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Chapter

Thiols: Role in Oxidative Stress-Related Disorders

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Abstract

The effects of oxidative stress occur as a result of peroxidative damage of the macromolecule and membranes of the cells and with the disruption of metabolic activities in the components of the cells in living organisms. Organ and tissue pathologies are known to occur when oxidative stress is excessive in the body. It is known that thiols are one of the main protective mechanisms of the body against oxidative stress. Thiols have been shown to play important roles in enzymatic reactions, apoptosis, detoxification and antioxidant protection in the body. Many studies have shown changes in thiol status and thiol/disulphide homeostasis in various diseases such as digestive system, respiratory system, reproductive system, urinary system, metabolic diseases and cancer. This also shows that the thiol state is very important in the pathogenesis of oxidative stress-mediated diseases. Therefore, it is thought that interventions that can improve thiol status may contribute to the prevention or treatment of oxidative stress-related diseases.

Keywords: antioxidant, glutathione, oxidative stress, oxidative stress-mediated disorders, taurine, thiol-disulphide homeostasis, thioredoxin

1. Introduction

Oxygen is a potentially toxic molecule, although the aerobic organisms must survive. During biochemical reactions vital to living organisms, oxygen reduced, resulting in intermediate metabolic products known as reactive oxygen species (ROS), which cause oxidative damage to many tissues. ROS is called “oxidant” or “free radical” due to the oxidative destruction they create and form in all living organisms that metabolize molecular oxygen [1] Free radicals are very short-lived reagents, separating other electrons around high-energy electrons and disrupting their structure. Therefore, free radicals are dangerous to the organism [2, 3].

There are many defense mechanisms in the organism to prevent ROS formation and the damage caused by them. These mechanisms are generally called “antioxidant defence systems” or “antioxidants” for shortly [4]. Antioxidants serve in the body by controlling the metabolization and levels of free radicals formed as a result of normal metabolism or pathological conditions and preventing or repairing the damage that may occur by these radicals [5, 6]. In the living organism, there is a balance between the rate of formation and elimination of free radicals. This balance is called the “oxidative balance” that prevents the body from being affected by free radicals. If the oxidative balance is disturbed in favor of free

radicals, oxidative stress occurs, which is one of the factors that ultimately causes damage to cells and tissues [7, 8].

All biomolecules are subject to free radical attack. But among them, lipids are the most easily affected [9]. The membranes and cell organelles that surround the cells contain a large amount of unsaturated fatty acids (PUFA). Due to the high affinity of the oxygen molecule to PUFA in the cell membrane, there is a close relationship between the two. Oxygen binds to double ligaments in PUFA found in tissues, causing lipid peroxidation [10, 11]. Lipid peroxidation is a harmful chain reaction. It can directly damage the membrane structure or damages by producing reactive aldehydes. These compounds are either metabolized at the cell or diffuse damage from initial domains to other parts. Thus, the structure of lipids in the cell membrane is disturbed, permeability for ions increases and cell death occurs [12].

Reactive nitrogen species (RNS) are another reactive species group that is as important as ROS. Nitric oxide (NO), a free radical, is the most substantial member of this group. It has the ability to directly or indirectly affect cells and tissues. As it can directly affect itself, while indirect are mediated RNS produced the interaction of NO with superoxide radicals ($O_2^{-\bullet}$) or oxygen (O_2). Most of its direct physiological effects are cyclic guanosine 3′,5’monophosphate-mediated (cGMP). It can also interact with proteins containing iron and zinc or create S-nitrosothiols through nitrosylation [2, 13–17]. Many antioxidants work in the organism to prevent damage caused by ROS and RNS. Antioxidants, present in considerably lower concentrations than the substrate, are substances that can protect an oxidation-sensitive substrate from peroxidative damage. Biological antioxidants contain all compounds that protect cellular lipids, proteins and nucleic acids from peroxidative damage. One of these compounds is thiols. Thiols play a crucial biologic role among these compounds due to their capacity to react with free radicals and their strong reducing capabilities [18].

Thiols are a member of the class of organic compounds containing sulfhydryl group (-SH). They consist of a hydrogen atom and a sulfur atom attached to a carbon atom [19]. In the organism, in the oxidation created by ROS, excess electrons pass to thiols and disulphide bonds are formed. Due to the oxidative balance, electrons in these reversible bonds can return to thiols. The antioxidant ability of thiol-disulphide homeostasis is important in enzymatic reactions, signal transduction, detoxification, transcription, regulation of enzymatic activation, cellular signaling mechanisms and apoptosis reaction [20–22]. With these in mind, in this chapter, reactive oxygen species, nitric oxide, lipid peroxidation, oxidative stress and the role of thiols in antioxidant defense is summarized and has been explained how thiol status changes in conditions associated with oxidative stress.

2. Biochemistry of reactive oxygen and nitrogen species

Free radicals and non-radical intermediates are commonly referred to as ROS. Species that contain unpaired electrons are free radicals. Species with unpaired electrons in their structure are free radicals, and because of this unpaired electron shell, free radicals have high reactivity. The most important sources of free radicals in biological systems are oxygen and nitrogen [23]. In the electron transfer chain, cells constantly convert small amounts of O_2 to ROS. ROS can be produced in many ways in the organism, including the respiratory burst that occurs in active phagocytes [24]. Respiratory burst, also known as “oxidative burst”, is the event of a rapid release of ROS such as $O_2^{-\bullet}$ and hydrogen peroxide (H_2O_2) from different cell types. Generally, these chemicals are produced by immune system cells such as neutrophils and macrophages as a result of infection of the organism by bacteria

and fungi [25, 26]. In phagocytes, the respiratory burst that occurs to break down bacteria plays an important role in the immune system. $O_2^{-\bullet}$ is produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a family of enzymes commonly found in many cells. In neutrophils and monocytes, myeloperoxidase is involved in combining H_2O_2 with CI-to produce hypochlorite, which plays a role in destroying bacteria [25].

Reactive oxygen species formation, as natural result of aerobic metabolism, has an important role in maintaining tissue oxygen homeostasis. $O_2^{-\bullet}$, H_2O_2 and hydroxyl ($^{\bullet}OH$) radicals are produced in mitochondria as normal metabolic by-products. Other important intracellular sources of ROS are peroxisomal enzymes, flavoprotein oxidases and microsomal cytochrome P450 enzymes [27]. ROS also play an important role in various physiological processes such as the functioning of normal vascular cells and maintenance of vessel diameter regulation [28]. It is stated that in biological systems, ROS participate in differentiation, proliferation, growth, apoptosis, cytoskeleton, migration and contraction regulation and play a role in the control of inflammatory response by stimulation of growth factor [29, 30].

Mitochondria are the main source of the $O_2^{-\bullet}$ anion most commonly found under physiological conditions. [31]. The $O_2^{-\bullet}$ anion is formed by adding an electron to dioxygen. However, it is unstable because it can react spontaneously in aqueous solutions and convert into H_2O_2 and O_2. [32]. In the respiratory chain, in particular, the $O_2^{-\bullet}$ anion is formed by the leakage of electrons from complex I and III into O_2. The rate of formation depends on the number of electrons and increases with hyperoxia and high glucose concentration. The decrease in oxygen availability, acting as the final electron acceptor for complex IV, causes the accumulation of electrons. Because the $O_2^{-\bullet}$ anion is charged, it cannot pass through the membrane and remains in the mitochondrial matrix [23]. $O_2^{-\bullet}$ anion can convert to O_2 by reducing Fe^{3+} ion to Fe^{2+}. $O_2^{-\bullet}$ is detoxified with superoxide dismutase (SOD) enzymes and converted into H_2O_2 [32, 33].

Hydrogen peroxide is not a free radical, but it is mentioned in ROS because it is closely related to the detoxification or generation of free radicals [32]. It is not polar, so it can easily pass through the membranes of cells and organelles and therefore acts as a secondary messenger in a wide range of signal transduction pathways. It is detoxified into the water by catalase (CAT) and glutathione peroxidase (GPx). Imbalances in $O_2^{-\bullet}$ and H_2O_2 levels can result in the formation of $^{\bullet}OH$ radicals, which are far more dangerous than them [4]. The main source of the $^{\bullet}OH$ radical is metal-catalyzed Haber-weiss reaction [34] and the second source is the Fenton-type reaction [35]. It has been reported that the $^{\bullet}OH$ radical can react with any biological molecule in its immediate vicinity and there is no known scavenger because it is very reactive [23].

2.1 Nitric oxide

Nitric oxide is produced during the reaction which arginine is converted to citrulline catalyzed by nitric oxide synthase (NOS) which is NADPH-dependent enzyme [36, 37]. There are three isoforms of NOS: neuronal (nNOS) endothelial (eNOS) and inducible (iNOS) and it is known to be present in every cell component [17, 38]. NO is an uncharged lipophilic molecule containing unpaired electron. Although NO is not a highly reactive radical, it is important in that it can form other reactive intermediates that have an impact on protein function and the function of all organisms, as well as trigger nitrosative damage in biomolecules [39]. Therefore; it can function as an antioxidant or as an oxidant. NO, blood pressure regulator and a neurotransmitter, can produce powerful oxidants during pathological conditions [28].

The interaction of excessive amounts of $O_2^{-\bullet}$ anion with NO leads to the formation of the peroxynitrite anion ($ONOO^-$). $ONOO^-$, a cytotoxic radical, causes tissue damage and oxidizes low-density lipoproteins (LDL) [4, 40, 41]. It can also directly cause protein oxidation and DNA oxidation. $ONOO^-$ can form prooxidant nitrogen dioxide (NO_2) and $^{\bullet}OH$ by self-decomposition [42]. It is suggested that NO can increase the production of reactive oxygen and nitrogen species and inhibit cytochrome C oxidase in mitochondria, which can alter the activity of various processes such as respiration, mitochondrial biogenesis and oxidative stress [37]. It plays a critical role in inflammation-related carcinogenesis by activating the redox-sensitive transcription factor with nitrosative stress caused by NO, which has an important regulatory role for cellular functions. It is stated that by increasing the level of NO in plasma, it can reduce the concentration of uric acid and ascorbic acid and cause lipid peroxidation [28].

3. Lipid peroxidation

Reactive oxygen species, produced in mitochondria and extramitochondrial regions, react with polyunsaturated fatty acids (PUFA) found in complex lipids and lipoproteins, such as phospholipids found in cellular membranes, which are highly sensitive to oxidative changes. The process that causes degradation of PUFAs by chemically modified by ROS is called lipid peroxidation [43].

Lipid peroxidation in membranes is initiated by the contribution of ROS or separation of the hydrogen atom by ROS from the methylene group located between two double bonds in the PUFA. Conjugated dienes made up of PUFA react with oxygen present in the membranes at a very high rate and form a peroxyl radical ($ROO^{\bullet}$). Since $ROO^{\bullet}$ radicals are particularly highly reactive to neighboring PUFA chains, they spread the lipid peroxidation process by removing hydrogen from them. In this reaction, carbon centred radicals and lipid hydroperoxide are formed. Lipid peroxides can react with transition metal ions (iron, copper ions) to form alkoxyl radicals ($RO^{\bullet}$) [4, 44]. Metal ions can cause the lipid peroxide molecule to become unstable, leading to its degradation into smaller products. These products range from simple hydrocarbons to various ketones and aldehydes. The decomposition products of lipid peroxides are aldehydes such as malondialdehyde (MDA), acrolein, 4-hydroxy-2-hexenal (HHE) and 4-hydroxy-2-nonenal (HNE) [43, 45]. Commonly used lipid peroxidation markers are MDA and HNE. HNE is formed as a peroxidation product of omega-6 unsaturated fatty acids, while MDA is essentially a PUFA peroxidation product with more than two double bonds such as arachidonic acid [4].

Biomolecules undergo a lipoxidation reaction by lipid peroxidation end products such as MDA, 4-HNE and acrolein. Irreversible nonenzymatic modifications occur when these products react with lysyl (ε-NH_2), histidyl (imidazole) and cysteinyl (-SH) groups in the polypeptide chain. MDA-lysine and HNE-protein compounds formed by lipoxidation are called advanced lipoxidation end-products (ALE) [46–48].

4. Antioxidant defense system

Antioxidants, when present in low concentrations, are generally defined as substances that significantly inhibit or delay oxidative processes while they oxidize themselves, in relation to oxidizable substrates [49]. They neutralize free radicals and oxidize themselves by accepting highly reactive unpaired electrons [4]. Various

transcription factors in the human body are activated or inhibited depending on the relative oxidant/antioxidant ratio. Thus, many signal paths are controlled by redox balance. The endogenous defense system consists of antioxidant compounds and specific enzymes that catalyze their antioxidant activities. There are a wide variety of powerful antioxidants that cells use, such as vitamins (C, E, A) and enzymes (CAT, GPx, SOD and thioredoxin reductase). Other non-enzymatic antioxidants available to cells include GSH, α-lipoic acid, taurine and coenzyme Q10, carotenoids and polyphenols. Especially GSH and taurine, which are thiol antioxidants, are of great importance in maintaining the redox balance [50–53].

4.1 Thiols and some of the important thiol antioxidants

Thiols are biological mercaptans (R-SH), while biological mercaptans are called biothiols. Biothiols can be classified as low molecular weight free thiols and large molecular weight protein thiols. Thiols found in biological systems play a role in the coordination of antioxidant defense systems [54]. It contains protein thiols in plasma, protein sulfhydryl groups and protein mix disulphides consisting of cysteine, cysteinylglycine, homocysteine and GSH. These thiols are also available in the form of low molecular mass disulphides, homocystine, cystinylglycine, cystine and GSSG. [19]. While GSH/GSSG, especially in reduced form, consists of the low molecular weight sulfhydryl/disulphide pool inside the cell, cysteine/cystine in the form of disulphide in plasma and outside the cell as a whole [55]. It has been reported that dynamic thiol disulphide balance plays a crucial role in antioxidant system [20]. Total thiol (TT), especially protein thiol (-SH) groups in the body are considered as the main plasma antioxidants of the living organism. Most of these thiol (-SH) groups are found in albumin and constitute the major reducing groups found in body fluids [56].

Thiols play important physiological roles in processes requiring sulfur and are highly reactive, the -SH groups are readily oxidized or reduced in the presence of a catalyst [57–59]. Thiols can act as electron acceptors, reducing unstable free radicals by oxidizing, so they are powerful antioxidants. Despite their high reactivity, thiols' antioxidant potential depends on environmental, structural and catalytic factors [60–62].

Cysteine can be synthesized endogenously from methionine. Methionine, an essential amino acid in the diet, is endogenously metabolized to homocysteine and then to cysteine; Its conversion is rate limited by a few enzymes [63]. As an amino acid, cysteine has important structural roles and can bind thiol side chains to metals such as zinc, copper and iron, which are crucial for enzymatic functions. The thiol side chain of cysteine also allows it to be included in the tri-peptide thiol antioxidant GSH. Besides, cysteine metabolism through the cysteine-sulfinic acid pathway can generate taurine, although enzymatically the rate is limited, this pathway is much more complex than that of GSH [64, 65]. Both GSH and taurine are formed from cysteine with bioactive thiol groups. Although intermediate levels of cysteine are important for cellular signaling pathways, high plasma levels have been associated with cardiovascular and neurological diseases [66–68]. Additionally, high intracellular levels can increase oxidative DNA damage through the Fenton reaction [69].

4.1.1 Thioredoxin system

Thioredoxin (Trx) was first discovered in E.coli in 1964 [70]. Trx's are proteins that act as regulators in redox reactions and are found in all eukaryotic and prokaryotic organisms [71]. The Cys-Gly-Pro-Cys division is located in its active region [72].

Cytosolic thioredoxin-1 (Trx1) and mitochondrial thioredoxin-2 (Trx2) are part of the thioredoxin system, an essential and important antioxidant system for the maintenance of intracellular redox state, and play an important role in cellular redox balance and normal cell and tumor cell signaling [73, 74]. Trx exerts its antioxidant effects primarily by acting as an electron donor for peroxiredoxins. Trx is a small molecular weight protein that functions as an antioxidant by facilitating the reduction of other proteins containing the thiol (-SH) group via cysteine thiol-disulphide (-S-S-) exchange, and ribonucleotide reductase, an essential enzyme in the replication of deoxyribonucleic acid (DNA) for a hydrogen donor [75].

Thioredoxin reductases (TrxR) is a member of the flavoprotein family of pyridine nucleotide-disulphide oxidoreductases such as glutathione reductase (GSR), lipoamide dehydrogenase, mercury ion reductases [75, 76]. Members of this family include the active site in each monomer comprising the FAD, NADPH binding site and redox-active disulphide. It has a selenocysteine residue in its active site [73]. The disulphides in the active part of the TrxR reduce the substrate by catalyzing the electron transfer from NADPH to FAD. TrxRs reduce the thioredoxin protein containing two different cysteine amino acids (Trx1; Cys32 and Cys35, Trx2; Cys31 and Cys34) in its catalytic region. TrxRs have been reported to be associated with lipoic acid, lipid hydroperoxidase, cytotoxic and antibacterial polypeptide NK-lysin, dehydroascorbic acid, vitamin K, ascorbyl free radical, tumor suppressor protein p53 as well as Trx protein [71, 76–80]. It has been stated that mammalian thioredoxin reductase has three different isoenzymes, cytosolic TrxR1, mitochondrial TrxR2 and TrxR3, which is specific to testicles containing glutaredoxin region in the N terminal region [81].

Thioredoxin system has various roles in organisms and reflects the importance of the -SH group together with disulphide (-S-S-) in many reactions that are crucial in cell regulation [82]. It was previously thought that Trx was mainly involved in protecting against oxidative stress, scavenging ROS through its interaction with peroxiredoxin and working to control cellular redox balance. As a result of the studies, it has been shown that Trx contributes to redox-dependent cellular processes such as signal transduction, gene expression, apoptosis and cell growth [83, 84]. The reduced Trx binds apoptosis signal kinase-1 (ASK-1) and stops apoptosis [85]. Trx is released in response to oxidative stress and extracellular Trx exerts cytoprotective effects in inflammatory and oxidative conditions [86].

4.1.2 Glutathione system

Glutathione (GSH = γ-glutamylcysteinylglycine) is abundant in the human body. It is a tripeptide synthesized from three amino acids (cysteine, glycine and glutamate). It is a low molecular weight intracellular thiol compound and is mostly synthesized in the liver and is found in all cell types. As the regulator of intracellular redox homeostasis, most of it is stored in reduced form in the nucleus, endoplasmic reticulum, and mitochondria. The thiol group (-SH) of glutathione reduces the number of free radicals by binding to the un-shared electrons of free radicals formed as a result of oxidative stress. There are two forms in the organism: reduced (GSH) and oxidized (GSSG). The thiol-containing cysteine molecule in GSH, which is predominantly in the cell, allows ROS to take part in antioxidant roles by taking part in both degradation and removal [87–89].

The glutathione system acts as a leading cellular defense mechanism against oxidants. GSH is not only a direct ROS scavenger but also an antioxidant that has an important act in the regulation of intracellular redox status. The system consists of GPx, GSR and GSH. GSH retains its antioxidant ability in its reduced form. GPx catalyzes the reduction of H2O2 to water using GSH as a cosubstrate. GSSG is then reduced to GSH by GSR using NADPH. The cycle between these two states aids in

free radical and toxic substance metabolism. The GSH/GSSG ratio is considered a sign of the redox state and relative oxidative stress level. The capability of organisms to regenerate GSH (through the synthesis of GSH or through reduction of GSSG) means the cell's success to withstand oxidative stress [90, 91].

The ability of GSH to act as an antioxidant is due to the thiol-containing cysteine part. GSH is located on both the first and second lines of ROS defense and requires GPx enzymes to catalyze the breakdown of H_2O_2 through the reduction of GSH to GSSG. GPx (GPx1), selenium-dependent, is found in the kidneys and mitochondria [92, 93]. Four other GSH peroxidases (GPx2-GPx5) have also been discovered, along with evidence of antioxidant properties in vivo [94]. Detoxified metabolites resulting from GPx defense are excreted from the cell via a glutathione S-conjugate transporter [87]. It has been reported that administration of a GSH enzyme inhibitor in rats reduces vitamin C levels in the kidney, liver, brain and lung [95]. It has been noted that GSH administration increases both vitamins C and E [96]. It is stated that vitamin C deficiency significantly decreases GSH levels in the blood [97], while vitamin C supplementation contributes to the formation of GSH [98].

4.1.3 Taurine

Cysteine can be metabolized to taurine, intracellular sulfonic acid, via cysteine-sulfinic acid. Taurine or 2-aminoethanesulfonic acid is abundant in the human body. Since there is not a carboxyl group in its structure, it is not an amino acid in theory, but it is usually referred to as proteins [99, 100]. As a result of this condition, it is released in the plasma of mammals and inside the cell [101]. Taurine is most often found where reduced O_2 molecules are produced and in locations where potentially toxic substances such as xenobiotics, retinoids and bile acids are found [102]. It is also found in high levels in white blood cells and platelets [103].

Although the mechanisms of taurine's antioxidant effects are not fully explained, possible mechanisms include regeneration of thiol groups, interfering with ROS activity and scavenging ROS [104]. It has been reported that Taurine suppresses superoxide production in mitochondria [105]. In general, taurine causes a significant reduction in ROS formation through its stimulatory effect on SOD, CAT and GPx enzyme activity [106–108]. Besides, taurine also contributes to the regulation of GSH concentrations. [109]. It is thought that taurine has limited or no direct scavenging and reaction ability with ROS, and shows its antioxidant effect by increasing the activities of antioxidant enzymes such as GPx and SOD [110, 111]. It has been recorded that taurine indirectly increases endogenous GSH levels. [112]. Studies have shown that taurine supplementation reduces lipid peroxidation and maintains GSH levels [113, 114].

Taurine can also inhibit free radical generation. Taurine's amino group is the direct scavenger of hypochlorous acid (HOCl) [105]. In the presence of myeloperoxidase, taurine reacts with the acid to form a less toxic oxidant, taurine chloramine (TauCl). Since neutrophils contain high levels of taurine, TauCl formation can continue as long as there is enough taurine [115]. TauCl not only plays a role in antioxidant systems by lowering HOCl levels but also inhibits O2 production and proinflammatory mediators in neutrophils and macrophages [115, 116].

5. Thiol status in oxidative stress-related various diseases

Thiol state and thiol-disulphide balance, which is an antioxidant defense system, may change due to oxidative stress in some diseases that may occur in various systems, organs and tissues in the organism.

5.1 Thiol status in digestive system diseases

In diseases of the digestive system, significant changes are observed in thiol state. For example, ROS formation in the liver increases due to alcohol intake. In this situation, serum protein thiol levels of alcohol drinkers decrease [117, 118]. It has also been determined that the level of thiol in the gallbladder increases in various gastrointestinal diseases [119]. A study showed that serum -SH levels of patients with helicobacter pylorus were significantly decreased [120]. Some studies have shown that native thiol (NT) and total thiol (TT) levels decrease and disulphide levels increase in celiac disease, acute pancreatitis, and inflammatory bowel disease [121–123]. In addition, the serum free thiol level has determined that non - alcoholic fatty liver disease (NAFLD) is associated with death from all causes in people with suspected NAFLD [124]. Impaired thiol-disulphide homeostasis has been reported in patients with hepatitis-B-induced chronic hepatitis and liver cirrhosis [125]. Again, in liver damage caused by pesticides, the thiol level was decreased, whereas black tea extract was found to improve thiol level in the liver tissue [126]. In experimental gastric damage induced by indomethacin, a non-steroidal anti-inflammatory drug, it was observed that ellagic acid treatment increased GSH levels and played a role in protecting against the harmful effects of indomethacin by reducing oxidative stress [127].

5.2 Thiol status in cardiovascular system diseases

Another situation in which thiol status changes is cardiovascular diseases. For example, in a study in preeclamptic patients characterized by high blood pressure, it was determined that the buffering function of SNO-albumin was impaired in patients in which the thiol of albumin acts as a scavenger for NO [128]. It was also observed that serum NT and TT levels of patients who had a heart attack decreased [129, 130]. In a study, it was determined that the level of mitochondria-specific thioredoxin increased, which increases NO bioavailability and reduces oxidative stress, thus protecting vascular endothelial cell function and preventing the development of atherosclerosis [131]. In rabbits, after experimental ischemia–reperfusion, it has been reported that thiol redox balance is impaired in myocardial cells and this causes abnormalities in cell function [132]. It has been reported that in case of cardiac damage caused by cyclophosphamide, thiol level decreases, but lupeol and its esters increase thiol level [133]. In sheep babesiosis, a tick-borne hemiparasitic disease, the parasite settles in the erythrocytes and causes a decrease in GSH levels in the blood. Therefore, the decrease in GSH levels indicates that excessive amounts of ROS are formed in cells [134].

5.3 Thiol status in nervous system diseases

In Parkinson's disease, oxidative stress plays an important role in the degeneration of dopaminergic neurons in the substantia nigra (SN) of patients. It was determined that the thiol antioxidant glutathione (GSH) significantly decreased in the neurons present in Substantia nigra and mitochondrial damage occurred as a result of this decrease [135, 136]. It has been observed that plasma GSH, C-SH and CG-SH levels decrease in patients with schizophrenia. However, it has been observed that Curcumin administration caused a significant increase in GSH level [137, 138]. It has been determined that TT and NT concentrations are decreased in Alzheimer's patients [139]. In the experimental Parkinson model with 6-hydroxydopamine, it was observed that the thiol level in the brain tissue decreased and the application of biarum carduchrum extract increased the thiol level [140]. In another

study, hesperidin administration in 6-hydroxydopamine-induced Parkinson's model was reported to improve thiol level in brain tissue [141].

5.4 Thiol status in urinary system diseases

Studies have shown that thiol status changes in excretory system diseases. A decrease in thiol status has been reported in chronic kidney disease [142, 143]. There was a negative correlation between serum creatine level and protein thiol level. This is an indicator that serum protein thiol level will decrease in case of renal failure [144]. It has been reported that plasma protein thiol level decreases in nephrotic syndrome [145]. In another study, it was revealed that the thiol-sulphide balance decreased and this balance shifted towards disulphide in patients with acute renal failure, and the decrease in total and native thiol concentrations was associated with the severity of the disease [146]. In renal damage induced by dimethylnitrosamine, thiol level in kidney tissue decreased, whereas Simvastatin (SMN) administration improved thiol level in kidney tissue, while Thymoquinone administration was found to have no effect on thiol level [147].

5.5 Thiol status in reproductive system diseases

In polycystic ovary syndrome study, it has been observed that native thiol, total thiol, disulphide levels in the ovary tissues of patients with polycystic ovary syndrome do not change compared to the control group [148]. It has been determined that arsenic and imidocarb reduce the total thiol level in the testicular tissue of rats with testicular damage [149]. In a study, it was concluded that chemotherapeutic agents cause ovarian damage in women and that the reduction of thiol level is very important in the mechanism of this damage [150].

5.6 Thiol status in metabolic diseases

In gestational diabetes, it was determined that pregnant women with gestational diabetes have higher disulphide/natural thiol and disulphide/total thiol levels compared to healthy pregnant women [151]. In addition, in a study, in the case of diabetic nephropathy, natural thiol and total thiol levels decreased [152]. In the pathogenesis of diabetic ketoacidosis, thiol/disulphide balance changed in favor of thiol and significant decreases in disulphide level were observed [153]. Diabetic cats have been reported to have lower erythrocyte membrane thiol level than control [154]. It has been determined that thiol/disulphide homeostasis is impaired in obesity [155].

5.7 Thiol status in respiratory system diseases

In experimental asthma disease, it was determined that inflammation in the lung tissue of rats with experimental asthma increased and thiol level decreased, On the other hand, it was determined that the application of Hydro-Ethanolic Extract of *Portulaca oleracea* increased thiol level [156]. It has been reported that oxidative stress occurs during acute pulmonary inflammation induced experimentally in rats and is associated with systemic thiol homeostasis [157].

5.8 Thiol status in cancer

A study in Norway shows that thiols play a preventive role against the development of the most common breast, lung, colorectal and prostate cancers [158].

It has been determined that thiol/disulphide homeostasis plays a crucial role in the pathogenesis of cervical cancer [159]. In one study, it was reported that disruption of thiol disulphide balance is likely to contribute to the etiopathogenesis of endometrial cancer [160]. In addition, it has been stated that irregularities in thiol/disulphide homeostasis may act a part in the pathogenesis of gastric cancer, and a higher oxidative stress level may cause advanced disease to become widespread and aggressive [161].

6. Conclusion

As a result, oxidative stress can cause serious damage to the cell. Thiol is a very important antioxidant in preventing oxidative stress-induced damage and protects the cell against oxidative stress. Glutathione and taurine are among the important thiols. It is observed that thiol status changes in various diseases and thiol/disulphide homeostasis is very important in the pathogenesis of various diseases such as digestive system, respiratory system, reproductive system, urinary system, metabolic diseases and cancer. This also shows that thiol state is very important in the pathogenesis of oxidative stress-mediated diseases. Therefore, it is thought that interventions that can improve thiol status may contribute to the prevention or treatment of oxidative stress-related diseases.

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