Inside the Genome: Understanding Genetic Influences on Oxidative Stress

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Conflicts of Interest

The authors have read the journal's policy and the authors of this manuscript have the following competing interests: Rajavelu and Pereira are paid employees of Vibrant America LLC. Jayaraman, Krishna, Wang, Bei, Rajasekaran, and Krishnamurthy are paid employees of Vibrant Sciences LLC. Vibrant Sciences or Vibrant America is a commercial lab that performs genetic testing for oxidative stress related gene polymorphisms. Vibrant Sciences or Vibrant America could benefit from increased testing based on the results. There are no patents, products in development, or marketed products to declare.

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Author Contributions

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Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Consent for publication

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Abstract

Genetics is a key factor that governs the susceptibility to oxidative stress. In the body, oxidative burden is regulated by the balance between the prooxidant genes that orchestrate processes that produce oxidant species, while the antioxidant genes aid those involved in scavenging these species. Repair genes help in detecting and repairing the damage caused by oxidant species. Together, the three components aid in maintaining the oxidative balance in the body. Genetic variations can influence the expression and activity of the encoded proteins which can then affect their efficiency in regulating redox processes, thereby increasing the risk of oxidative stress. This review studies single nucleotide polymorphisms (SNPs) that bear relevance to oxidative stress by exploring the variations in the prooxidant genes, such as XDH, CYBA, CYP1A1, PTGS2, NOS, and MAO and antioxidant genes including SOD, CAT, GPX, GSS, GLUL, GSR, GSTM1, GSTM5, GSTP1, TXN and HMOX1. The review also assesses the complexities of DNA repair genes including OGG1, NEIL1, NEIL2, MUTYH, APEX1, PARP1, XRCC1, XPD, XRCC3, and the protein repair gene, MSRA. Early identification of individuals at the increased risk of oxidative stress is possible from the assessment of these genes. Integrating genetic insights into oxidative stress management measures can pave the way for personalized medicine that tailors' healthcare approaches to individual genetic profiles. Effective genetic assessment along with routine quantification of biological markers can improve and monitor treatment strategies, enhancing mitigation approaches that maintain cellular health and promote longevity.

Keywords: oxidative stress, reactive oxygen species, genetic polymorphisms, superoxides

Introduction

Oxygen is a fundamental element for life and plays a crucial role in extracting energy through oxidation processes in the human body. This metabolic necessity, while essential, concurrently gives rise to transient entities, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), primarily originating from the mitochondria [1]. Although pivotal for immune defense and cellular signaling, an excess of ROS and RNS can harm the body by modifying lipids, DNA, RNA, and proteins, instigating detrimental oxidative reactions [2]. To counteract oxidative damage, the human body has evolved a sophisticated antioxidant defense mechanism comprising endogenous and exogenous antioxidants. Antioxidants play a crucial role in protecting against oxidative stress by preventing the formation of reactive species, scavenging, neutralizing, and removing reactive species, inhibiting oxidative chain reactions, and chelating reactive metals, therefore combatting oxidative stress. [3]. Oxidative stress (OS) is defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and molecular damage" [4]. Infections and inflammatory processes can endogenously contribute to the generation of oxidant species. In addition, exogenous sources such as toxins, ultraviolet (UV) radiation, cigarette smoking, alcohol consumption, and ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) can also result in the increased generation of oxidant species [5].

The delicate equilibrium between oxidants and antioxidants has garnered attention due to its association with the onset and/or progression of several diseases, including cancer, diabetes, metabolic disorders, atherosclerosis, and cardiovascular diseases (CVD) [6]. Elevated levels of ROS and RNS attack cellular macromolecules which can trigger fundamental changes at the cellular level, leading to chronic inflammation, DNA damage, and disruptions in cell signaling pathways. Alterations in these critical pathways can be associated with the pathogenesis of various diseases [2]. For instance, in cardiovascular diseases like atherosclerosis, oxidative stress can contribute to the development of arterial plaques [8]. In diabetes, oxidative stress is implicated in insulin resistance and pancreatic beta-cell dysfunction [8]. Persistent oxidative stress can also contribute to the development and promotion of cancer by causing genetic mutations, promoting angiogenesis, and facilitating metastasis [7]. The global prevalence of these disorders underscores the significance of screening for oxidative stress.

Oxidative stress is known to be influenced by intrinsic elements such as genetic predispositions and epigenetic modifications [9]. Prooxidant genes such as XDH, CYBA, CYP1A1, and PTGS2 encoding the enzymes, xanthine oxidase, NADPH oxidase, CYP1A1 enzyme, and cyclooxygenase-2, respectively, are involved in the generation of reactive species. The various forms of nitric oxide synthase encoded by NOS1, NOS2, and NOS3, while monoamine oxidases encoded by the MAO genes also produce oxidant species. Variations in these genes might pose the risk of higher oxidant production. Antioxidant genes, such as SOD, CAT, and GPX encode to the primary antioxidant enzymes, superoxide dismutase, catalase, and glutathione peroxidase, respectively. Enzymes involved in the glutathione system including glutathione synthetase (GSS gene), glutamate-cysteine ligase (GLUL), glutathione reductase (GSR), and glutathione transferases (GSTM1, GSTM5, GSTP1) play critical roles in maintaining the glutathione antioxidant pool. Additionally, the enzymes, thioredoxins (TXN) and heme oxygenase – 1 (HMOX1) contribute to the body's antioxidant system by maintaining redox homeostasis. Polymorphisms in these antioxidant genes can affect their activity and efficiency, thereby affecting the body's antioxidant defences. For instance, variations in the

SOD gene influence the enzyme's function and reduce its activity, increasing the susceptibility to oxidative stress [10].

Lipids are highly susceptible to oxidative damage, leading to lipid peroxidation and the formation of reactive aldehydes and lipid hydroperoxides. To counteract lipid peroxidation, the body employs repair mechanisms involving antioxidant enzymes and lipid repair proteins. However, research on genes involved in lipid repair is currently limited [11]. In contrast, the body has developed robust repair mechanisms against oxidative DNA damage, crucial for maintaining genomic integrity and preventing mutagenesis. Key genes involved in various DNA repair pathways, such as OGG1, NEIL1, NEIL2, MUTYH, APEX1, PARP1, XRCC1, XPD, and XRCC3 play essential roles in repairing oxidative DNA lesions. Polymorphisms in these genes can disrupt the efficiency or fidelity of DNA repair mechanisms, leading to the accumulation of oxidative DNA damage and impairing the cell's ability to cope with oxidative stress [12]. Similarly, repair mechanisms safeguard protein integrity, involving molecular chaperones and proteolytic systems. The MSRA gene, responsible for regulating protein oxidation, plays a crucial role in the reversible oxidation-reduction of methionine sulfoxide in proteins to methionine. Polymorphisms in the MSRA gene can impair this process, affecting protein function and integrity [13].

Understanding the genetics of prooxidants, antioxidants, and oxidative repair mechanism genes can provide insights into the genetic factors influencing oxidative stress-related disease risk. Genetic assessment for these genes might enable the early identification of individuals at higher risk of oxidative stress. Moreover, the exploration into the genetic landscape opens a promising avenue for personalized medicine, where interventions can be tailored based on an individual's unique genetic profile.

Overview of Oxidative stress

Oxidants, Free Radical Production, and Antioxidants

The generation of oxidant species involves both enzymatic and nonenzymatic reactions [14]. Enzymatic reactions in the respiratory chain, prostaglandin synthesis, phagocytosis, and the cytochrome P450 system significantly contribute to ROS production. Key enzymes, including NADPH oxidase, and xanthine oxidase play crucial roles in synthesizing superoxide radicals ($O_2^{\bullet-}$), leading to the formation of hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl). H_2O_2 is a nonradical compound, generated by various oxidase enzymes, such as amino acid oxidase and xanthine oxidase. The highly reactive hydroxyl radical ($^{\bullet}OH$) is formed through the interaction of $O_2^{\bullet-}$ with H_2O_2, catalysed by Fe^{2+} or Cu^+ in the Fenton reaction. Additionally, the nitric oxide radical ($NO^{\bullet}$) is enzymatically synthesized from the oxidation of arginine to citrulline by nitric oxide synthase (NOS) [14] (Figure 1). Nonenzymatic reactions also contribute to free radical production, especially during mitochondrial respiration, where oxygen reacts with organic compounds. Exposure to toxins and ionizing radiation trigger nonenzymatic free radical formation [14].

Free radicals originate from both endogenous and exogenous sources [15]. Endogenous production is linked to immune cell activation, inflammation, ischemia, infection, cancer, excessive exercise, mental stress, and aging. Exogenous sources include exposure to toxins such as environmental pollutants, heavy metals (Cd, Hg, Pb, Fe, and as), certain drugs (cyclosporine, tacrolimus, gentamycin, and bleomycin), chemical solvents, cigarette smoke,

alcohol consumption, and radiation exposure [15-16]. In the case of exogenous substances, these substances upon entering the body, undergo degradation or metabolism, resulting in the generation of free radicals as by-products. At low or moderate concentrations, ROS and RNS act as weapons for the host defence system. Phagocytes release $O_2^{\bullet-}$ during immune responses to destroy invading pathogens, underscoring the dual nature of reactive species [16]. Nitric oxide ($^{\bullet}NO$) is an important vasodilator and a cellular redox regulator [16].

To counteract oxidative stress, the body employs mechanisms involving antioxidants, either endogenously generated or externally supplied through foods. Antioxidants neutralize excess free radicals, protecting cells and contributing to disease prevention [17]. Endogenous antioxidants are classified as enzymatic antioxidants and non-enzymatic antioxidants. The primary antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) directly neutralize ROS and RNS. SOD catalyzes the dismutation of $O_2^{\bullet-}$ into H_2O_2, which is then transformed into water (H_2O) and oxygen (O_2) by CAT or GPx. Glutathione is an integral antioxidant in the body and it orchestrates its antioxidant functions with the help of various enzymes that together form the 'glutathione system.' Glutamate-cysteine ligase (GLUL) catalyzes the formation of the precursor to GSH while glutathione synthetase (GSS) is one of the enzymes participating GSH synthesis. GPx removes H_2O_2 by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG) [17] (Figure 1).

Glutathione reductase (GR) regenerates GSH from GSSG utilizing NADPH as a source of reducing power [18]. The glutathione enzyme family, glutathione S-transferases (GSTs) also contribute to glutathione-mediated antioxidant actions. Additionally, the thioredoxin system comprising thioredoxin (Trx) and thioredoxin reductase (TR) mediate antioxidant functions by using NADPH. Heme oxygenase (HO) is another important enzyme that regulates oxidative stress by maintaining heme homeostasis (Figure 1). In addition to these internal enzymatic antioxidant defences, the body also has non-enzymatic antioxidants that are further divided into endogenous non-enzymatic antioxidants (e.g., glutathione, alpha- lipoic acid, coenzyme Q10, melatonin, uric acid, bilirubin,) and exogenous non-enzymatic antioxidants (e.g., vitamin A, E, C, selenium, zinc, carotenoids, trace metals, flavonoids, omega-3 and omega-6 fatty acids) [18].

The enzymatic and non-enzymatic antioxidants together mount effective antioxidant defences against oxidant species in the body. The antioxidant process operates through chain-breaking or prevention mechanisms. In chain-breaking, antioxidants stabilize free radicals formed during reactions, preventing further damage, while in prevention, antioxidant enzymes reduce the rate of chain initiation, scavenging initiating free radicals or stabilizing transition metal radicals [19]. This intricate process is critical for maintaining redox homeostasis and preventing oxidative damage [19].

Prooxidant genes in oxidative stress

Xanthine Oxidase

Xanthine oxidase (XO) is a molybdoflavoprotein hydroxylase that can act both as an oxidase (XO) and reductase (called xanthine dehydrogenase). It is encoded by the XDH gene. Both forms of the enzyme aid in the final stage of purine catabolism. They catalyze the last two oxidative reactions that convert hypoxanthine to xanthine and xanthine to uric acid, a well-

known antioxidant. However, this process results in the generation of $O_2^{\bullet-}$ and H_2O_2 [20] (Figure 2). Additionally, XO is involved in the hydroxylation of various substrates and the production of $NO^{\bullet}$ under hypoxic conditions from nitrates and nitrites [21]. This increases the availability $NO^{\bullet}$ to react with $O_2^{\bullet-}$ to give $ONOO^-$ radicals [21]. This dual functionality of XO, in participating in the synthesis of uric acid and also in being a source of ROS, underscores its significance in oxidative stress pathways.

Polymorphisms in the prooxidant, XDH gene associated with its increased activity results in higher ROS and RNS production leading to oxidative stress. Increased production of ROS by XDH has been described in experimental models of salt-sensitive, and glucocorticoid-induced hypertension [22]. Some studies have suggested that XDH activity is enhanced in patients with hypertension and a higher production of H_2O_2 mediated by XDH in hypertensives as compared with controls has been described [23]. Among several XDH polymorphisms, variants at positions 565+64CT and -337GA are of particular interest. Individuals carrying specific genotypes, such as the CC genotype of the 565+64CT polymorphism, have been found to exhibit higher levels of oxidative stress markers, including malondialdehyde (MDA) and 8-oxo-deoxyguanosine (8-oxo-dG) as compared to individuals with the CT and TT genotypes. This suggests that C allele enhances oxidase function and may predispose individuals to increased oxidative stress, potentially contributing to a range of oxidative stress-related conditions [24]. Similarly, the -337GA polymorphism has shown associations with oxidative stress markers, primarily through elevated MDA levels seen among individuals with AA and AG genotypes in comparison with the GG genotypes. These studies strengthen the potential role of XDH variants in the risk of oxidative stress and related diseases such as hypertension [25].

NADPH oxidase

NADPH oxidase (NOX) is a transmembrane enzyme located in intracellular organelles. The CYBA gene that encodes the p22phox subunit of NOX. NOX is a transmembrane enzyme and is involved in the production of reactive species. It is present in intracellular organelles and comprises several isoforms, including NOX1–5, NOX oxidase 1 and 2, NOX organizer 1, and NOX activator 1. All of these, under normal conditions produce modest levels of $O_2^{\bullet-}$, contributing to fundamental cellular processes. However, exposure to diverse stimuli can amplify ROS production, triggering intracellular signalling pathways and consequently, oxidative stress. The p22phox subunit, originating from the CYBA gene, plays a vital role in NOX function by stabilizing the catalytic subunit and providing a docking site for cytosolic factors, thereby facilitating NADPH oxidase activity [26].

Upon translocation to the membrane and co-localization with p22phox and other NADPH subunits (p67phox, p47phox, and p40phox), NADPH oxidase stands out as the sole known enzyme family dedicated to producing ROS as its primary function. NOX orchestrates the transfer of electrons from cytosolic NADPH, traversing through FAD to penetrate the membrane via hemes, reaching oxygen and resulting in $O_2^{\bullet-}$ generation in the cytoplasm. Therefore, the CYBA gene through NADPH oxidase is involved in maintaining cellular processes by the generation of ROS [27] (Figure 2).

Numerous genetic polymorphisms have been reported within the promoter and exonic regions of the CYBA gene. Some of these polymorphisms influence gene expression and subsequently, NADPH oxidase activity, leading to elevated free radical formation. Among several CYBA

polymorphisms, rs4673 (C242T), rs9932581 (A-930G), and rs8854 variants have been extensively studied [28]. In the promoter region, G alleles of rs9932581 and T alleles of rs8854 are associated with increased promoter activity, resulting in elevated oxidative stress [29]. These polymorphisms are in the potential binding site of C/EBP (CCAAT/enhancer-binding protein) transcription factors, suggesting their role in modulating CYBA promoter activity and influencing CYBA transcription [30]. Studies have linked these genetic variations to susceptibility to oxidative stress-related diseases like hypertension, accompanied with increased oxidative stress markers such as 8-isoprostaglandin $F_2\alpha$ (8-isoPGF2α) levels, along with reduced antioxidant CAT activity [29].

For the rs4673 polymorphism, different rates of $O_2^{\bullet-}$ production have been demonstrated depending on the genotype. The T allele is associated with reduced NADPH oxidase activity, both at basal levels and when stimulated. This allele has been suggested to confer protection against oxidative stress pathologies [31]. Studies in patients with obstructive sleep apnea indicate that the CC genotype associates with higher oxidative marker levels, such as 8-Isoprostane levels, while the TT genotype associates with lower 8-isoPGF2α levels. This suggests that individuals with the CC genotype exhibit higher CYBA activity and experience increased oxidative stress compared to those with TT genotypes [32]. These genetic variations exert a significant influence on oxidative stress markers, antioxidant activity, and disease susceptibility.

Cytochrome P450 family 1 subfamily A member 1

Cytochrome P450 (CYP) enzymes, specifically the CYP1A subfamily constitute a diverse group that plays pivotal roles in metabolizing both, internally generated (endobiotic) and foreign (xenobiotic) substances within the human body [33]. CYP1A1 belongs to this subfamily and it is mainly in extrahepatic tissues where it participates in the metabolism of a vast number of endobiotics and xenobiotic such as toxins and drugs. However, CYP1A1's metabolic activity also results in the generation of ROS as byproducts, particularly when metabolizing certain procarcinogens like polycyclic aromatic hydrocarbons (PAHs) found in environmental pollutants and food contaminants. The overexpression of CYP1A1 usually caused due to exposure to PAHs results in the increase in ROS generation (Figure 2). As a result, variations in this gene might have implications in oxidative stress [34].

The CYP1A1 gene exhibits the polymorphism, rs4646903, located in the 3'-UTR. In rs4646903, the T>C alteration influences the enzyme's activity which results in the increase in CYP1A1 activity [35]. As a result, individuals with variant genotypes (CC and TC) may experience higher ROS production during metabolic reactions as opposed to those with the wild-type genotype (TT) having optimum CYP1A1 activity [35]. It is fair to infer that the rs4646903 polymorphism predisposes the CC and TC genotypes to increased oxidative stress. This inference was supported by the observed increase in the levels of the oxidative marker, MDA and the decrease in the antioxidant, GPx [36]. The SNP can predispose these individuals to diseases associated with oxidative damage, such as chronic obstructive pulmonary disease (COPD) and coronary artery disease [37].

Cyclooxygenase-2

The PTGS2 gene which is responsible for encoding the cyclooxygenase-2 (COX-2) enzyme, plays a crucial role in susceptibility to oxidative stress. The enzyme contributes to the

production of inflammatory molecules by catalysing the conversion of arachidonic acid into prostaglandins, specifically, prostaglandin G2 and prostaglandin H2. This process results in the generation of $O_2^{\bullet-}$ and subsequently other oxidant species. Moreover, COX-2 expression is upregulated during oxidative stress and inflammation. This creates a positive feedback loop where COX-2 activity is further boosted increasing the production of pro-inflammatory prostaglandins, which exacerbate oxidative stress and tissue damage [38,39]. Variations in the COX-2 gene can be implicated in oxidative stress-related conditions such as cancer, cardiovascular diseases, and neurodegenerative disorders.

Polymorphisms within the COX-2 gene, such as rs20417 (−765G > C) significantly influence oxidative stress [40]. The rs20417 polymorphism situated upstream from the transcription start site of the COX-2 gene introduces a critical alteration in a stimulatory protein binding site. This genetic variation leads to a consequential increase in transcription activity, resulting in elevated expression of the COX-2 enzyme [41]. The heightened expression of COX-2, in turn, is known to play a significant role in the intricate relationship between oxidative stress and cancer susceptibility [41]. By converting arachidonic acid into prostaglandins, COX-2 becomes a key player in oxidative stress-mediated inflammation and cytokine production. The CC genotype of rs20417 is associated with a higher incidence of oxidative stress [42,43]. This polymorphism has been linked to a higher risk of colorectal and gastric diseases, potentially due to increase in oxidative stress levels [44, 45].

Nitric oxide synthase

The family of nitric oxide synthase (NOS) proteins, which includes neuronal NOS (nNOS or NOS 1), inducible NOS (iNOS or NOS 2), and endothelial NOS (eNOS or NOS 3), plays a crucial role in catalyzing the oxidation of L-arginine, producing $^{\bullet}$NO and L-citrulline (Figure 3). These enzymes, encoded by separate genes, significantly contribute to cellular redox balance and various cellular functions. Understanding the role of NOS proteins is essential, especially considering that their genetic variations can impact $^{\bullet}$NO production.

$^{\bullet}$NO, a multifaceted molecule, acts as a chain-breaking antioxidant in free radical-mediated lipid peroxidation. Optimal levels of $^{\bullet}$NO are important for vasodilation, host defence, and other cellular signaling processes in the body. Generally, concentrations ranging from pico to nanomolar levels are considered the optimum range for $^{\bullet}$NO, where it positively influences various physiological processes. However, the oxidative status of the underlying tissue can affect $^{\bullet}$NO synthesis and bioavailability. Elevated endogenous tissue oxidant levels can reduce $^{\bullet}$NO levels aggravating NO-dependent oxidative stress. When tissue $O_2^{\bullet-}$ levels are higher, they attack $^{\bullet}$NO to form the cytotoxic, $ONOO^-$ (Figure 3). This indicates that low levels of $^{\bullet}$NO contribute to oxidative stress. However, studies have proposed $^{\bullet}$NO to represent a ‘double-edged sword’ with its overproduction leading to a multitude of $^{\bullet}$NO by-products implicated in mutational events and carcinogenesis. It is hypothesized that metabolic oxygen and nitrogen species from $^{\bullet}$NO may attack DNA bases, resulting in point mutations, strand breaks and interactions with sulfhydryl groups potentially leading to carcinogenesis [46]. Therefore, maintaining an optimum range of $^{\bullet}$NO levels is crucial. Exceedingly high or low $^{\bullet}$NO levels can pose risks to cellular health, leading to oxidative stress-related conditions.

Exercise significantly impacts •NO production, especially concerning energy demand. •NO, released by endothelial cells, plays a vital role in improving vascular function, leading to reductions in blood pressure during physical activity. Chemical and physical stimuli regulate

NO production during exercise [47]. Individuals with high •NO expression levels, engaging in short bouts of exercise can quickly increase NO biological activity, suggesting that less intense exercise may be sufficient to maintain NO levels. Conversely, for those with low •NO expression levels, prolonged training is beneficial as it leads to NO-dependent arterial remodeling and normalization of shear stress response, potentially compensating for their lower baseline NO levels. This understanding underscores the importance of tailoring exercise interventions based on an individual's NO expression levels to optimize vascular health. [47-48].

Nitric oxide synthase - 1

In the intron region of the NOS1 gene, the rs1879417 (g.117803515C > T) SNP has been studied in the context with oxidative stress. The C allele at this intronic SNP may be associated altered NOS1 function linked to an increased risk of oxidative stress-related conditions, such as stroke, when compared to individuals with T alleles [49]. The diverse polymorphisms within the NOS gene family, along with their associated genotypes underscore their significance in modulating oxidative stress and their intricate involvement in various diseases.

Nitric oxide synthase – 2

In the NOS2 gene, three SNPs in the promoter region namely, -1659 C>T (rs8078340), -1026G>T (rs2779249), and -277A>G (rs2779248) contribute to increase •NO production [47]. Specifically, the T alleles of rs8078340 and rs2779249, along with G alleles of rs2779248, lead to higher •NO production. These "high •NO expressor" variants raise •NO levels, potentially resulting in the generation of ROS and contributing to oxidative stress. Elevated concentrations of •NO under certain circumstances can generate $ONOO^-$ which is toxic and has carcinogenic potential [47]. These polymorphisms are associated with conditions such as hypertension, diabetes mellitus, stroke, hypercholesterolemia, atherosclerosis, cardiovascular diseases, and kidney diseases.

Nitric oxide synthase - 3

Within the NOS3 gene, several notable polymorphisms, such as T-786C [50], G894T (Glu298Asp) [51], and 27bp-VNTR [52] are linked to altered •NO production leading to oxidative stress. For the SNPs, T-786C and G894T, the homozygous (NOS3−786 CC) and/or heterozygous (NOS3 894 GT+TT) states are significantly associated with the with low •NO and high oxidative stress [47]. Similarly, 27bp-VNTR is seen to result in low •NO bioavailability leading to disease progression [47]. These polymorphisms, identified as low NO expressor alleles/genotypes, result in a global reduction in •NO production due to a 50% reduction in promoter activity. This reduction in •NO levels contribute to the observed heightened oxidative stress in individuals carrying these risk alleles/genotypes.

Monoamine oxidase - B

Monoamine oxidases (MAOs) are mitochondrial enzymes that oxidize monoamines, producing H_2O_2 and reactive aldehydes. There are two isoforms: MAO-A and MAO-B, with MAO-B playing a key role in regulating intracellular redox balance. Disruptions in monoamine metabolism and genetic variations in the MAO genes can cause oxidative stress, affecting cellular redox balance [53, 54]. Among the MAO-B gene polymorphisms, rs1799836 is of great importance. This polymorphism is in intron 13 of the MAO-B gene and is thought to disrupt

monoamine metabolism, leading to increased ROS production and oxidative stress within the central nervous system [55]. In this polymorphism, the enzymatic activity of MAO-B is affected; the A allele is associated with elevated MAO-B activity, while the G allele is linked to lower MAO-B activity. Studies consistently show that individuals with the AA genotype exhibit higher MAO-B enzyme activity and protein levels, confirming the involvement of the A allele in heightened oxidative stress through increased MAO-B expression [55]. The implications of rs1799836 extends to various neurodegenerative diseases such as Parkinson's Disease (PD) and mental health conditions like bipolar disorder and panic disorder, mediated by the A allele's effect in oxidative stress [56]. Table 1 provides a gist of the mechanisms by which genetic polymorphisms influence prooxidant genes.

Antioxidant genes in oxidative stress

Superoxide Dismutase

Superoxide dismutase (SOD) is a group of enzymes found in oxygen-dependent organisms that convert the highly reactive, $O_2^{\bullet-}$ into less reactive, H_2O_2 and oxygen (O_2) through redox reactions of metal ions within their active sites [57] (Figure 2). This is the integral mechanism by which SOD reduces oxidative stress in the body. Humans have three distinct SOD isoforms: copper-zinc superoxide dismutase (Cu/ZnSOD) or SOD1, manganese superoxide dismutase (MnSOD) or SOD2, and extracellular superoxide dismutase (ECSOD) or SOD3 [58]. Higher levels of SOD can enhance the antioxidant defense system, reducing oxidative damage to cells and potentially lowering the risk of various diseases, including cancer and neurodegenerative disorders such as Alzheimer's disease [59-60].

Superoxide Dismutase 1

The SOD1 gene encodes for the enzyme, superoxide dismutase 1, present in cellular compartments, including the cytosol, lysosomes, mitochondria, and endoplasmic reticulum. Along with quenching $O_2^{\bullet-}$, SOD1 also functions as a transcription factor in the nucleus, responding to oxidative stress by activating genes involved in ROS resistance [61]. Polymorphisms in the SOD1 gene have garnered attention due to their impact on oxidative stress regulation. One extensively studied polymorphism is rs2234694 (+35A/C), situated at the junction site between the intron and exon 3 [62]. The AA genotype is associated with an increase in SOD1 enzyme activity, while the CC genotype correlates with a reduction in enzymatic activity. This reduction in enzyme activity can lead to a compromised ability to catalyze the conversion of $O_2^{\bullet-}$ into H_2O_2 and O_2. As a result, the balance in the ROS levels is disrupted, contributing to an increased susceptibility to oxidative stress [63]

Another notable polymorphism, rs36232792 is the 50 bp Insertion/Deletion (Ins/Del) located 1684 base pairs upstream of the ATG start codon in the SOD1 gene promoter region. The Del allele in this polymorphism is linked to a reduction in promoter activity which can result in decreased synthesis of the SOD1 enzyme, compromising the its ability to neutralize $O_2^{\bullet-}$ radicals [64]. This reduction in enzymatic activity and compromised ROS detoxification might contribute to an elevated oxidative stress environment within the cell [65]. The implications of these SOD1 gene polymorphisms extend to various diseases such as heart failure, cancer, diabetes, Down's syndrome, and amyotrophic lateral sclerosis owing to their roles in altered redox signaling.

Superoxide dismutase 2

SOD2 encodes superoxide dismutase 2, that neutralizes $O_2^{\bullet-}$ generated during oxidative phosphorylation [66]. As an antioxidant enzyme primarily localized in mitochondria, SOD2 plays a pivotal role in mitigating the harmful effects of $O_2^{\bullet-}$ byproducts produced during cellular respiration [67-68]. The SOD2 polymorphism, rs4880 located in exon 2, introduces a T to C substitution at position 2734, resulting in the SOD2 Ala16Val genotype. The Val allele, a product of this SNP, significantly reduces SOD2 activity within the mitochondria via the accelerated degradation of SOD2 Val mRNA. As a result, individuals with the Val variant may experience higher oxidative stress. On the other hand, the Ala variants are associated with higher SOD2 Ala mRNA synthesis in cells, thereby having optimum antioxidant function. Additionally, the mitochondrial targeting sequence (MTS) of the SOD2 Ala precursor facilitates efficient mitochondrial import through an α-helix conformation while the MTS of the SOD2 Val precursor, adopting a β-sheet structure, results in a less efficient transport. Consequently, SOD2 activity is approximately 40% higher following the mitochondrial import in the SOD2 Ala precursor compared to its Val counterpart [69]. The SOD2 rs4880 polymorphism is believed to be associated with the susceptibility to various diseases, including cancer, neurodegenerative disorders, chronic kidney disease (CKD), and cardiovascular diseases [70].

Superoxide Dismutase 3

The SOD3 gene encodes for superoxide dismutase 3, playing a pivotal role as an extracellular antioxidant enzyme. SOD3 is present in various body fluids, including plasma, lymph, and synovial fluid where it neutralizes $O_2^{\bullet-}$ [71]. Particularly abundant in the lungs, it contributes significantly to SOD activity in the airways and blood vessels protecting lung tissues from oxidative stress.[72]. The SOD3 gene, particularly in exon 3, is linked to a commonly studied SNP, specifically rs1799895 (R213G polymorphism). This SNP occurs in the heparin-binding domain of the SOD3 gene, leading to an arginine-to-glycine amino acid substitution at position 213 (R213G). The genetic variations among CC genotypes resulting from this polymorphism witness an impaired binding of ECSOD to the extracellular matrix, leading to lower tissue levels of the enzyme in comparison to individuals carrying CG and GG genotypes [73]. This reduction in ECSOD levels results in decreased protection of lung matrix components against oxidative damage, indicating a potential involvement in the progression of chronic obstructive pulmonary disease (COPD) and a decline in lung function over time [74-75].

Catalase

The CAT gene encodes the catalase enzyme, primarily found in cell peroxisomes and the cytoplasm. It plays a crucial role in breaking down H_2O_2 produced during cellular respiration into oxygen and water (Figure 2). Catalase is consistently active in systems involved in electron transport with cytochromes, where H_2O_2 formation poses a threat to cellular integrity. Although catalase is essential for eliminating excess H_2O_2, its effectiveness decreases at low substrate concentrations due to low affinity. In such cases, catalase requires additional hydrogen donors like ethanol, formic, or ascorbic acids to effectively reduce H_2O_2 [76]. Genetic variations within the CAT gene, particularly in its promoter region and coding sequence, can affect catalase activity and may influence an individual's susceptibility to oxidative stress-related diseases [77].

Variations in the CAT gene, including, -262C>T (rs1001179) [78], -844C/T or -844G/A (rs769214) [79], and C111T (rs769217) [80] polymorphisms, are of significant interest due to

their implications in oxidative stress. These polymorphisms, located in the promoter region, have been associated with alterations in catalase expression levels and activity. Specifically, the rs1001179 polymorphism has been linked to variations in catalase levels and activity, affecting the enzyme's ability to neutralize intracellular H_2O_2. Carriers of the TT-genotype of the CAT gene rs1001179 polymorphism exhibited lower levels of catalase activity compared to carriers of CT- and CC-genotypes, suggesting a potential role in oxidative stress [78]. The other polymorphism, rs769214 has been associated with higher CAT activity in basal conditions, depending on the binding site of the transcriptional factor PAX6. The T allele of this polymorphism has been linked to increased CAT transcriptional activity [79, 81]. The rs769217 is responsible for alterations in CAT activity, with individuals carrying the TT genotype associated with lower CAT activity compared to those with the wild-type allele [80]. While the variant allele in rs769214 is improving the enzyme's activity, the variant allele of rs769217 is reducing CAT activity reading to oxidative stress.

Glutathione Peroxidase

Glutathione Peroxidase (GPx) catalyzes the reduction of H_2O_2 to water and oxygen (Figure 2). It also reduces peroxide radicals (ROO•) to alcohols and oxygen. Inactivity of GPx can result in oxidative damage and trigger inflammatory pathways associated with nuclear factor-κB (NF-κB) [82]. GPx comprises at least eight different members in humans, labeled GPx1 to GPx8. These enzymes are found in various cellular compartments: GPx1 in the cytosol, GPx2 in the gastrointestinal system, GPx4 in membranes, and GPx3 in mitochondria/extracellular space [83]. Most GPx enzymes use selenocysteine as a cofactor. While not all of them have selenocysteine, they all rely on GSH in their active sites. GPx5, GPx7, and GPx8 lack selenocysteine and instead use cysteine (CysGPxs). They are called thioredoxin-dependent peroxidases and use cysteine (Cys) in their redox-active sites. This choice between cysteine and selenocysteine offers a biological advantage by acting as an active site for redox actions [84]. Due to their integral role in antioxidant activity, polymorphisms in GPx are implicated in various conditions, including cancer, hypertension, vitiligo, neurodegenerative diseases, and cardiovascular disease. [85].

Glutathione Peroxidase 1

Glutathione Peroxidase 1 (GPx1), also known as cellular GPx, is encoded by the GPX1 gene and plays a crucial role in antioxidant defense mechanisms.[86]. Its significance is underscored by its association with various health conditions, including coronary atherosclerosis in type 2 diabetic patients, as well as breast, lung, and bladder cancer. Furthermore, GPX1 has been linked to vascular calcifications [87-88]. A notable polymorphism in the GPX1 gene, rs1050450, is a leucine to proline change at codon position 198 (GPX1 Pro198Leu genotype). This SNP involves a C>T substitution at position 198, resulting in the replacement of proline (Pro) with leucine (Leu). The presence of the Leu allele in the GPX1 gene can affect the protein's catalytic enzyme activity, substrate affinity, and structural stability. Specifically, the GPX1 Leu variant exhibits lower enzymatic activity compared to the GPX1 Pro enzymes which may weaken its ability to combat oxidative stress [89].

Glutathione Peroxidase 3

Glutathione Peroxidase 3 (GPx3) is primarily released into the extracellular space. It is encoded by the GPX3 gene. GPx3 serves as a crucial antioxidant enzyme in the vasculature. Its main

function involves maintaining a delicate balance between various oxidant species and •NO, a key vasorelaxant maintaining endothelial health. This equilibrium orchestrated by GPx3 is vital for preserving the vascular bioavailability of NO, as other ROS can quickly react and deactivate •NO [90]. Therefore, GPx3's role is essential in establishing an antithrombotic vascular environment, averting endothelial dysfunction, and reducing the likelihood of diseases associated with oxidative stress. Studies have identified the GPX3 gene to be associated with the risk of arterial ischemic stroke, cerebral venous thrombosis, and sudden sensorineural hearing loss (SSNHL), potentially due to its genetic influence on ROS [91]. For the rs3805435 in the GPX3 gene, individuals with the AA genotypes exhibited a deficiency in the GPx3 enzyme, leading to heightened extracellular oxidant stress, platelet activation, poor antioxidant defenses, and potential oxidative modification of fibrinogen compared to the AG and GG genotypes [92]. This sequence of events increases the risk of oxidative stress-related diseases, including acute ischemic stroke, hypertension, platelet-dependent thrombosis, coronary artery disease, and SSNHL [93].

Glutathione Peroxidase 4

Glutathione Peroxidase 4 (GPx4) encoded by the GPX4 gene, is a crucial enzyme essential for cellular protection against oxidative stress. It plays a key role in reducing H_2O_2 and lipid peroxides (LOOH) by utilizing GSH [94]. Variations in GPX4 gene is associated with the risk of oxidative stress. The rs713041 SNP within the GPX4 gene introduces a C-T substitution, specifically located in the 3′ untranslated region (3′UTR) of the mRNA. This region plays a crucial role in selenoprotein synthesis facilitating the incorporation of Secys. A genetic variation in this region has the potential to influence GPx4 activity, particularly under conditions of low selenium intake, rendering individuals more susceptible to oxidative stress-related diseases [95]. The rs713041 polymorphism in GPX4 gene presents three distinct genotypes, CC (Homozygous wild), CT (Heterozygous), TT (Homozygous mutant). In this polymorphism, the C allele appears to confer a protective role against oxidative damage, particularly when selenium levels are sufficient. It also contributes to maintaining GPx4 concentrations in lymphocytes, particularly for individuals with the CC genotype, compared to those with the TT genotype in situations of inadequate selenium intake [95]. The substitution of C allele with T allele has been linked to conditions such as obesity, endometriosis, thyroid diseases, Alzheimer's disease, depression, multiple sclerosis, and various possibly owing to its implication in oxidative stress [96].

Glutathione system

The glutathione system, anchored by glutathione (GSH), stands as a critical defense mechanism against oxidative stress. GSH, a tripeptide composed of L-glutamate, L-cysteine, and glycine, plays a pivotal role in maintaining cellular redox balance, essential for overall health [97] (Figure 4). Its synthesis is orchestrated by two key enzymes, γ-Glutamyl cysteine synthase and glutathione synthetase (GSS), fueled by ATP hydrolysis within the cytosol [98,101]. Additionally, glutamate-cysteine ligase (GLUL) catalyzes the formation of gamma-glutamylcysteine, a precursor to GSH, in the initial stage of GSH synthesis. GSH functions as a crucial substrate for enzymes like GPx, which scavenge peroxides to protect cells from oxidative damage. Glutathione reductase (GR) aids in GSH regeneration by converting oxidized glutathione (GSSG) back to its active form, thereby maintaining an optimal cellular pool of GSH for antioxidant defense and redox homeostasis [99] (Figure 4). Furthermore,

glutathione S-transferases (GSTs), including GSTM, GSTP, and GSTA, among others, contribute to detoxification processes within cells. These enzymes facilitate the conjugation of GSH with electrophilic compounds, enhancing their solubility and facilitating their removal from the cell. By neutralizing and eliminating harmful substances, GSTs play a crucial role in protecting cells from oxidative damage and maintaining overall cellular health [100][102] (Figure 4). Together, these elements form the robust, glutathione defense network crucial for cellular health and resilience against oxidative insults. Polymorphisms in these enzymes have been associated with various diseases.

Glutathione synthetase

The GSS gene encodes the glutathione synthetase enzyme (GSS), a critical player in the synthesis of GSH [98]. GSS catalyzes the final step in GSH biosynthesis, using ATP to ligate γ-glutamylcysteine with glycine. This is the final step in the synthesis of GSH [103] Polymorphisms rs121909307 in the GSS gene can impact the activity of the GSS enzyme, influencing the production of GSH and, consequently, the cellular response to oxidative stress. Individuals with CC genotype exhibit optimum GSS activity, resulting in a lower risk of oxidative stress. In contrast, those with CT or TT genotypes experience reduced GSS activity, leading to decreased GSH production and a higher susceptibility to oxidative stress. The polymorphic variations in the GSS gene directly correlate with the enzyme's function, influencing the cellular antioxidant capacity and the ability to combat oxidative stress [104]. Individuals carrying the CT or TT genotypes may face an increased risk of conditions where oxidative stress plays a pivotal role, such as neurodegenerative disorders, cardiovascular diseases, or certain types of cancers [105].

Glutamate ammonia ligase

The GLUL gene encodes the enzyme glutamate ammonia ligase, also known as glutamine synthetase. This enzyme is vital for maintaining cellular levels of glutamine, an amino acid with various functions, including antioxidant properties [106]. Glutamine is a precursor for GSH synthesis, crucial for controlling cellular redox status, highlighting the importance of the GLUL gene. [106]. Polymorphisms in the GLUL gene, particularly, rs10911021 contribute to variations in oxidative stress susceptibility. Homozygous wild individuals (TT) have sufficient levels of glutamine synthetase and glutathione experience lower oxidative stress. Heterozygous individuals (TC) with decreased levels of glutamine synthetase enzyme and glutathione may face an increased risk of oxidative stress. Homozygous mutant individuals (CC) with reduced levels of glutamine synthetase enzyme and glutathione exhibit heightened susceptibility to oxidative stress [107].

Glutathione reductase

The GSR gene produces the glutathione-disulfide reductase protein, also known as the glutathione reductase (GR) enzyme. This enzyme plays a crucial role in maintaining the reduced form of GSH. This action mediated by GR is integral for replenishing the pool of GSH [108]. Mutations in the GSR gene can cause hereditary glutathione reductase deficiency, affecting cellular redox potential and increasing oxidative stress levels, especially in red blood cells. This deficiency is linked to conditions such as hereditary hemolytic anemia. [108]. In the polymorphism, rs8190955 in the GSR gene, individuals with the C allele have optimum levels of GR while individuals with T allele are associated with a GR deficiency. As a result,

homozygous wild individuals with the CC genotype have appropriate antioxidant function and lower levels of oxidative stress in red blood cells. On the other hand, heterozygous individuals and homozygous mutant individuals with the CT and TT genotypes, respectively, have impaired cellular redox potential and increased oxidative stress levels in red blood cells, owing to the GR deficiency. This deficiency is associated with hereditary hemolytic anemia [108].

Glutathione transferases

Glutathione transferases (GST) form a critical enzyme family in cellular detoxification and defense against oxidative stress. They facilitate the conjugation of GSH with electrophilic compounds, aiding in the elimination of harmful substances. These enzymes are categorized into cytosolic, mitochondrial, and microsomal members and are classified into multiple classes including Alpha (A), Mu (M), and Pi (P), each with distinct subtypes. GSTs are expressed predominantly in the liver and are involved in metabolizing various compounds. Their primary function lies in rendering substances more water-soluble for excretion [109-110]. GSTs are crucial for maintaining cellular homeostasis and preventing the accumulation of toxic compounds, highlighting their role in cellular health maintenance. Genetic polymorphisms in GST genes can alter enzyme activity and may exhibit altered detoxification capacities and altered redox state, affecting susceptibility to diseases such as cancer, neurodegenerative disorders, and cardiovascular diseases [111].

Glutathione S-transferase Mu 1

The GSTM1 gene produces an enzyme called glutathione S-transferase Mu 1 (GSMT1). The enzyme is involved in detoxifying toxic compounds by catalyzing the conjugation of GSH with a variety of electrophilic substrates, which makes the compounds more water-soluble and facilitating their elimination from the body. Found in cellular compartments such as mitochondria, lysosomes, and nuclei, this GSTM1 safeguards organelles, especially the mitochondria from oxidative stress. It achieves this by preventing cardiolipin peroxidation and cytochrome c release, making it a key regulator in fighting ROS [112]. Polymorphisms in the GSTM1 gene contribute to variations in oxidative stress susceptibility. The rs366631 polymorphism is characterized by the T>C change. Individuals with the TT genotype exhibit normal GSTM1 activity and have normal ROS scavenging abilities. On the other hand, individuals with the CT and CC genotypes display reduced GSTM1 activity, making them prone to oxidative stress due to the gene's diminished ability to scavenge oxidant species [113].

Glutathione S-transferase 5

Similarly, the GSTM5 gene is part of the GST family and encodes the enzyme, glutathione S-transferase 5 (GSTM5) found in cellular compartments, such as the mitochondria. The enzyme is crucial for protecting cell organelles from oxidative stress. For rs3754446 polymorphism in GSTM5 individuals with TT genotypes exhibit normal GSTM5 activity, associated with normal mitochondrial function and a lower risk of oxidative stress. In contrast, individuals with GT and GG genotypes have altered GSTM5 activity and experience heightened oxidative stress due to ROS accumulation in the mitochondria. [114]

Glutathione S-transferase P1

Glutathione S-transferase P1 (GSTP1) encoded by the GSTP1 gene, is a crucial enzyme found throughout various cellular compartments such as the cytoplasm, mitochondria, lysosomes, and

nucleus. Its mitochondrial form plays a vital role in protecting organelles from oxidative stress by inhibiting cardiolipin peroxidation and preventing cytochrome c release [109]. Polymorphisms within the GSTP1 gene, such as rs1138272 contribute to variations in oxidative stress susceptibility. Individuals with the AA genotype exhibit normal gene activity, leading to appropriate antioxidant activity and a lower risk of oxidative stress. In contrast, those with the AG genotype show partially abnormal gene activity, resulting in decreased antioxidant activity and an elevated risk of oxidative stress. Homozygous GG individuals experience decreased gene activity, reduced antioxidant capacity, and a higher risk of oxidative stress. These polymorphic variations directly impact the enzyme's activity, influencing the cellular response to oxidative stress conditions [115].

Thioredoxin system

The thioredoxin system is crucial for regulating redox processes. It consists of thioredoxin (Trx) and its partner, thioredoxin reductase (TR or TrxR), which uses NADPH to reduce Trx [116] (Figure 5). Trx acts as an antioxidant by transferring electrons and protons, converting disulfides into dithiols [116]. Trx maintains its active state mainly through the action of TR. It can also be reactivated by glutaredoxin (Grx) within the glutathione system. Trx serves as an antioxidant by directly quenching singlet oxygen ($^1O_2$) and hydroxyl radicals ($^{\bullet}OH$) or indirectly by reducing oxidized proteins. A significant target of Trx is peroxiredoxin (Prx), which directly reduces peroxides including H_2O_2 and various alkyl hydroperoxides. After Prx reduces its target, Trx recycles the oxidized form of Prx back to its reduced state [117] (Figure 5). Overall, the thioredoxin system collaborates with the glutathione system to maintain the organism's redox balance and protect against oxidative stress.

Thioredoxin-2

The TXN2 gene encodes thioredoxin-2, that reduces Prx dimers that are formed upon reaction with H_2O_2, thereby keeping Prx in their reduced and active state (Figure 5). TXN2 is essential in particular for the efficient cycling of PRDX3, which indicates its importance in the body's antioxidant defences [116]. Genetic variations within the TXN2 gene, particularly the rs35045487 polymorphism is known to be crucial in modulating of oxidative stress. This polymorphism, located in the proximal promoter region, involves an insertion/deletion impacting the transcriptional activity [117]. Alleles A2 (GA insertion), A4 (G insertion), and A5 (GGGA insertion) display decreased transcriptional activity, attributed to additional SP1 binding sites. This suggests a potential association with heightened oxidative stress, indicating that individuals carrying these alleles may be predisposed to an imbalance in redox homeostasis [118]. Similarly, the rs4485648 polymorphism in intron 1 of the TXN2 gene is known to modulate oxidative stress-risk. The variant, 'TT' and 'CT' alleles of this polymorphism may have altered TXN2 expression which may compromise its functionality leading to oxidative stress. On the other hand, the 'CC' genotypes have appropriate gene expression associated with optimum antioxidant function. A study showed that the TT and CT genotypes were associated with the increased risk of diabetic retinopathy which could be mediated by elevated oxidative stress [119-120].

Heme oxygenase - 1

Heme oxygenase (HO) plays a crucial role in regulating oxidative stress by maintaining heme homeostasis. There are three isoforms of heme oxygenase: HO-1, HO-2, and HO-3. Among

these, HO-1 is upregulated in response to various stress stimuli, including oxidative stress. Its activation is a protective response against oxidative stress, as it helps to degrade heme, a pro-oxidant molecule, and generates products like biliverdin, which possess antioxidant properties HO-1 expression is regulated by the transcription factor, Nrf2, which activates antioxidant response elements (AREs) in the promoter region of the HMOX1 gene, encoding HO-1[121-122]. One notable polymorphism in the HMOX1 gene is rs2071746, where the A>T change is linked to various oxidative stress-related diseases like sickle cell anemia, ischemic heart disease, hypertension, and rheumatoid arthritis. Particularly in sickle cell anemia, the rs2071746 TT genotype in the HMOX1 gene's promoter is associated with elevated fetal hemoglobin (Hb F) levels. The T allele of rs2071746 is linked to reduced gene expression, potentially leading to higher free heme concentration and stress-induced erythropoiesis, consequently increasing Hb F levels. This association may contribute to the heightened oxidative stress observed in sickle cell anemia. [123]. Table 2 summarizes the mechanisms by which genetic polymorphisms influence antioxidant genes.

Repair mechanisms in oxidative stress

Biomolecules such as lipids, DNA, and proteins are prime targets of oxidative damage, leading to significant cellular dysfunction and disease pathogenesis. Understanding the intricate interplay between oxidative damage and the repair mechanisms that counteract the damage is crucial for deciphering the molecular basis of diseases. This also aids in the development of targeted interventions. Lipids, as integral components of cell membranes, are susceptible to oxidative damage, resulting in lipid peroxidation and the generation of reactive aldehydes and LOOH [124]. Repair mechanisms, including antioxidant enzymes and lipid repair proteins, act to counteract lipid peroxidation damage [125]. In contrast, DNA, the fundamental repository of genetic information, is continuously exposed to oxidative insults leading to various forms of damage such as base alterations, single-strand breaks, and DNA-protein crosslinks. Robust DNA repair mechanisms, including base excision repair (BER), nucleotide excision repair (NER), and double-strand break repair (DSBR) play pivotal roles in maintaining genomic integrity and mitigating the deleterious effects of oxidative DNA damage. Similarly, proteins are also vulnerable to oxidative modifications like carbonylation, nitration, and disulfide bond formation. Repair mechanisms, including molecular chaperones and proteolytic systems help maintain protein integrity [126].

Despite significant strides in understanding the genes mediating repair mechanisms against oxidative damage, a critical gap persists in our knowledge regarding the impact of genetic polymorphisms on these processes. DNA repair mechanisms play critical roles in repairing DNA, reducing the accumulation of DNA lesions, and maintaining the integrity of the genome. Owing to this, considerable research has been dedicated to elucidating the role of genetic variations in DNA repair pathways, while studies investigating polymorphisms in lipid and protein repair mechanisms are relatively scarce [125]. In this review, we mainly focus on DNA repair polymorphisms along with an additional polymorphism associated with protein repair. Polymorphisms in various DNA repair genes can modulate individual DNA repair capacity, thereby influencing genetic susceptibility to diseases. The limited information available for lipid and protein repair pathways underscores the pressing need for further research in these areas.

DNA repair genes in oxidative stress

OGG1

OGG1 is a vital DNA glycosylase in mammals. It plays a crucial role in the BER of oxidative DNA damage, particularly the removal of 8-hydroxyguanine (8-OHG) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) lesions formed during oxidative stress. The human OGG1 gene gives rise to multiple isoforms, with the primary variants, type 1a and 2a, exhibiting distinct localizations in the nucleus and mitochondria, respectively [125].

The Ser326Cys polymorphism (rs1052133) in OGG1 is a well-studied genetic variation associated with oxidative stress [126]. This SNP leads to a Ser-to-Cys substitution in the C-terminal domain of OGG1, impacting its catalytic activity. Individuals with the Cys/Cys genotype exhibit reduced BER repair rates of 8-OHG lesions, possibly due to lower enzymatic activity associated with the Cys326 variant. The oxidation of Cys326, forming a disulfide bond contributes to the diminished function of OGG1-Cys326. This polymorphism has been linked to increased DNA damage, suggesting a higher susceptibility to oxidative stress [127]. A significant association has been reported between the Ser326Cys polymorphism and lung cancer risk, emphasizing OGG1's role in maintaining genomic stability [128]. Additionally, OGG1 has implications in age-related diseases like Huntington's disease, where the Cys326 allele is linked to an earlier onset of the condition [129]. OGG1-Cys326 has also been identified as a risk factor for bladder cancer and tumor recurrence in non-muscle invasive bladder cancer patients [130]. Another OGG1 gene variant, Arg154His, with genotypes Arg/Arg, Arg/His, and His/His, represents different combinations of alleles at the position 154 locus, potentially influencing susceptibility to oxidative stress-related conditions. A gastric cancer cell line study revealed that the His variant affects the recognition of cytosine paired with 8-OHG leading to the inability to repair the DNA site, suggesting its potential involvement in disease progression [131].

NEIL1

The NEIL1 gene belongs to the Nei-like protein family. It is a DNA glycosylase that plays a crucial role in recognizing and excising oxidized bases from DNA, including 4,6-diamino-5-formamidopyrimidine (FapyA) and FapyG. Unlike OGG1, NEIL1 does not specifically target 8-OHG. It exhibits a strong affinity for oxidized bases in single-stranded DNA as well as in transcription and replication bubble DNA. NEIL1 operates in BER, utilizing a unique elimination mechanism that establishes an apurinic/apyrimidinic endonuclease 1 enzyme (APE1)-independent pathway, involving the APE1 enzyme responsible for repairing DNA lesions within the BER pathway [132].

Relevant SNPs in the NEIL1 gene, such as Gly83Asp (rs5745906) and Cys136Arg (rs5745907), impact the catalytic efficiency of the enzyme [132]. The Asp/Asp genotypes of the rs5745906 SNP exhibit impaired function in excising certain DNA lesions in duplex DNA while retaining the activity in single-stranded DNA. On the other hand, individuals with the Arg/Arg genotype of the rs5745907 variation, have reduced DNA glycosylase activity for oxidative base damage repair, altering protein folding and potentially affecting the enzyme's capability to interact with nucleotides that have undergone a flipping motion or structural change [132]. These genetic alterations in NEIL1 leading to inefficient DNA damage repair can result in accumulation of oxidized DNA lesions. These lesions can interfere with DNA replication and transcription, leading to mutations, and ultimately contributing to cellular dysfunction and oxidative stress [133]. While no direct associations with specific diseases have

been established, the impact of NEIL1 polymorphisms on oxidative stress response underscores their potential role in influencing overall health and disease susceptibility. Further research is needed to elucidate the specific disease associations and clinical implications of NEIL1 gene polymorphisms.

NEIL2

NEIL2 is another member of the DNA glycosylase family, and this gene consists of five exons. NEIL2 functions as both, a DNA glycosylase integral to BER and an AP (apurinic/apyrimidinic) lyase, primarily targeting oxidative cytosine products with its highest efficiency in 5-hydroxyuracil (5OHU) removal [132]. In terms of polymorphisms, relevant SNPs in the NEIL2 gene include the following two in the 5' UTR region: ss74800505 (C > A) and rs8191518 (C > G). These SNPs, when co-occurring, reduce NEIL2 expression levels and affect DNA repair, potentially modifying disease susceptibility [131, 134]. The hypothesis suggests that these polymorphisms may disrupt the binding of crucial transcriptional proteins. Moreover, cultured lymphocytes carrying the heterozygous or homozygous ss74800505 variant show heightened mutagen sensitivity, implying that changes in NEIL2 expression levels could affect DNA repair processes, potentially increasing induced mutagenesis [131].

MUTYH

MUTYH is a crucial DNA glycosylase integral to BER, playing a pivotal role in addressing oxidative stress-induced DNA damage. Its primary function involves the elimination of adenine bases paired with 8-OHG and 2-hydroxyadenine (2OHA) when erroneously paired with guanine (G), leading to the formation of an AP site. The MUTYH gene, comprising sixteen exons, generates various mature transcripts and gives rise to two distinct proteins with distinct cellular localizations: mitochondrial (type 1 protein) and nuclear (type 2 protein). The N-terminal domain of MUTYH interacts with the DNA strand containing the adenine substrate, extruding adenine from the DNA helix. The C-terminal domain of MUTYH facilitates the recognition of DNA strands containing 8-OHG and interacts with downstream BER proteins [135].

Various human MUTYH variants, primarily arising from missense or insertion/deletion mutations, exhibit significantly reduced DNA glycosylase activity. These mutations often involve residue substitutions in the catalytic domain or the substrate recognition region, highlighting their role in oxidative stress-induced diseases [136]. In humans, MUTYH germline mutations have been linked to a recessive form of familial adenomatous polyposis and colorectal cancer predisposition known as MUTYH-associated polyposis (MAP). One notable variant, Tyr165Cys (rs34612342), causes the Tyr residue to intercalate directly into the DNA duplex between 8-OHG and the nucleoside, resulting in structural changes and reduced interaction capabilities. Individuals with this variant might exhibit increased risk for oxidative stress-induced DNA damage due to reduced DNA glycosylase activity [136].

APEX1 Gene

The APEX1 gene, also referred to as the apurinic/apyrimidinic endonuclease 1 gene, encodes the multifunctional protein, APEX1. This protein is a key player in the BER pathway which is an essential mechanism for repairing DNA damage. Specifically, APEX1 is responsible for addressing DNA lesions resulting from oxidative stress. Acting as an endonuclease, it targets and cleaves DNA at sites of apurinic/apyrimidinic (AP) damage which is a common

consequence of oxidative stress. By initiating the incision of damaged DNA strands, APEX1 commences the repair process, enabling other enzymes to remove and replace the affected nucleotides, ultimately restoring the integrity of the DNA molecule [137].

Various genetic alterations in the APEX1 gene have been identified, including the 468 T>G (rs1760944), c.444 T>G (rs1130409), and rs3136817 polymorphisms. Among these, the rs1760944 polymorphism involves a T to G substitution at position 468 within the APEX1 gene's promoter region. Notably, individuals with the TT genotype may experience altered DNA repair efficiency under oxidative stress compared to those with GG or GT genotypes [138]. Another significant polymorphism, rs1130409, represents a T>G transversion at position 2197 in exon 5, resulting in the substitution of aspartate with glutamate. This substitution has been linked to the increased frequency of chromosomal aberrations. Functional studies suggest that the variant allele G affects APEX1's endonuclease and DNA-binding activity. This may result in reducing APEX1's interaction with other BER proteins and lowering its DNA repair efficiency in comparison to T variants [139]. Similarly, the rs3136817 (T>C) polymorphism is associated with variations in the DNA repair capacity, particularly under oxidative stress-induced DNA damage. This SNP affects specific base pairs within the APEX1 gene sequence, with TC and CC genotypes linked to enhanced DNA repair capacity in comparison to TT genotypes [140].

PARP1

PARP-1 is a key gene that encodes the enzyme Poly (ADP-ribose) polymerase 1 responsible for DNA repair. It plays a crucial role in BER and the repair of single-strand breaks induced by ionizing radiation and oxidative damage. One of the significant SNPs investigated in relation to PARP1 activity and the risk of oxidative stress-related diseases such as cataract is rs1136410 (A>G). Individuals with AG and GG genotypes exhibit lower activity of the PARP enzyme leading to increased susceptibility to oxidative DNA damage compared to those with AA genotypes. [141].

XPD

The XPD gene (also known as ERCC2) encodes the helicase protein, Xeroderma Pigmentosum group D. It is crucial for transcription-coupled NER, contributing to unwinding DNA and excising damaged DNA fragments. Genetic variations influencing enzyme activity can impact the protein’s capacity to repair DNA damage caused by environmental and endogenous factors. One notable polymorphism in the XPD gene is rs13181 (Lys751Gln (A/C)). Individuals with the CC and CA genotypes may have impaired NER function affecting the recognition and repair of DNA damage. Studies show that individuals with CC and CA genotypes exhibit decreased DNA repair capacity, whereas the AA variant is associated with enhanced protection against oxidative DNA damage. As a result, CC and CA genotypes are at an increased risk for oxidative DNA damage [142].

XRCC1

The XRCC1 gene encodes for X-ray cross-complementing group 1, a DNA repair protein involved in single-strand breaks (SSBs) and the BER pathway. It has been reported to be responsible for the efficient repair of DNA damage caused by active oxygen, ionization, and alkylating agents. Its multidomain protein structure interacts with the nicked DNA and participates with at least three different enzymes to repair SSBs. These enzymes include poly-

ADP-ribose polymerase (PARP), DNA ligase III, and DNA polymerase b [143]. Many polymorphisms have been detected in the XRCC1 gene, and three of them received most attention.

A functional SNP rs25487 caused due to single base change from G to A results in the substitution of glutamine amino acid in place of arginine. This single base change variation causes complete disturbance in the functioning of XRCC1 gene resulting in its lower capability to mediate BER repair. When DNA repair proteins become deficient, probably due to genetic alterations, it can lead to the initiation or can further aggravate oxidative stress related disease development [143]. Another notable polymorphism in XRCC1 is the rs1799782 exon 6, C>T polymorphism. The T allele results in amino acid substitutions that modify protein function and alters cellular ability to repair endogenous and exogenous DNA damage, leading to oxidative stress-related disease susceptibility [143].

XRCC3

The X-ray repair cross-complementing group 3 (XRCC3) gene belongs to the RAD51 family. It encodes a protein crucial for participating in homologous recombination (HR) double-strand break repairs (DSBRs), essential for maintaining chromosomal stability. In HR-DSBR, when a DNA double-strand break occurs, an undamaged sister chromatid or homologous chromosome serves as a template for accurately repairing the break. Variations in the XRCC3 gene can affect its repair function. Among the notable polymorphisms within the XRCC3 gene is Thr241Met (rs861539), characterized by a C to T transition leading to an amino acid substitution from threonine to methionine at codon 241. This substitution may alter DNA repair capacity by affecting the ability of the HR machinery to recognize and bind to the DNA template, promote strand invasion, and facilitate DNA synthesis and ligation. Consequently, individuals carrying the TT genotype may exhibit decreased or lost DNA repair capacity compared to those with CT and CC genotypes [143]. The gist of the mechanisms by which genetic polymorphisms affect DNA repair genes have been enlisted in Table 3.

Protein repair genes in oxidative stress

Methionine sulfoxide reductase A

The MSRA gene encodes for Methionine sulfoxide reductase A, an enzyme crucial for repairing oxidative damage to proteins. It operates by reducing methionine sulfoxide (MetO), the oxidized form of methionine, back to methionine, therefore restoring biological activity. This repair mechanism helps counteract the harmful effects of oxidative stress on proteins, preventing misfolding and dysfunction [144]. In the context of chronic obstructive pulmonary disease (COPD), the protein alpha-1-antitrypsin (A1AT) plays a key role in protecting lung tissue from damage by neutrophil elastase. However, oxidation of methionine residues in A1AT can impair its function, leading to a deficiency in protecting the lung parenchyma. Studies have shown that MSRA can partially restore the function of oxidized A1AT, indicating its role in repairing oxidative damage in proteins. Research on the rs10903323 polymorphism in the MSRA gene has indicated a potential link to COPD severity. The minor G allele of rs10903323 is associated with higher levels of oxidized A1AT in COPD smokers, particularly in severe COPD cases in comparison to A allele. This indicates that the G allele is associated with altered MSRA activity which may influence the susceptibility to COPD by affecting the repair efficiency of oxidatively damaged proteins, including A1AT. This underscores the

interplay between genetic variations and susceptibility to COPD mediated by oxidative damage [144] (Table 3).

Conclusion

The review has explored the intricate relationship between genetic predispositions and oxidative stress which could be associated with the pathogenesis of various conditions. Through the assessment of single nucleotide polymorphisms (SNPs) relevant to oxidative stress, we have highlighted the significant impact of genetic variations in the prooxidant genes, XDH, CYBA, CYP1A1, PTGS2, NOS, MAO and the antioxidant genes, SOD, CAT, GPX, GSS, GLUL, GSR, GSTM1, GSTM5, GSTP1, TXN, and HMOX1 on oxidative stress susceptibility. These polymorphic variations can influence the expression and activity of the encoded proteins, thereby disrupting the delicate redox balance in the body. Furthermore, our exploration of DNA repair genes, including OGG1, NEIL1, NEIL2, MUTYH, APEX1, PARP1, XRCC1, XPD, XRCC3, and the protein repair gene, MSRA, has underscored their critical roles in maintaining genomic and proteomic integrity in the face of oxidative challenges. Alterations in these genes contribute to the intricate network regulating DNA and protein repair mechanisms, ultimately impacting an individual's susceptibility to oxidative stress-related diseases.

Genetic assessment of the three integral gene categories can help in understanding variations in the enzymes and pathways associated with oxidative stress. This information can provide insights into the individual’s innate potential to produce and combat oxidant species as well as repair oxidative stress damage. Additionally, genetic assessment allows the early detection of individuals at a higher risk of oxidative stress, potentially predisposing them to oxidative stress-related conditions. This enables the timely implementation of mitigation strategies. The integration of genetic insights into treatment measures allows the employment of personalized medicine, interventional strategies that are designed to cater to one’s genetic profile. While understanding genetics can help in deciphering the body’s innate potential to combat oxidative stress, assessment of biological markers can provide the actual representation of the degree of oxidative stress in the body. Quantification of the oxidative damage markers, lipid peroxidation, DNA, RNA, and protein damage markers, can evaluate the extent of oxidative damage caused to these biomolecules. In addition, measuring the levels of endogenous and exogenous antioxidants can indicate the body’s antioxidant capacity and its ability to counteract oxidative stress. Therefore, genetic assessment along with routine testing for oxidative damage and antioxidant markers is important in managing oxidative stress. While genetics can drive the formulation of personalized interventions, routine biomarker assessment can monitor the effectiveness of the interventions in reducing oxidative stress. Effective assessment of oxidative stress and the implementation of personalized medicine can to optimize cellular function, and reduce the risk of age-associated chronic diseases, thereby promoting longevity.

In conclusion, this review sheds light on the current understanding of genetic determinants of prooxidants, antioxidants, and repair genes, offering a comprehensive perspective on how variations in these genes can modulate the risk of oxidative stress. Moving forward, further research is warranted to elucidate the precise molecular mechanisms underlying these genetic associations and to develop targeted interventions for mitigating the adverse effects of oxidative stress on health.

References:

1. Di Meo, S., & Venditti, P. (2020). Evolution of the knowledge of free radicals and other oxidants. *Oxidative Medicine and Cellular Longevity*, *2020*.
2. Checa, J., & Aran, J. M. (2020). Reactive oxygen species: drivers of physiological and pathological processes. *Journal of Inflammation research*, 1057-1073.
3. Huchzermeyer, B., Menghani, E., Khardia, P., & Shilu, A. (2022). Metabolic pathway of natural antioxidants, antioxidant enzymes and ROS providence. *Antioxidants*, *11*(4), 761.
4. Hajam, Y. A., Rani, R., Ganie, S. Y., Sheikh, T. A., Javaid, D., Qadri, S. S., ... & Reshi, M. S. (2022). Oxidative stress in human pathology and aging: Molecular mechanisms and perspectives. *Cells*, *11*(3), 552.
5. Bhattacharyya, A., Chattopadhyay, R., Mitra, S., & Crowe, S. E. (2014). Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiological reviews*, *94*(2), 329-354.
6. Ramírez-Expósito, M. J., & Martínez-Martos, J. M. (2019). The delicate equilibrium between oxidants and antioxidants in brain glioma. *Current neuropharmacology*, *17*(4), 342-351.
7. Reuter, S., Gupta, S. C., Chaturvedi, M. M., & Aggarwal, B. B. (2010). Oxidative stress, inflammation, and cancer: how are they linked?. *Free radical biology and medicine*, *49*(11), 1603-1616.
8. Andreadi, A., Bellia, A., Di Daniele, N., Meloni, M., Lauro, R., Della-Morte, D., & Lauro, D. (2022). The molecular link between oxidative stress, insulin resistance, and type 2 diabetes: A target for new therapies against cardiovascular diseases. *Current opinion in pharmacology*, *62*, 85-96.
9. Scandalios, J. G. (2005). Oxidative stress: molecular perception and transduction of signals triggering antioxidant gene defenses. *Brazilian journal of medical and biological research*, *38*, 995-1014.
10. Gusti, A. M., Qusti, S. Y., Alshammari, E. M., Toraih, E. A., & Fawzy, M. S. (2021). Antioxidants-Related Superoxide Dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione-S-transferase (GST), and nitric oxide synthase (NOS) gene variants analysis in an obese population: A preliminary case-control study. *Antioxidants*, *10*(4), 595.
11. Ayala, A., Muñoz, M. F., & Argüelles, S. (2014). Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxidative medicine and cellular longevity, 2014.
12. Santos, L. F. D. S. S. (2021). DNA repair SNPs as genetic modulators of individual susceptibility to differentiated thyroid cancer and response to radioiodine therapy.
13. Oien, D. B., & Moskovitz, J. (2007). Substrates of the methionine sulfoxide reductase system and their physiological relevance. Current Topics in Developmental Biology, 80, 93-133.
14. Sachdev, S., Ansari, S. A., Ansari, M. I., Fujita, M., & Hasanuzzaman, M. (2021). Abiotic stress and reactive oxygen species: Generation, signaling, and defense mechanisms. *Antioxidants*, *10*(2), 277.
15. Martemucci, G., Costagliola, C., Mariano, M., D'andrea, L., Napolitano, P., & D'Alessandro, A. G. (2022). Free radical properties, source and targets, antioxidant consumption and health. *Oxygen*, *2*(2), 48-78.

16. Pham-Huy, L. A., He, H., & Pham-Huy, C. (2008). Free radicals, antioxidants in disease and health. *International journal of biomedical science: IJBS*, *4*(2), 89.
17. Chaudhary, P., Janmeda, P., Docea, A. O., Yeskaliyeva, B., Abdull Razis, A. F., Modu, B., ... & Sharifi-Rad, J. (2023). Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases. *Frontiers in chemistry*, *11*, 1158198.'
18. He, L., He, T., Farrar, S., Ji, L., Liu, T., & Ma, X. (2017). Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. *Cellular Physiology and Biochemistry*, *44*(2), 532-553.
19. Santos-Sánchez, N. F., Salas-Coronado, R., Villanueva-Cañongo, C., & Hernández-Carlos, B. (2019). Antioxidant compounds and their antioxidant mechanism. *Antioxidants*, *10*, 1-29.
20. Kumar, R., Joshi, G., Kler, H., Kalra, S., Kaur, M., & Arya, R. (2018). Toward an understanding of structural insights of xanthine and aldehyde oxidases: an overview of their inhibitors and role in various diseases. *Medicinal Research Reviews*, *38*(4), 1073-1125.
21. Harrison, R. (2002). Structure and function of xanthine oxidoreductase: where are we now?. *Free Radical Biology and Medicine*, *33*(6), 774-797.
22. Laakso J, Mervaala E, Himberg JJ, Teravainen TL, Karppanen H, Vapaatalo H, Lapatto R. Increased kidney xanthine oxidoreductase activity in salt-induced experimental hypertension. Hypertension 1998; 32:902–906
23. Suzuki H, DeLano FA, Parks DA, Jamshidi N, Granger DN, Ishii H, et al. Xanthine oxidase activity associated with arterial blood pressure in spontaneously hypertensive rats. Proc Natl Acad Sci U S A 1998; 95:4754–4759.
24. Alderman, M. H., Cohen, H., Madhavan, S., & Kivlighn, S. (1999). Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension*, *34*(1), 144-150.
25. Chaves, F. J., Corella, D., Blesa, S., Mansego, M. L., Marín, P., Portoles, O., ... & Redon, J. (2007). Xanthine oxidoreductase polymorphisms: influence in blood pressure and oxidative stress levels. *Pharmacogenetics and genomics*, *17*(8), 589-596.
26. Aviello, G., & Knaus, U. G. (2018). NADPH oxidases and ROS signaling in the gastrointestinal tract. *Mucosal immunology*, *11*(4), 1011-1023.
27. Kumar, R., Kohli, S., Ali, Z., Duhan, K., Ram, R., Gupta, M., ... & Pasha, M. A. (2015). CYBA (p22phox) variants associate with blood pressure and oxidative stress markers in hypertension: a replication study in populations of diverse altitudes. *Hypertension Research*, *38*(7), 498-506.
28. Ortega-Loubon, C., Martínez-Paz, P., García-Morán, E., Tamayo-Velasco, Á., López-Hernández, F. J., Jorge-Monjas, P., & Tamayo, E. (2021). Genetic susceptibility to acute kidney injury. *Journal of Clinical Medicine*, *10*(14), 3039.
29. Tupurani, M. A., Padala, C., Puranam, K., Galimudi, R. K., Kupsal, K., Shyamala, N., ... & Hanumanth, S. R. (2018). Association of CYBA gene (-930 A/G and 242 C/T) polymorphisms with oxidative stress in breast cancer: a case-control study. *PeerJ*, *6*, e5509.
30. San José, G., Fortuno, A., Beloqui, O., Diez, J., & Zalba, G. (2008). NADPH oxidase CYBA polymorphisms, oxidative stress and cardiovascular diseases. *Clinical Science*, *114*(3), 173-182.

31. Najafi, M., Alipoor, B., Shabani, M., Amirfarhangi, A., & Ghasemi, H. (2012). Association between rs4673 (C/T) and rs13306294 (A/G) haplotypes of NAD (P) H oxidase p22phox gene and severity of stenosis in coronary arteries. *Gene*, *499*(1), 213-217.
32. Kheirandish-Gozal, L., & Gozal, D. (2013). Genotype–phenotype interactions in pediatric obstructive sleep apnea. *Respiratory physiology & neurobiology*, *189*(2), 338-343.
33. Danielson, P. Á. (2002). The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. Current drug metabolism, 3(6), 561-597.
34. Stading, R., Chu, C., Couroucli, X., Lingappan, K., & Moorthy, B. (2020). Molecular role of cytochrome P4501A enzymes in oxidative stress. Current opinion in toxicology, 20, 77-84.
35. Kiyohara, C., Washio, M., Horiuchi, T., Asami, T., Ide, S., Atsumi, T., ... & Kyushu Sapporo SLE (KYSS) Study Group. (2012). Risk modification by CYP1A1 and GSTM1 polymorphisms in the association of cigarette smoking and systemic lupus erythematosus in a Japanese population. Scandinavian journal of rheumatology, 41(2), 103-109.
36. Peddireddy, V., Badabagni, S. P., Gundimeda, S. D., Mamidipudi, V., Penagaluru, P. R., & Mundluru, H. P. (2016). Association of CYP1A1, GSTM1 and GSTT1 gene polymorphisms with risk of non-small cell lung cancer in Andhra Pradesh region of South India. European journal of medical research, 21, 17.
37. Kim, H. J., Park, J. H., Seo, Y. S., Holsen, T. M., Hopke, P. K., Sung, J., ... & Kim, J. I. (2018). CYP1A1 gene polymorphisms modify the association between PM10 exposure and lung function. Chemosphere, 203, 353-359.
38. Jaén, R. I., Prieto, P., Casado, M., Martín-Sanz, P., & Boscá, L. (2018). Post-translational modifications of prostaglandin-endoperoxide synthase 2 in colorectal cancer: An update. World journal of gastroenterology, 24(48), 5454.
39. Simmons, D. L., Botting, R. M., & Hla, T. (2004). Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacological reviews*, *56*(3), 387-437.
40. Kim, J. H., Lee, M. R., & Hong, Y. C. (2016). Modification of the association of bisphenol A with abnormal liver function by polymorphisms of oxidative stress-related genes. Environmental research, 147, 324-330.
41. Benelli, R., Venè, R., & Ferrari, N. (2018). Prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2), a complex target for colorectal cancer prevention and therapy. Translational Research, 196, 42-61.
42. Katkam, S. K., Indumathi, B., Naushad, S. M., & Kutala, V. K. (2019). Impact of genetic and epigenetic factors on the oxidative stress in cardiovascular disease. Modulation of Oxidative Stress in Heart Disease, 107-128.
43. Roberts, R. A., Laskin, D. L., Smith, C. V., Robertson, F. M., Allen, E. M., Doorn, J. A., & Slikker, W. (2009). Nitrative and oxidative stress in toxicology and disease. Toxicological sciences, 112(1), 4-16.
44. Gholamalizadeh, M., Majidi, N., Tajaddod, S., Abdollahi, S., Poorhosseini, S. M., Ahmadzadeh, M., ... & Houshiar-Rad, A. (2022). Interactions of Colorectal Cancer, Dietary Fats, and Polymorphisms of Arachidonate Lipoxygenase and Cyclooxygenase Genes: A Literature Review. Frontiers in Oncology, 12, 865208.

45. Rudnicka, K., Backert, S., & Chmiela, M. (2019). Genetic polymorphisms in inflammatory and other regulators in gastric cancer: risks and clinical consequences. molecular mechanisms of inflammation: induction, resolution and escape by helicobacter pylori, 53-76.
46. Cinel, L., Polat, A., Aydin, Ö., Düşmez, D., & Eğilmez, R. (2002). Bcl-2, iNOS, p53 and PCNA expression in normal, disordered proliferative, hyperplastic and malignant endometrium. Pathology international, 52(5-6), 384-389.
47. Chaaben, A. B., Mariaselvam, C., Salah, S., Busson, M., Dulphy, N., Douik, H., ... & Tamouza, R. (2015). Polymorphisms in oxidative stress-related genes are associated with nasopharyngeal carcinoma susceptibility. Immunobiology, 220(1), 20-25.
48. Nosarev, A. V., Smagliy, L. V., Anfinogenova, Y., Popov, S. V., & Kapilevich, L. V. (2015). Exercise and NO production: relevance and implications in the cardiopulmonary system. *Frontiers in cell and developmental biology*, *2*, 73.
49. Synowiec, E., Wigner, P., Cichon, N., Watala, C., Czarny, P., Saluk-Bijak, J., ... & Bijak, M. (2021). Single-nucleotide polymorphisms in oxidative stress-related genes and the risk of a stroke in a Polish population—A preliminary study. Brain Sciences, 11(3), 391.
50. Pacanowski, M. A., Zineh, I., Cooper-DeHoff, R. M., Pepine, C. J., & Johnson, J. A. (2009). Genetic and pharmacogenetic associations between NOS3 polymorphisms, blood pressure, and cardiovascular events in hypertension. American journal of hypertension, 22(7), 748-753.
51. Kondkar, A. A., Azad, T. A., Sultan, T., Osman, E. A., Almobarak, F. A., & Al-Obeidan, S. A. (2020). Association of endothelial nitric oxide synthase (NOS3) gene polymorphisms with primary open-angle glaucoma in a Saudi cohort. PLoS One, 15(1), e0227417.
52. Nath, S. D., He, X., Voruganti, V. S., Blangero, J., MacCluer, J. W., Comuzzie, A. G., ... & Thameem, F. (2009). The 27-bp repeat polymorphism in intron 4 (27 bp-VNTR) of endothelial nitric oxide synthase (eNOS) gene is associated with albumin to
53. Kaludercic, N., Mialet-Perez, J., Paolocci, N., Parini, A., & Di Lisa, F. (2014). Monoamine oxidases as sources of oxidants in the heart. Journal of molecular and cellular cardiology, 73, 34-42.
54. Ramsay, R. R. (2016). Molecular aspects of monoamine oxidase B. Progress in neuro-psychopharmacology and biological Psychiatry, 69, 81-89.
55. Leko, M. B., Perković, M. N., Erjavec, G. N., Klepac, N., Štrac, D. Š., Borovečki, F., ... & Šimič, G. (2021). Association of the MAOB rs1799836 Single Nucleotide Polymorphism and APOE ε4 Allele in Alzheimer's Disease. Current Alzheimer Research, 18(7), 585-594.
56. Angelopoulou, E., Bougea, A., Papageorgiou, S. G., & Villa, C. (2022). Psychosis in Parkinson's Disease: A Lesson from Genetics. Genes, 13(6), 1099.
57. Barry, H. (2018). SUPEROXIDE DISMUTASE AND THE SUPEROXIDE THEORY OF OXYGEN TOXICITY. A CRITICAL APPRAISAL. Copper Proteins and Copper Enzymes: Volume II, 2.
58. Ściskalska, M., Ołdakowska, M., Marek, G., & Milnerowicz, H. (2020). Changes in the activity and concentration of superoxide dismutase isoenzymes (Cu/Zn SOD, MnSOD) in the blood of healthy subjects and patients with acute pancreatitis. Antioxidants, 9(10), 948.

59. Aranda-Rivera, A. K., Cruz-Gregorio, A., Arancibia-Hernández, Y. L., Hernández-Cruz, E. Y., & Pedraza-Chaverri, J. (2022). RONS and oxidative stress: An overview of basic concepts. Oxygen, 2(4), 437-478.
60. Saxena, P., Selvaraj, K., Khare, S. K., & Chaudhary, N. (2022). Superoxide dismutase as multipotent therapeutic antioxidant enzyme: Role in human diseases. Biotechnology Letters, 1-22.
61. Eleutherio, E. C. A., Magalhães, R. S. S., de Araújo Brasil, A., Neto, J. R. M., & de Holanda Paranhos, L. (2021). SOD1, more than just an antioxidant. *Archives of Biochemistry and Biophysics*, *697*, 108701.
62. Ben Anes, A., Ben Nasr, H., Garrouche, A., Bchir, S., Dhaouefi, Z., Chabchoub, E., ... & Chahed, K. (2019). The Cu/Zn superoxide dismutase+ 35A/C (rs2234694) variant correlates with altered levels of protein carbonyls and glutathione and associates with severity of COPD in a Tunisian population. Free Radical Research, 53(3), 293-303.
63. Gallegos-Arreola, M. P., Ramírez-Hernández, M. A., Figuera, L. E., Zúñiga-González, G. M., & Puebla-Pérez, A. M. (2020). The rs2234694 and 50 bp Insertion/Deletion polymorphisms of the SOD1 gene are associated with breast cancer risk in a Mexican population. European Review for Medical & Pharmacological Sciences, 24(15).
64. Sedaghat, M. R., Shiri, H., Tavakkol-Afshari, J., Norouzmahani, M. E., Bahri, F., Fooladi, S., ... & Sadeghi, J. (2024). Impact of a 50bp insertion/deletion polymorphism of the superoxide dismutase-1 on oxidative stress status and risk of keratoconus. Experimental Eye Research, 238, 109742.
65. Mirsadraee, N., & Saadat, M. (2019). Association between a 50bp Ins/Del polymorphism at the promoter region of the superoxide dismutase-1 and age of onset of schizophrenia. EXCLI journal, 18, 204.
66. Zelko, I. N., Mariani, T. J., & Folz, R. J. (2002). Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. *Free Radical Biology and Medicine*, *33*(3), 337-349.
67. Flynn, J. M., & Melov, S. (2013). SOD2 in mitochondrial dysfunction and neurodegeneration. *Free Radical Biology and Medicine*, *62*, 4-12.
68. Dong, L. (2009). Development and validation of in vivo sensors of mitochondrial redox status (Doctoral dissertation, University of South Carolina).
69. Pourvali, K., Abbasi, M., & Mottaghi, A. (2016). Role of superoxide dismutase 2 gene Ala16Val polymorphism and total antioxidant capacity in diabetes and its complications. *Avicenna journal of medical biotechnology*, *8*(2), 48.
70. Holley, A. K., Bakthavatchalu, V., Velez-Roman, J. M., & St. Clair, D. K. (2011). Manganese superoxide dismutase: guardian of the powerhouse. International journal of molecular sciences, 12(10), 7114-7162.
71. Gao, F., Kinnula, V. L., Myllärniemi, M., & Oury, T. D. (2008). Extracellular superoxide dismutase in pulmonary fibrosis. Antioxidants & redox signaling, 10(2), 343-354.
72. Bezerra, F. S., Lanzetti, M., Nesi, R. T., Nagato, A. C., Silva, C. P. E., Kennedy-Feitosa, E., ... & Valenca, S. S. (2023). Oxidative Stress and Inflammation in Acute and Chronic Lung Injuries. Antioxidants, 12(3), 548.

73. Griess, B., Tom, E., Domann, F., & Teoh-Fitzgerald, M. (2017). Extracellular superoxide dismutase and its role in cancer. Free Radical Biology and Medicine, 112, 464-479.
74. Gongora, M. C., Lob, H. E., Landmesser, U., Guzik, T. J., Martin, W. D., Ozumi, K., ... & Harrison, D. G. (2008). Loss of extracellular superoxide dismutase leads to acute lung damage in the presence of ambient air: a potential mechanism underlying adult respiratory distress syndrome. The American journal of pathology, 173(4), 915-926.
75. Sørheim, I. C., DeMeo, D. L., Washko, G., Litonjua, A., Sparrow, D., Bowler, R., ... & Hersh, C. P. (2010). Polymorphisms in the superoxide dismutase-3 gene are associated with emphysema in COPD. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *7*(4), 262-268.
76. Ighodaro, O. M., & Akinloye, O. A. (2018). First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria journal of medicine, 54(4), 287-293.
77. Kodydková, J., Vávrová, L., Kocík, M., & Zak, A. (2014). Human catalase, its polymorphisms, regulation and changes of its activity in different diseases. Folia biologica, 60(4), 153.
78. McCullough, L. E., Santella, R. M., Cleveland, R. J., Bradshaw, P. T., Millikan, R. C., North, K. E., ... & Gammon, M. D. (2012). Polymorphisms in oxidative stress genes, physical activity, and breast cancer risk. Cancer Causes & Control, 23, 1949-1958.
79. Wu, J., Jiang, Z., Huang, X., Luo, Z., & Peng, H. (2023). Association of polymorphisms in the catalase gene with the susceptibility to noise-induced hearing loss: A meta-analysis. American Journal of Otolaryngology, 44(2), 103699.
80. Hebert-Schuster, M., Fabre, E. E., & Nivet-Antoine, V. (2012). Catalase polymorphisms and metabolic diseases. Current Opinion in Clinical Nutrition & Metabolic Care, 15(4), 397-402.
81. Sirivarasai, J., Kaojarern, S., Chanprasertyothin, S., Panpunuan, P., Petchpoung, K., Tatsaneeyapant, A., ... & Sritara, P. (2015). Environmental lead exposure, catalase gene, and markers of antioxidant and oxidative stress relation to hypertension: an analysis based on the EGAT study. BioMed research international, 2015.
82. Kim, S. K., Kang, S. W., Chung, J. H., Park, H. J., Cho, K. B., & Park, M. S. (2015). Genetic polymorphisms of glutathione-related enzymes (GSTM1, GSTT1, and GSTP1) and schizophrenia risk: a meta-analysis. International Journal of Molecular Sciences, 16(8), 19602-19611.
83. Shaparov, M. G., Gudkov, S. V., Lankin, V. Z., & Novoselov, V. I. (2021). Role of glutathione peroxidases and peroxiredoxins in free radical-induced pathologies. Biochemistry (Moscow), 86, 1418-1433.
84. Flohé, L., & Brigelius-Flohé, R. (2011). Selenoproteins of the glutathione peroxidase family. In Selenium: Its Molecular Biology and Role in Human Health (pp. 167-180). New York, NY: Springer New York.
85. Toppo, S., Vanin, S., Bosello, V., & Tosatto, S. C. (2008). Evolutionary and structural insights into the multifaceted glutathione peroxidase (Gpx) superfamily. Antioxidants & redox signaling, 10(9), 1501-1514.
86. Zhao, Y., Wang, H., Zhou, J., & Shao, Q. (2022). Glutathione peroxidase GPX1 and its dichotomous roles in cancer. Cancers, 14(10), 2560.

87. Mohammedi, K., Patente, T. A., Bellili-Muñoz, N., Driss, F., Le Nagard, H., Fumeron, F., ... & Velho, G. (2016). Glutathione peroxidase-1 gene (GPX1) variants, oxidative stress and risk of kidney complications in people with type 1 diabetes. Metabolism, 65(2), 12-19.
88. Lubos, E., Loscalzo, J., & Handy, D. E. (2011). Glutathione peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities.
89. Jerotić, Đ. (2021). Association of NRF2, SOD2 and GPX1 gene polymorphisms with markers of oxidative stress and prognosis in patients with end stage renal disease. Универзитет у Београду.
90. Zhang, F., Li, X., & Wei, Y. (2023). Selenium and Selenoproteins in Health. Biomolecules, 13(5), 799.
91. Chang, C., Worley, B. L., Phaëton, R., & Hempel, N. (2020). Extracellular glutathione peroxidase GPx3 and its role in cancer. Cancers, 12(8), 2197.
92. Chien, C. Y., Huang, T. Y., Tai, S. Y., Chang, N. C., Wang, H. M., Wang, L. F., & Ho, K. Y. (2017). Glutathione peroxidase 3 gene polymorphisms and the risk of sudden sensorineural hearing loss. The Kaohsiung Journal of Medical Sciences, 33(7), 359-364.
93. Voetsch, B., Jin, R. C., Bierl, C., Deus-Silva, L., Camargo, E. C., Annichino-Bizacchi, J. M., ... & Loscalzo, J. (2008). Role of promoter polymorphisms in the plasma glutathione peroxidase (GPx-3) gene as a risk factor for cerebral venous thrombosis. Stroke, 39(2), 303-307.
94. Weaver, K., & Skouta, R. (2022). The Selenoprotein Glutathione Peroxidase 4: From Molecular Mechanisms to Novel Therapeutic Opportunities. Biomedicines 2022, 10, 891.
95. Barbosa, P., Abo El-Magd, N. F., Hesketh, J., & Bermano, G. (2022). The Role of rs713041 Glutathione Peroxidase 4 (GPX4) Single Nucleotide Polymorphism on Disease Susceptibility in Humans: A Systematic Review and Meta-Analysis. International journal of molecular sciences, 23(24), 15762.
96. Crawford, A., Fassett, R. G., Geraghty, D. P., Kunde, D. A., Ball, M. J., Robertson, I. K., & Coombes, J. S. (2012). Relationships between single nucleotide polymorphisms of antioxidant enzymes and disease. Gene, 501(2), 89-103.
97. Deponte, M. (2022). Glutathione and glutathione-dependent enzymes. In Redox Chemistry and Biology of Thiols (pp. 241-275). Academic Press.
98. Lu, S. C. (2013). Glutathione synthesis. Biochimica et Biophysica Acta (BBA)-General Subjects, 1830(5), 3143-3153.
99. Sarıkaya, E., & Doğan, S. (2020). Glutathione peroxidase in health and diseases. Glutathione system and oxidative stress in health and disease, 49.
100. Nissar, S., Sameer, A. S., Rasool, R., Chowdri, N. A., & Rashid, F. J. J. C. M. (2017). Glutathione S transferases: biochemistry, polymorphism and role in colorectal carcinogenesis. J. Carcinog. Mutagen, 8(2), 287.
101. Vašková, J., Kočan, L., Vaško, L., & Perjési, P. (2023). Glutathione-Related Enzymes and Proteins: A Review. Molecules, 28(3), 1447.
102. Tretter, V., Hochreiter, B., Zach, M. L., Krenn, K., & Klein, K. U. (2021). Understanding cellular redox homeostasis: A challenge for precision medicine. International Journal of Molecular Sciences, 23(1), 106.

103. Dickinson, D. A., & Forman, H. J. (2002). Cellular glutathione and thiols metabolism. Biochemical pharmacology, 64(5-6), 1019-1026.
104. Kalamkar, S. D., Thorve, A. M., Gajjar, V., Divate, U., Karandikar-Iyer, S., Goel, P., ... & Ghaskadbi, S. (2023). Single nucleotide polymorphism in glutathione synthetase gene in Indian population with type 2 diabetes. Chronicle of Diabetes Research and Practice, 2(2), 67-72.
105. Bentley, A. R., Emrani, P., & Cassano, P. A. (2008). Genetic variation and gene expression in antioxidant-related enzymes and risk of chronic obstructive pulmonary disease: a systematic review. Thorax.
106. Halama, A., & Suhre, K. (2022). Advancing cancer treatment by targeting glutamine metabolism—a roadmap. Cancers, 14(3), 553.
107. Morieri, M. L., & Doria, A. (2023). Genetics of Coronary Artery Disease in Diabetes Mellitus. In Diabetes and Cardiovascular Disease (pp. 129-157). Cham: Springer International Publishing.
108. Vyas, B., Bhowmik, R., Akhter, M., & Ahmad, F. J. (2022). Identification, analysis of deleterious SNPs of the human GSR gene and their effects on the structure and functions of associated proteins and other diseases. Scientific Reports, 12(1), 5474.
109. Hayes, J. D., & McLellan, L. I. (1999). Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. Free radical research, 31(4), 273-300.
110. Fujikawa, Y., Terakado, K., Nezu, S., Noritsugu, K., Maemoto, Y., Ito, A., & Inoue, H. (2023). Improving reactivity of naphthalimide-based GST probe by imparting TPP cation: Development and application for live cell imaging. Bioorganic & Medicinal Chemistry Letters, 80, 129109.
111. Grussy, K., Łaska, M., Moczurad, W., Król-Kulikowska, M., & Ściskalska, M. (2023). The importance of polymorphisms in the genes encoding glutathione S-transferase isoenzymes in development of selected cancers and cardiovascular diseases. Molecular Biology Reports, 50(11), 9649-9661.
112. Mortazavi, Y., Rahimi, R., Azimi, F., Rostami, S., Moghimi, M., Faghihzadeh, S., & Mazloomzadeh, S. (2020). Role of Glutathione S-transferase (GSTM1, GSTT1) and CYP1A1 (cytochrome p450) Gene polymorphisms in susceptibility to acute myeloid leukemia. Middle East Journal of Cancer, 11(1), 12-20.
113. Dai, X., Bui, D. S., & Lodge, C. (2021). Glutathione S-transferase gene associations and gene-environment interactions for asthma. Current Allergy and Asthma Reports, 21(5), 31.
114. Butrym, A., Łacina, P., Bogunia-Kubik, K., & Mazur, G. (2021). ABCC3 and GSTM5 gene polymorphisms affect overall survival in Polish acute myeloid leukaemia patients. Current Problems in Cancer, 45(5), 100729.
115. Santric, V., Djokic, M., Suvakov, S., Pljesa-Ercegovac, M., Nikitovic, M., Radic, T., ... & Savic-Radojevic, A. (2020). GSTP1 rs1138272 polymorphism affects prostate cancer risk. Medicina, 56(3), 128
116. Lee, S., Kim, S. M., & Lee, R. T. (2013). Thioredoxin and thioredoxin target proteins: from molecular mechanisms to functional significance. *Antioxidants & redox signaling*, *18*(10), 1165-1207.
117. Hanschmann, E. M., Godoy, J. R., Berndt, C., Hudemann, C., & Lillig, C. H. (2013). Thioredoxins, glutaredoxins, and peroxiredoxins—molecular mechanisms and

health significance: from cofactors to antioxidants to redox signaling. *Antioxidants & redox signaling*, *19*(13), 1539-1605.

118. Wen, S., Lu, W., Zhu, H., Yang, W., Shaw, G. M., Lammer, E. J., ... & Finnell, R. H. (2009). Genetic polymorphisms in the thioredoxin 2 (TXN2) gene and risk for spina bifida. American Journal of Medical Genetics Part A, 149(2), 155-160.

119. Domingues, A., Jolibois, J., Marquet de Rougé, P., & Nivet-Antoine, V. (2021). The emerging role of TXNIP in ischemic and cardiovascular diseases; a novel marker and therapeutic target. International Journal of Molecular Sciences, 22(4), 1693.

120. Ramus, S. M., Cilensek, I., Petrovic, M. G., Soucek, M., Kruzliak, P., & Petrovic, D. (2016). Single nucleotide polymorphisms in the Trx2/TXNIP and TrxR2 genes of the mitochondrial thioredoxin antioxidant system and the risk of diabetic retinopathy in patients with Type 2 diabetes mellitus. Journal of Diabetes and its Complications, 30(2), 192-198.

121. Chiang, S. K., Chen, S. E., & Chang, L. C. (2021). The role of HO-1 and its crosstalk with oxidative stress in cancer cell survival. *Cells*, *10*(9), 2401.

122. Ryter, S. W. (2022). Heme oxygenase-1: an anti-inflammatory effector in cardiovascular, lung, and related metabolic disorders. *Antioxidants*, *11*(3), 555.

123. Pandey, H., Singh, K., Ranjan, R., Dass, J., Tyagi, S., Seth, T., ... & Mahapatra, M. (2023). Prevalence and Impact of HMOX1 Polymorphism (rs2071746: A> T) in Indian Sickle Cell Disease Patients. *Journal of Laboratory Physicians*.

124. Gibson, B. W. (2005). The human mitochondrial proteome: oxidative stress, protein modifications and oxidative phosphorylation. The international journal of biochemistry & cell biology, 37(5), 927-934.

125. Kołodziej, U., Maciejczyk, M., & Zalewska, A. (2018). Oxidative stress–repair systems of oxidatively damaged biomolecules. Progress in Health Sciences, 8, 141-150.

126. Charlier, C. F. (2018). Deciphering the Crosstalk: Characterisation of the Regulation of the ER Stress Response by the DNA Repair Enzyme AAG. University of Surrey (United Kingdom).

127. Daimon, M., Oizumi, T., Toriyama, S., Karasawa, S., Jimbu, Y., Wada, K., ... & Kato, T. (2009). Association of the Ser326Cys polymorphism in the OGG1 gene with type 2 DM. Biochemical and biophysical research communications, 386(1), 26-29.

128. Okasaka, T., Matsuo, K., Suzuki, T., Ito, H., Hosono, S., Kawase, T., ... & Tajima, K. (2009). hOGG1 Ser326Cys polymorphism and risk of lung cancer by histological type. Journal of human genetics, 54(12), 739-745.

129. Berger, F., Vaslin, L., Belin, L., Asselain, B., Forlani, S., Humbert, S., ... & Hall, J. (2013). The impact of single-nucleotide polymorphisms (SNPs) in OGG1 and XPC on the age at onset of Huntington disease. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 755(2), 115-119.

130. Gangwar, R., Ahirwar, D., Mandhani, A., & Mittal, R. D. (2009). Do DNA repair genes OGG1, XRCC3 and XRCC7 have an impact on susceptibility to bladder cancer in the North Indian population?. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 680(1-2), 56-63.

131. Simonelli, V., Mazzei, F., D'Errico, M., & Dogliotti, E. (2012). Gene susceptibility to oxidative damage: from single nucleotide polymorphisms to function.

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 731(1-2), 1-13.

132. Albelazi, M. S., Martin, P. R., Mohammed, S., Mutti, L., Parsons, J. L., & Elder, R. H. (2019). The biochemical role of the human NEIL1 and NEIL3 DNA glycosylases on model DNA replication forks. Genes, 10(4), 315.

133. Wilson III, D. M., Kim, D., Berquist, B. R., & Sigurdson, A. J. (2011). Variation in base excision repair capacity. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 711(1-2), 100-112.

134. Kinslow, C. J. (2008). Genetic determinants of NEIL2 transcription (Doctoral dissertation).

135. Nakamura, T., Okabe, K., Hirayama, S., Chirifu, M., Ikemizu, S., Morioka, H., ... & Yamagata, Y. (2021). Structure of the mammalian adenine DNA glycosylase MUTYH: insights into the base excision repair pathway and cancer. Nucleic acids research, 49(12), 7154-7163.

136. Curia, M. C., Catalano, T., & Aceto, G. M. (2020). MUTYH: Not just polyposis. World Journal of Clinical Oncology, 11(7), 428.

137. Lu, Z., Li, S., Ning, S., Yao, M., Zhou, X., Wu, Y., ... & Xie, Y. (2018). Association of the rs1760944 polymorphism in the APEX1 base excision repair gene with risk of nasopharyngeal carcinoma in a population from an endemic area in South China. *Journal of clinical laboratory analysis*, *32*(2), e22238.

138. AlMutairi, F., Ali Khan Pathan, A., Alanazi, M., Shalaby, M., Alabdulkarim, H. A., Alamri, A., ... & Reddy Parine, N. (2015). Association of DNA repair gene APE1 Asp148Glu polymorphism with breast cancer risk. *Disease Markers*, *2015*

139. Wang, T., Wang, H., Yang, S., Guo, H., Zhang, B., Guo, H., ... & Su, H. (2018). Association of APEX1 and OGG1 gene polymorphisms with breast cancer risk among Han women in the Gansu Province of China. *BMC Medical Genetics*, *19*, 1-9.

140. Kaur, K., & Kaur, R. (2018). Absence of APE1 (Asp148Glu) gene polymorphism in North-West Indian population: A comparison with world population. *Meta gene*, *16*, 208-212.

141. Cui, N. H., Qiao, C., Chang, X. K., & Wei, L. (2017). Associations of PARP-1 variant rs1136410 with PARP activities, oxidative DNA damage, and the risk of age-related cataract in a Chinese Han population: A two-stage case-control analysis. *Gene*, *600*, 70-76.

142. Wlodarczyk, M., & Nowicka, G. (2012). XPD gene rs13181 polymorphism and DNA damage in human lymphocytes. Biochemical genetics, 50, 860-870.

143. Yan, L., Li, Q., Li, X., Ji, H., & Zhang, L. (2016). Association studies between XRCC1, XRCC2, XRCC3 polymorphisms and differentiated thyroid carcinoma. Cellular Physiology and Biochemistry, 38(3), 1075-1084

144. Milovanovic, V., Topic, A., Milinkovic, N., Lazic, Z., Ivosevic, A., Radojkovic, D., & Rankov, A. D. (2021). Association of the methionine sulfoxide reductase A rs10903323 gene polymorphism with functional activity and oxidative modification of alpha-1-antitrypsin in COPD patients. *Pulmonology*.

TABLES

Table 1

Prooxidant enzyme	Gene Name	rsID	Function of Mutation	References
Xanthine Oxidase	XDH	565+64CT, -337GA	Enhanced XDH activity, shifting towards oxidase function, and disrupting redox balance	[24, 25]
NADPH oxidase	CYBA	rs9932581, rs8854, rs4673	Increased CYBA promoter activity leading to enhanced NADPH oxidase function giving rise to high $O_2^{\bullet-}$ levels	[29-32]
Cytochrome P450 enzymes	CYP1A1	rs4646903	Increased CYP1A1 activity resulting in higher ROS production	[35,36]
Cyclooxygenase-2	PTGS2	rs20417	Altered protein binding site and increased transcriptional activity result in the elevated expression of COX-2 enzyme leading to increased ROS production	[40-43]
Nitric oxide synthase	NOS1	rs1879417	Altered NOS1 function leading to increased oxidative stress	[49]
	NOS2	rs8078340, rs2779249, rs2779248	Altered NOS2 activity leading to higher $^{\bullet}NO$ production implicated in oxidative stress	[47]
	NOS3	T-786C, G894T, 27bp-VNTR	Altered NOS3 activity leading to lower $^{\bullet}NO$ production implicated in oxidative stress	[47,50-52]
Monoamine oxidases	MAO-B	rs1799836	Disrupted monoamine metabolism associated with elevated MAO-B activity leading to increased ROS production	[55]

Table 1. Mechanisms of genetic polymorphisms affecting prooxidant genes

Abbreviations: $O_2^{\bullet-}$ - superoxide; ROS – Reactive oxygen species; $^{\bullet}NO$ – Nitric oxide; NOS1 - Nitric oxide synthase – 1; NOS2 - Nitric oxide synthase – 2; NOS3 - Nitric oxide synthase – 3; MAO-B - Monoamine oxidase - B

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Table 2

Antioxidant enzyme	Gene Name	rsID	Function of Mutation	References
Superoxide dismutase	SOD1	rs2234694	Reduced SOD1 enzyme activity hampers the conversion of $O_2^{\bullet-}$ to H_2O_2 and O_2, dysregulating redox balance	[62,63]
		rs36232792	Decreased promoter activity results in lower SOD1 enzyme synthesis, impairing its ability to neutralize $O_2^{\bullet-}$ radicals	[64]
	SOD2	rs4880	Accelerated degradation of SOD2 mRNA lowers SOD2 activity, potentially leading to increased oxidative stress	[69]
	SOD3	rs1799895	Impaired SOD3 (ECSOD) binding to the ECM reduces tissue SOD3 levels, leading to decreased protection against oxidative damage	[73]
Catalase	CAT	rs1001179, rs769217	Lower catalase activity and expression affects the enzyme's ability to neutralize intracellular H_2O_2	[78, 80]
		rs769214	Increased catalase transcriptional activity resulting in improved antioxidant function	[79,81]
Glutathione Peroxidase	GPX1	rs1050450	Affected catalytic enzyme activity, substrate affinity, and structural stability which may lower GPx1's ability to combat oxidative stress	[89]
	GPX3	rs3805435	Reduced GPx3 enzyme levels resulting in poor antioxidant defenses and heightened oxidative stress	[92]
	GPX4	rs713041	Affected selenoprotein synthesis impacting GPx4 activity and potentially increasing susceptibility to oxidative stress	[95]
Glutathione synthetase	GSS	rs121909307	Altered GSS enzyme activity, influencing the production of GSH and consequently, affecting cellular response to oxidative stress	[104]
Glutamate ammonia ligase	GLUL	rs10911021	Decreased levels of the glutamine synthetase enzyme and GSH, resulting in the increased risk of oxidative stress	[107]
Glutathione reductase	GSR	rs8190955	Lower GR levels leading to impaired cellular redox potential caused by the affected antioxidant pool; results in increased oxidative stress levels, especially in red blood cells	[107]
Glutathione transferases	GSTM1	rs366631	Reduced GSTM1 activity affects the conjugation of GSH to toxic products leading to their poor elimination and compromising GSTM1's ROS scavenging abilities	[113]
	GSTM5	rs3754446	Reduced mitochondrial GSTM5 activity affects GSH's conjugation to toxic products resulting in their poor elimination, thereby compromising GSTM5's ability to quench ROS in the mitochondria	[114]
	GSTP	rs1138272	Abnormal GSTP1 activity decreases cellular antioxidant capacity	[115]
Thioredoxin	TXN2	rs35045487, rs4485648	Decreased transcriptional activity leads to altered TXN2 gene expression reducing its antioxidant function	[118-120]

Heme-oxygenase	HO-1	rs2071746	Reduced gene expression raises free heme concentration, promoting stress-induced erythropoiesis and increasing Hb F levels, thereby leading to oxidative stress, especially in sickle cell anemia	[123]

Table 2. Mechanisms of genetic polymorphisms affecting antioxidant genes

Abbreviations: SOD1 - Superoxide Dismutase 1; $O_2^{\bullet-}$ - Superoxide; H_2O_2 - Hydrogen peroxide; O_2 – Oxygen; SOD2 - Superoxide Dismutase 2; SOD3 - Superoxide Dismutase 3; ECSOD - Extracellular superoxide dismutase; ECM - Extracellular matrix; GPx1 – Glutathione peroxidase 1; GPx3 - Glutathione peroxidase 3; GPx4 - Glutathione peroxidase 4; GSS - Glutathione synthetase; GSH – Glutathione; GR - Glutathione reductase; GSTM1 - Glutathione S-transferase Mu 1; ROS – Reactive oxygen species; GSTM5 - Glutathione S-transferase 5; GSTP1 - Glutathione S-transferase P1; TXN2 - Thioredoxin-2; Hb F - Fetal hemoglobin

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Table 3

Repair enzyme	Gene Name	rsID	Function of Mutation	References
DNA repair				
DNA glycosylase	OGG1	rs1052133	Impaired catalytic activity lowers enzyme activity resulting in reduced BER repair rates of 8-OHG lesions	[126-127]
		Arg154His	Affected recognition of cytosine paired with 8-OHG leading to the enzyme's inability to repair the DNA site	[131]
	NEIL1	rs5745906	Dysregulated enzyme function leads to its impaired ability in excising DNA lesions in duplex DNA	[132]
		rs5745907	Reduced enzyme activity for oxidative base damage repair results in altering protein folding and thereby affecting the enzyme's capability to interact with nucleotides that have undergone a flipping motion or structural change; leads to the accumulation of oxidized DNA lesions	[132]
	NEIL2	ss74800505, rs8191518	Disrupted binding of crucial transcriptional proteins reduces the gene's expression levels, consequently affecting DNA repair	[131,134]
	MUTYH	rs34612342	Tyrosine residue intercalates directly into the DNA duplex between 8-OHG and the nucleoside, resulting in structural changes and reduced enzyme interaction, decreasing DNA repair capabilities	[136]
Apurinic/apyrimidinic endonuclease 1	APEX1	rs1760944	Altered DNA repair efficiency under oxidative stress	[138]
		rs1130409	Affected DNA-binding activity results in lowered APEX1's interaction with other BER proteins, affecting DNA repair; accompanied with increased frequency of chromosomal aberrations	[139]
		rs3136817	Alteration in the gene sequence results in enhanced DNA repair capacity	[140]
Poly (ADP-ribose) polymerase 1	PARP-1	rs1136410	Reduced enzyme activity leading to increased susceptibility to oxidative DNA damage	[141]
Xeroderma Pigmentosum group D	XPD	rs13181	Impaired NER function affects the recognition and repair of damaged DNA, thereby reducing DNA repair capacity	[142]
X-ray cross-complementing group 1	XRCC1	rs25487	Affected gene function resulting in the reduced capability to mediate BER repair	[143]

		rs1799782	Altered gene modifies protein function and affects cellular ability to repair endogenous and exogenous DNA damage	[143]
X-ray repair cross-complementing group 3	XRCC3	rs861539	Affected ability of the HR machinery to recognize and bind to the DNA template, promote strand invasion, and facilitate DNA synthesis and ligation, thereby reducing DNA repair capacity	[143]
Protein repair				
Methionine sulfoxide reductase A	MSRA	rs10903323	Altered gene activity affecting the repair efficiency of oxidatively damaged proteins	[144]

Table 3. Mechanism of genetic polymorphisms affecting DNA and protein repair genes

Abbreviations: BER - Base excision repair; 8-OHG - 8-hydroxyguanine; NER - Nucleotide excision repair; HR - homologous recombination; Prx - Peroxiredoxins

FIGURES

Figure 1

OXIDATIVE BALANCE GOVERNED BY PROOXIDANTS, ANTIOXIDANTS, & OXIDATIVE DAMAGE REPAIR GENES

Figure 1. Oxidative balance is governed by prooxidants, antioxidants, & oxidative damage repair genes. This illustration indicates the interplay between prooxidant, antioxidant, and repair genes in regulating the oxidative burden in the body. Prooxidant genes regulate processes that generate oxidant species which are beneficial at low to moderate levels. However, increased levels of these species are detrimental to the body. To scavenge reactive species the body has antioxidant genes encoding antioxidants that help in combatting oxidative stress. In addition, the repair genes in the body encode repair enzymes that help cope with oxidative damage. Therefore, the action of the three classes of genes is known to govern the oxidative balance in the body.

Figure 2

OVERVIEW OF CELLULAR OXIDATIVE STRESS PATHWAYS AND ANTIOXIDANT DEFENSE MECHANISMS

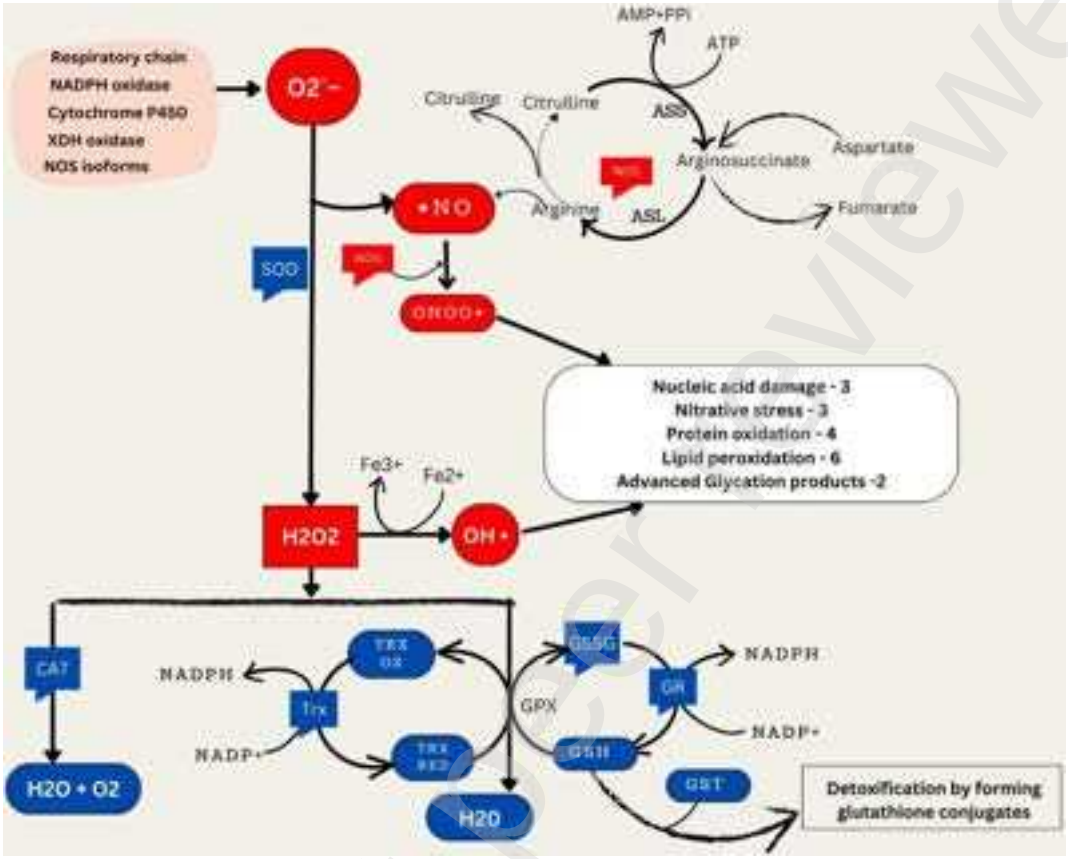

Figure 2. Overview of Cellular Oxidative Stress Pathways and Antioxidant Defense Mechanisms

Abbreviations

•NO - Nitric oxide
NOS - Nitric oxide synthase
$O_2^{\bullet -}$ - Superoxide
$ONOO^-$ - Peroxynitrite
SOD - Superoxide dismutase
H_2O_2 - Hydrogen peroxide
•OH - Hydroxyl radicals
Fe^{2+} - Ferrous iron
CAT – Catalase
GPx - Glutathione peroxidase
GSH - Reduced glutathione
TPx - Thioredoxin peroxidase
GST - Glutathione S-transferase
ROS - Reactive oxygen species

Figure 2. Antioxidant system in OS. NADPH oxidase, an essential component of the immune response, generates superoxide. Similarly, xanthine oxidase produces superoxide during purine metabolism. The respiratory chain, integral to cellular energy production, generates superoxide as a byproduct of

electron transport. Cytochrome P450 enzymes, involved in metabolic processes, also contribute to superoxide production. Under certain conditions, nitric oxide synthase isoforms can produce superoxide, particularly when uncoupled.

•NO is synthesized from the citrulline cycle by NOS enzymes. These enzymes catalyze the conversion of L-arginine to L-citrulline and NO, a process involving the oxidation of L-arginine's guanidino nitrogen. When NO reacts with $O_2^{\bullet -}$, $ONOO^-$ forms, a highly reactive nitrogen species implicated in oxidative damage to biomolecules.

SOD enzymes convert superoxide radicals into H2O2. These include cytosolic Cu/Zn-SOD (SOD1), mitochondrial Mn-SOD (SOD2), and extracellular SOD (SOD3). Hydrogen peroxide can produce •OH through the Fenton reaction, a process catalyzed by transition metal ions such as Fe^{2+}. This reaction initiates chain reactions leading to oxidative damage.

Catalase (CAT), located in peroxisomes, breaks down hydrogen peroxide into water and oxygen. This catalysis facilitates the conversion of hydrogen peroxide molecules into water and oxygen molecules. Moreover, the glutathione and thioredoxin systems directly reduce H2O2 to water. In the glutathione system, glutathione peroxidase (GPx) reduces H2O2 using reduced glutathione (GSH) as a cofactor. Similarly, thioredoxin peroxidase (TPx) reduces hydrogen peroxide using thioredoxin as a cofactor. Both systems protect cells from oxidative damage by detoxifying hydrogen peroxide.

GSH and glutathione S-transferase (GST) are crucial in detoxifying harmful compounds. Through conjugation, GSH binds to electrophilic centers on toxic molecules, enhancing their water solubility and facilitating excretion from cells. This detoxification process aids in protecting cells from the damaging effects of xenobiotics and reactive oxygen species (ROS).

Figure 3

THE NOS PATHWAY IN OXIDATIVE STRESS

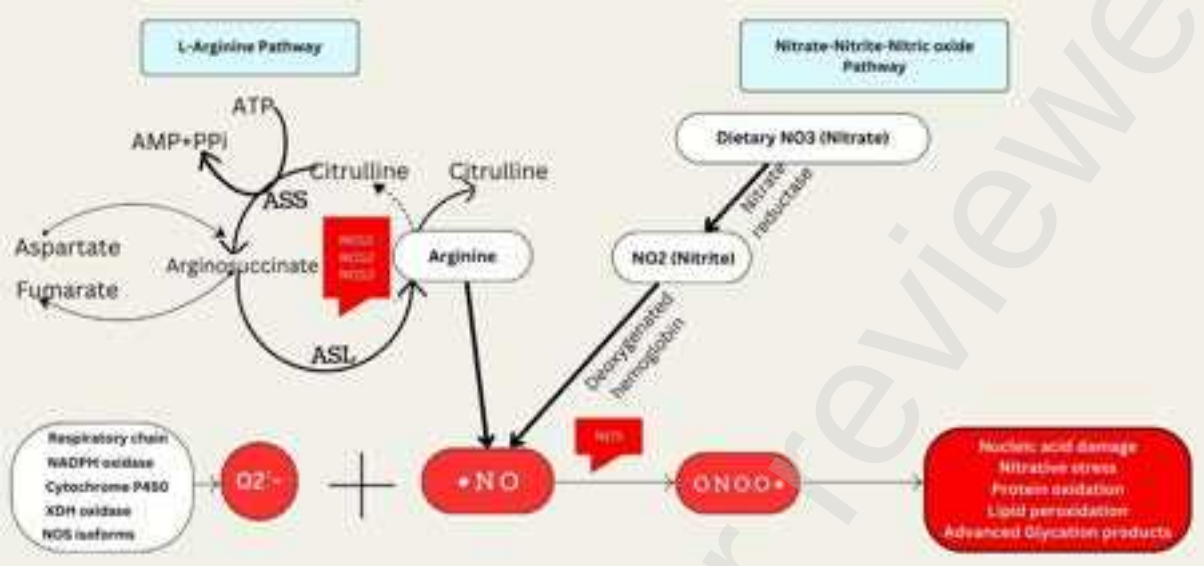

Figure 3. The NOS Pathway in Oxidative Stress

Abbreviations

NOS - Nitric oxide synthase

•NO - Nitric oxide

$O_2^{\bullet -}$ - Superoxide

$ONOO^-$ - Peroxynitrite

Figure 3. The NOS Pathway in Oxidative Stress. The figure illustrates the multifaceted pathway involving NOS in oxidative stress conditions. Under normal circumstances, NOS catalyzes the conversion of L-arginine to L-citrulline, producing •NO, a crucial signaling molecule. Additionally, dietary intake of nitrate and nitrite can contribute to •NO production through the nitrate-nitrite-NO pathway. However, in the presence of $O_2^{\bullet -}$, generated during oxidative stress, •NO reacts to form $ONOO^-$, a potent oxidant. This reaction leads to the synthesis of peroxynitrite, exacerbating oxidative stress and its detrimental effects on cellular components. The intricate interplay between NOS, $O_2^{\bullet -}$, and NO underscores the significance of oxidative stress in various pathological conditions.

Figure 4

GLUTATHIONE PATHWAY IN OXIDATIVE STRESS

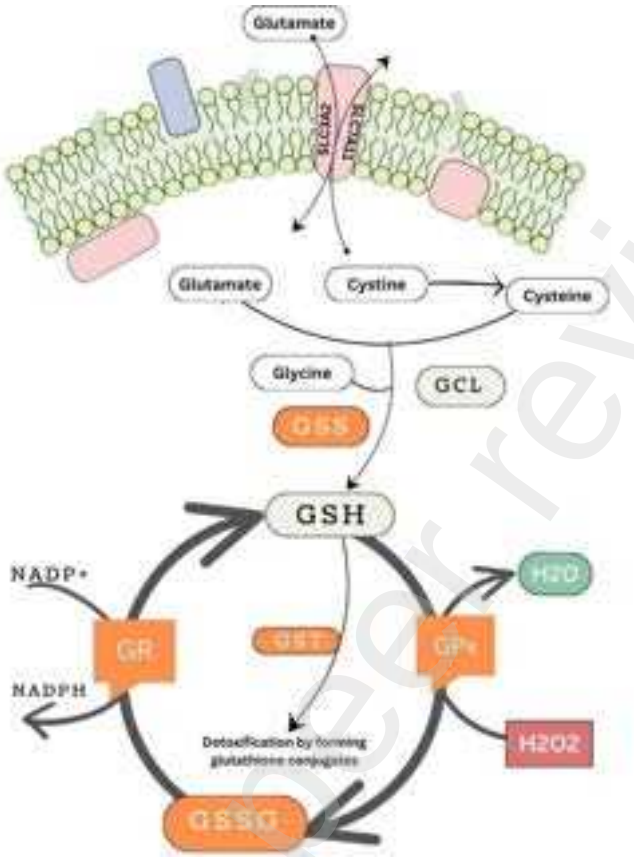

Figure 4: Glutathione Pathway in Oxidative Stress

Abbreviations

GSH – Glutathione
GCL - Glutamate-cysteine ligase
GSS - Glutathione synthetase
H_2O_2 - Hydrogen peroxide
ROS - Reactive oxygen species
GSSG - Oxidized glutathione
GR – Glutathione Reductase

Figure 4: Glutathione Pathway in Oxidative Stress. This schematic illustrates the GSH pathway in oxidative stress, showcasing the synthesis of GSH and its role in the glutathione cycle. Glutamate enters the cell membrane from the extracellular space via specific transporters. Inside the cell, glutamate combines with cysteine and glycine, facilitated by the enzymes GCL and GSS, to form GSH. GSH is a critical antioxidant involved in cellular defense against oxidative stress. In the glutathione cycle, GSH reacts with ROS such as H_2O_2, catalyzed by the enzyme glutathione peroxidase GPx, to form GSSG and water. GSSG is then converted back to GSH through the action of GR, utilizing NADPH as a cofactor. This regeneration of GSH enables its continued function in scavenging ROS and maintaining redox balance within the cell. Overall, the glutathione pathway plays a crucial role in mitigating oxidative stress by synthesizing GSH, which acts as a potent antioxidant, and by recycling GSSG back to GSH, thus efficiently neutralizing harmful ROS like H_2O_2 to harmless water.

Figure 5

THIOREDOXIN PATHWAY IN OXIDATIVE STRESS REGULATION

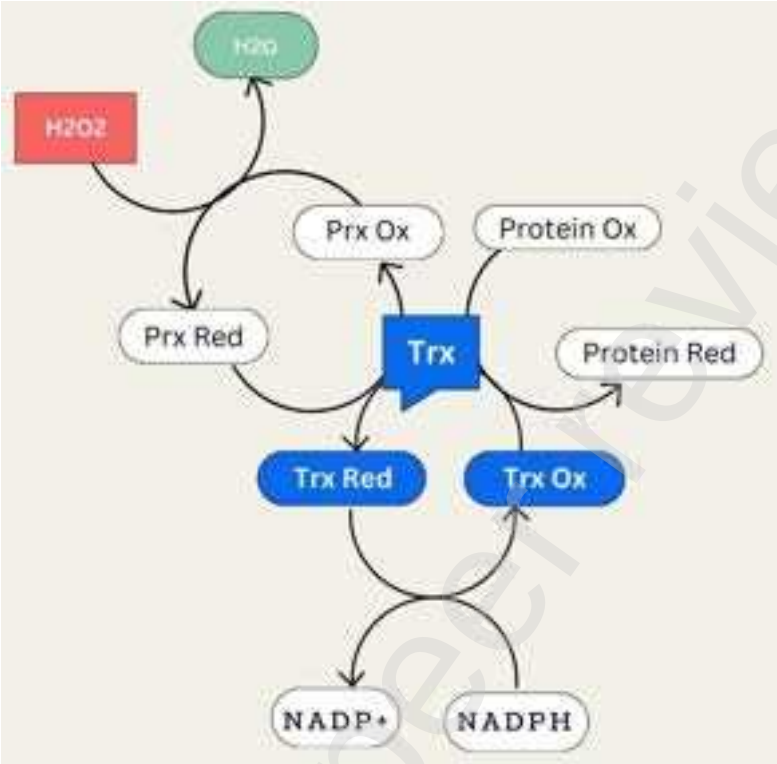

Figure 5: Thioredoxin Pathway in Oxidative Stress Regulation.

Abbreviations

Trx – Thioredoxin
ROS - Reactive oxygen species
Trx-S2 - Oxidized state
Trx-SH - Reduced form
Prx Ox - Oxidized peroxiredoxins
Prx Red – Reduced peroxiredoxins
H_2O_2 - Hydrogen peroxide
H_2O - Water

Figure 5: Thioredoxin Pathway in Oxidative Stress Regulation. The diagram illustrates the Trx pathway, a crucial cellular defense mechanism against oxidative stress. In response to elevated ROS, Trx undergoes reduction by NADPH-dependent thioredoxin reductase, transforming from its Trx-S2 to its reduced form Trx-SH. The reduced Trx-SH, in turn, functions as a potent electron donor for the reduction of Prx Ox to Prx Red, essential peroxidases involved in ROS detoxification. Concurrently, Trx activates various redox-sensitive proteins by reducing their disulfide bonds, restoring their functional state. Notably, this pathway plays a pivotal role in maintaining cellular homeostasis by facilitating the conversion of H_2O_2 to H_2O, thereby mitigating oxidative damage and preserving cellular integrity.