induced overexpression of mitochondrial Mn-superoxide dismutase extends the life span of adult Drosophila melanogaster. *Genetics* **2002**, 161(2), 661-72.
64. H. Ruan, X.D. Tang, M.L. Chen et. al. High-quality life extension by the enzyme peptide methionine sulfoxide reductase. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, 99(5), 2748-53.
65. S.E. Schriner, N.J. Linford, G.M. Martin et. al. Extension of Murine Life Span by Overexpression of Catalase Targeted to Mitochondria. *Science* **2005**, 308(5730), 1909-11.
66. J.R. McConaghy, A. Decker, S. Nair. Peptic Ulcer Disease and H. pylori Infection: Common Questions and Answers. *Am. family physician* **2023**, 107(2), 165-72.
67. B. Halliwell. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *Lancet* **1994**, 344(8924), 721-4.
68. B. Halliwell, J.M. Gutteridge. Role of free radicals and catalytic metal ions in human disease: an overview. *Methods Enzymol* **1990**, 1861-85.
69. D. Das, D. Bandyopadhyay, R.K. Banerjee. Oxidative inactivation of gastric peroxidase by site-specific generation of hydroxyl radical and its role in stress-induced gastric ulceration. *Free Radic Biol Med* **1998**, 24(3), 460-9.
70. D. Das, D. Bandyopadhyay, M. Bhattacharjee, R.K. Banerjee. Hydroxyl radical is the major causative factor in stress-induced gastric ulceration. *Free Radic Biol Med* **1997**, 23(1), 8-18.
71. S. Kwiecien, T. Brzozowski, S.J. Konturek. Effects of reactive oxygen species action on gastric mucosa in various models of mucosal injury. *J Physiol Pharmacol* **2002**, 53(1), 39-50.
72. P.S. Phull, C.J. Green, M.R. Jacyna. A radical view of the stomach: the role of oxygen-derived free radicals and anti-oxidants in gastroduodenal disease. *Eur J Gastroenterol Hepatol* **1995**, 7(3), 265-74.
73. D. Das, R.K. Banerjee. Effect of stress on the antioxidant enzymes and gastric ulceration. *Mol Cell Biochem* **1993**, 125(2), 115-25.
74. H. Suzuki, M. Mori, K. Seto et. al. Helicobacter pylori-associated gastric pro- and antioxidant formation in Mongolian gerbils. *Free Radic Biol Med* **1999**, 26(5-6), 679-84.
75. A. Hassan, E. Martin, P. Puig-Parellada. Role of antioxidants in gastric mucosal damage induced by indomethacin in rats. *Methods Find Exp Clin Pharmacol* **1998**, 20(10), 849-54.
76. T. Yoshikawa, Y. Naito, A. Kishi et. al. Role of active oxygen, lipid peroxidation, and antioxidants in the pathogenesis of gastric mucosal injury induced by indomethacin in rats. *Gut* **1993**, 34(6), 732-7.

77. G.R. Davies, N.J. Simmonds, T.R. Stevens et. al. Helicobacter pylori stimulates antral mucosal reactive oxygen metabolite production in vivo. *Gut* **1994**, 35(2), 179-85.
78. M. Bhattacharjee, S. Bhattacharjee, A. Gupta, R.K. Banerjee. Critical role of an endogenous gastric peroxidase in controlling oxidative damage in H. pylori-mediated and nonmediated gastric ulcer. *Free Radic Biol Med* **2002**, 32(8), 731-43.
79. P.C. Konturek, T. Brzozowski, Z. Sulekova et. al. Enhanced expression of leptin following acute gastric injury in rat. *J Physiol Pharmacol* **1999**, 50(4), 587-95.
80. S. Kwiecien, T. Brzozowski, P. Konturek, S.J. Konturek. The role of reactive oxygen species in action of nitric oxide-donors on stress-induced gastric mucosal lesions. *J Physiol Pharmacol* **2002**, 53(4 Pt 2), 761-73.
81. P. Maity, S. Bindu, V. Choubey et. al. Lansoprazole protects and heals gastric mucosa from non-steroidal anti-inflammatory drug (NSAID)-induced gastropathy by inhibiting mitochondrial as well as Fas-mediated death pathways with concurrent induction of mucosal cell renewal. *J Biol Chem* **2008**, 283(21), 14391-401.
82. S. Somasundaram, R. Simpson, S. Rafi et. al. 2, 4-diamino-6- hydroxy pyrimidine inhibits NSAIDs induced nitrosyl-complex EPR signals and ulcer in rat jejunum. *BMC Gastroenterol* **2002**, 28.
83. H. Devarbhavi, S.K. Asrani, J.P. Arab et. al. Global burden of liver disease: 2023 update. *J. hepatology* **2023**, 79(2), 516-37.
84. P.E. Starke, J.L. Farber. Endogenous defenses against the cytotoxicity of hydrogen peroxide in cultured rat hepatocytes. *J Biol Chem* **1985**, 260(1), 86-92.
85. H. Jaeschke, Y.S. Ho, M.A. Fisher et. al. Glutathione peroxidase-deficient mice are more susceptible to neutrophil-mediated hepatic parenchymal cell injury during endotoxemia: importance of an intracellular oxidant stress. *Hepatology* **1999**, 29(2), 443-50.
86. K. Ollinger, K. Roberg. Nutrient deprivation of cultured rat hepatocytes increases the desferrioxamine-available iron pool and augments the sensitivity to hydrogen peroxide. *J Biol Chem* **1997**, 272(38), 23707-11.
87. P.J. Ferret, R. Hammoud, M. Tulliez et. al. Detoxification of reactive oxygen species by a nonpeptidyl mimic of superoxide dismutase cures acetaminophen-induced acute liver failure in the mouse. *Hepatology* **2001**, 33(5), 1173-80.
88. B. Yerushalmi, R. Dahl, M.W. Devereaux et. al. Bile acid-induced rat hepatocyte apoptosis is inhibited by antioxidants and blockers of the mitochondrial permeability transition. *Hepatology* **2001**, 33(3), 616-26.
89. M.J. Czaja. Induction and regulation of hepatocyte apoptosis by oxidative stress. *Antioxid Redox Signal* **2002**, 4(5), 759-67.
90. S. Dey, M. Guha, A. Alam et. al. Malarial infection develops mitochondrial pathology and mitochondrial oxidative stress to promote hepatocyte apoptosis. *Free radical biol. Med.* **2009**, 46(2), 271-81.
91. N.J. Siddiqi, V.C. Pandey. Studies on hepatic oxidative stress and antioxidant defence systems during arteether treatment of Plasmodium yoelii nigeriensis infected mice. *Mol Cell Biochem* **1999**, 196(1-2), 169-73.
92. I.A. Clark, G. Chaudhri, W.B. Cowden. Some roles of free radicals in malaria. *Free radical Biol. Med.* **1989**, 6(3), 315-21.
93. P. Srivastava, S.K. Puri, G.P. Dutta, V.C. Pandey. Hepatic superoxide-scavenging system during Plasmodium berghei infection and chloroquine treatment. *Med. Sci. Res.* **1991**, 19(10), 307-8.
94. A. Meister, M.E. Anderson. Glutathione. *Annu Rev Biochem* **1983**, 52711-60.
95. A.L. Dimore, Z.K. Edosa, A.A. Mitiku. Glycemic control and diabetes complications among adult type 2 diabetic patients at public hospitals in Hadiya zone, Southern Ethiopia. *PloS one* **2023**, 18(3), e0282962.
96. C. Ruiz, A. Alegria, R. Barbera et. al. Lipid peroxidation and antioxidant enzyme activities in patients with type 1 diabetes mellitus. *Scand J Clin Lab Invest* **1999**, 59(2), 99-105.
97. G. Marra, P. Cotroneo, D. Pitocco et. al. Early increase of oxidative stress and reduced antioxidant defenses in patients with uncomplicated type 1 diabetes: a case for gender difference. *Diabetes Care* **2002**, 25(2), 370-5.
98. B.S. Chhikara, K. Parang. Global Cancer Statistics 2022: the trends projection analysis. *Chem. Biol. Lett.* **2023**, 10 (1), 451.
99. O. Canli, A.M. Nicolas, J. Gupta et. al. Myeloid Cell-Derived Reactive Oxygen Species Induce Epithelial Mutagenesis. *Cancer cell* **2017**, 32(6), 869-83 e5.
100. Y. Rose Li, K.D. Halliwill, C.J. Adams et. al. Mutational signatures in tumours induced by high and low energy radiation in Trp53 deficient mice. *Nature communications* **2020**, 11(1), 394.
101. J.G. Gill, E. Piskounova, S.J. Morrison. Cancer, Oxidative Stress, and Metastasis. Cold Spring Harbor symposia on quantitative biology **2016**, 81163-75.
102. J.D. Hayes, A.T. Dinkova-Kostova, K.D. Tew. Oxidative Stress in Cancer. *Cancer cell* **2020**, 38(2), 167-97.
103. M.B. Hampton, K.A. Vick, J.J. Skoko, C.A. Neumann. Peroxiredoxin Involvement in the Initiation and Progression of Human Cancer. *Antioxid Redox Signal* **2018**, 28(7), 591-608.
104. B. Halliwell, J.M. Gutteridge. Free radicals in biology and medicine, Oxford university press, USA, **2015**.
105. S.V. Torti, D.H. Manz, B.T. Paul et. al. Iron and Cancer. *Annual review of nutrition* **2018**, 3897-125.
106. V. Shafirovich, N.E. Geacintov. Removal of oxidatively generated DNA damage by overlapping repair pathways. *Free Rad. Biol. Med.* **2017**, 10753-61.
107. Y. Chen, E. Johansson, Y. Fan et. al. Early onset senescence occurs when fibroblasts lack the glutamate-cysteine ligase modifier subunit. *Free Rad. Biol. Med.* **2009**, 47(4), 410-8.
108. J. Morry, W. Ngamcherdtrakul, W. Yantasee. Oxidative stress in cancer and fibrosis: Opportunity for therapeutic intervention with antioxidant compounds, enzymes, and nanoparticles. *Redox biology* **2017**, 11240-53.
109. M. Schieber, N.S. Chandel. ROS function in redox signaling and oxidative stress. *Current biology* **2014**, 24(10), R453-62.
110. M. Hasanuzzaman, M.B. Bhuyan, F. Zulfiqar et. al. Reactive oxygen species and antioxidant defense in plants under abiotic stress: Revisiting the crucial role of a universal defense regulator. *Antioxidants* **2020**, 9(8), 681.
111. E.A.M. Saleh, F. Al-dolaimy, S. Baymakov et. al. Oxidative stress affects the beginning of the growth of cancer cells through a variety of routes. *Pathology-Research and Practice* **2023**, 154664.
112. Z. Yan, Q. Chen, Y. Xia. Oxidative Stress Contributes to Inflammatory and Cellular Damage in Systemic Lupus Erythematosus: Cellular Markers and Molecular Mechanism. *J. inflammation res*. **2023**, 16453-65.

AUTHOR'S BIOGRAPHY

Dr. Chinmay Pal received his B.Sc. from Calcutta University in 2005 and completed his M.Sc. in chemistry in 2007, from Indian institute of Technology Roorkee. He obtained his Ph.D. from Indian Institute of Chemical Biology under the guidance of Dr. Uday Bandyopadhyay in 2012. After his postdoctoral research with Professor Steven Tannenbaum at the Singapore-MIT Alliance for Research and Technology (SMART), Singapore he joined Jadavpur University, West Bengal, in 2014 as Inspire Faculty. After that Dr. Pal joined Gobardanga Hindu College as an Assistant Professor in 2015. His research project covers the field of Design, synthesis and biological evaluation of some novel antioxidant–antiapoptotic molecules to protect organ damage due to oxidative stress.