Broad overview of oxidative stress and its complications in human health

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ABSTRACT

There is extensive literature dealing with toxicity and human health. A goodly portion puts focus on involvement of electron transfer, reactive oxygen species and oxidative stress involving body organs. There is evidence for prevention or amelioration by antioxidants. This is one mechanism which is part of a multifaceted mode of action. This review comprises an update of earlier literature.

Keywords: Health; Organ Toxicity; Oxidative Stress; Reactive Oxygen Species; Electron Transfer
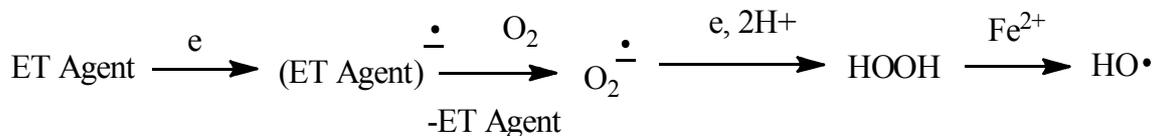
1. INTRODUCTION

Abundant literature exists on involvement of reactive oxygen species (ROS) and oxidative stress (OS) on human health. Various reviews (see main text) in the past have addressed the topic in relation to organ toxicity. The present review provides a literature update including the following organs: lungs, skin, kidney, heart, reproductive and mitochondria. The preponderance of bioactive substances or their metabolites incorporate electron transfer (ET) functionalities, which, we believe, play an important role in physiological responses. These main groups include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). *In vivo* redox cycling with oxygen can occur giving rise to OS through generation of ROS (**Scheme 1**), such as hydrogen perox-

ide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide). In some cases, ET results in interference with normal electrical effects, e.g., in respiration or neurochemistry. Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, *i.e.*, more positive than −0.5 V. ET, ROS, and OS have been increasingly implicated in the mode of action of drugs and toxins (toxicants), e.g. anti-infective agents [1], anticancer drugs [2,3], carcinogens [4], and toxins [5].

There is a plethora of experimental evidence supporting the theoretical framework, including generation of the common ROS, lipid peroxidation, degeneration products of oxidation, depletion of AOs, effect of exogenous AOs, DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is in keeping with the frequent observations that many ET substances display a variety of activities, e.g., multiple drug properties, as well as toxic effects.

Diverse mechanisms have been proposed for these agents. However, there has not been recognition for a unifying theme involving ET-ROS-OS. The unifying relationships lend credence to the proposed involvement of ET-ROS-OS in the physiological effects addressed in this review, and comprise an extension of the prior mechanistic framework. However, it should be emphasized that physiological activity is often complex and multifaceted, with various modes of action involved. A number of original references may be found in the reviews and articles cited; in many cases, references are representative.

$$\text{ET Agent} \xrightarrow{\text{e}} \text{(ET Agent)}^{\bullet} \xrightarrow[\text{-ET Agent}]{O_2} O_2^{\bullet -} \xrightarrow{\text{e, 2H+}} \text{HOOH} \xrightarrow{Fe^{2+}} \text{HO}^{\bullet}$$

Scheme 1. Formation of ROS and RNS. Shown is ET resulting in formation of superoxide which serves as precursor of other ROS.

2. DISCUSSION

2.1. Neurodegenerative Diseases

There has been treatment of neurotoxicity and neurodegenerative diseases involving ROS and OS. A recent review represents an update of neurodegenerative diseases based on extensive literature [6]. The redox approach comprises a unifying theme which can be applied to a large number of illnesses in this class, including Parkinson's, Huntington's, Alzheimer's, prions, Down's syndrome, ataxia, multiple sclerosis, Creutzfeldt-Jacob disease, amyotrophic lateral sclerosis, schizophrenia, and tardive dyskinesia. An earlier review addressed neurodegeneration from a similar mechanistic viewpoint based on ROS-OS [7].

The brain consumes more oxygen under physiological conditions than other organs, thereby increasing its susceptibility to OS since generation of higher levels of ROS can lead to pathological changes when these are in excess of the buffering capacity of endogenous antioxidant systems [8]. Extensive data on OS, signaling pathways, cell death and neuroprotection have been generated in many studies.

Hyperoxia produces toxicity, including that of the nervous system. The mammalian brain appears to be particularly sensitive to oxidative damage, one reason being the high oxygen consumption. Rises in calcium interfere with mitochondrial function (including neural), increasing formation of superoxide which can react with nitric oxide (NO) to form the potent oxidant peroxynitrite ($ONOO^-$), accompanied by lipid peroxidation. Several neurotransmitters, including dopamine, L-DOPA, serotonin and norepinephrine, can produce ROS, evidently via quinone/semiquinone metabolites. Iron is found throughout the brain as complexes with various proteins (see Role of Iron below). Neural membrane lipids are replete with polyunsaturated fatty acids whose oxidation products, such as 4-hydroxynonenal and 4-oxononenal [9], can act as sources of ROS, and are especially cytotoxic to neurons. Brain metabolism generates an abundance of hydrogen peroxide via SODs (superoxide dismutases) and other enzymes [7]. AO defenses are modest, such as catalase levels. Brain microglia can become activated to produce superoxide, hydrogen peroxide and cytokines. Microglia and astrocytes are major players in brain inflammation which is associated with ROS [10]. Some cytochromes leak electrons during the catalytic redox cycle, thus providing ROS [7]. An- other source of brain ROS is NADPH oxidase enzymes. Hemoglobin, a neurotoxin, can release heme which is a powerful promoter of lipid peroxidation. The complex of hemoglobin with NO can also generate OS [11]. The Halliwell review presents various means for defense against neurotoxins [7]. There is also reference to earlier treatment of neurodegenerative diseases.

A broad overview of neurotoxins was presented based on electron transfer (ET), reactive oxygen species (ROS), and oxidative stress (OS) [12]. It is relevant that metabolites from toxins generally posses ET functionalities which can participate in redox cycling. Toxic effects at the molecular level include lipid peroxidation, DNA attack, adduction, enzyme inhibition, oxidative attack on the CNS, and cell signaling. The toxins fall into many categories. Beneficial effects of AOs are documented. A related update was reported in 2012 [13]. A similar article deals with nitric oxide (NO), catecholamine and glutamate [14]. The review treats the mechanism of these agents as important neurotransmitters and as neurotoxins, based on involvement of ET-ROS-OS.

Role of Iron

A recent review presents a unifying theme for cellular death and neurotoxicity by iron agents [6,15]. The basic theme involves continuing and autocatalytic generation of hydroxyl radicals by way of the Fenton reaction involving poorly liganded iron.

3. PULMONARY TOXICITY

The pulmonary system is one of the main targets for toxicity. In the industrial age, there has been a large increase in atmospheric pollutants. Many adverse reactions can occur, some of the principal ones being asthma, COPD and cancer.

It is often unclear what role natural components play in the mechanism of pathogenesis. However, a common factor appears to be the upregulation of ROS in lung cells upon exposure. *In vivo* redox cycling with oxygen can occur giving rise to OS through generation of ROS. ROS can arise from diverse sources, both endogenous and exogenous [16]. Reduction of O_2 to ROS, e.g., superoxide, occurs as a by-product of metabolism. When cellular injury occurs, release of species, such as iron, into extracellular space can lead to generation of deleterious ROS. Neutrophils and macrophages are adept at transforming oxygen into ROS which eliminate foreign organisms, accompanied by the undesirable effect of OS on normal cells. The lung is especially susceptible to injury by this gas. For example, hyperoxia damages endothelial and alveolar epithelial cells [17]. A recent review deals with the consequence of hyperoxia and toxicity of oxygen in the lung [18]. Exposure results in increased intracellular generation of superoxide and, hence, of other ROS, with ensuing autoxidation reactions.

A dramatic example of lung toxicity involving ROS is adult respiratory distress syndrome (ARDS) which is brought about by trauma, shock, sepsis, vomiting, and inhalation of toxins. Inflammation, a common result of

lung insult by toxic substances, is a precursor of subsequent events triggered by ROS. There is considerable evidence that OS is a contributing factor in ARDS [17]. We wish to emphasize the following quote: "In general, free radicals represent an important component in the pathogenesis of lung disease" [16]. The role of ROS in lung damage is further buttressed by the increased activeity of free radical-scavenging enzymes in lungs challenged by a variety of toxins.

There is appreciable literature on ROS, OS and pulmonary toxicity. In our 2009 review, we surveyed a number of pulmonary toxicants [16]. In this review only those toxicants from more recent years will be cited.

3.1. Role of Nanomaterials

In recent years, a wide range of nanomaterials have been developed for various applications. Increasing evidence suggests that the special physicochemical properties of these nanomaterials pose potential risk to human health. Recent reviews in this area deal with the biomechanism and toxicity of nanoparticles, including pulmonary insults [19,20].

Data indicate that the composition and size of nanomaterials, as well as the target cell type, are critical determinants of intracellular responses, degree of cytotoxicity and potential mechanism of toxicity [21]. ROS plays a major role in its toxicity. Alveolar epithelial cells exposed to manganese (II,III)oxide nanoparticles generated ROS leading to OS and apoptosis [22]. Copper oxide nanoparticles induce OS and cytotoxicity in airway epithelial cells [23].

A study correlated the conduction band energy with cellular redox potential of Co_3O_4, Cr_2O_3, Ni_2O_3, Mn_2O_3 and CoO nanoparticles and its ability to induce oxygen radicals, OS, and inflammation [24]. A review deals with the mammalian toxicity of ZnO nanoparticles, through inhalation results in ROS generation which plays an important role in inflammatory response [25]. A 2012 review covers toxicity induced by nanoparticles [26]. Multiwalled carbon nanotubes induce OS, with increased ROS production and depletion of intracellular GSH. Multiwalled carbon nanotubes also induce a fibrogenic response by stimulating ROS production [27]. Data showed that exposure of cultured RAW 264.7 cells and A549 human lung cells to multiwalled carbon nanotubes led to OS induced cytotoxicity [28].

3.2. Role of Organic Toxins

OS and oxidative effects on DNA are increased in mice exposed to styrene or styrene oxide, and these may play a role in the lung tumorigenesis [29]. In a related study N-acetylcysteine and GSH were shown to act as AOs in preventing OS in mice exposed to styrene [30].

Chlorobenzene and 1,2-dichlorobenzene cause OS and induce apoptosis in lung epithelial cells at non-acute toxic concentrations [31]. 2-Chloroethyl ethyl sulfide, a sulfur mustard, causes a significant increase in mitochondrial dysfunction, involving increase in ROS in lung cell injury [32]. Metalloporphyrin acts as an AO in decreasing mitochondrial ROS, DNA oxidation and the increasing intracellular GSH. A study revealed diallyl trisulfide, a major constituent of garlic oil, induces apoptosis of U937 human leukemia cells by generation of ROS [33].

Research showed that wood dust from pine, birch and oak is cytotoxic, being able to increase the production of ROS [34].

4. DERMAL TOXICITY

Insults to the skin may be mild, serious or lethal. Various constituents of the skin may be affected by dermal toxicants. Cutaneous damage may also result from inhalation or ingestion of toxins, in addition to direct skin contact. Similarly, substances that induce toxicity through absorption by the skin can also migrate to and adversely affect other organs.

In this review, we draw lines of evidence to support the concept that the ET-ROS-OS unifying theme, which has been successful in describing the means by which many other classes of toxins induce their effects, can also be applied to dermatotoxins [35]. Such toxin classes include a variety of structurally diverse substances.

Exposure to the chemical warfare agent sulfur mustard is reported to cause depletion of GSH, which plays an important role in sulfur mustard-linked OS and skin injury. Cultured skin epidermal cells and SKH-1 mouse skin when exposed to 2-chloroethyl ethyl sulfide, an analog of mustard gas, led to amelioration by GSH and induction of toxicity [36]. N-Acetyl cysteine, a GSH analog, acts as an AO and shows both protective and therapeutic effects. The sulfur mustard analog 2-chloethyl ethyl sulfide induced oxidative DNA damage in skin epidermal cells and fibroblasts [37]. A related study also revealed that the sulfur mustard analog induces OS and activates transcription factors AP-1 and NF-κB via upstream signaling pathways including MAPKs and Akt in SKH-I hairless mouse skin [38].

Cr(IV) induced apoptosis with involvement of reactive oxidants [39]. Data indicated that topical exposure to unpurified single walled carbon nanotubes induced free radical generation, OS, and inflammation, depletion of glutathione, oxidation of protein thiols and carbonyls, elevated myeloperoxidase activity and skin thickening [40]. Amorphous nanosilica induces endocytosis-dependent ROS generation and DNA damage in human keratinocytes [41]. Cytotoxicity of uranium, has been in the spotlight in recent decades. Uranyl acetate induces

OS [42].

Carotenoids are known to be potent quenchers of singlet molecular oxygen. Solar light-induced photooxidative stress causes skin photoaging by accelerating the generation of ROS. Intake of carotene lowered the metalloproteinase family which is responsible for wrinkles and sagging of skin, and helps in slowing down ultraviolet-A-induced photoaging in human skin by acting as a singlet oxygen quencher [43]. A 2012 review deals with protective mechanisms of green tea AOs polyphenols in skin [44]. Another article deals with the ROS-mediated skin damage and skin protection by AOs [45].

5. NEPHROTOXICITY

Toxic processes have been implicated in the pathogenesis of several systemic diseases including kidney, which induces OS in the kidney [46]. A 2012 review summarizes the induction of OS in kidney [46]. Much of the nephrotoxicity can be attributed to OS-induced by drugs, and reports address the role of prescription drug-induced OS and toxicity [47,48].

Drug-induced OS is implicated as a mechanism of toxicity in numerous organs, including liver. Well characterized drugs associated with OS, include cancer therapies, anti-inflammatory drugs, antiviral agents, antipsychotics and analgesics [48]. Metabolism of a drug may generate a reactive intermediate that can induce ROS generation, leading to OS in various organs. Cisplatin is an example of a drug that exhibits multi organ toxicity, acting as an antineoplastic agent. Clinically, renal injury has been described. The kidney accumulates cisplatin to a greater degree than other organs [48]. The disproportionate accumulation of cisplatin in kidney tissue contributes to free radical generation, depletion of antioxidants leading to OS and nephrotoxicity [48,49]. Research also indicated that cisplatin nephrotoxicity is associated with mutual mitochondrial/lysosomal potentiation (cross talk) of OS in renal proximal tubular cells [50]. This cross-talk results in release of lysosomal digestive protease and phospholipases and mitochondrial permeability transition pore opening leading to cytochrome c release and activation of caspase cascade, which signals apoptosis.

Several reports exist for AO action against cisplatin nephrotoxicity. Selenium nanoparticles functionalized with 11-mercapto-1-undecanol inhibit ROS-mediated apoptosis [51]. Captopril, an angiotensin-converting enzyme inhibitor containing the sufhydryl group can protect against cisplatin-induced nephrotoxicity in rats [52]. Canabidiol attenuates cisplatin-induced nephrotoxicity by decreasing OS, inflammation and cell death [53].

Data demonstrate a key role of lysosomal iron and early ROS production in gentiomicin-induced lysosomal membrane premeabilization and apoptosis [54]. Salicylic acid was found to attenuate the nephrotoxicity in rats [55]. Ifosfamide, an antineoplastic drug, causes severe nephrotoxicity. The metabolite chloroactaldehyde is believed to be the chemical responsible for the nephrotoxicity [56]. N-Acetyl cysteine acts as an AO in decreasing the nephrotoxicity. A study showed that ROS, OS, and MAPK signaling is involved in promoting cyclosporine-induced glomerular dysfunction and subsequent nephrotoxicity [57].

Increased production of ROS by anticancer drugs trichostatin and 5-aza-deoxycytidine, has been described in patients with various malignancies, which is attributed to their nephrotoxicity.

A study showed uric acid attenuates toxicity by preventing systemic and renal oxidative stress and tissue damage induced by mercuric chloride in rats [58]. Cadmium (Cd) is a well known human carcinogen and potent nephrotoxin. Cd caused renal toxicity by inducing lipid peroxidation and morphological alterations [59]. Curcumin, a natural product from turmeric protects Cd-induced nephrotoxicity in rats. Colistin (polymyxin E), a cationic polypeptide antibiotic, causes OS-induced nephrotoxicity. Melatonin was found to attenuate colistin-induced nephrotoxicity in rats [60]. Zinc oxide and cadmium sulfide nanoparticles generate ROS that leads to OS-induced nephrotoxicity [61].

6. CARDIOVASCULAR TOXICITY

As described in drug-induced OS and nephrotoxicity, many antibiotic drugs also induce cardiotoxicity [48,62]. The antineoplastic activity of doxorubicin is mediated by interaction with DNA [48]. Reduction of doxorubicin by one electron via mitochondrial reductase may generate anthracycline semiquinone free radicals that produce ROS [48]. Reaction between iron and doxorubicin may also generate ROS. Extensive data have been generated in numerous model systems showing that administration of AOs protects cardiomycetes from doxorubicin-induced damage. The range of molecules explored is diverse, including plant extracts, vitamins C and E, N-acetylcycteine, L-carnitine, beta-blocker carvedilol, coenzyme Q10, and dexrazonxane [48,63].

Adriamycin is another antineoplastic anthracycline used to treat solid tumors and various forms of cancer, but it displays cardiac toxicity [64]. Adriamycin is well known to produce large amounts of ROS, which may be lethal to cancerous cells. However, unchecked ROS generation typically leads to OS. Adriamycin has been documented to cause oxidative damage in several organs, including heart [64]. Gamma-glutamycysteine ethyl ester was found to suppress the OS induced by adriamycin. Several reviews deal with the mechanism and protection

in anthracycline-induced cardiotoxicity [65-68].

Platinum-based compounds are commonly used cyto-toxic agents in the treatment of several solid tumors. However, their application is still limited in elderly patients, due to the risk in cardiovascular toxicity. The increased risk is mainly due to ROS production [69]. AOs have been involved in cancer treatment by their property to suppress the oxidant injury [69,70].

Administration of glucose degradation products increased cardiovascular damage in rat models [71]. A related study showed that glucose degradation products and advanced glycation end (AGEs) products play a role in the pathophysiolgy of cardiotoxicity [72]. Mechanistic aspects of AGEs have been addressed [73].

Cocaine is one of the most common illicitly used drugs in the world and causes the most frequent drug-related deaths in young adults. Chronic cocaine consumption is associated with serious cardiovascular complications. Chronic cocaine administration causes severe myocardial OS through increased ROS production [74]. Cocaine cardiotoxicity may be mediated indirectly through its sympathomimetic effect, inhibiting reuptake and increasing the levels of neuronal catecholamines.

Exposure to nanoparticles significantly impairs endothelium-dependent vasoreactivity in coronary arterioles, and this may be due in large part to increases in microvascular ROS [75]. Another study showed that exposure to ambient particulate pollution induces arrhythmia via OS and calcium calmodulin kinase II activation [76].

In recent years two reviews have appeared dealing with heavy metal (Ar, Pb, Cd, Hg) poisoning and cardiovascular disease. The reviews implicate ROS and OS as major players in the pathophysiology of atherosclerosis [77,78].

7. REPRODUCTIVE TOXICITY

Several earlier reviews have addressed this topic [79-81]. The present contribution provides recent developments. There is evidence that several teratogens affect the developing embryo by increasing OS resulting in severe embryonic damage. This mechanism seems to operate in diabetic-induced embryonic damage, as well as in the mechanism of teratogenicity caused by ionizing radiation, hypoxia, alcohol and cocaine use and cigarette smoking. Under diabetic conditions, there was a significant decrease in the activity of endogenous AO enzymes and of vitamins C and E in the embryos. Human and animal studies show that the main mechanism of fetal damage induced by high levels of ionizing irradiation, cocaine and alcohol abuse, hypoxia and cigarette smoking is also by increased embryonic OS. Similarly, several drugs exert their teratogenic activity via embryonic OS. Abnormal placentation may also cause enhanced placental OS, resulting in embryonic death. Animal studies also

show that a variety of AOs are effective in decreasing the damaging effects of hightened OS induced by teratogens. Concurrent administration of chloroamphenicol (CAP) with multivitamin-haematinics complex (MHC) is a common practice to cushion anticipated anaemic effects in reproductive toxicity [82]. Alone, MHC treatment markedly decreased catalase (CAT) and glutathione S-transferase (GST) activities, whereas it resulted in significant increase in superoxide dismutase (SOD) activity. Significant increase in testicular lipid peroxidation and sperm abnormalities were accompanied by reduction in sperm number, sperm motility and live-dead ratio in all treatment groups. MHC-induced testicular toxicity occurred vis OS.

Mequindox (MEQ) is a synthetic antimicrobial chemical [83]. A study was designed to investigate the hypothesis that MEQ exerts testicular toxicity by causing OS. Superoxide dismutase (SOD), reduced glutathione (GSH) and 8-hydroxydeoxyguananosine (8-OHdG) levels were elevated, whereas the malondialdehyde (MDA) level was slightly increased. The findings provide evidence *in vivo* for the formation of free radicals.

Reports document the protective effect of AOs, such as vitamin E [84] and Ginko biloba [85]. Various studies on reproductive toxicity deal with the role of metals: Pb [86], Cr [87,88], and Se [89].

8. MITOCHONDRIA

Mitochondrial OS has long been implicated in normal aging, and a host of human diseases, including cancer and neurodegenerative disorders. Mitochondria are the major source of oxygen free radicals in most cell types. Low concentrations of ROS can serve as signaling functions, triggering the activation of specific pathways [90]. However, high concentrations of ROS cause lipid peroxidation, damage to cell membranes, proteins, and DNA. Mitochondria are, therefore, a major source of ROS and a major target of ROS-induced OS and damage. A high rate of mitochondrial DNA mutation eventually exacerbates mitochondrial dysfunction and reduces mitochondrial energy production [90].

Under OS conditions, mitochondria release various pro-apoptoic factors. This release is caused by the permeabilization of the mitochondrial outer membrane, which accompanies the depolarization of the mitochondrial intermembrane potential. Aldehydes are generated during numerous physiological processes. Aldehydes are highly reactive agents, which form adducts with lipids, proteins, and DNA, affecting the function of these macromolecules. Aldehyde dehydrogenases are important enzymes that eliminate toxic aldehydes by catalyzing their oxidation to non-reactive acids. A review discusses the mitochobdrial aldehyde dehydrogenase and cardiac diseases [91]. Inhibition of aldehyde dehydrogenase 2 by

OS is associated with cardiac dysfunction in diabetic rats [92]. A study demonstrated that TNF-α-induced OS alters redox homeostasis by impairing the membrane permeability transition pore opening proteins adenine nucleotide translocator and voltage-dependent anion channel, thereby resulting in the pore opening, causing mitochondrial dysfunction and attenuated cardiac function [93].

A recent review deals with the mitochondria death/survival signaling pathways in cardiotoxicity induced by anthracyclines [94]. Data shows that inhibition of mitochondrial transition permeability prevents doxorubicin-induced cardiotoxicity. OS and mitochondrial dysfunction have been implicated in atherosclerosis [95]. Authors suggest mitochondria-targeted AOs as potential therapy. Alzheimer's disease, the most common form of dementia with a progressive course, evidences neuronal damage in specific vulnerable brain regions and circuits involved in memory and language [96]. Two recent reviews deal with mitochondrial- and endoplasmic reticulum-associated OS in Alzheimer's disease [96,97].

There is an emerging consensus that aging is a multifactorial process, which is genetically determined and influenced epigenetically by environment. OS induced DNA damage, oxidation of proteins, lipid peroxidation and ROS have been implicated as causative factors of aging [98]. Two reviews deal with the OS, mitochondrial dysfunction and aging [98,99].

9. CONCLUSION

This review presents recent reports dealing with electron transfer, reactive oxygen species and oxidative stress as part of the mechanism of toxicity involving organs in human health. Various portions of the organ cells may be involved in the insults. Antioxidants may play a role in prevention.

10. ACKNOWLEDGMENTS

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ABREVIATIONS

OS, oxidative stress;
ROS, reactive oxygen species;
RNS, reactive nitrogen species;
ET, electron transfer;
AO, antioxidant;
COPD, chronic obstructive pulmonary disease;
GABA, gamma amino butyric acid;

HSP, heat shock proteins;
LPP, lipid peroxidation products;
CIS, cisplatin;
SOD, superoxide dismutase;
GSH, glutathione;
8-OHdG, 8-hydroxydeoxyguanosine;
MDA, malondialdehyde;
MEQ, Mequindox.