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Cellular Red-Ox system in health and disease: The latest update

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ABSTRACT

Cells are continually exposed to reactive oxygen species (ROS) generated during cellular metabolism. Apoptosis, necrosis, and autophagy are biological processes involving a feedback cycle that causes ROS molecules to induce oxidative stress. To adapt to ROS exposure, living cells develop various defense mechanisms to neutralize and use ROS as a signaling molecule. The cellular redox networks combine signaling pathways that regulate cell metabolism, energy, cell survival, and cell death. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are essential antioxidant enzymes that are required for scavenging ROS in various cell compartments and response to stressful situations. Among the non-enzymatic defenses, vitamin C, glutathione (GSH), polyphenols, carotenoids, vitamin E, etc., are also essential. This review article describes how ROS are produced as byproducts of oxidation/reduction (redox) processes and how the antioxidants defense system is directly or indirectly engaged in scavenging ROS. In addition, we used computational methods to determine the comparative profile of binding energies of several antioxidants with antioxidant enzymes. The computational analysis demonstrates that antioxidants with a high affinity for antioxidant enzymes regulate their structures.

1. Introduction

Living cells generate reactive oxygen species (ROS) as a metabolic byproduct. Under high-stress conditions, cells produce a large number of ROS. Consequently, living organisms evolutionary acquire a set of response mechanisms to adapt to ROS exposure and use it as a signaling molecule. Endogenous and physiological ROS are mainly produced as byproducts of normal cellular metabolism during the oxidative reaction process of the mitochondrial respiratory chain [1]. Moderate levels of ROS have beneficial effects such as pathogen killing, wound healing, and mending activities [2].

On the other hand, ROS molecules would cause oxidative stress as part of a feedback mechanism involving several biological processes such as apoptosis, necrosis, and autophagy. Overproduction of ROS can disrupt the structure of organelles and biomolecules, resulting in an inflammatory response, which is the critical mechanism for developing diabetes and cancer. Growing evidence suggests ROS is vital as signaling molecules throughout the cell death cascade [3]. The primary source of oxidative stress indicators, cytochrome P450 enzymes (CYP) convert hazardous metabolites into ROS, such as superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide(H_2O_2), and hydroxyl radical (OH^-), which can cause cell damage [4]. As a result, cells have evolved a balanced system to neutralize excess ROS levels via enzymatic and non-enzymatic antioxidant defense action. The primary antioxidant systems include enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thioredoxin (Trx), as well as non-enzymatic antioxidants such as vitamin C, E, catechin, curcumin, and carotenoids, which collectively reduce the oxidative state (Fig. 1). Although catechin and curcumin possess direct antioxidant activity, recent research has revealed that this activity is not necessarily the primary mechanism of their biological activity. Instead, they are believed to exert their effects via various signaling pathways that regulate gene expression, cell cycle progression, and inflammation. Furthermore, they may act as pro-oxidants under certain conditions, inducing oxidative stress in cancer cells and contributing to their death. However, enzymatic antioxidants provide more effective protection against oxidative assaults due to their ability to degrade ROS [4].

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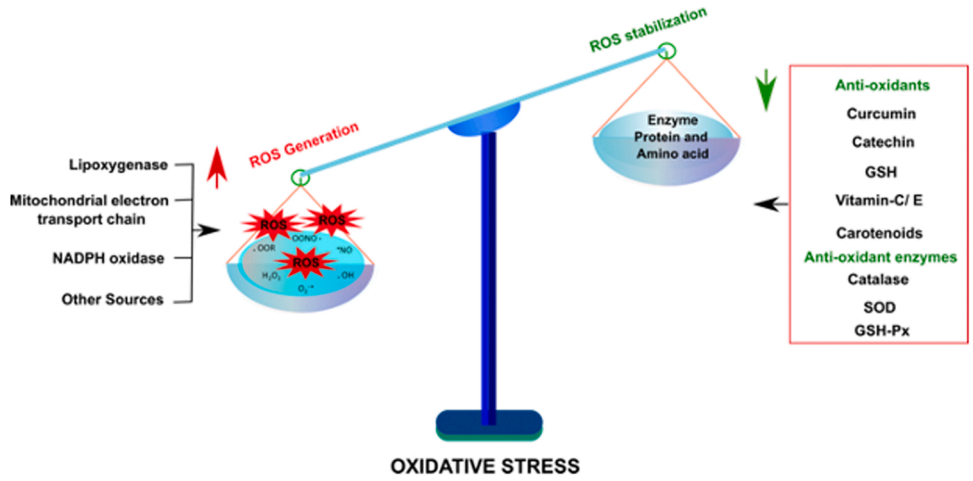

Fig. 1. Imbalance between ROS and anti-oxidants causes Oxidative stress.

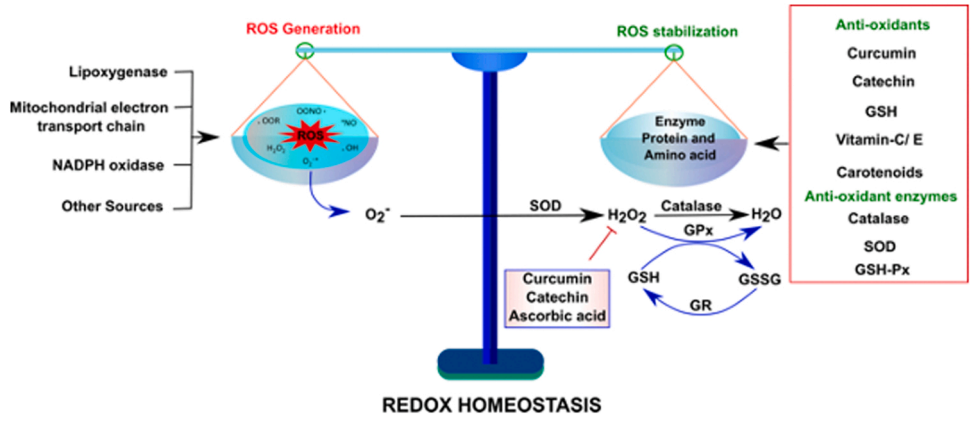

Fig. 2. Mechanism of redox homeostasis. The balance between ROS and exogenous and endogenous anti-oxidants.

2. Redox balance

Cellular redox balance, an oxidant/antioxidant equilibrium condition, greatly influences cell viability, proliferation, differentiation, bioenergetics, and apoptosis. This is greatly aided by redox-dependent post-translational protein changes, which modify their functional activity [5]. The body maintains a continual balance of oxidants and antioxidants, maintaining "redox homeostasis" (Fig. 2). Therefore the generation of ROS increases, body's response boosts the activity of endogenous antioxidant systems via a redox signaling pathway [6]. Furthermore, antioxidants may be generated from exogenous sources; these exogenous antioxidants and the endogenous antioxidant system play a crucial role in maintaining redox equilibrium. Endogenous antioxidant systems include antioxidant enzymes (such as CAT, SOD, and GPx) as well as antioxidant compounds (e.g., GSH and Trx) [7].

3. Oxidative stress and diseases

Essentially, life evolved without oxygen throughout the early phases of the prehistoric period. However, when oxygen-producing living forms evolved, the amount of oxygen in the atmosphere steadily grew. The species either started to build up resistance to oxidative stress or searched for environmental niches with low oxygen concentrations. Another key benefit was utilizing oxygen metabolically in synthetic and degradative processes and for oxidation-reduction type reactions and energy generation. However, ROS damage must also be considered with the preamble of an oxygen-rich environment. Therefore, it became necessary for organisms to build defenses against the leading causes of oxidative stress with the emergence of an oxygen-rich environment. As a result, enzymes were created to detoxify the most common oxidants.

ROS is often used to denote molecules that can lead to oxidative stress. Reactive species made of oxygen and nitrogen are involved in the chemistry of oxidative stress. ROS are crucial to both physiological and pathological processes. Since superoxide anion is formed when oxygen reacts with an electron that has migrated from the inner membrane of the electron transport chain, mitochondria are highly vulnerable to oxidative damage. Although this anion cannot traverse membranes due to its instability, it is quickly transformed into hydrogen peroxide, which allows passage through the membrane. The hydroxyl radical, produced by the Fenton reaction, is highly reactive in the mitochondrial matrix, which in the mitochondrial matrix has a high level of reactivity. Increased mitochondrial DNA (mtDNA) damage is caused by elevated ROS levels [8]. All macromolecules, including lipids, proteins, and nucleic acids, can be harmed by excessive ROS, which can cause an overall cumulative deterioration in physiological activity [9]. Oxidative stress causes disease primarily through two different mechanisms. The first is the direct oxidation of macromolecules, such as membrane lipids, structural proteins, enzymes, and nucleic acids, by reactive species produced during oxidative stress, especially •OH, ONOO, and HOCl, which results in abnormal cell function and death (Fig. 3). Aberrant redox signaling is the second mechanism of oxidative stress.

Numerous disorders, including atherosclerosis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease, and cancer, have demonstrated the involvement of oxidative stress, illuminating the

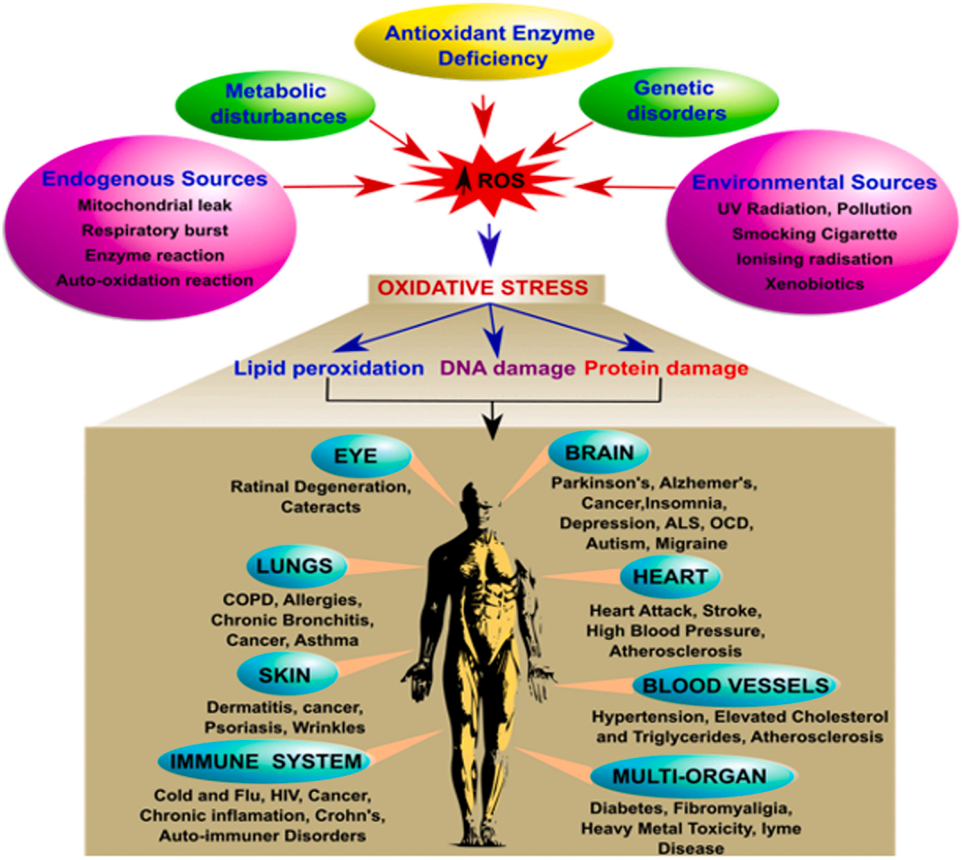

Fig. 3. ROS causes multiple diseases.

various processes by which oxidants contribute to cellular damage [10–13] (Fig. 3). A major contributing cause of toxicity and disease can be oxidative stress. A key caveat is that once damage occurs, antioxidant treatment frequently fails to stop the course of tissue harm as other variables take control of the pathophysiology [10].

It helps validate developing treatment methods for antioxidant defense by studying which ROS causes harm to macromolecules. Even though several small compounds tested as antioxidants showed therapeutic promise in preclinical research, clinical trial outcomes have been underwhelming. A more thorough comprehension of the processes by which antioxidants function and the conditions under which and when they are most effective may offer a logical framework that boosts pharmaceutical effectiveness.

4. Maintenance of cellular redox homeostasis by neutralization of ROS: roles of antioxidants

In addition to ROS, reactive nitrogen species (RNS) such as nitrogen dioxide (NO_2), nitric oxide (NO), dinitrogen trioxide (N_2O_3), peroxynitrite (OONO-), and nitrous acid (HNO_2) also contribute to the oxidative stress [14]. NO is formed by three separate isoforms of nitric oxide synthases (NOs), which catalyze the conversion of L-arginine to L-citrulline by generating NO [15]. Interestingly, NO has been shown to operate as a small molecule in activating AMP-activated protein kinase (AMPK), a vital kinase that regulates energy and metabolic balance homeostasis [16]. Cellular NO interacts with ROS to produce numerous RNS involved in oxidative and nitrosative damage [16]. Drugs, as well as natural antioxidants such as SOD, GPx, GSH, and vitamin E, have been identified that play an essential role in reducing the excess level of ROS. The inhibition of ROS-induced cell injury by natural antioxidants or synthetic chemicals should be studied further to understand better their potential use in treating diseases caused by excessive ROS exposure.

Antioxidants can neutralize oxidants and counteract free radicals (Fig. 2). Antioxidants may also be categorized according to their source, including endogenous production, such as enzymes and small molecules, and exogenous foods, such as phenolics, flavonoids, phenolic acids, carotenoids, vitamins, and minerals [17,18]. Non-enzymatic antioxidants include vitamins C and E, plant polyphenols (such as curcumin and catechin), carotenoids, and GSH [17,19]. As a result, this group of antioxidants plays critical roles in diseases such as acute hyperoxia damage, radiation injury, lung transplantation, and inflammation. Non-enzymatic antioxidants interfere with the chain reactions of free radicals [20]. The antioxidant systems, including enzymatic and non-enzymatic antioxidants, adjust the ROS level by modulating gene expression and associated signaling pathways to maintain redox balance and cellular component integrity. Therefore, antioxidant therapeutics will offer a viable method of preventing and treating diseases caused by excessive ROS exposure [18].

This paper reviews recent findings of ROS-induced cellular processes and the roles of endogenous cellular antioxidant systems and natural anti-oxidative compounds in preventing several human diseases caused by oxidative stress.

5. Repercussion of oxidative stress in the cellular environment

Oxidative stress is attributed to the imbalance between ROS levels and the availability and activity of antioxidants or antioxidant enzymes (Fig. 1). The imbalance is induced by increased generation of free radicals or decreased antioxidant activity [21]. However, oxidative stress plays a pivotal role in the development of pathogenesis of inflammatory airway diseases, asthma, chronic obstructive pulmonary disease (COPD), Alzheimer's disease, Parkinson's disease, and vascular dementia [22,23]. The current progression of these disorders necessitates the development of appropriate biomarkers to evaluate oxidative stress

in *vivo* conditions. The role of these biomarkers as an integrator and their high correlation with the pathophysiological process of the disease has been the prime focus for current researchers. The plausible biomarkers such as Malondialdehyde (MDA), hydrogen peroxide (H_2O_2), and isoprostanes (IsoPs) hydroxyl radicals (OH^-) evolved as potential predictors for prognosis or response to treat diseases associated with the severity [24].

5.1. Malondialdehyde (MDA)

MDA was formed through the decomposition of highly reactive lipid hydroperoxides during lipid peroxidation and acted as a promising marker of oxidative stress and an appropriate measurement of lifestyle-related diseases [25]. In many progressive disorders like cancer, asthma, chronic obstructive pulmonary disease, and cardiovascular diseases, MDA is the most frequently used biomarker; however, the high reactivity and its cross interactions with other biological fluids draw limitations as a reliable marker [26]. Earlier patients with bipolar disorder were examined with high serum levels of MDA than healthy control by showing increased susceptibility to oxidative stress [27]. The elevated MDA levels in oral squamous cell carcinoma plasma, serum, and saliva samples accurately reflect the increased oxidative stress level [28]. As a result, MDA evaluation expresses the degree of lipid peroxidation and free radical-mediated oxidative damage. MDA levels have previously been found to be elevated in inflamed periodontal tissue. They may play a role in the destructive processes of periodontitis, implying a role for ROS in periodontal pathogenesis [29].

Furthermore, MDA levels in the blood have been linked to mortality in Human immunodeficiency virus (HIV) patients [30]. At the same time, MDA contents in the diabetic group were significantly higher than those in the control group, while antioxidant enzymes like SOD activities were significantly lower in the diabetic group [31]. Finally, the critical role of MDA was linked to schizophrenic patients, where plasma MDA levels in both first-episode schizophrenics and chronic schizophrenic patients were significantly higher than in healthy individuals due to increased lipid peroxidation [32]. Hence, the study suggested the role of MDA as a valuable oxidative marker in different disease pathologies.

5.2. Hydrogen peroxide (H_2O_2)

H_2O_2 can also be a plausible oxidative biomarker due to its cryptic and synergetic influence on disorders induced by oxidative stress. However, the control balance of physiological intracellular H_2O_2 concentrations is critical for cell function and viability. Extracellular H_2O_2 levels can rise due to environmental stresses such as radiation, toxicants, tobacco smoke, immune system activity, or metabolic disorders in surrounding tissues [33]. In diseases like cancer, the cytoplasmic H_2O_2 level in cancer cells was hundreds of times lower than the extracellular level at high H_2O_2 concentrations. At the same time, the extracellular-to-intracellular gradient in normal cells was thousands of times more significant [34]. FMRFamide-related neuropeptide (FLP-1) secretion induced by mitochondrial H_2O_2 activates the oxidative stress response transcription factor SKN-1/Nrf2 in distal tissues, protecting animals from ROS-mediated toxicity, indicating that H_2O_2 plays a vital role in linking diet-induced changes in mitochondrial homeostasis with neuropeptide secretion [35]. The progression of diseases like vitiligo is

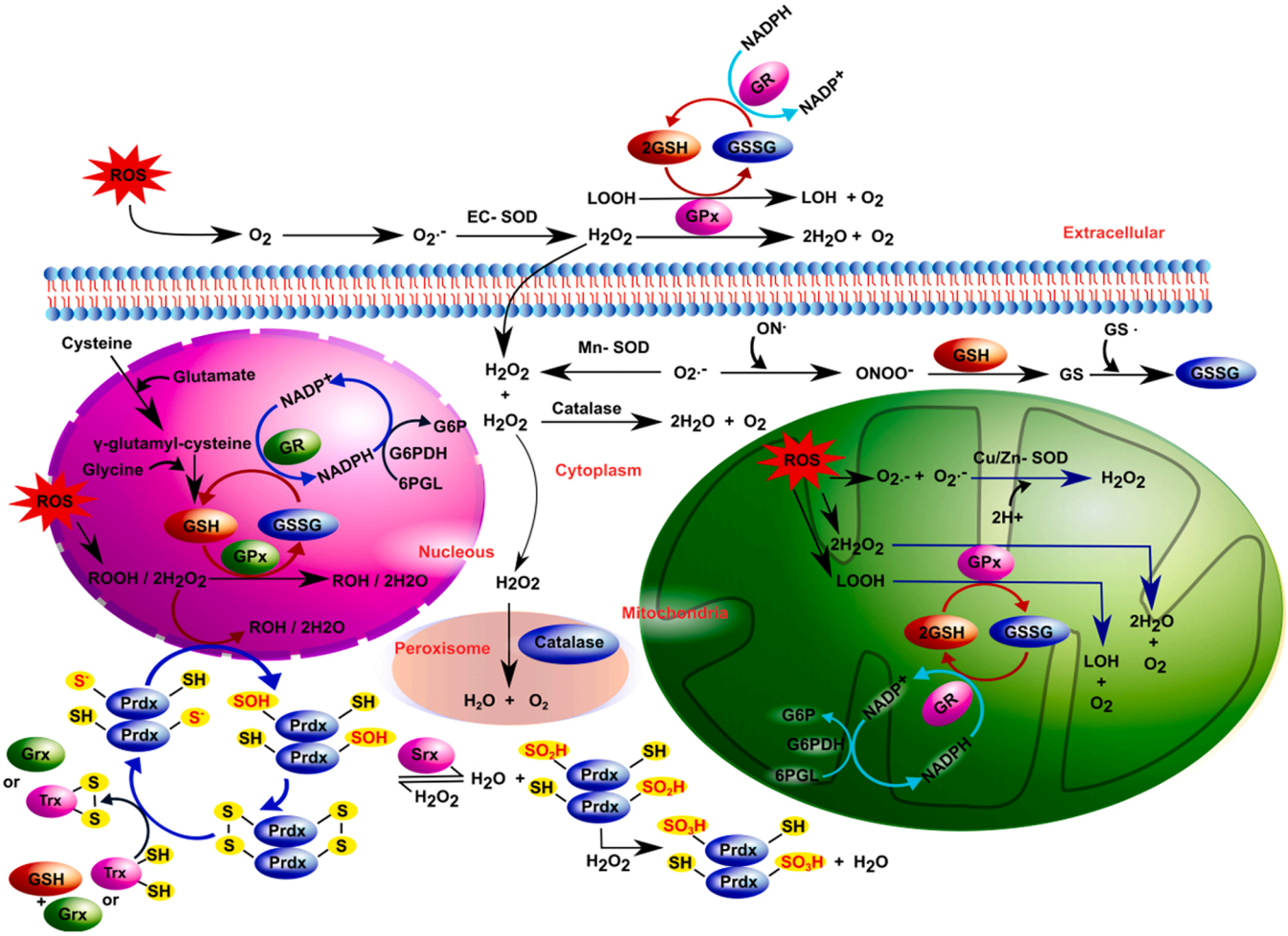

Fig. 4. The counteract defense action of enzymatic antioxidants against the free radicals.

also influenced by H_2O_2-induced oxidative stress where impaired activation of nuclear factor E2-related factor 2-antioxidant response element (Nrf2-ARE) pathway, elevated lipid peroxidation, CAT, and SOD was observed [36]. Since H_2O_2 has been established as an essential signaling molecule for the growth and regulation of the microbial, role of H_2O_2 is frequently endorsed to reduce the cyanobacterial abundance and organic pollutants because it is more effective with cyanobacteria than other phytoplankton [37]. The acute and chronic H_2O_2 treatments induced oxidative stress in HeLa cells by significantly decreasing aconitase and antioxidant enzyme activity [38]. However, H_2O_2 can freely cross membranes and is prone to participating in the Fenton reaction in the presence of Fe^{2+} (or Cu^{+}) [39]. Current researchers are particularly interested in the concentration- and time-dependent effects of H_2O_2-induced oxidative stress on MnSOD, Se: GPx, CAT, and aconitase.

5.3. Hydroxyl radical (OH˙)

The Fenton reaction, catalyzed by iron II (or copper I), can generate the $OH^{\cdot}$ radical, the three-electron reduction state of O_2, in vivo, which can react aggressively with organic and inorganic molecules resulting in more severe cell damage [40]. Furthermore, due to interactions between H_2O_2 and metal ions (Fe+2 or Cu+), which are frequently bound in complex forms with various proteins like ferritin or ceruloplasmin, OH• is produced in the Fenton reaction [41]. Excessive $O_2^{\bullet -}$ may cause these metal ions to break free from their corresponding complexes under stressful circumstances. The Haber-Weiss response involves interactions between O2•− and H2O2 and can also produce OH•. The $OH^{\cdot}$radical cannot be destroyed by an enzymatic reaction, unlike $O_2^{\bullet -}$ and H_2O_2, as this would require diffusion to the enzyme's active site. Since diffusion is slower than the half-life of the radical, the $OH^{\cdot}$ radical is neutralized by adverse interactions with any surrounding oxidizable molecules [42].

Furthermore, $OH^{\cdot}$ radicals can weaken disulfide bonds in proteins, particularly fibrinogen, causing them to unfold and refold abnormally with strange spatial arrangements [40]. The action of non-reducing substances can stop the consequences of this reaction, which are seen in many diseases like atherosclerosis, cancer, and neurological disorders [43]. The risk of cardiovascular disease is raised by forming $OH^{\cdot}$ radicals, which affect platelet activation and thrombosis in the blood vessels. The production of $O^{2\cdot}$ radicals is triggered by hyperglycemia, and these radicals can then combine with H_2O_2 to create $OH^{\cdot}$ radicals [44]. The $OH^{\cdot}$ radical reacts most readily with mtDNA. It can cause several DNA modifications, including strand breaks, the formation of abasic sites when bases from the deoxyribose backbone are broken, and the addition of oxygen to DNA to produce a variety of mutagenic molecules [45]. Hence, $OH^{\cdot}$ radical is not a key species participating in endogenous oxidative DNA damage but other disorders induced by oxidative damage.

5.4. Isoprostanes (IsoPs)

Isoprostanes are a class of prostaglandin-like compounds formed from arachidonic acid oxidation. They are produced by non-enzymatic lipid peroxidation and often act as important biomarkers of oxidative stress in humans and animals. Isoprostanes have been implicated in several physiological processes, including inflammation, vasoconstriction, and platelet aggregation [46]. The association of Isoprostanes as the marker of oxidative stressor was established in various diseases, such as atherosclerosis, cancer, and neurodegenerative disorders. Measuring levels of isoprostanes in biological fluids such as urine, blood, or cerebrospinal fluid can help assess oxidative stress and identify potential health risks [47]. Interestingly, recent findings highlighted the role of F2-isoprostane as an indicator, implying that F2-isoprostanes may contribute to obesity-induced cardiovascular risk in Black women by increasing inflammatory cytokine IL-6 production [48].

6. Enzymatic antioxidant enzymes: indispensable role in redox homeostasis

This review is centered on the major antioxidant enzymes, including catalases, SODs, peroxiredoxins (PRDXs), and GPXs, which work cooperatively to protect cells from an excess of ROS derived from endogenous metabolism or external hazardous microenvironment [49–51] (Fig. 4). The antioxidant enzymes react thousands to millions of times more rapidly with those oxidants than small molecules and provide the predominant antioxidant defense [10].

6.1. Catalase: has the highest turnover numbers of all enzymes

Among these enzymes, Catalase, one of the oldest known enzymes, has been studied extensively as a critical defense system in reactive oxygen and radical formation studies [52]. This multi-domain enzyme plays a vital role in the metabolism of H_2O_2 by disproportioning the toxic H_2O_2 into oxygen and water [49]. The excess cellular H_2O_2 leads to colonic inflammation in patients with ulcerative colitis and plays a significant role in developing sepsis conditions [53,54]. In addition, H_2O_2 formed other ROS, like $O^{2\cdot}$ and $OH^{\cdot}$ radicals [55]. These ROS mainly found to be highly lethal and causes extensive damage to protein, DNA, and lipids, thereby affecting normal cellular functioning [56]. Therefore, the primary goal is to understand the biological consequences of chronic exposure of cells to ROS and their counteraction by catalase which would enhance longevity and protect the functionality of the cells. Thus, the defense mechanism activation by catalase against ROS can lead to potential therapeutic extrapolation for various pathologies.

Several studies have elucidated the molecular mechanisms regulating catalase expression in response to increased levels of ROS in cancer cells [57]. Cancer cells have a higher metabolism than normal cells, producing a high level of ROS. Activators such as IB kinase (IKK) and NF-B induce continuous production and maintain higher ROS concentrations for a high rate of proliferation [58]. The higher proliferation rate enhances the processes of ageing and carcinogenesis by ROS-induced activation of the c-Jun N-terminal kinase (JNK) pathway. In addition, it induces the progression of mitochondrial dysfunction with subsequent initiation of apoptosis [58,59]. Therefore, manipulating ROS levels by redox modulation is essential to selectively inhibit cancer cell proliferation by implementing antioxidant enzymes. The potentiality of catalase during the acquisition of cancer cell resistance to chemotherapeutic agents was explored by over-expressing the human enzyme in MCF-7 cells [60]. Cells over-expressing catalase showed no specific resistance to conventional chemotherapies such as doxorubicin, cisplatin, and paclitaxel. Still, they were more resistant to the pro-oxidant effect induced by an H_2O_2-generating system [61]. Hence, targeting the redox status of cancer cells through modulation of catalase expression evolved as an emerging field in developing potentiate chemotherapy strategies.

Similarly, an examination of diabetic and acatalasemic patients revealed that diabetes patients have a higher frequency of catalase gene mutations [49]. Diabetes-associated compromised antioxidant systems lead to increased renal oxidative stress and hypertension, indicating an increased risk of type 2 diabetes mellitus in people with inherited catalase deficiency [62]. Certainly, catalase overexpression protected cardiomyocyte contractility in the agouti model of type 2 diabetes. Catalase deficiency demonstrated that both type 1 and type 2 diabetes cause damage at the level of individual myocytes via ROS utilization, which can be mitigated by catalase activation [49,63,64]. Catalase was found in mouse oocytes and is thought to protect the genome from oxidative damage during meiotic maturation [65]. As a requirement, catalase could play an essential role in detoxifying or activating toxic and anti-tumor compounds. The indispensable part of catalase in oxidative stress conditions highlights the importance of regulating this crucial antioxidant enzyme. Notably, catalase results in peroxisomal localization in mammalian cells, whereas a construct lacking the

targeting signal remains in the cytosol. During the demonstration of subcellular localization of catalase in *C. reinhardtii* in fatty acid metabolism, the microscopy findings revealed the presence of CAT1 (catalase isoform 1) in the peroxisomes while CAT2 (catalase isoform 2) is localized in the endoplasmic reticulum [66].

6.2. Superoxide dismutase: first-line antioxidant defense system

Among the potential ROS scavengers, SOD acted as the first line of defense, counteracting free radicals and preserving cellular redox homeostasis [67,68]. SOD is present throughout the human body, including the skin and appendages. Notably, copper/zinc SOD is found in human skin, which protects the skin and its appendages from damage caused by ROS. This enzyme is located in the cytoplasm of keratinocytes, where most ROS are produced. The enzyme's location in skin tissues is influenced by cell type and factors such as age, gender, and disease state [67].

Furthermore, MnSOD is the primary enzyme responsible for scavenging ROS in cells. Any factors that affect the expression or activity of MnSOD, leading to a decrease in the cell's antioxidant capacity can have significant repercussions on the overall health of the cell. This can alter mitochondrial metabolic function, contributing to the onset and advancement of numerous diseases [50]. A comprehensive comprehension of how MnSOD safeguards cells from the detrimental impacts of excessive ROS, specifically the effects on mitochondrial metabolic enzymes, may facilitate the creation of innovative therapies for conditions where ROS plays a crucial role [51]. An extensive study should be investigated to understand better their potential in treating diseases that originate from excessive ROS exposure. SOD scavenging potency was investigated by lowering MDA, an oxidative stress indicator produced by lipid peroxidation, during the effects of statin treatment [69]. The phenomenon indicates that higher circulating concentrations of SOD and other antioxidant enzymes significantly reduce the risk of coronary heart disease. However, an impaired SOD mechanism promotes oxidative stress and develops endothelial dysfunction, vascular damage, and atherosclerosis [70]. SOD also prevents the formation of peroxide anion, which has tumorigenic properties. The reduction in SOD activity is associated with cluster degradation, loss of the catalytic iron and enzymatic activity, and the elimination or removal of $O_2^{\bullet -}$ [68]. Thus, restoring SOD and other antioxidants could be a practical pathway in organisms with oxidative damage.

Furthermore, SOD is utilized as a ROS scavenger and reduces its toxicity ROS throughout the intra-erythrocytic stage of parasite survival in *Plasmodium falciparum* [71]. Since the massive accumulation of ROS was reported in mitochondria which induces oxidative damage and destructive tissue activity during ischemia-reperfusion injury and lung allograft rejection, elevated expression of Mn-SOD was required to inhibit the ROS production [72]. Similarly, autophagy dysregulation in cells lacking a functional electron transport chain indicated an excess of mitochondrial ROS, where SODs play an essential role in clarifying the signaling functions of $O_2^{\bullet -}$ and H_2O_2 [73]. SOD being the key player against free radicals, the altered expression of SOD leads to various pathological conditions like age-dependent diseases such as cancer and neurodegenerative and cardiovascular diseases [74].

6.3. Glutathione peroxidase: an intracellular unique antioxidant enzyme

Glutathione peroxidase exists in various forms. These forms differ in their amino acid sequences, cellular localization, and biochemical properties. Some common forms of glutathione peroxidase include GPx1, GPx2, GPx3, GPx4, and GPx6 [74,75]. Each form has a unique function in the body and is critical in protecting cells from oxidative damage by catalyzing the reduction of hydrogen peroxide and organic hydroperoxides. Additionally, these forms of glutathione peroxidase regulate cellular signaling pathways and modulate immune responses [74].

Further research is necessary to elucidate each form of glutathione peroxidase's specific functions and mechanisms of action. Glutathione peroxidase-1 (GPx-1) is an intracellular antioxidant enzyme that enzymatically reduces H_2O_2 to water to limit its harmful effects [58]. Specific ROS, such as H_2O_2, is also essential for growth factor-mediated signal transduction, mitochondrial function, and maintenance of average thiol redox balance [75]. Thus, by limiting H_2O_2 accumulation, GPx-1 also modulates these processes. This review explores the molecular mechanisms involved in regulating the expression and function of GPx-1, emphasizing the role of GPx-1 in modulating cellular oxidant stress and redox-mediated responses. As a selenocysteine-containing enzyme, GPx-1 expression is regulated uniquely by the trace mineral selenium and selenocysteine incorporation during translation [74,76]. GPx-1 has also been linked to developing and preventing a wide range of common and complex diseases, including cancer and cardiovascular disease [77].

Furthermore, the expected intracellular and extracellular redox balance disruptions contribute to susceptibility and pathology in other difficult human conditions. Thus, the antioxidant GPx-1 has been studied for its role in modulating processes in which oxidants play an essential role as average cellular growth and proliferative responses, adaptive pathological responses, involved in atherogenesis, drug toxicity, and ischemia-reperfusion injury [78,79]. This review summarised the current knowledge of the molecular determinants influencing the expression and function of GPx-1, emphasizing the role of GPx-1 in modulating cellular oxidant stress and redox-mediated signaling responses. Importantly, GPx-1 may protect against oxidative stress by regulating cellular hydroperoxides and RNS, but in excess, GPx-1 may have adverse effects due to a lack of essential cellular oxidants [80]. Thus, the crucial role of enzymatic antioxidant enzymes in response to free radicals and the counteract defense mechanism was demonstrated in Fig. 4.

6.4. Peroxiredoxins

Peroxiredoxins are crucial enzymes for hydroperoxide detoxification; they have only gained significant attention in recent years compared to other major players, such as heme-containing catalases and peroxidases, and glutathione peroxidases, in peroxide detoxification. These peroxidases, which depend on cysteine, exhibit high reactivity with organic hydroperoxides, hydrogen peroxide, and peroxynitrite and have a significant role in peroxide defense. Additionally, peroxiredoxins play a crucial role in regulating peroxide-mediated cell signaling. The emphasis is on their catalytic mechanism, regulation, and biological function. Peroxiredoxins are present in most organisms and expressed ubiquitously, with several isoforms. They possess a conserved active site architecture that is highly specialized for peroxide reduction, enabling them to exhibit very high rates of peroxide reduction on the order of 106–108 M^{-1} s^{-1} [81]. However, their reactivity with other thiol reagents is modest due to their specificity for peroxide reduction. Despite being present at high levels and able to clear peroxides quickly, these enzymes exhibit an extraordinary range of variations in their oligomeric states and susceptibility to regulation via hyperoxidative inactivation and other post-translational modifications. The active site of these enzymes contains critical conserved residues that promote catalysis by stabilizing the transition state required for transferring the terminal oxygen of hydroperoxides to the peroxidatic cysteine residue within the active site [82]. Ongoing extensive research efforts are aimed at broadening our understanding of the scope of their importance and the structures and forces governing these crucial defense and regulatory enzymes.

7. Antioxidant enzymes and their cofactor

The initial line of cellular defense against reactive oxygen species (ROS) and other free radicals is provided by antioxidant enzymes like catalase, glutathione peroxidase, and superoxide dismutase. These

enzymes are distinct in their need for cofactors and cellular location, and they have different metals in their active sites. For example, GPx uses selenium in one of its isoforms; soluble SOD uses Cu (copper) and Zn (zinc), and heme protein CAT uses Fe (iron). While considering their function, metals at their active sites offer rapid electron transition along the substrate, which is essential for their anti-ROS defense function [83]. As a result, H_2O_2 is transformed into O_2 and H_2O by GPx and CAT. No enzymatic defense exists against OH. While it is dramatically different in bacteria and plants, antioxidant enzyme regulation in tissues of higher animals depends on many factors, including organ specificity, age, developmental stage, prevailing hormone profile, and the availability of active site cofactors. Therefore, those metals' intracellular levels are critical for their catalytic activity. There is no convincing data that cofactor metals not only affect the activity of enzymes by their presence but also control the amount of protein at the expression level [84].

Free radicals induce oxidative stress, balanced by the body's endogenous antioxidant systems with input from co-factors and by ingesting exogenous antioxidants. Therefore, if the generation of free radicals exceeds the protective effects of antioxidants and some co-factors, this can cause oxidative damage, which accumulates during the life cycle and has been implicated in ageing and age-dependent diseases such as cardiovascular disease, cancer, neurodegenerative disorders, and other chronic conditions [85].

Selenium, copper, zinc, and manganese are essential since they act as cofactors for antioxidant enzymes. Selenium is considered particularly important in protecting the lipid environment against oxidative injury, as it is a cofactor for GSH-Px [86]. The antioxidant enzymes – GPx, heme peroxidase, CAT, and SOD – metabolize oxidative toxic intermediates and require micronutrient cofactors such as selenium, iron, copper, zinc, and manganese for optimum catalytic activity.

Antioxidant enzymes can stabilize or deactivate free radicals before they attack cellular components. They act by reducing the energy of the free radicals or by giving up some of their electrons for their use, thereby causing them to become stable. In addition, they may also interrupt the oxidizing chain reaction to minimize the damage caused by free radicals. For the past decade, countless studies have been devoted to the beneficial effects of antioxidant enzymes. It has been found that an important link exists between free radicals and more than sixty different health conditions, including the ageing process, cancer, diabetes, Alzheimer's disease, strokes, heart attacks, and atherosclerosis.

7.1. Cofactors controlling oxidative reaction

Cofactors play an essential role in regulating oxidative reactions in biological tissues. Flavin mononucleotide (FMN) is a known cofactor of respiratory complex I occupy a crucial position in the electron transport chain. According to the findings, FMN protects *Azotobacter vinelandii* flavodoxin from H_2O_2-induced oxidation, resulting in significantly improved flavodoxin stability against unfolding and strong protection against oxidative stress [87]. Similarly, essential metals, including copper, iron, and manganese, functioned as cofactors and actively participated in oxidant/antioxidant mechanisms. Copper (Cu) exhibited antioxidant properties and served as a cofactor in several essential enzymes, including cytochrome C oxidase and copper, zinc-superoxide dismutase (Cu, ZN-SOD) [88]. Unregulated Cu, conversely, is a well-known pro-oxidant that can be activated by transporter proteins such as metallothionein and ceruloplasmin [89]. The deficiency of Cu leads to an imbalanced redox system by reducing the antioxidant enzymes selenium-dependent glutathione peroxidase (Se-GPX) and catalase [90]. The deficiency in Cu causes alteration in the scavenging properties of ROS, including metallothionein, which further leads to the development of oxidative stress [91]. Other metals, such as selenium (Se) and manganese (Mn), have been discovered to be involved in antioxidant defense mechanisms and play an essential role in protecting mitochondria from free radical attacks. Se deficiency can increase the risk of cancer and the development of neurodegenerative and cardiovascular diseases [92]. However, the moderate level of Se is associated with the upregulation of glutathione peroxidases, which are known to protect DNA and other cellular damage from oxidative stress [93]. Since Mn-SOD is the first-line antioxidant defense enzyme, Mn plays a crucial role in binding to the catalytic site and modulating the enzymatic activity of these enzymes. The presence of Mn and Zn in SOD contributed to its free radical scavenging ability, which aids in protecting the vascular and immune systems from the damaging effects of free radical species [94]. Ageing and other skin problems may be associated with the deficiency of vital metals incorporated within the catalytic site of antioxidant enzymes to regulate the function of these enzymes [95,96]. Iron (Fe) is present in the hem group of enzymes such as catalase, hemoglobin, and myoglobin and plays a critical role in maintaining the redox equilibrium. The excess level of Fe can act as a pro-oxidant by accumulating free radicals, which can be a supportive factor for inducing cancer. Other co-factors such as thiamine, riboflavin, and carnitine are well known for their property to scavenge free radicals and protect against oxidative damage [97].

8. Antioxidants and antioxidant enzymes restore antioxidant activity to maintain redox homeostasis

Incorporating a functional, balanced antioxidant system to combat the effects of imbalanced ROS generation in tissue is one of the most difficult challenges in the cellular environment. Antioxidants, both enzymatic and non-enzymatic, evolved as a balanced system to neutralize excess ROS and reduce oxidative state. Supplementation with ubiquinone, lycopene, lutein, N-acetylcysteine, resveratrol, and other flavonoid-like polyphenols acted as a potential inhibitor of ROS-induced cell injury in conditions such as acute hyperoxia injury, radiation injury, lung transplantation, and inflammation. Polyphenols possess potent antioxidant properties due to the hydroxyl groups in their chemical structures, allowing them to neutralize ROS effectively. Consequently, they can be useful in combating human illnesses or pathological conditions caused by oxidative stress. In vitro studies have provided evidence that dietary sources of polyphenols may confer benefits in protecting against various diseases, including neurodegenerative diseases, cardiovascular diseases, diabetes, cancer, inflammatory diseases, and infectious illnesses[98]. Several nutritional polyphenols, including EGCG, gallic acid, ellagic acid, quercetin, myricetin, rutin, kaempferol, and resveratrol, exhibit both pro- and anti-oxidant properties. However, the advantageous antioxidant activity of green tea polyphenols (EGCG, ECG) is primarily accountable for their anticancer, antiobesity, and antibacterial effects.

In contrast, their harmful toxic effects arise from their pro-oxidative impact [99]. Other antioxidant-rich vitamins, such as vitamin A (retinoids, carotenes), vitamin C, and E (tocopherols), aided standard treatment regimens by removing excess ROS during DNA damage repair. Natural antioxidants such as curcumin significantly reduced the increase in plasma and hepatic MDA and total oxidant status (TOS) in rats fed high fructose and high-fat diets. Curcumin reduced the oxidative stress index (OSI) in both diet groups' plasma, liver, and kidney tissues [100]. Catechins are also potent antioxidants, but they act as prooxidants under pathological conditions, modulating signal transduction, inflammation, and cell death regulation pathways [101]. The enzymatic antioxidants have the potential to protect cells against ROS-induced damage. Catalase played a critical role in human retinal cell lines, where high glucose-induced peroxide production was significantly reduced after catalase transduction.

Furthermore, in the peroxisome-rich livers of treated mice, catalase enzyme activity increased while oxidative damage decreased [63]. In addition to catalase, SOD acted as a potential ROS inhibitor in restoring antioxidant properties to maintain redox balance. ROS accumulation can cause mitochondrial permeability transitions and disrupt mitochondrial membrane stability, which can be prevented by increasing Mn-SOD expression [102]. Furthermore, the members of the GPx family

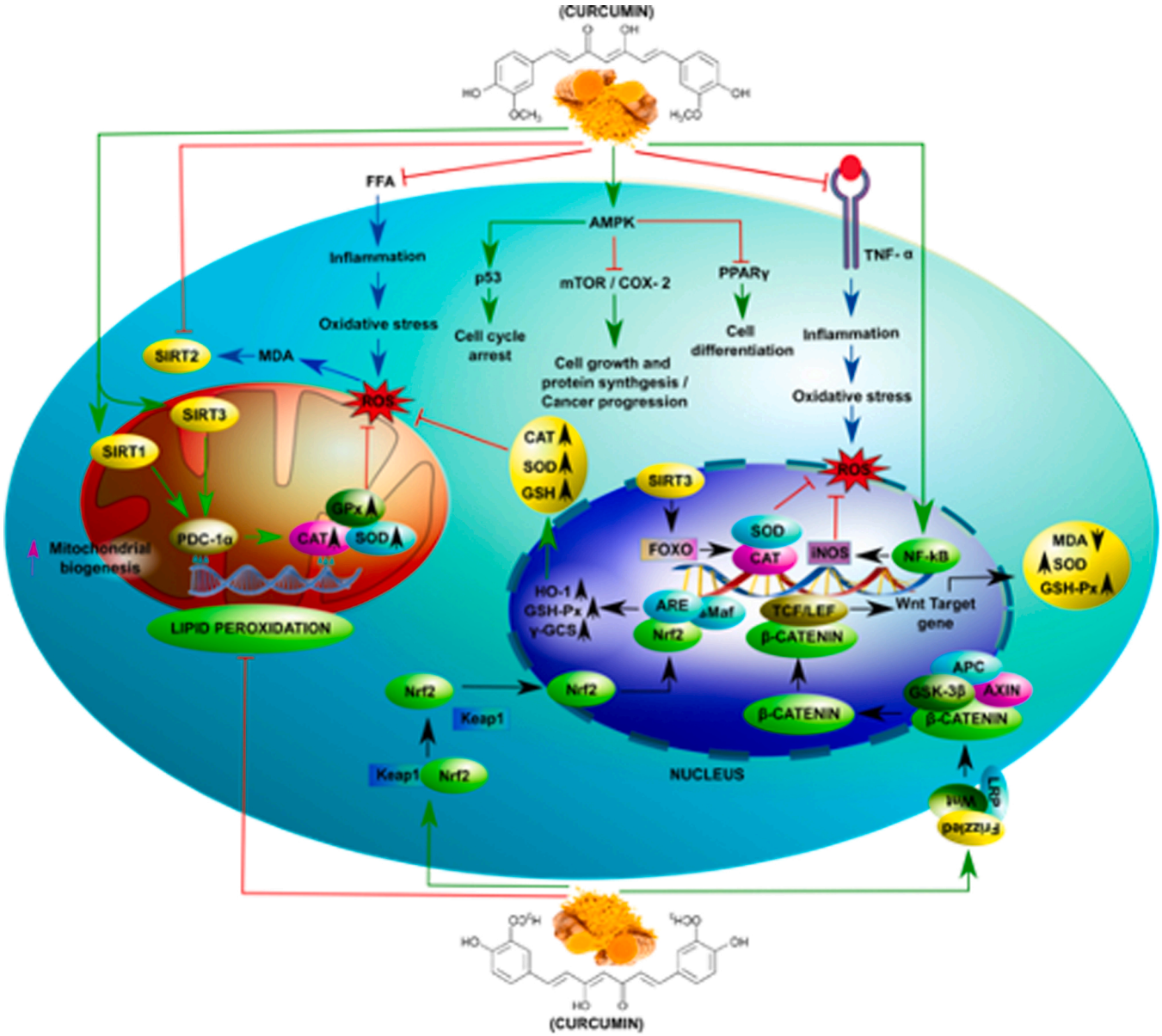

Fig. 5. The mechanistic role of curcumin as an inhibitor and activator in protecting oxidative stress.

have anti-oxidative functions in various cellular components; GPx1 is found in the cytosol and mitochondria, GPx2 in the cytosol and nucleus, and GPx3 in the plasma; GPx4 is membrane-associated and appears to protect membranes from oxidative stress. The role of GSH in catalyzing the conversion of H_2O_2 or organic hydroperoxides into water or the corresponding alcohols is well established [103,104]. This was discovered to help regulate the concentration of hydroperoxide mediators, which affects several physiological pathways, including GPx1 in insulin signaling, GPx4 in cell survival/proliferation, and GPx5 in spermatogenesis [77]. As an endogenous antioxidant system, the Trx antioxidant system, which consists of NADPH, thioredoxin reductase (TrxR), and Trx, is critical in the fight against oxidative stress. Trx antioxidants aid in DNA and protein repair by inhibiting ribonucleotide reductase and methionine sulfoxide reductase and play a vital role in immune response [105]. Since the homeostatic setting is determined by the oxidation and reduction rates of independent reactions, both enzymatic and non-enzymatic antioxidants aid in maintaining redox homeostasis.

9. Non- enzymatic antioxidants: indispensable role in redox homeostasis

9.1. Curcumin

Curcumin is primarily derived from the rhizomes of turmeric (*Curcuma longa*). It is a hydrophobic polyphenol with lipid solubility that is yellow. It is a natural antioxidant and anti-inflammatory substance used to treat inflammatory bowel disease (IBD), rheumatoid arthritis, Alzheimer's disease (AD), and colon, lung, stomach, skin, and breast malignancies. In addition, it provides various health advantages demonstrated in multiple experimental and pharmacologic trials [106, 107].

Curcumin and the curcuminoids contained in turmeric may be extracted to create supplements with far greater effectiveness than turmeric [108]. However, because curcumin is poorly absorbed during digestion, many different formulations have been developed to boost its bioavailability. Curcumin supplementation consistently decreases inflammation indicators and increases endogenous antioxidant levels [109]. More extensive research on curcumin is needed in many areas of

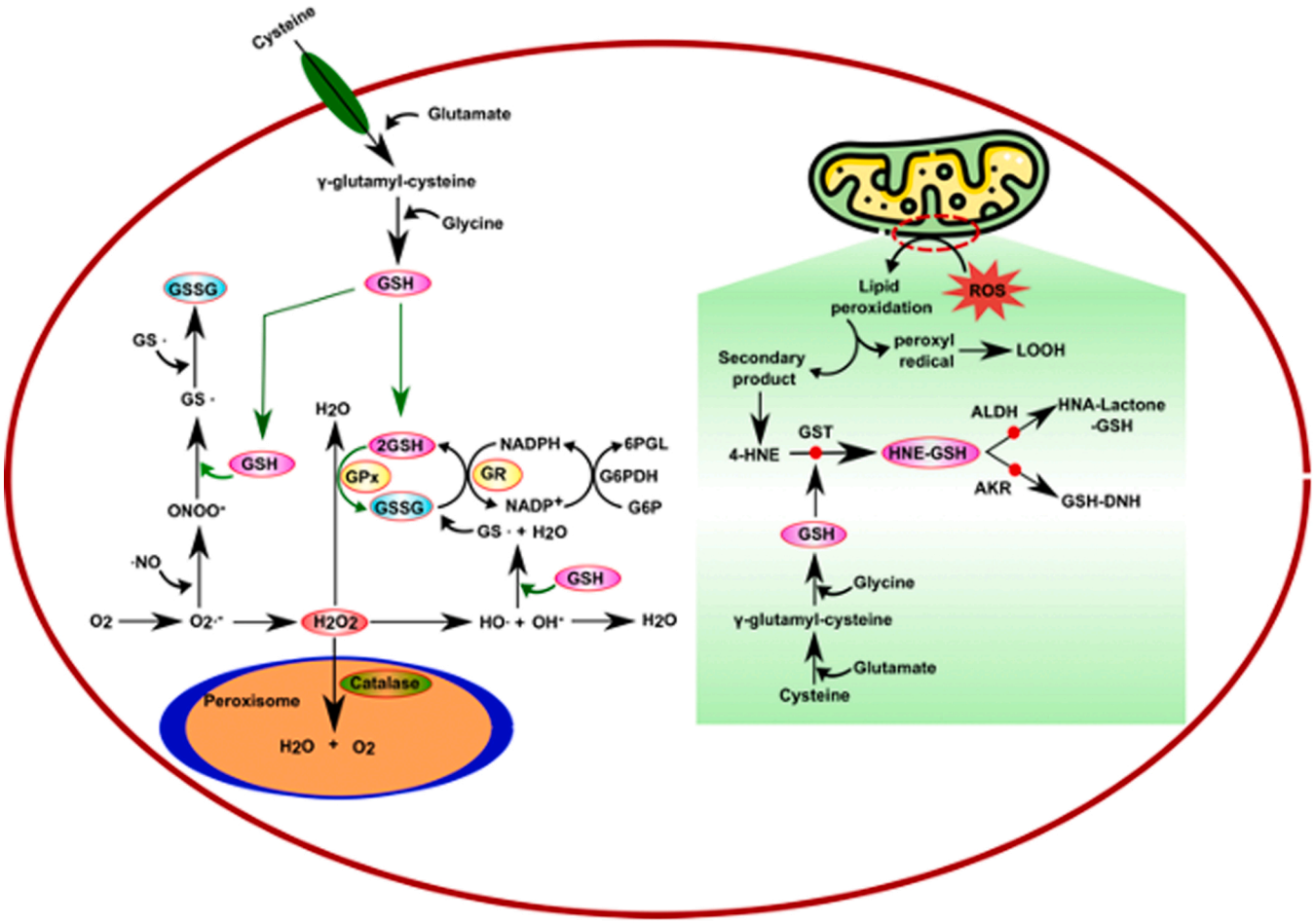

Fig. 6. : Mechanism of GSH in the stabilization of Reactive oxygen species.

health to understand its physiochemical properties. The potential role of curcumin has been investigated during direct or indirect interaction with different molecular targets, including transcription factors, enzymes, cell cycle proteins, receptors, cell surface adhesion molecules, growth factors, and protein kinases.

Apart from an antioxidant and anti-inflammatory agent, this potent, non-enzymatic exogenous antioxidant, curcumin, has a wide range of pharmacological effects. The ability to scavenge the free radicals, decrease the production of ROS, and function as a potent inhibitor of lipid peroxidation and advanced glycation end products [110]. Thus, the numerical clinical trials have indicated curcumin's role as an oxidative stress inhibitor in several chronic diseases [111]. The potential role of curcumin as an inhibitor or activator by involving different pathways is demonstrated in Fig. 5. Curcumin inhibits the signaling of Tumour Necrosis Factor-alpha (TNF-α), Free Fatty acid (FFA), and Peroxisome proliferator-activated receptor gamma (PPAR-γ) that induce oxidative stress and inflammation in cells.

It also promotes AMPK- induces P53 that causes cell cycle arrest and inhibits mammalian targets of rapamycin (mTOR) and Cyclooxygenase-2 (COX-2), which have a significant role in cell proliferation and cancer progression. Curcumin also reduced MDA and sirtuin 2 (SIRT2) expression, resulting in a lower production of H_2O_2-induced ROS. Curcumin may reduce MDA and increase antioxidant levels by activating or inhibiting the sirtuins 1, 2, and 3 [112,113]. Sirtuin 1 (SIRT1) facilitates the acetylation of the Forkhead box O (FOXO) 3a protein, activating the FOXO transcription factors that control the FOXO genes that regulate antioxidant genes like SOD and CAT to lower cellular levels of ROS [114]. Curcumin inhibited the SIRT2 gene, which decreased the amount of H_2O_2-induced ROS produced in the cytoplasm [113]. In a rat model of COPD (Chronic obstructive pulmonary disease), curcumin also increased the mRNA and protein expression of Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) and sirtuin 3 (SIRT3), which lowered oxidative stress by lowering MDA and raising SOD, GPx, and CAT levels in skeletal muscle mitochondria [115]. Hexahydrocurcumin drastically reduced oxidative stress, MDA, and NO levels in rats. The increased expression of nuclear factor erythroid 2–related factor 2 (Nrf2) and HO-1 expression, along with antioxidative enzymes, was reported in animal model research [116]. In addition, Curcumin activates Wnt/β-catenin and Keap1-Nrf2-ARE pathways, which promote anti-oxidant production and reduce ROS-mediated stress [117]. However, neither the antioxidant defense system nor the effects of curcumin on several antioxidant variables, including GSH, CAT, TAC, and GR, have been well-reviewed.

9.2. GSH

GSH is an essential antioxidant that aids in the battle against free radicals, unstable molecules that develop in response to environmental variables. GSH is a naturally occurring molecule in the body formed from the amino acid glycine, L-cysteine, and L-glutamate. It is generated by the liver and nerve cells in the central nervous system. The essentiality of GSH was reported during tissue formation and repair, detoxification, and the generation of enzymes and hormones [118].

Thus, GSH is established as the most abundant antioxidant and a key detoxification agent in cells. It is synthesized by a two-enzyme reaction catalyzed through glutamate cysteine ligase (GCL) and glutathione synthetase (GCS), and its level is well controlled in response to redox changes [119]. Evidence shows that GSH may play crucial functions in

cell signaling [120]. Over the last few decades, research on free radicals, oxidative stress, and, more recently, redox signaling has substantially enhanced the physiological activities of the tripeptide glutathione [121]. GSH undoubtedly plays a vital trigger role (γ-glutamyl-L-cysteinyl glycine, GSH), a water-soluble tripeptide consisting of the amino acids L-glutamate, L-cysteine and glycine, which is widely present in both eukaryotes and prokaryotes [122]. GSH is engaged explicitly in food metabolism, antioxidant defense, and the control of cellular metabolic activities ranging from gene expression and DNA and protein synthesis to signal transmission, cell proliferation, and apoptosis [121]. It also plays an essential function in the immunological system [123]. GSH supplements are frequently advised for various health issues, including Alzheimer's and heart disease [124]. It is also used in dermatology to brighten skin and battle apparent indications of ageing.

Under the physiological state, reduced GSH is the dominant form, with concentrations ranging from 10 to 100-fold greater than oxidized GSH (oxidized GSH, GSSG, mixed disulfide, GSSR). GSSG is primarily formed by the catalysis of GPx and through direct interactions of GSH with electrophilic molecules, such as radical species [121]. Usually, the ratio of reduced GSH to oxidized glutathione (GSSG), GSH/GSSG, which characterizes the cellular redox status, is 100/1 in the cytoplasm, 10/1 in mitochondria, and 3/1–1 in the endoplasmic reticulum [5]. This ratio varies based on the physiological condition of the cell, such as proliferation, differentiation, or death, and its disruption causes significant alterations in cellular signaling processes [121]. This involvement of GSH/GSSG primarily derives from its regulatory influence on the functional activities of protein thiols [125]. The GSH/GSSG ratio is a critical redox sensor that dictates redox-dependent changes in protein functional activity via necessary post-translational modifications such as S-glutathionylation and S-nitrosylation. The improvement of the activity of these reactions in response to a change in the GSH/GSSG ratio due to an increase or decrease in RONS levels contributes significantly to functional cell adaptability to redox changes in the environment [126,127]. GSH stabilizes ROS and RNS in the presence of the enzyme GPx which catalyzes the conversion between GSH and GSSH. HNE (4-hydroxy-2-nonenal) conjugate with GSH by glutathione transferases (GST) is the primary detoxification step in mitochondria. The cellular GSH pool's renewal depends on cysteine content and cystine/glutamate antiporter (xCT) regulation. The oxidation pathway via the eukaryotic aldehyde dehydrogenases (ALDHs) family is supposed to be activated when stress is moderate. The reduction pathway with the aldo-keto reductases (AKRs) family is thought to be activated in case of acute stress. Redox equilibrium is critical for sustaining cellular signaling and activation. GSH is an important intracellular antioxidant that scavenges excess ROS, and the role of GSH as a stabilizer against free radicals generation is demonstrated in Fig. 6.

Redox-dependent mechanisms substantially determine cell viability, which controls the division, bioenergetics, and programmed death. Low-molecular-weight markers characterize the cellular redox state (GSH, NADH). Because their oxidized/reduced form ratio fluctuates in response to variations in reactive oxygen and nitrogen species (RONS) levels, they can trigger the redox-dependent control of biological activities. GSH is less vulnerable to oxidation than Cys, making it the best candidate for maintaining an intracellular redox state [128]. In addition, the γ-peptide bond at the Glu residue shields GSH from peptidase activity.

In contrast, the SH group at the Cys residue makes GSH an excellent electron donor, allowing it to interact with strong electrophiles [5]. Additionally, it should be noted that the Trx systems play significant roles in the immune response, viral infection, and cell death by interacting with thioredoxin-interacting protein. The regulation of cellular redox state in human cells is primarily carried out by the cytosolic and mitochondrial Trx systems, with TrxRs serving as high molecular weight selenoenzymes and the glutathione-glutaredoxin (Grx) system also contributing to this process [129].

9.3. Catechin

Catechin is naturally present in many nutritional products, plants, fruits (such as apples, blueberries, gooseberries, grape seeds, kiwi, and strawberries), red wine, green tea, cacao liquor, chocolate, beer, cocoa, etc. Tea and red wine are among the world's most popular beverages containing many catechins [130,131]. Several in vitro, in vivo, and physical approaches have proven the antioxidant activity of Catechin. Catechin influences the molecular pathways in cancer and associated diseases, such as angiogenesis, extracellular matrix breakdown, cell death control, and multidrug resistance [132]. According to epidemiological and experimental research, there is a positive correlation between green tea intake and cardiovascular health due to many effects such as antioxidative, antihypertensive, anti-inflammatory, antiproliferative, anti-thrombogenic, and anti-hyperlipidemic [133]. Furthermore, Catechin has been found in clinical tests to have positive benefits due to its antioxidant activity.

The antioxidant properties of catechins have yet to be thoroughly demonstrated. However, the role of catechins as an excellent free radical scavenger was well established in cell culture studies [134]. Catechin, in conjunction with vitamins C and E and antioxidant enzymes such as SOD and CAT, may operate as indirect antioxidants, increasing the overall antioxidant capacity of plasma. Although catechins may generally inhibit vitamin E oxidation, green tea catechins do not appear to change the plasma status of vitamins E and C in vivo [135]. However, catechins have limited antioxidant activity due to their relatively low distribution. Nonetheless, the role of catechin was found to have cell signaling action, such as activation of Nrf2 and inhibition of Nuclear factor-κB(NF-κB). EGCG is the most efficient antioxidant among the catechins, especially regarding quenching ROS [17,136].

Catechins can be obtained from various sources, including numerous plants, fruits, vegetables, drinks, algae, and confectionery foods. However, the contents and kinds of these sources differ significantly. The availability of varied sources varies worldwide, which is a primary factor for nonuniform nutrient consumption. Geographic variations affect the quantity and diversity of catechins in each source, such as tea leaves and other seeds from various areas with differing catechin levels. Green tea polyphenols, including EGCG, are thought to alter cellular signal transduction pathways involved in preventing various diseases, including cancer, diabetes, and cardiovascular disease [130]. Therefore, recently, EGCG has attracted much interest as a possible cancer chemo-preventive [137]. It was the first polyphenol to be identified as a covalent topoisomerase toxin. In the family of green tea polyphenols, EGC has been identified as a covalent topo2 toxin, as opposed to ECG and EC, which do not affect topo2-induced DNA breakage. Moreover, the critical role of catechin on DNA integrity was established during interaction with topoisomerase isoenzymes [130].

Catechins are widely known antioxidants; however, they may also act as pro-oxidants and produce ROS. ROS may disrupt the functioning of cellular proteins, lipids, and nucleic acids, resulting in various diseases. Mutation and genomic instability are vital contributors to the initiation, development, and advancement of carcinogenesis when DNA is oxidized. As a result, depending on catechin bioavailability and the context of the cellular environment, catechins' antioxidant and pro-oxidative actions can impact cancer signaling [134]. Although the antioxidant activity of tea catechins has been extensively established in vitro, such activity is only shown in vivo when the animals are subjected to oxidative stress. EGCG treatment, for example, has reduced lipid peroxidation and protein carbonylation levels in aged but not young rats [138]. Tea polyphenols may have critical roles in quenching endogenously generated ROS at various phases of carcinogenesis, as these species are vital in promoting carcinogenesis. Green tea administration to smokers for 4 weeks has been found in human trials to lower the number of 8-oxo-dG-positive cells [139] considerably.

The antioxidant effectiveness of catechin is mediated by two different mechanisms: (1) direct mechanisms (scavenging ROS and

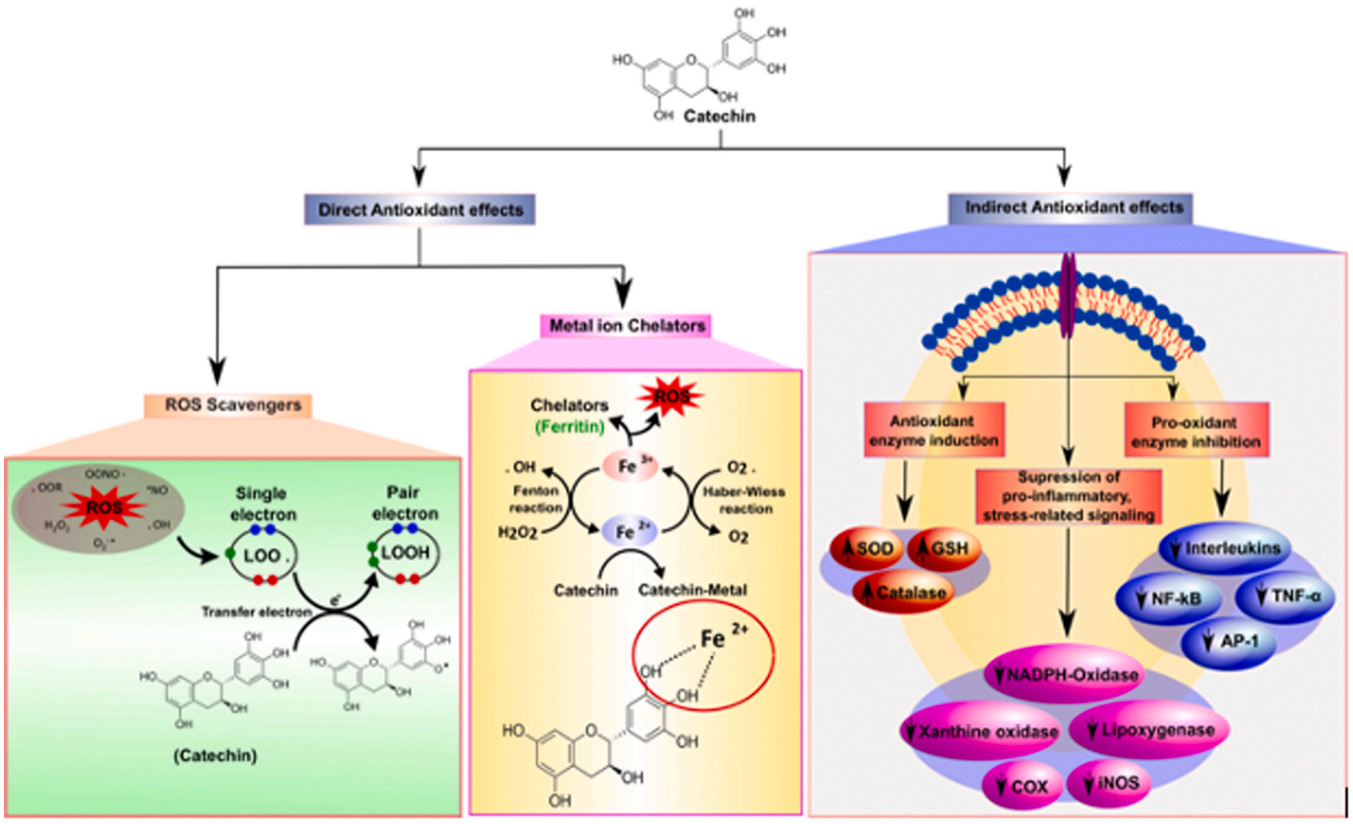

Fig. 7. The direct and indirect antioxidant effects of catechin in response to ROS.

chelating metal ions) and (2) indirect mechanisms (producing phase II detoxification enzymes and antioxidant enzymes while inducing antioxidant enzymes and inhibiting pro-oxidant enzymes [140]. The defense mechanism of catechin through this direct and indirect action in response to an increased level of ROS was presented in the scheme (Fig. 7). Catechin and its di-stereoisomers have phenolic hydroxyl groups in their chemical compositions, which can stabilize free radicals [141]. This characteristic gives catechins their antioxidant properties, which include the ability to scavenge free radicals. The phenolic hydroxyl groups of catechin can engage in a termination reaction with ROS and RNS to stop the cycle of producing new radicals. This property is responsible for their antioxidant activities, where catechins can act as free radical scavengers. Catechins reduce free radicals by donating one electron to the phenolic OH group, and the aromatic group is kept stable by the resonance of the resulting peroxyl radicals [142]. The amount of hydroxyl groups a molecule contains correlates favorably with the antioxidant activity of phenolic compounds [143,144]. As free radical scavengers, catechins can halt radical chain reactions, which stop the oxidation of cellular lipids.

The ability of phenolic compounds to bind metal ions in forming free radicals is another factor contributing to their antioxidant capability [141]. The adjacent hydroxyl groups of molecules may serve as iron chelation sites [145]. Catechins dramatically boosted the activities of GPx, CAT, and SOD, which play critical roles in scavenging ROS [134]. Catechins can inhibit the pro-oxidant enzyme nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) and alter how ligands interact with receptors like TNF-α; they also block several pathways linked to oxidative stress that is involved in the inflammatory processes [142]. NF-κB and activator protein-1 (AP-1) are redox-sensitive transcription factors that play critical roles in response to oxidative stress induced by disease counteracted by the catechin's effect to neutralize the increased ROS level [146] (Fig. 7).

Catechins appear capable of producing and scavenging free radicals, and their therapeutic effects appear to be owing to a combination of the two methods. Catechins are ROS scavengers and metal ion chelators. Their indirect antioxidant actions include activating antioxidant enzymes, inhibiting pro-oxidant enzymes, and synthesizing phase II detoxifying and antioxidant enzymes. Catechins may help prevent and guard against disease induced by.

9.4. *Vitamins C*

Vitamin C (ascorbic acid, ascorbate) is an essential micronutrient that must be obtained via food or as a supplement because humans lost the capacity to synthesize it owing to mutations in the gene encoding a terminal enzyme in the vitamin C biosynthetic pathway [147]. Furthermore, as a cofactor for enzymes engaged in processes and effects critical for cancer transformation, vitamin C plays a role in various activities, including antioxidant defense, transcription, and epigenetic control of gene expression [148].

Vitamin protects cells from the effects of free radical molecules formed when the body digests food or is exposed to cigarette smoke and radiation from the sun, X-rays, or other sources [20]. Vitamin C aids in the management of infections and the healing of wounds, and it is a potent antioxidant capable of neutralising damaging free radicals. The requirement of vitamin C was essential for the production of collagen, a fibrous protein found in connective tissue [149]. In addition, the vitamin is helpful in the production of many hormones and chemical messengers that are employed in the brain and nerves [150]. The activity of white blood cells was boosted by vitamins indicating the potentiality of vitamin C in response to the body's immune system [151].

Vitamin C can potentially scavenge ROS, reducing DNA damage and other consequences that are critical in cancer transformation [152]. Dietary Vitamin C from natural sources is consumed with other molecules, which affects its absorption and biological effects. Prooxidant effects of high therapeutic vitamin C dosages may harm cancer cells

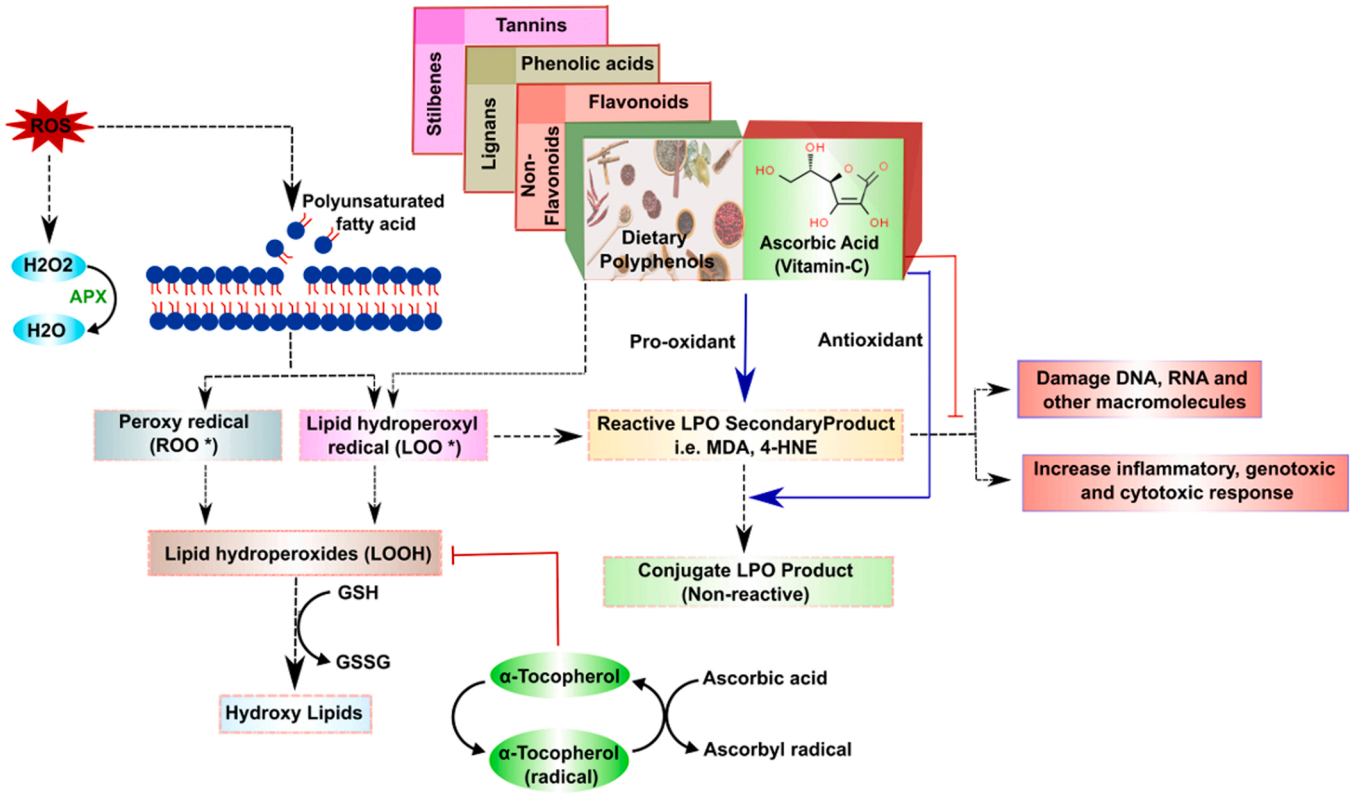

Fig. 8. : Role of Vitamin C (Ascorbic acid) as a prooxidant and antioxidant.

[150]. However, dehydroascorbate, an oxidized vitamin C, is transported through glucose transporters. Cancer cells switch from oxidative phosphorylation to glycolysis, and excess vitamin C may limit glucose transport and ATP production, resulting in an energetic crisis and cell death [152]. In addition, vitamin C may alter cancer cells' metabolomic and epigenetic profiles and kill cancer stem cells by activating ten-eleven translocation (TET) proteins and downregulating pluripotency factors. It also promotes the breakdown of the hypoxia-inducible element (HIF-1), which is required for tumor cell viability in hypoxic environments [152].

Although ascorbic acid is commonly utilized in medical practice, particularly for enhancing iron absorption and as an adjuvant treatment in iron chelation therapy, its mode of action and consequences in iron metabolism and toxicity remains unknown. It operates biologically as a reducing agent and coenzyme in some metabolic pathways and as an antioxidant. As a radical scavenger, Ascorbic acid effectively protects membranes and proteins against oxidation by ROS: $O_2^{\bullet -}$, H_2O_2, $OH^{\cdot}$ radicals, peroxyl radicals (•OOH), and singlet oxygen $_1O^2$, especially at high concentrations [153]. Vitamin C stabilizes ROS and ROS-mediated lipid peroxidation. Ascorbate peroxidase reduces H_2O_2 to water by using ascorbate as an electron donor. As a prooxidant, it induces a proactive secondary product (reactive) that cause DNA, and RNA damage, cell toxicity, and tissue toxicity. It stabilizes these secondary products as an antioxidant by forming a conjugate with that Proactive Secondary product (non-reactive). The role of vitamin C as a pro-oxidant and antioxidant is presented in Fig. 8.

Ascorbic acid, on the other hand, is a multifaceted molecule that may function as a chelator and a producer of free radicals [154]. The significance of ascorbic acid as a chelator in iron and copper overload circumstances is highly debated [153,155,156]. However, the evidence that ascorbic acid might benefit human cancer patients is still shaky and warrants further investigation.

Exogenous antioxidant molecules consumed in the food include vitamins C, E, and flavonoids. In addition, some molecules serve as metal chelators (for example, lactoferrin and transferrin), preventing the formation of the •OH via the Fenton and Haber-Weiss reactions [6]. It has also been proven that ascorbate is more efficient than thiols, tocopherol, and urate in preventing lipid peroxidation in plasma.

The pharmacokinetic features of Ascorbate have intimately associated with its functions in tissues since its circulation and concentration in the different body organs depend on their requirements of vitamin C. Furthermore, the distinction between physiological and pharmacological doses of vitamin C, determined by the route of absorption as well as by the pro-oxidant and antioxidant effect of different doses of vitamin C dependent on the redox balance of the individual, allows us to understand why some previous studies have failed to demonstrate the health benefits of vitamin C. Finally, the significance of vitamin C in health is connected to the preservation of the internal microenvironment, which is changed in diseases such as obesity, cancer, neurodegenerative disorders, hypertension, and autoimmune diseases [157].

9.5. *Vitamin E*

Vitamin E is the cell's most critical lipid-soluble component antioxidant defense mechanism and can be obtained entirely from food [158]. Because of its antioxidant action, it plays various critical roles in the body. There are eight naturally occurring forms of vitamin E, notably the alpha, beta, gamma, and delta classes of tocopherol and tocotrienol, which plants synthesize from homogentisic acid [158]. Vitamin E can protect cells from free radical damage and limit radical formation in specific settings. However, inconsistent trial results have dimmed some of the promises of high-dose vitamin E in preventing chronic diseases. It also improves immunological function and prevents blood clots from developing in the heart's arteries. Skin-care products containing vitamin E and its derivatives (such as tocopheryl linoleate and tocopherol acetate) have been linked to allergic contact dermatitis. Vitamin E is beneficial against oxidation and has been related to various potential ailments and diseases, including cancer, ageing, arthritis, and cataracts

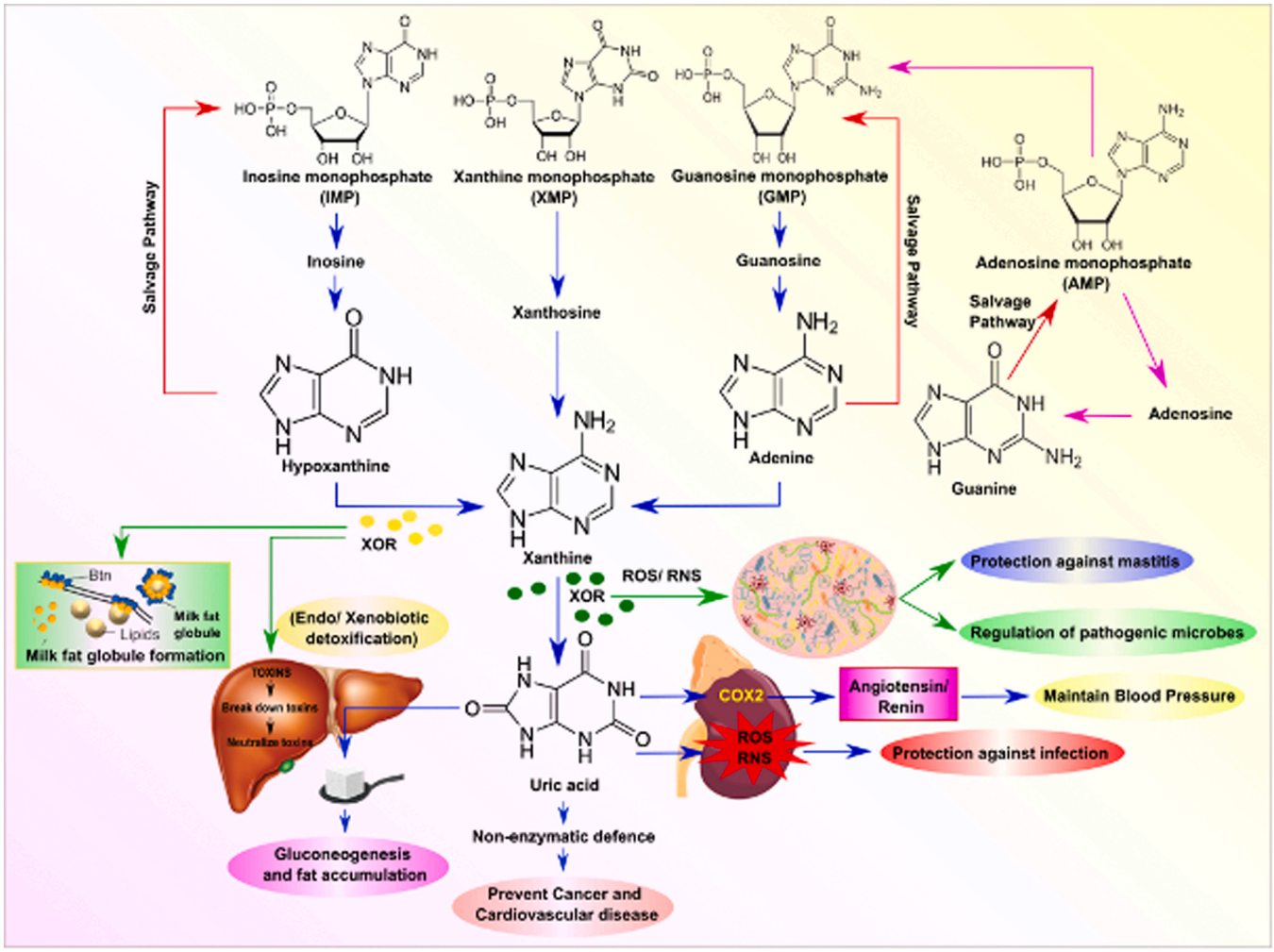

Fig. 9. : Catabolism of Xanthine and physiological role of Xanthine oxidoreductase (XOR) and uric acid.

[158].

Vitamin E is recognized to control redox equilibrium in the body due to its high concentration among lipid-soluble vitamin groups. It occurs ubiquitously throughout the body, including cell membranes and lipoproteins. However, it has been noted that the positive qualities of vitamin E, particularly its antioxidative actions, are only seen in vitro and not in vivo. As a result, there is an ongoing controversy about the biological roles of vitamin E and its link to redox equilibrium [159].

The first line of protection against the peroxidation of lipids in cell membranes is vitamin E, and the second line of defense is selenium [158]. Tocopherols work as antioxidants by interrupting free-radical chain reactions. In general, the antioxidative actions of vitamin E isomers are determined by the number of methyl groups on the chroman ring [159]. For example, α-TocH has three methyl groups in the chroman ring, whereas -tocopherol has one. It is generally recognized that the strength of antioxidative activity is in the order of $\alpha > \beta > \gamma > \delta$ among vitamin E isomers and that tocopherol is stronger than tocotrienol [160]. It is a potent chain-breaking antioxidant that prevents the formation of ROS molecules during fat oxidation and the propagation of free radical reactions [158]. It protects cell membranes from free radical assault by acting as the initial line of defense against lipid peroxidation [161]. It also preserves the polyunsaturated fatty acids found in membrane phospholipids and plasma lipoproteins due to its •OOH radical-scavenging action [158]. It may have anti-inflammatory properties and a role in enzyme regulation and gene expression. Humans seldom suffer from vitamin E insufficiency, which manifests clinically as hemolytic anemia [161].

9.6. Carotenoids

Carotenoids are structurally and functionally diverse groups of natural polyenescolors [162]. Carotenoids are an important class of isoprenoid pigments. Carotenoids are essential components of the photosynthetic organelles of all higher plants, including mosses, ferns, and algae. They can also be found in phototropic bacteria and cyanobacteria photosynthetic membranes [163]. They are excellent physical quenchers of singlet oxygen and scavengers of other ROS. Carotenoids can also operate as chemical quenchers in situations when oxygenation is irreversible. The molecular mechanisms behind these reactions remain unknown, particularly in the context of the anti- and pro-oxidant activity of carotenoids, which, while not synthesized by people or animals, are present in their blood and tissues and contribute to a variety of biochemical processes. The antioxidant capability of carotenoids is significant for human health because a loss of antioxidant-ROS equilibrium leads to oxidative stress, a vital element in the pathogenic processes of many chronic diseases [164]. Carotenoids and specific metabolites are thought to have a protective role in various ROS-mediated ailments, including cardiovascular disease, cancer, neurological disorders, and photosensitive or eye-related conditions [165].

9.7. Xanthene

Another significant family of heterocyclic compounds found in bioactive natural items and medicines and demonstrating a wide range of biological and pharmacological activity is xanthene derivatives, such

Table 1
Molecular Docking of enzymatic antioxidants with natural antioxidants.

Enzymatic Antioxidants	Natural Antioxidants	Binding affinity (kcal/mol)	Interacting AA Name; AA No;
Catalase	GSH	-6.6	**van der waals:** Pro69, Glu70, Glu118, Lys168, Arg169, Pro171, His174, Asn323, Tyr324, Phe325, Arg387, Asp388, Asn402 **Hydrogen bond:** Ile68, Ser119 **Attractive charge:** Glu329
	Vitamin E	-7.2	**van der waals:** Arg65, Gly366, Ile68, Pro69, Arg362, His363, Leu365, Pro367, Pro390, Met391 **Hydrogen bond:** His363 **Alkyl:** Pro390, Pro397
	Vitamin C	-6.7	**van der waals:** Glu66, His165, Lys168, Arg169, Pro171, His174, Asn323, Tyr324, Phe325, Arg387, Asn402 **Hydrogen bond:** Asp388, Asn396 **Unfavourable Donor-Donor:** Arg67
	Carotenoids	-9.6	**van der waals:** Gly120, Ser121, Val 125, Asp127, Gln167, Arg169, Lys176, Val181, Trp185, Leu 198, Phe199, Ala253, His 254 **Alkyl:** Ala122, Val125, Arg126, Lys176, Pro257, His465
	Catechin	-10.0	**van der waals:** Ile68, Pro69, Arg362, His363, Arg 364, Gly366, Pro367, Pro390, Met391, **Alkyl:** Pro69, Pro367, Pro390 **Hydrogen bond:** Arg 65, Arg67, Arg362, His363, Leu 365 **Unfavourable Donor-Donor:** Arg 65, His363
	Curcumin	-9.6	**van der waals:** Met60, Phe63, Arg111, Val72, Val73, Ser216, His217, Leu298, Leu331, Ala332, Phe333, Ala356, Thr360, His361 **Hydrogen bond:** Arg71, Asn147 **Carbon hydrogen bond:** His74, Tyr357 **Pi-cation:** Arg353 **Pi-Sulfur:** Met349 **Pi-Pi Stacked:** Phe152, Phe160
	Xanthine	-7.3	**van der waals:** Lys168, Asn170, Tyr324, Phe325 **Hydrogen bond:** Pro171, His174, Asn323, Asp388, Asn396, Asn402 **Pi-cation:** Asp388 **Pi-Sigma:** Pro171 **Alkyl:** Arg169, Arg387
SOD	GSH	-5.2	**van der Waals:** Leu106, Ser107, Gly108, Cys111, Ile113, Ile151, **Hydrogen bond:** Ala1, Leu106, Gly108, Cys111 **Unfavourable Positive-Positive:** Ala1
	Vitamin E	-6.9	**van der Waals:** Ser107, Gly108, Asp109, Asp109, Cys111, Ile113, Arg115, Ile151, **Alkyl:** Cys111, Ile113
	Vitamin C	-6.6	**van der Waals:** Val5, Cys6, Val7, Asp52, Gly147, Val148, Gly150 **Hydrogen bond:** Val7, Asn53, Gly147, Val148
	Carotenoids	-9.5	**van der Waals:** Thr2, Lys3, Leu106, Ser107, Glu49, Phe50, Gly108, Asp109, Cys111, Arg115, Ala152, Gln153 **Alkyl:** Cys111, Ile113, Ile151
	Catechin	-8.8	**van der Waals:** Cys6, Lys9, Gly10, Gly56, Cys57, Cys146 **Hydrogen bond:** Gly10, Asn53, Cys146, Gly147, **Pi-Alkyli:** Lys9, Val148
	Curcumin	-7.4	**van der Waals:** Ser107, Ile113, Ile151 **Hydrogen bond:** Ala1, Gly108, Asp109, Cys111 **Unfavourable Donor-Donor:** Ala1 **Pi-Alkyli:** Ile113
	Xanthine	-6.2	**van der Waals:** Cys6, Val7, Cys146, Gly147 **Hydrogen bond:** Val7, Asn53, Val148 **Unfavourable Donor-Donor:** Val148 **Pi-Alkyli:** Val148
GPX	GSH	-4.9	**van der Waals:** Lys137, Gly138, Asn141, Gly142, Ser170, Trp171, Asp172 **Hydrogen Bond:** Asn102, Gln103, Glu143, Lys144, **Salt Bridge:** Asp139
	Vitamin E	-5.6	**van der Waals:** Gly164, Thr165, Ser168, His158, Arg180, His200, **Hydrogen Bond:** Ser160 **Pi-Sigma:** Ile162 **Pi-Carbon:** Arg201 **Pi-Alkyl:** Trp181
	Vitamin C	-4.9	**van der Waals:** Ile162, Gly164, Thr165, Arg180, Trp181, His200, Arg201 **Hydrogen Bond:** Leu163, Ser168
	Carotenoids	-7.2	**van der Waals:** Gly105, Pro159, Ser160, Gly164, Ser168, Ser199, Arg201 **Alkyl:** Ile162, Lys167, Trp181, Arg180, His200,
	Catechin	-8.1	**van der Waals:** Leu75, Gly105, Ile162, Gly164, Thr165, Lys167, Ser168, Arg201 **Hydrogen Bond:** Gln107, Leu163 **Pi-Sigma:** Trp181 **Pi-Alkyl:** Arg180 **Unfavourable Acceptor-Acceptor:** His200
	Curcumin	-6.7	**van der Waals:** Gly74, Ser160, Leu163, Thr165, Arg180, His200 **Hydrogen Bond:** Leu75, Gln107, Gly164, Ser168, Arg201, **Pi-Sigma:** Ile162 **Alkyl:** Cys73 **Pi-Pi Stacked:** Trp181
	Xanthine	-5.1	**van der Waals:** Asn141, Gly142, Trp171 **Hydrogen Bond:** Gln103, Asp139, Glu143, Lys144, Ser170, Asp172

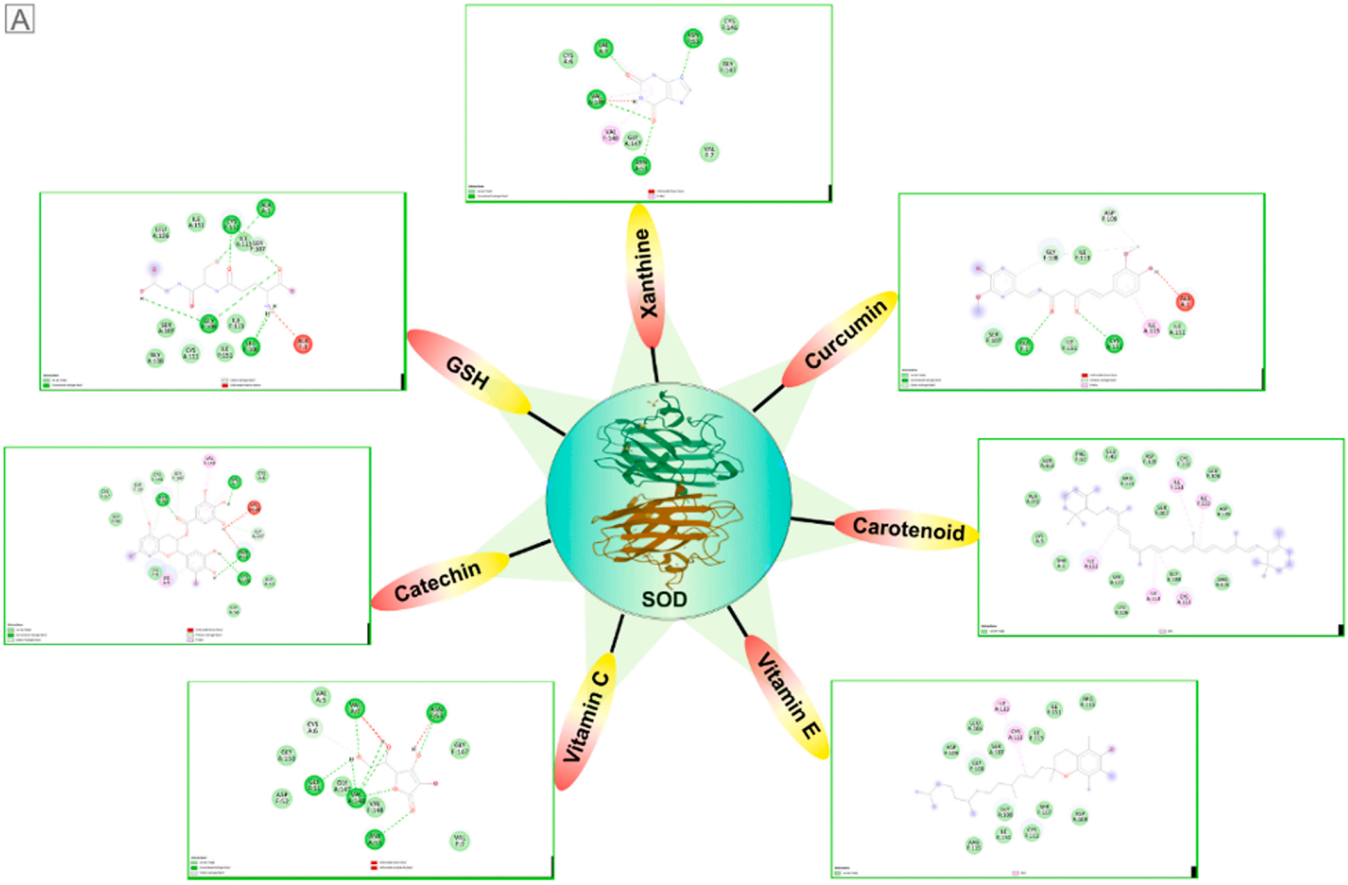

Fig. 10. : Molecular interaction study of antioxidants with SOD (A), Catalase (B), GPx (C).

as antimicrobial [166], antiproliferative [167], antibacterial [168], antiviral and antinociceptive activities [169], and antioxidant activity [170]. Moreover, xanthenes can be utilized to make stable laser dyes [171], fluorescent sensors [172] and protein labeling fluorophores [173] used in laser technology [174], functional materials for visualization of biomolecular assemblies [175], photodynamic therapy [176], and as antagonists [177].

Adenosine monophosphate (AMP), Guanosine monophosphate (GMP), Inosine monophosphate (IMP), and Xanthine monophosphate (XMP) are the monophosphate nucleotides involved in the catabolism of xanthine. Purine salvage pathways involve this process. Hypoxanthine-guanine phosphoribosyl transferase (HPRT) catalyzes the conversion of hypoxanthine and guanine to IMP and GMP, respectively, and adenine phosphoribosyltransferase (APRT) catalyzes the conversion of adenine to AMP. Xanthine oxidoreductase (XOR) catalyzes the conversion of Hypoxanthine to xanthine and then to uric acid. XOR and uric acid have different roles on the other side of the human body.

XOR aids in the secretion of apocrine lipids by apical membrane remodeling and enables Btn clustering and membrane docking of milk-fat droplets in the breast [22]. Lactoperoxidase uses the hydrogen peroxide (H_2O_2) and nitric oxide (NO) produced by XOR in milk to form hypothiocyanite and nitrogen dioxide. These compounds inhibit opportunistic bacteria's development, hence preventing breast mastitis. Additionally, the commensal flora of the newborn oral cavity, stomach, and intestine are unaffected by milk's bactericidal activity, which controls the intestinal microbiome. Therefore, XOR controls the newborn's development [44]. Reactive oxygen and nitrogen species (ROS and RNS) produced by XOR protect against opportunistic infections in the intestine. Most purine degradation occurs in the kidney; XOR is in charge of uricosuria, affecting uricemia levels. By increasing COX-2 expression and the renin/angiotensin pathway, XOR also helps to control blood pressure. The urinary system is kept sterile by XOR oxidant products. The uric acid generated by XOR affects lipids and glucose metabolism in the liver, promoting gluconeogenesis and fat accumulation [42]. Serum XOR derives from the physiological hepatic cell turnover, triggering liver enzymes' release from dead cells. Endothelial cells can be bound by circulating XOR, which promotes endothelial activation during inflammation, modifies vascular tone, and therefore aids in controlling blood pressure [36] (Fig. 9).

Numerous bioactive compounds, both natural and synthetic, include xanthene derivatives. For instance, benzoxanthenes are significant physiologically active oxygen-containing heterocycles with anticancer properties [2], antimycobacterial [3], and potent modulators of intestinal P-glycoprotein [4]. In addition, the useful spectroscopic features of these xanthene derivatives also made them valuable for laser technology [5], in fluorescent materials for the visualization of biomolecules [6], and as dyes [7]. Furthermore, xanthene derivatives, such as fluorescein and its derivatives, have been found to possess antioxidant properties and are effective in combating oxidative stress caused by ROS. They act by directly scavenging ROS and preventing oxidative damage to cellular components such as lipids, proteins, and DNA [22]. Additionally, some xanthene derivatives have been found to activate endogenous antioxidant systems, such as the Nrf2-Keap1 pathway, leading to an increase in the production of antioxidant enzymes. This dual action of xanthene derivatives makes them potential candidates for treating and preventing oxidative stress-related diseases, such as neurodegenerative disorders, cardiovascular diseases, and cancer [44].

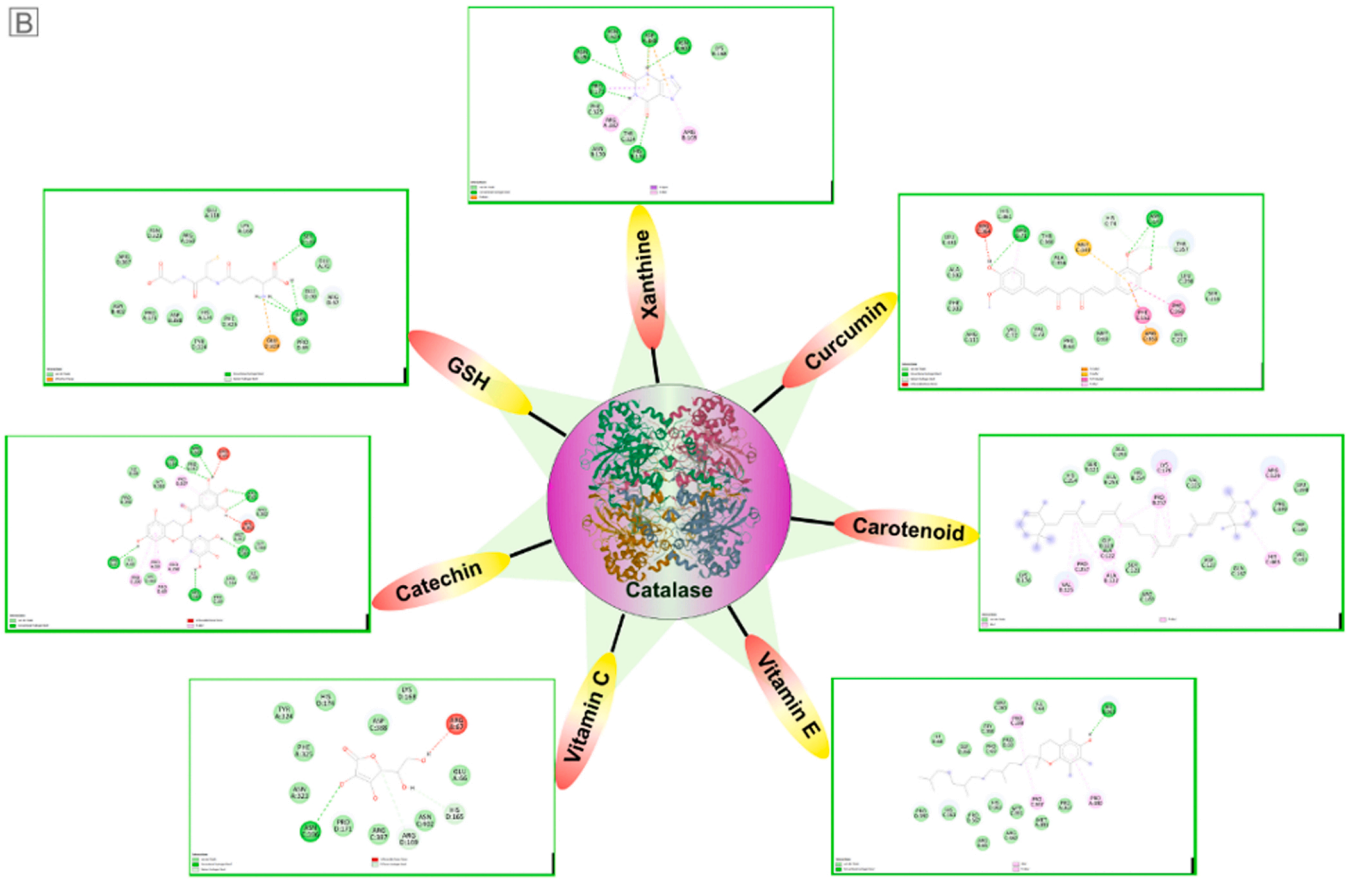

Fig. 10. (*continued*).

10. Action of antioxidants at the cellular and molecular level

In the current communication, a comparative docking study was conducted to evaluate the binding affinities of natural antioxidants with powerful antioxidant enzymes (Table 1). The interactions mentioned above were assessed using the molecular docking tool AutoDock 4.2 [178]. Following the AutoDock 4.2 interaction, the conformer with the lowest energy was chosen for investigation. The crystal structure of catalase (1tgu), Glutathione Peroxidase (2i3y), and SOD (2c9v) were retrieved from the Protein Data Bank (https://www.rcsb.org/) with resolution 2.8, 2.00 and 1.07 Å. Antioxidants' canonical SMILES ids were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and transformed into 3D structures using Chimera 1.11.2. Then, the binding site of antioxidants and binding energy were contrasted. Numerous factors were investigated to identify the ligands' binding areas in antioxidant enzymes, including binding affinity, receptor-ligand interaction site, atomic contact energy (ACE), and side amino acid residues. The analysis and visualization of results were complied with by Discovery Studio 2017 R2 Client (Fig. 10).

The above-mentioned natural antioxidants were docked with selected antioxidants enzymes. Catechin had the highest binding relationship towards catalase, i.e., − 10.0 kcal/mol, among other antioxidants. The findings also indicated that carotenoids and curcumin exhibited similar affinities while forming the complex with catalase. On the contrary, in the case of molecular interaction with SOD, carotenoids showed the highest binding affinity than other antioxidants, i.e., − 9.5 kcal/mol. The order of binding affinities of natural antioxidants towards SOD was followed by carotenoids>catechin>curcumin> Vitamin E > vitamin C>GSH. By catalase molecular interaction, similar binding affinities towards GPx were obtained. The highest affinity between GPx and catechin was found to be − 8.1 kcal/mol (Table 1). However, the binding affinities of natural antioxidants towards specific enzyme is independent of the nature of the antioxidants and their mode of binding.

From the docking scores, it can be surmised that all antioxidants have a strong binding affinity for antioxidant enzymes. The amino acid residues of antioxidant enzymes that form different chemical bonds (such as van der Waals forces, hydrogen bonds, and alkyl bonds, etc.) with selected antioxidants differ among enzymes. However, molecular docking investigations have suggested that binding affinities of catechin, curcumin, and carotenoids are higher than other antioxidants. Due to more functional OH groups than other antioxidants, catechin, curcumin, and carotenoids have a significant binding affinity towards the receptor.

11. Conclusion

Numerous defense mechanisms are implicated in the battle against these highly reactive molecules. Among them, both enzymatic and non-enzymatic antioxidants are the requisites for neutralizing the damaging effects of free radicals. In the current review, an attempt was made to summarize the potentiality of both enzymatic and non-enzymatic against the increased/imbalanced generation of free radicals, which is the key inducer of many pathological disorders, including cancer, diabetes, inflammatory joint disease, and asthma. However, the precise roles of free radicals in the pathogenesis of various diseases are still unknown. Since many issues concerning the use of antioxidant supplements in disease prevention remain unresolved, the current assessment is based on elucidating the defense mechanism of both enzymatic and non-enzymatic antioxidants against the toxic effect of free radicals as the cryptic role of these antioxidants in maintaining redox homeostasis.

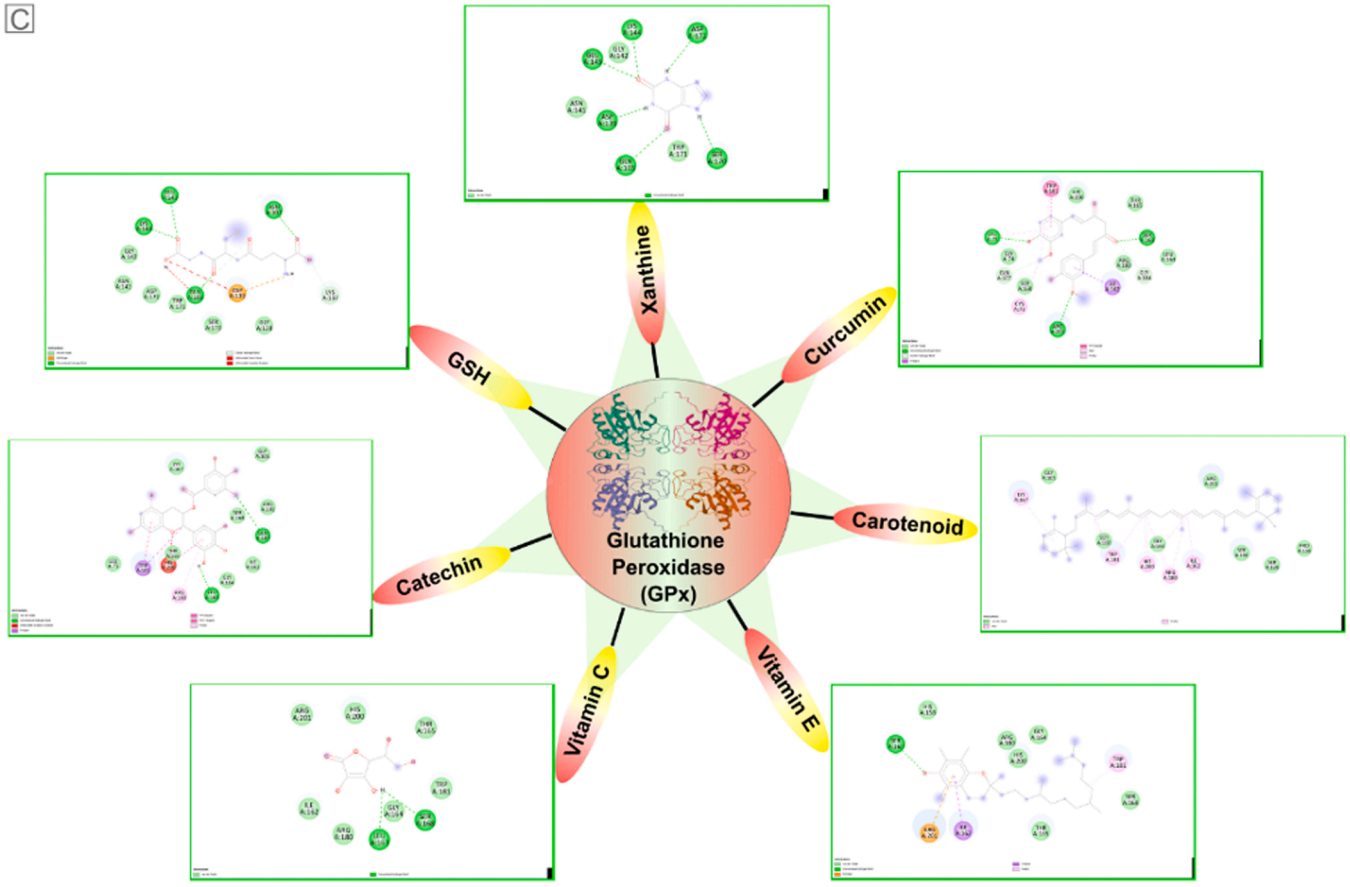

Fig. 10. (*continued*).

Ethical approval

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

AB and AKDR conceived the project. AB, RRS, and NKB participated in data extraction and analysis, prepared figures, and wrote the manuscript. AB and AKDR revised the manuscript. All the authors read and approved the final manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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None.

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