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Review Article

Drug-Induced Oxidative Stress: Mechanisms, Major Drugs, and Antioxidant Therapy

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ABSTRACT

Drug-induced oxidative stress is an important mechanism involved in drug toxicity and adverse drug reactions. It occurs when the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds the capacity of the body's antioxidant defence systems, leading to cellular damage. Several therapeutic drugs, including doxorubicin, paracetamol, diclofenac, and isoniazid, can induce oxidative stress through mechanisms such as redox cycling, reactive metabolite formation, glutathione depletion, mitochondrial dysfunction, and impairment of antioxidant defence pathways. These mechanisms may cause lipid peroxidation, protein oxidation, DNA damage, inflammation, and cell death, contributing to organ toxicity, particularly in the liver, heart, and kidneys. The body protects itself through enzymatic antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase, and non-enzymatic antioxidants, including glutathione and vitamins C and E. Exogenous antioxidants, such as N-acetylcysteine and selected natural plant-derived compounds, have also been investigated for their potential to reduce oxidative injury. This review discusses the mechanisms of drug-induced oxidative stress, major drugs associated with oxidative damage, its cellular and organ-specific consequences, and the potential role of antioxidant therapy in reducing drug-related toxicity. A better understanding of these mechanisms may support the development of safer therapeutic strategies and improve drug safety.

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INTRODUCTION:

An imbalance between the body's antioxidant defence systems and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is known as oxidative stress. These reactive species are involved in immune defence, cellular signalling, and the regulation of many biological activities under normal physiological settings. However, redox equilibrium can be disturbed by excessive ROS/RNS generation or inadequate antioxidant defences, damaging cellular constituents such as lipids, proteins, and nucleic acids.[1,2,3]

Drug-induced oxidative stress is an important mechanism involved in adverse drug reactions and organ toxicity. Through different mechanisms, a variety of therapeutic drugs, including as antibiotics, anticancer agents, non-steroidal anti-inflammatory drugs (NSAIDs), anti-tubercular medicines, and antiepileptic medications, can increase oxidative stress. These include the production of reactive metabolites, mitochondrial malfunction, redox cycling, glutathione depletion, and inflammatory pathway activation. For example, isoniazid may contribute to liver damage by metabolic and oxidative pathways, doxorubicin can produce reactive oxygen species through redox cycling, and paracetamol can cause oxidative damage through its reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).[3,4,5]

A number of organs, including the liver, kidneys, heart, lungs, and nervous system, can be damaged by drug-induced oxidative stress. Inflammation, cellular damage, cell death, and mitochondrial dysfunction can all be caused by persistent oxidative stress. Therefore, detecting possible toxicity pathways, enhancing drug safety, and establishing effective preventive strategies all depend on an understanding of the molecular mechanisms causing drug-induced oxidative stress.

Antioxidant therapy has attracted significant attention as a possible approach for reducing oxidative damage caused by drugs. Cellular redox equilibrium is maintained by endogenous antioxidants such as glutathione, glutathione peroxidase, catalase, and superoxide dismutase (SOD). Exogenous antioxidants have also been studied for their ability to prevent oxidative damage, including N-acetylcysteine, vitamins C and E, and several natural phytochemicals. Antioxidant therapy does not entirely remove drug-induced toxicity, and its effectiveness varies depending on the drug, dose, mechanism of injury, and clinical status.

This review discusses the mechanisms underlying drug-induced oxidative stress, major therapeutic drugs associated with oxidative injury, the molecular pathways involved in organ-specific toxicity, and the role of antioxidant therapies in preventing or reducing cellular damage.

HISTORICAL BACKGROUND:

The concept of oxidative stress has evolved over several decades through significant discoveries in redox and free radical biology. Rebeca Gerschman and colleagues claimed in 1954 that the adverse effects of oxygen were directly related to the generation of free radicals, which was one of the first scientific links between oxygen toxicity and oxidative cellular damage. This important discovery cleared the way for further studies into the biological consequences of reactive oxygen species.[6] Helmut Sies' 1985 formally established definition of oxidative stress—a disturbance in the equilibrium between oxidants and antioxidants in favour of oxidants, potentially leading to cellular and tissue damage—constituted a significant turning point. This term, which is still commonly used in biomedical research, provides a conceptual framework for understanding the role of oxidative stress in human health and medical conditions.[6,7,8] Research conducted during the 1990s and early 2000s showed that reactive oxygen species are not only hazardous metabolic by products but also important signalling molecules that control immunological responses, inflammation, cellular death, cell proliferation, and differentiation. The idea of redox signalling was established by this paradigm shift, which also brought attention to the dual function of ROS in preserving physiological homeostasis and, when produced in excess, contributing to pathogenic processes.[9,10] Oxidative stress has been recognized as a major factor in the development and progression of many diseases, including cancer, diabetes mellitus, neurodegenerative diseases, chronic kidney disease, liver disorders, pulmonary diseases, and cardiovascular disorders, because of recent advances in

molecular biology and analytical techniques. By leading to mitochondrial dysfunction, lipid peroxidation, DNA damage, protein oxidation, and inflammatory responses, oxidative stress has also been shown to play a major role in drug-induced toxicity.[11,12] The importance of drug-induced oxidative stress is receiving growing attention in pharmacology and toxicology over the last two decades. Several therapeutic compounds have been reported to generate reactive metabolites that can disturb the redox balance of cells and result in organ-specific toxicities as hepatotoxicity, nephrotoxicity, cardiotoxicity, and neurotoxicity. The development of antioxidant therapy, natural product-based interventions, and advanced approaches to drug delivery designed to reduce oxidative damage while maintaining therapeutic efficacy was helped by these discoveries.[1–12]

Today, oxidative stress is recognized as a fundamental mechanism linking drug exposure to adverse biological effects. Ongoing research continues to improve our understanding of redox regulation, identify reliable biomarkers of oxidative damage, and develop innovative strategies for the prevention and management of drug-induced oxidative stress.

MECHANISM OF OXIDATIVE STRESS:

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the antioxidant defence system, resulting in disruption of cellular redox homeostasis and oxidative damage to biomolecules.[9] Under physiological conditions, ROS and RNS act as important signalling molecules regulating cell proliferation, immune responses, and apoptosis.[13] However, excessive production of reactive species or depletion of antioxidant defences causes oxidative modification of lipids, proteins, carbohydrates, and nucleic acids, ultimately contributing to numerous pathological conditions.[9, 13-32]

Generation of ROS/RNS: The most important endogenous source of reactive oxygen species (ROS) is mitochondria, where electron leakage from complexes I and III of the electron transport chain produces superoxide anion ($O_2^{\bullet -}$).[14] Superoxide is actively produced by NADPH oxidase (NOX) enzymes as part of intracellular interaction and host defence, but excessive activation leads to oxidative stress and inflammation.[15] During fatty acid β-oxidation, peroxisomes produce hydrogen peroxide, which is usually detoxified by catalase.[16] ROS is generated by cytochrome P450 enzymes during xenobiotic metabolism, particularly when enzyme uncoupling occurs.[19] During ischemia-reperfusion injury, xanthine oxidase becomes a significant generator of ROS.[18] In order to eliminate infections, activated neutrophils and macrophages produce significant levels of ROS and RNS through respiratory burst mechanisms.[29] Intracellular ROS formation is also increased by exogenous factors such UV radiation, cigarette smoke, environmental contaminants, heavy metals, pesticides, alcohol, and pharmaceuticals.[1-3] **Formation of Reactive Species:** The primary ROS generated when molecular oxygen is decreased by a single electron is superoxide anion ($O_2^{\bullet -}$).[2] Superoxide dismutase rapidly transforms superoxide into hydrogen peroxide ($H2O_2$).[21] The highly reactive hydroxyl radical (•OH), which indiscriminately damages biological molecules, is produced when hydrogen peroxide goes through the Fenton reaction with ferrous iron.[2] Peroxynitrite ($ONOO^-$), a potent oxidizing and nitrating species that causes DNA damage and protein nitration, is produced when nitric oxide (NO), which is produced by nitric oxide synthases, reacts with superoxide.[22] **Initiation of Oxidative Reactions:** By removing hydrogen atoms or moving electrons from biological molecules, reactive oxygen and nitrogen species initiate an oxidative reaction that produce secondary free radicals and initiate by chain reactions.[2] Because of their many double bonds, polyunsaturated fatty acids found in cellular membranes are particularly susceptible to lipid peroxidation.[23] These radical chain reactions are stopped and redox balance is maintained under physiological conditions by antioxidant enzymes including glutathione peroxidase, catalase, and superoxide dismutase as well as non-enzymatic antioxidants such vitamins C and E.[21]

Damage to Biomolecules: Toxic aldehydes including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which damage membrane integrity and cellular function, are produced as a consequence of lipid peroxidation.[23] Carbonyl formation, amino acid residue

oxidation, enzyme deactivation, and protein aggregation are all consequences of protein oxidation.[24] DNA strand breakage, base oxidation, and the production of 8-hydroxy-2′-deoxyguanosine (8-OHdG), recognized as a biomarker of oxidative DNA damage, are all common outcomes of oxidative DNA damage.[25] Advanced glycation end products (AGEs), which trigger RAGE-mediated inflammatory signalling pathways, are produced when carbohydrates undergo oxidative alteration.[26]

Cellular Consequences: By damaging respiratory chain proteins and mitochondrial DNA, oxidative stress causes mitochondrial dysfunction, which leads to ATP depletion and increased ROS generation.[2] Increased production of inflammatory cytokines occurs due to ROS activating redox-sensitive signalling pathways such as NF-κB, MAPKs, and PI3K/Akt.[27] While excessive oxidative damage causes necrotic cell death, severe oxidative stress triggers mitochondrial apoptotic pathways via cytochrome c release and caspase activation.[19] **Outcomes of Oxidative Stress:** Persistent oxidative stress contributes to aging[28], Carcinogenesis[25], Cardiovascular diseases[29], Neurodegenerative disorders[28], Diabetes Mellitus, Liver and Kidney Diseases, and Immune Dysfunction.[2]

FREE RADICAL IN OXIDATIVE STRESS:

Free radicals are highly unstable, short-lived atoms, molecules, or ions characterized by one or more unpaired electrons in their outermost electron shell, making them extremely reactive species that readily donate or accept electrons to trigger damaging chain reactions across biological systems. They are systematically classified into reactive oxygen species (ROS)—such as superoxide anions, hydroxyl radicals (the most reactive), proxy radicals, and non-radical counterparts like hydrogen peroxide—and reactive nitrogen species (RNS) like nitric oxide and peroxynitrite. These entities are continuously generated through normal endogenous metabolic processes, including the mitochondrial electron transport chain, NADPH oxidase, and cytochrome P450 enzymes, as well as via exogenous exposures like cigarette smoke, radiation, heavy metals, and therapeutic drugs such as paracetamol, doxorubicin, and cisplatin that promote oxidative stress and redox cycling. Mechanistically, free radicals form through the sequential reduction of molecular oxygen into superoxide and hydrogen peroxide, which subsequently undergoes the Fenton reaction in the presence of ferrous iron to yield highly destructive hydroxyl radicals. While physiological concentrations are vital for normal cellular signalling, gene expression regulation, immune defence, apoptosis, and wound healing, excessive production drastically overwhelms the body's antioxidant defence mechanisms—which consist of enzymatic defences like superoxide dismutase, catalase, and glutathione peroxidase, alongside non-enzymatic agents including glutathione, vitamins C, E, and A, and polyphenols. When this imbalance occurs, it results in severe oxidative stress where free radicals aggressively attack crucial molecular targets, initiating lipid peroxidation, protein oxidation and enzyme inactivation, DNA strand breaks, and the formation of advanced glycation end products from carbohydrates. This widespread cellular damage drives mitochondrial dysfunction, inflammation, cellular senescence, apoptosis, and tissue fibrosis, ultimately contributing to the pathogenesis of major clinical conditions such as cardiovascular diseases, diabetes mellitus, neurodegenerative disorders, cancer, chronic organ diseases, and drug-induced toxicities. To evaluate and monitor this damage, researchers rely on established biomarkers of oxidative and nitrosative stress, including malondialdehyde, 4-hydroxynonenal, 8-hydroxy-2′-deoxyguanosine, protein carbonyls, nitro tyrosine, and the overall GSH/GSSG redox ratio alongside antioxidant enzyme activities.[11,12,14,25]

Some Important Free Radicals – some important free radicals that play crucial role in generation of oxidative stress are as follow. .

Superoxide Anion Radical ($O_2^{\bullet -}$): Superoxide anion radical is the primary and most widely distributed reactive oxygen species generated in biological systems. It is formed by the one-electron reduction of molecular oxygen during enzymatic reactions, auto-oxidation processes, and non-enzymatic electron transfer reactions. Mitochondria are the principal intracellular source of superoxide due to electron leakage from the electron transport chain during oxidative phosphorylation. Other enzymatic sources include xanthine oxidase, NADPH oxidase, cyclooxygenase, and

lipoxygenase. At physiological pH, superoxide exists predominantly as the superoxide anion ($O_2^{\bullet -}$), whereas under acidic conditions it is protonated to form the hydroperoxyl radical ($HO_2^{\bullet}$), which is more lipid-soluble and readily penetrates biological membranes. Although superoxide is relatively less reactive than other ROS, it serves as the precursor of several highly reactive oxidants. It acts as both a reducing and an oxidizing agent by reducing ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) and oxidizing antioxidants such as ascorbic acid and α-tocopherol. Under physiological conditions, superoxide is rapidly converted into hydrogen peroxide by the antioxidant enzyme superoxide dismutase (SOD), thereby limiting its accumulation and preventing excessive oxidative damage.[2,12,13,14]

Hydroxyl Radical (•OH): The hydroxyl radical is considered the most reactive and destructive oxygen-derived free radical in biological systems. It reacts almost instantaneously with DNA, proteins, lipids, carbohydrates, and nucleic acids, causing irreversible cellular damage. Because of its extremely short half-life, hydroxyl radicals react at the site of their formation and cannot diffuse over long distances. They are primarily generated through the Fenton reaction, in which hydrogen peroxide reacts with transition metal ions such as ferrous iron (Fe^{2+}) or cuprous copper (Cu^{+}), producing hydroxyl radicals and hydroxide ions. Hydroxyl radicals are also formed through the Haber–Weiss reaction involving the interaction of superoxide with hydrogen peroxide. During oxidative stress, excess superoxide releases iron from intracellular storage proteins like ferritin, making more catalytic iron available for the production of hydroxyl radicals. Lipid peroxidation, protein oxidation, DNA strand breakage, and mutagenesis are all caused by the hydroxyl radical's extraordinarily high reactivity.[2,12,13,14]

Proxy Radical (ROO•): When organic molecules, such as lipids, undergo oxidation, oxygen-cantered free radicals called proxy radicals are formed. The hydroperoxyl radical (HOO•), which is formed when superoxide is protonated under acidic conditions, is the most basic member of this group. Although only a small proportion of intracellular superoxide exists in this protonated form, hydroperoxyl radicals possess greater membrane permeability and initiate lipid peroxidation by abstracting hydrogen atoms from polyunsaturated fatty acids. The resulting lipid radicals propagate chain reactions that damage cellular membranes, alter membrane fluidity, and impair cellular function. Proxy radicals have also been implicated in chronic inflammation, aging, and tumour development.[12,13,14,15]

Hydrogen Peroxide (H_2O_2): Hydrogen peroxide is a non-radical reactive oxygen species, which is formed mainly due to the disputation of superoxide mainly by the catalytic interaction with superoxide dismutase. Whereas there is no unpaired electron, hydrogen peroxide is an important biological phenomenon because of its relative stability, diffusion across biological membranes and the capacity to produce highly reactive hydroxyl radicals using transition metal ions. While hydrogen peroxide possesses no unpaired electron, at physiological level it functions as a vital signalling molecule which plays a major role in cell proliferation, differentiation, apoptosis, and immune responses. However, high intracellular concentrations can inactivate essential metabolic enzymes, undermine mitochondrial functionality and induce oxidative damage. Antioxidants like catalase, glutathione peroxidase and peroxiredoxins, convert hydrogen peroxide into water and molecular oxygen present in cells which inhibit hydrogen peroxide.[2,12,13,14]

Singlet Oxygen ($^1O_2$): Singlet oxygen is an electronically excited, highly reactive form of molecular oxygen produced during photochemical reactions, inflammatory processes, and various enzymatic reactions. Activated neutrophils and eosinophils can also synthesize active oxidant during immune response. Due to its high reactivity singlet oxygen can oxidize various biological molecules including lipids, proteins, and nucleic acids, thereby contributing to cellular and tissue damage. It has been linked with oxidative injury inflammatory disease, ischemia-reperfusion injury, and photo oxidative damage.[2,12,13,14]

Ozone (O_3): Ozone is a powerful oxidizing agent that can be generated in vivo through antibody-catalysed oxidation reactions during inflammation. It reacts rapidly with biological macromolecules that initiated lipid peroxidation and oxidizing functional groups present in proteins, carbohydrates, and nucleic acids. Ozone

exposure also induces the development of chromosomal malignancies and injury of a cell or tissue, by oxidation – either by direct oxidation or through secondary reactive oxygen species. Due to its strong oxidative capacity, ozone contributes significantly to inflammatory tissue damage and oxidative stress-related disorders.[2,12,13,14]

Hypochlorous Acid (HOCl): Hypochlorous acid is the potent oxidizing molecule produced by the active neutrophils by the myeloperoxidase-catalysed reaction between hydrogen peroxide and chloride ions at the respiratory swarm. It plays an important role in immune function by killing off bacteria, viruses and fungi. But excessive production of HOCl can aggravate the wounds within host tissues through oxidization of thiol group, amino acids, nucleotides, and membrane lipids. It also chlorinates proteins, cholesterol, unsaturated lipids and DNA; resulting in structural changes, enzyme dysfunction, and inflammatory tissue injury.[12,13,14,15]

Nitric Oxide (NO•): Nitric oxide (NO) is an enzymatically formed reactive nitrogen species originating from L-arginine via nitric oxide synthase (NOS). NO is generated in different tissues by three isoforms of NOS: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). Nitric oxide is lipid- and water soluble and can therefore diffuse rapidly across the cell membrane and act as an important intracellular messenger. It stimulates guanylate cyclase, regulating vascular tone and promoting relaxation of smooth muscle, it participates in neurotransmission, modulates immune responses, and regulates cellular redox signalling by protein nitrosylation. Nitric oxide has several physiological roles but excessive production leads to oxidative and nitrosative stress.[2,12,13,14]

Peroxynitrite ($ONOO^-$) and Other Reactive Nitrogen Species: Nitric oxide reacts with the superoxide anion at diffusion-controlled rates to form peroxynitrite. It is one of the most potent reactive nitrogen species and may further react with carbon dioxide to form highly reactive intermediates or decompose to hydroxyl radicals and nitrogen dioxide. Peroxynitrite oxidizes lipids in membranes, nitrates tyrosine residues in proteins, damages mitochondrial enzymes and oxidizes DNA. This leads to impaired cellular function and cell death. Formation of nitro tyrosine residues is widely accepted as a biomarker of oxidative damage by peroxynitrite. Other reactive nitrogen species like nitrosonium (NO+), nitroxyl (NO-), nitrogen dioxide (NO2•), dinitrogen trioxide (N2O3), nitrite (NO2-) and nitrate (NO3-) are generated in the metabolism of nitric oxide and are involved in a variety of oxidation, nitration and nitrosation reactions that are implicated in cellular damage during pathological conditions.[2,12,13,14]

Sources of Free Radicals: Free radicals and reactive oxygen species originate from both endogenous and exogenous sources. Endogenously, mitochondria represent the primary source of intracellular ROS, where electron leakage from complexes I and III of the electron transport chain leads to the one-electron reduction of oxygen and generation of superoxide radicals. Additional intracellular sources include peroxisomes, endoplasmic reticulum, and enzyme systems such as NADPH oxidase, xanthine oxidase, cyclooxygenase, lipoxygenase, and nitric oxide synthase. Exogenous sources include environmental pollutants, cigarette smoke, ultraviolet and ionizing radiation, heavy metals, pesticides, industrial chemicals, alcohol, and numerous therapeutic drugs. Excessive production of free radicals from these sources overwhelms endogenous antioxidant defence mechanisms, resulting in oxidative stress, biomolecular damage, inflammation, and the progression of numerous acute and chronic diseases.[1-14]

MAJOR DRUGS ASSOCIATED WITH OXIDATIVE STRESS:

Doxorubicin-Mediated Oxidative Stress: Doxorubicin (DOX)-induced cellular damages including cardiotoxicity is due to Doxorubicin (DOX) mediated oxidative stress as a major mechanism. DOX promotes the overproduction of reactive oxygen species (ROS) through various interrelated mechanisms. The Quinone molecule of DOX is reduced by NADPH-dependent reductases such as cytochrome P450 reductase, by a one-electron reduction to a semi Quinone radical. The semi Quinone transfers its electron to molecular oxygen, regenerating DOX and producing a superoxide anion ($O_2•^-$). Superoxide is then converted to hydrogen peroxide (H 2 O 2) by superoxide dismutase (SOD). H 2 O 2 can produce highly reactive hydroxyl radicals (•OH) via iron-dependent Fenton chemistry. These ROS cause oxidation of lipids, proteins and nucleic

acids which leads to cellular dysfunction and death [1]. Another major mechanism is the high affinity of DOX with iron and the formation of DOX-Fe complexes. DOX–Fe 3+ reduction to DOX–Fe 2+ is favourable for ROS generation and lipid peroxidation. DOX also disrupts cellular and mitochondrial iron homeostasis, promoting the accumulation of free mitochondrial iron and enhancing oxidative damage. Iron accumulation along with increased lipid peroxidation can lead to ferroptotic cell death [31, 32]. DOX also stimulates ROS production by NADPH oxidases, particularly NOX2 and NOX4 in cardiomyocytes. The increase in NOX activity results in superoxide and hydrogen peroxide production, which increases oxidative stress. At the same time, accumulation of DOX in mitochondria, primarily via its interaction with cardiolipin within the inner mitochondrial membrane, disrupts electron-transport-chain function and mitochondrial integrity, leading to increased ROS generation and ATP depletion [33]. DOX also affects the antioxidant defense system. Oxidative stress might initially activate the Keap1–Nrf2 pathway as a compensatory response, but some studies show that DOX can inhibit Nrf2 signaling in some settings, which might limit the expression of antioxidant and detoxifying enzymes including glutathione S-transferase (GST), hem oxygenase-1 (HO-1) and NAD (P)H Quinone dehydrogenase 1 (NQO1). Therefore, ROS accumulation, mitochondrial dysfunction, lipid peroxidation and activation of apoptotic, inflammatory and ferroptotic pathways contribute to DOX-induced cellular and cardiac injury.[31,32,33]

Paracetamol-Mediated Oxidative Stress: Oxidative stress mediated by paracetamol (acetaminophen; APAP) is one of the principal mechanisms of APAP-induced hepatotoxicity, particularly following an overdose. At therapeutic doses, most of the APAP has become glucuronidated and sulfated, but a small amount is metabolized by the cytochrome P450 enzymes, especially CYP2E1, to form the highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). In normal conditions, NAPQI is rapidly detoxified by conjugation with reduced glutathione (GSH). However, in the case of APAP overdose, excessive formation of NAPQI may result in significant depletion of hepatic GSH and covalent binding of NAPQI to cellular proteins, especially mitochondrial proteins.[35,36] Mitochondrial protein adduction impairs mitochondrial respiration and antioxidant defenses, leading to increased electron leakage from the mitochondrial electron transport chain (ETC) and generation of superoxide (O2−).[34,35,36] Following APAP overdose, mitochondrial superoxide is converted to hydrogen peroxide (H_2O_2) by manganese superoxide dismutase (MnSOD/SOD2), which is normally detoxified by antioxidant systems including glutathione peroxidase, catalase and peroxiredoxins. However, excessive depletion of GSH reduces the ability of the cell to neutralize these reactive species. Superoxide can also react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), a highly reactive oxidant and nitrating species. Peroxynitrite promotes oxidative modification of mitochondrial proteins, mitochondrial DNA damage, and nitration/inactivation of MnSOD, thereby damaging mitochondrial antioxidant defenses and enhancing oxidative and nitrosative stress.[34,35,36] Mitochondrial oxidative stress also stimulates stress-signaling pathways, including c-Jun N-terminal kinase (JNK), which transports molecule into mitochondria and further amplifies mitochondrial dysfunction and oxidant stress. The resulting mitochondrial permeability transition, loss of ATP synthesis and oxidative damage ultimately result in nuclear DNA fragmentation and necrotic hepatocyte death.[34,35] Based on the current evidence, the major source of ROS in APAP hepatotoxicity is mitochondrial electron transport, while ROS produced by cytochrome P450 during the initial metabolism and ROS from immune cells appear to have a minor role in the initiation of hepatocyte death.[34,36]

Diclofenac-Mediated Oxidative Stress: Diclofenac (DIC), a widely used non-steroidal anti-inflammatory drug (NSAID), can cause oxidative stress through a number of mechanisms. Diclofenac has been reported to increase oxidative stress by inhibiting cyclooxygenase (COX)-1 and COX-2. Mitochondria are an important source and target of reactive oxygen species (ROS).[37] Experimental studies have reported that Diclofenac expose increase ROS production in several cell types, including cardiomyocytes, and cause mitochondrial dysfunction.[38] Increased ROS may stimulate the ERK1/2 component of the mitogen-activated protein kinase (MAPK) pathway, leading to cardiac fibroblast proliferation, fibrosis and cardiac

dysfunction.[39] Mitochondrial oxidative stress due to diclofenac is also characterized by depolarization of the mitochondrial membrane potential, decreased mitochondrial Ca 2+ uptake and impaired oxidative phosphorylation resulting in decreased ATP production.[38] Diclofenac also has the ability to inhibit L-type Ca^{2+} channels leading to disruption of intracellular Ca^{2+} handling and communication between the sarcoplasmic reticulum and mitochondria.[37,38] Thus, chronic exposure to diclofenac has been associated to enhanced ROS, mitochondrial dysfunction, inflammatory signaling, and reduced cardiac contractility

Isoniazid-Mediated Oxidative Stress: Isoniazid (INH) can cause an increase in reactive oxygen species (ROS) generation, leading to oxidative stress and hepatotoxicity. INH induced formation of ROS in a concentration dependent manner in HepG2 and THLE-2 liver cells. Higher amounts of ROS attacks the mitochondrial membrane resulting in the loss of mitochondrial integrity and the release of cytochrome c, which activates caspase-9 and then caspase-3 leading to intrinsic apoptosis.[39] Impairment of the Keap1–Nrf2 antioxidant pathway is one of the primary reasons. Normally, oxidative stress activates Nrf2, which migrates into the nucleus and attaches itself to antioxidant response elements (ARE) to trigger antioxidant and cytoprotective genes. On the other hand, INH decreases nuclear Nrf2 while increasing PKCδ phosphorylation and releasing Nrf2 from Keap1. Because INH suppresses Karyopherin-β1, an importer essential to Nrf2 nuclear translocation, Nrf2 stays mostly in the cytoplasm and is unable to adequately activate antioxidant genes such NQO1.[39] Additionally, INH decreases ERK phosphorylation, which increases Nrf2 activation and translocation. As a result, the antioxidant defense system fails, resulting in liver cells more susceptible to damage from ROS. DNA damage, apoptosis, cytochrome-c release, caspase activation, and mitochondrial dysfunction are all associated to this oxidative stress. INH-induced hepatic oxidative stress and apoptosis were further supported in INH-treated animals by elevated ALT, AST, and ALP as well as increased cytochrome c and caspase-9.[39]

ANTIOXIDANT DEFENCE SYSTEM:

Antioxidant : Antioxidants are compounds that neutralize reactive oxygen species (ROS), inhibit their generation or enhance the endogenous antioxidant defence mechanisms and significantly delay or prevent oxidation at lower concentrations than those of oxidizable substrates.[40]

Types of Antioxidant defence system: Both physiological and biological defence mechanisms have been established by biological systems in oxygenated conditions. Among these are the microvascular system at the physiological level, which maintains the tissues' oxygen levels stable, and the antioxidant defence system at the biological level, which can be either enzymatic or non-enzymatic and is known as a molecular repair mechanism.[41] Thus types of antioxidant defence system are as follow- .

Primary enzymatic system: Antioxidant enzymes like glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD), and DT-diaphoresis have been produced by aerobic organisms. SOD is in responsible of the disputation reaction between O2 and H2O2, which is then transformed into H2O and O2 in further reactions that are catalysed by either GPx or catalase. The most significant and potent detoxification enzyme in the cell is SOD. Because SOD is a metalloenzymatic, it needs a metal as a cofactor for it to perform its function. There are many kinds of SOD depending on the type of metal ion that the enzyme needs as a cofactor.[42,43] CAT completes the detoxification process initiated by SOD by catalysing the reduction or oxidation of hydrogen peroxide (H2O2) to produce water and molecular oxygen using iron or manganese as a cofactor.[44,45] A million of H2O2 molecules can be broken down by CAT in just a few seconds. The primary purpose of CAT, which is mostly present in peroxisomes, is to remove the H2O2 produced during fatty acids are oxidized. GPx is a key intracellular enzyme that, mainly found in the mitochondria and sometimes in the cytoplasm, breaks down lipid peroxides in their corresponding alcohols and H2O2 in water.[46] Selenium is necessary for GPx activity. At least eight GPx enzymes, GPx1–+-GPx8, can be detected in humans.[47] GPx1 is the most frequently produced selenoperoxidase among glutathione peroxidases and can be found

in almost all cells. The enzyme plays an essential role in preventing lipid peroxidation, which protects cells from oxidative damage.[48] Low GPx activity causes oxidative damage to the cell membrane's fatty acids and functional proteins. Numerous diseases, including cancer and cardiovascular disorders, have been associated to the formation and prevention of GPx, especially GPx1.[49] DT-diaphoresis is responsible for the reduction of drugs with Quinone structures and catalyses the reduction of Quinone to quinol [50]. The synthesis of these enzymes in cells is controlled by DNA.

Non-enzymatic system: This system of antioxidants consists of antioxidants that trap FR. To prevent the radical initiation response, they capture FR. The antioxidants become free radicals in the process of neutralizing or capturing the radicals by donating electrons, even though they are less reactive than the original FR. Other antioxidants in this class readily neutralize FR from antioxidants. Vitamin E, vitamin C, carotenes, ferritin, ceruloplasmin, selenium, reduced glutathione (GSH), manganese, ubiquinone, zinc, flavonoids, coenzyme Q, melatonin, bilirubin, taurine, and cysteine are among the antioxidants or free radical scavengers used by the cells. In some foods, the flavonoids act as a co-substrate in the catalytic action of specific enzymes, whereas in other foods, they interact directly with the reactive species to produce stable complexes or complexes with reduced reactivity.[41]

Repair system: The biomolecules, including lipids, proteins, and DNA, that have been damaged by ROS are either repaired or removed by enzymes. Mammalian cells' cytosol and mitochondria contain systems of proteolytic enzymes (proteinases, proteases, and peptidases) and DNA repair enzymes (polymerases, glycosylases, and nucleases). These type of enzymes include, for example, methionine sulfoxide reductase (MSR), glutathione reductase (GR), and GPx. These enzymes function as mediators in the process of repair oxidative damage generated by excessive amounts of reactive oxygen species. Any environmental influence that prevents or modifies a normal biological activity produces an environment that promotes oxidative stress to manifest or be repeated.[41]

Characteristics of Antioxidants: The main characteristic of a compound or antioxidant system is the inhibition or recognition of a chain of oxidative propagation, by stabilizing the resulting free radical, thus helping to decrease oxidative damage in the human body [51]. This characteristic was mentioned in Gordon's classification of antioxidants. Antioxidants fall into two categories: primary antioxidants, which break chain reactions and scavenge free radicals, and secondary or preventive antioxidants. The deactivation of metallic elements, inhibition of lipid hydro peroxides by preventing the formation of unwanted volatiles, regeneration of primary antioxidants, and removal of singlet oxygen are examples of secondary antioxidant processes. Therefore, antioxidants can be defined as "those substances that, in low quantities, act by preventing or greatly retarding the oxidation of easily oxidizable materials such as fats"[41]

Various Medicinal Plant With Antioxidant Potential TABLE 1. VARIOUS MEDICINAL PLANT WITH ANTIOXIDANT POTENTIAL

Sr.No	Plant source	Part used	Major antioxidant compound
1.	Maringa (*Maringa oleifera*)	Leaves	Quercetin[52]
2.	Green tea (*Camellia sinensis*)	Leaves	Catechins (EGCG)[53]
3.	Turmeric (*Curcuma longa*)	Rhizome	Curcumin[54]
4.	Cinnamon (*Cinnamomum verum*)	Bark	Polyphenols[55]
5.	Rosemary (*Salvia rosmarinus*)	Leaves	Rosmarinic acid[56]
6.	Tulsi (*Ocimum tenuiflorum*)	Leaves	Eugenol[57]
7.	Blueberry (*Vaccinium species*)	Fruit	Anthocyanins[58]
8.	Beetroot (*Beta vulgaris*)	Root	Betalains[59]
9.	Amla (*Phyllanthus emblica*)	Fruit	Vitamin C and polyphenols[60]
10.	Cocoa (Theobroma cacao)	Seeds	Flavanols[61]

CONCLUSION:

Drug-induced oxidative stress is an important mechanism contributing to adverse drug reactions and cellular injury. Drugs such as doxorubicin, paracetamol, diclofenac, and isoniazid can disturb cellular redox balance through excessive ROS production, glutathione depletion, mitochondrial dysfunction, and impaired antioxidant defences. These changes may lead to lipid peroxidation, protein and DNA damage, inflammation, and organ toxicity. The body's enzymatic and non-enzymatic antioxidant defence systems play a vital role in maintaining redox homeostasis and protecting cells against oxidative damage. Antioxidant agents, including N-acetylcysteine, vitamins C and E, and selected natural plant-derived compounds, may offer protective benefits in specific conditions. However, their effectiveness depends on the drug involved, the mechanism of toxicity, and the clinical situation. Therefore, further research is needed to establish the safety, efficacy, and appropriate clinical applications of antioxidant therapies. Understanding drug-induced oxidative stress may help improve the prevention and management of drug-related toxicity while supporting safer and more effective pharmacotherapy.

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