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Review Article

Antioxidant-enzyme Interaction in Non-communicable Diseases

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Abstract

Free radicals are produced in the body during normal cellular metabolic activities, and their excessive accumulation can overwhelm the natural antioxidant mechanisms. This leads to oxidative stress, which is associated with the development and progression of non-communicable diseases (NCDs) such as liver and kidney diseases, cardiovascular diseases, neurodegenerative diseases, cancer, and diabetes. Enzymes play a significant role in maintaining a balance between antioxidants and free radicals by either enhancing the production of antioxidants or slowing down the generation of free radicals in the body. There is no up-to-date review on how antioxidant-enzyme interactions modulate the development and progression of NCDs. This review, therefore, discusses the mechanisms of antioxidant-enzyme interactions in the control of oxidative stress, as well as the implications and prospects of these interactions in the management of NCDs. Therapeutic strategies targeting antioxidant-enzyme interactions in the natural defense mechanisms of the body against oxidative stress can provide targeted benefits in the management of various NCDs. The mechanisms of interaction of some antioxidants with catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, glutathione S-transferases, thioredoxin protein, and thioredoxin reductase suggest their strong involvement in mitigating the development and progression of NCDs. Moreover, understanding the specific interactions and signaling pathways involved in antioxidant-enzyme interactions could facilitate the emergence of novel and effective therapeutic strategies for the management of NCDs and should be considered a primary goal of future studies. This study provides the necessary template, encourages discussion, and creates more opportunities for the next stage in the development of antioxidant therapies.

Introduction

Antioxidants are enzymatic (endogenous) or non-enzymatic (exogenous) chemicals that form a major line of defense against reactive oxygen species (ROS) by inhibiting the propagation of free radicals or interrupting their formation, resulting in reduced oxidative stress, improved immune function, and increased healthy longevity.[1,2] While endogenous antioxidants are produced inside animal cells, exogenous enzymes must be supplemented through the diet due to the lack of a synthetic pathway for the latter.[1] Both endogenous antioxidants and free radicals are products of physiological activities and are present in biological systems, although the former keeps the latter in check. However, when ROS is produced at a higher concentration than antioxidants, pathological conditions such as oxidative stress and the associated diseases occur.[3] These diseases, including obesity, neurodegenerative diseases, cardiovascular diseases, certain types of cancer, type-2 diabetes, and aging, which result from the impact of oxidative stress, are classified as non-communicable diseases (NCDs).[4] Additionally, lifestyle factors such as tobacco and alcohol abuse, physical inactivity, and unhealthy diets have been identified as the main risk factors contributing to NCDs.[4]

Non-communicable diseases are known to cause slow, progressive damage to target cellular tissues, with high morbidity and mortality rates globally.[5] Low- and middle-income countries have been reported to have higher mortality rates from NCDs, with an eightfold increase projected by 2030 compared to developed coun-

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tries.[5] According to Bao *et al*., the intervention in NCDs depends on identifying, preventing, and controlling modifiable behavioral risk factors such as smoking, diabetes, hypertension, overweight, and alcohol use.[5] However, the use of medicinal plants with antioxidant properties has been explored for their ability to treat or prevent several human pathologies, with oxidative stress being one of the underlying causes. In a review elsewhere, the authors suggested that antioxidants in diets can prevent NCDs.[6] The bioavailability of these antioxidants, which determines their effectiveness in combating NCDs or oxidative stress-related diseases, depends on their interactions with certain proteins/enzymes in the biological system. It is also believed that antioxidants, when co-ingested with proteins or other food nutrients, can either enhance or reduce the bioavailability of antioxidants, depending on the type of antioxidant and/or food nutrient.[7]

Apart from antioxidant bioavailability, some antioxidant-protein interactions lead to protein modifications that alter protein function, which becomes medically significant depending on the type of protein involved. For instance, antioxidant interaction with the protein responsible for cancer onset and progression alters its function, resulting in anticancer effects.[7] The function of certain protein enzymes, as well as some antioxidants, has been enhanced through antioxidant-protein interactions. The protein modification resulting from interactions with antioxidants makes the protein resistant to oxidation, thereby preventing disease conditions arising from protein oxidation. According to some authors, the interaction between dietary antioxidants and enzyme antioxidants forms an integrated antioxidant system that can help manage immune-mediated oxidative stress.[8] It appears that antioxidant-protein interactions play a significant role in the control and management of oxidative stress-related diseases such as NCDs. Therefore, this review focuses on exploring the role of antioxidant interactions in the control and management of NCDs.

Mechanism of scavenging ROS

Oxidative stress represents an imbalance between free radical production and the system's ability to mitigate its negative impacts on DNA, proteins, and lipids. This situation has been shown to lead to the onset and progression of various NCDs, including rheumatoid arthritis, Alzheimer's disease (AD), and cancer.[2,3,9] Antioxidants can reduce the harmful effects of ROS and prevent the processes that cause cellular damage. As a result, cells have networks of antioxidants to scavenge excess ROS in the system. Two types of antioxidants are produced by living organisms: enzymatic and non-enzymatic. Both types of antioxidants participate in the process of scavenging ROS (oxidants).

Non-enzymatic antioxidants act directly on oxidative agents by either donating electrons or hydrogen atoms to free radicals to neutralize their harmful effects. This group includes ascorbate, α-tocopherols, carotenoids, flavonoids, polyphenols, etc. Vitamin E (α-tocopherol) has been shown to inhibit the generation of new ROS, while γ-tocopherol captures and neutralizes existing ROS.[10] Vitamin C is an effective electron donor that reacts with oxygen (O_2) to form a more stable compound, thus preventing oxidative damage.[9] It donates electrons to free radicals, scavenges their damaging reactions, and plays a major role in the detoxification of oxidants in the brain. Vitamin C helps regenerate other antioxidants, such as vitamin E, by stabilizing them when they are engaged in neutralizing oxygen radicals. This interplay between vitamins C and E radicals occurs not only in homogeneous solutions but also in the transmembrane system, where they reside on different sides of the membrane, with Vitamin C providing a synergistic effect that helps prevent membrane oxidation.[11] This is achieved through the continuous regeneration of vitamin E. This interaction is capable of protecting brain cells during stress conditions.[12]

Another important antioxidant is β-carotene, which inhibits the lipid peroxidation process. β-carotene traps and neutralizes free radicals of carbon origin (organic) and deactivates ROS produced during metabolic reactions.[13] There is evidence suggesting that carotene-rich foods can protect against cancer.[14] The potential of β-carotene to mop up free radicals depends on oxygen concentration. Under low oxygen tension, β-carotene acts as an antioxidant, but under higher oxygen concentrations and more oxidizing conditions, it acts as a pro-oxidant.[15] β-carotene combines with peroxy radicals to form a carbon-entered radical and then combines with another lipid peroxide to form a stable compound.[10]

Other endogenous antioxidants are produced by cells that bind to redox metals and prevent them from indirectly causing oxidative damage. One of the most important endogenous scavengers is melatonin. Melatonin is involved in scavenging hypochlorous acid and deactivating chemical agents such as H_2O_2, OH*, peroxyl radical, and reactive nitrogen species through electron donation, hydrogen donation, addition, substitution, and nitrosation, thus preventing oxidative stress.[16,17] Ubiquinol (coenzyme Q), glutathione, and 3,4-dihydroxyphenylalanine are other endogenous scavengers. 3,4-dihydroxyphenylalanine is currently used in the management of Parkinson's disease (PD).[18]

Enzymatic antioxidants (scavengers) include catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx), glutathione S-transferases, thioredoxin protein, and thioredoxin reductase. Catalase deactivates H_2O_2 to produce water and oxygen, with Fe or Mn serving as cofactors. The enzymes of the glutathione system contribute to the deactivation of H_2O_2 and hydroperoxides, utilizing selenium as a cofactor.[19] The activities of these enzymes help break down H_2O_2 into H_2O and O_2, thus preventing oxidative stress. The thioredoxin system acts as a scavenger for ROS, while SOD uses Cu, Zn, and Mn as cofactors to break down superoxide anions into H_2O_2 and O_2.[20]

Antioxidant-enzyme interaction

Free radicals are continuously produced during cellular metabolism. These free radicals are generated from molecules of oxygen, nitrogen, and sulfur, which, because of their unpaired electrons, react vigorously with other molecules to generate ROS and RNS. When allowed to accumulate in the body, these free radicals can damage nucleic acid bases, the side chains of amino acids in proteins, and unsaturated lipids. This results in damage to DNAs, RNAs, lipid cell membranes, and proteins, which subsequently leads to the onset of several NCDs.[21]

Antioxidants are compounds that can decrease the damage caused by ROS and RNS by converting them into less harmful molecules. The interaction between antioxidants and enzymes plays a vital role in the defense system against oxidative damage. Antioxidants neutralize free radicals and stabilize them, while enzymes catalyze reactions that convert ROS into less harmful substances. Antioxidants also indirectly reduce oxidative damage by preventing the expression of enzymes responsible for generating ROS, such as NAD(P)H oxidase and xanthine oxidase, or by promoting the activity or expression of free radical scavengers.

The antioxidant molecules can also interact with other physiological enzymes to either increase or decrease their activities. These interactions between antioxidants, enzymatic antioxidants,

Table 1. Implications of antioxidants and metabolic enzymes (and other biological molecules) interactions in the management of NCDs

Antioxidants	Interaction with enzymes and protein	Implication in the management of NCDs
Phenolics[24,25]	Inhibits the activity of Fatty acid synthase, acetyl CoA carboxylase and HMG CoA reductase	Reduction in the cholesterol level. Reduces risk of cardiovascular disease. Reduces the synthesis of fats
Terpenoids[23]	Enhances phosphoinositol-dependent kinase-1 (PDK-1) protein kinase B activities	Increased glucose uptake and reduced chances of diabetes
Flavonoids[22]	Inhibits the activities of Inflammatory enzymes such as Nitric oxide synthase, cyclooxygenase- 2, lipoxygenase (LOX)	Prevent inflammation
Melatonin[27]	Inhibits glucose-6-phosphate dehydrogenase (GPDH) activity	Limit energy metabolism in prostate cancer and suppress cancer growth
Polyphenol[28]	Inhibits the estrogen receptors and human epidermal growth factor receptor 2	Suppression of tumor cells
(−)-Epigallocatechin-3-gallate (EGCG)[29]	Enhance the activities of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), protein kinase B, and insulin receptor substrate 1(IRS)	It enhances insulin activity, increases glucose uptake, and reduces the chances of diabetes
Quercetin[26]	Binds to the poly-ADP-ribose polymerase (PARP) and telomerase	Stabilize the DNA and reduce the risk of non-communicable such as cancer, and cardiovascular diseases
Resveratrol[30]	Binds the estrogen receptor-α	Modulate the inflammatory process
(+)-Catechin[31]	Inhibits pro-oxidant enzymes such as nitric oxide synthase, lipoxygenases, cyclooxygenases, and xanthine oxidase	Reduces free radical generation and risk of NCD
(−)-Epigallocatechin-3-gallate (EGCG)[32]	Increase the level of E-cadherin and decrease the levels of β-catenin, cellular Myc (c-Myc), and phosphor-AKT (AK strain transforming)	Tumor suppression
Anthocyanins (flavonoids)[33]	Inhibit COX-1 and COX-2 and LOX	Reduces inflammatory process
Flavone and flavanols[34]	Inhibits xanthin oxidase	Reduce the risk of atherosclerosis
Tannin, flavonoids, and phenolic acids[35]	Inhibits alpha glucosidase	Reduce sugar level and risk of type 2 diabetes

COX, cyclooxygenase; HMG-CoA, hydroxymethylglutaryl-coenzyme A; LOX, lipoxygenases; NCDs, non-communicable diseases.

and other physiological enzymes are crucial for developing strategies to promote a healthy life and prevent or manage diseases arising from oxidative stress. The management of NCDs may be influenced by the interactions between antioxidants and metabolic enzymes (Table 1).[22–35] As the mechanisms involved in antioxidant-enzyme interactions are better understood, more information about cellular defense systems and potential therapeutic interventions will emerge.

Mechanism of antioxidant-enzyme interaction

The regulation of antioxidant enzyme activity serves therapeutic purposes in managing NCDs. Antioxidant enzymes help neutralize excessive ROS, thus reducing oxidative damage to cells and tissues. They achieve this by transforming harmful ROS into less reactive or non-toxic by-products. This section focuses on how interactions between antioxidant enzymes and other molecules can either prevent the production of ROS or enhance their efficient deactivation. To protect cells against oxidative damage, organisms have developed self-defense mechanisms, which depend primarily on the availability of antioxidant enzymes and their substrates (oxidants).[20] The concentration of oxidants determines whether these defenses are upregulated or downregulated, maintaining the capacity to deactivate oxidants and repair oxidative damage. Any agents or cellular activities that alter this defense mechanism become potential targets for antioxidant therapy. Antioxidant enzymes play a crucial role in neutralizing excessive ROS, protecting cells and tissues from oxidative damage, and reducing the onset or progression of NCDs. Over the past few decades, the regulation of antioxidant enzyme activities has been the focus of extensive research. These enzymes are mainly modulated by the concentration of oxidants in the cells. These oxidants are the primary modulators of antioxidant enzymes. The interactions of some antioxidant enzymes with oxidants, antioxidants, or other bioactive molecules contribute to the management of NCDs, as briefly described below.

Antioxidant-glutathione peroxidase interactions

Reports have shown that melatonin (an antioxidant) interacts with and modulates the enzymatic antioxidant activities and their translation from mRNA.[36] Some of the enzymes whose interactions with melatonin have been studied include glutathione reductase (GRd), GPx), and glucose-6-phosphate dehydrogenase.[1] It has been established that melatonin stimulates GPx *in vivo*, enhancing GPx activity, during which H_2O_2 is metabolized to H_2O, and glutathione (GSH) is oxidized to its disulfide form GSSG (Fig. 1). Glutathione is then regenerated from GSSG via a reaction pathway catalyzed by GRd, which is also stimulated by melatonin.[37] This

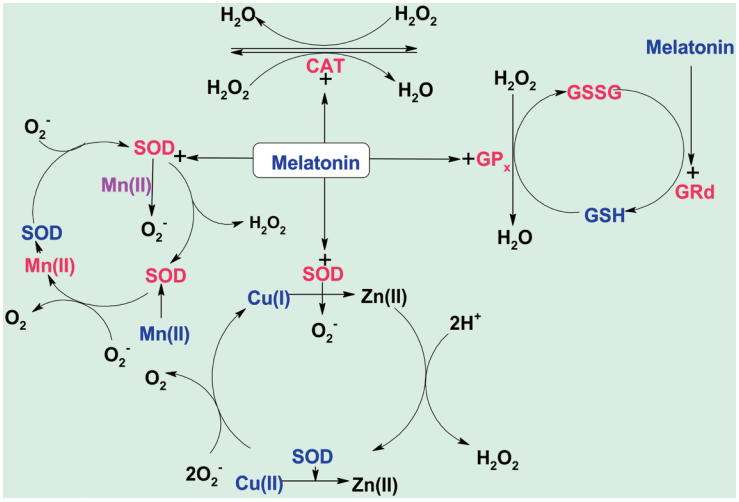

Fig. 1. Interactions of melatonin with antioxidant enzymes. CAT, Catalase; SOD, superoxide dismutase; GPx, glutathione peroxidase; GRd, glutathione reductase; GSH, glutathione; GSSG, oxidized glutathione.

regeneration of GSH from GSSG is one of the roles of melatonin in reducing or preventing free radical damage. The capacity of melatonin to control the GSH/GSSG balance through its influence on enzyme activities requires melatonin to bind to the nuclear binding site, thereby increasing enzyme expression.

Ma *et al*. observed that melatonin enhances the production and activity of GPx and GRd by binding to nuclear receptors.[38] The binding is facilitated by receptors such as retinoic acid receptor-related orphan receptors α, β, and γ.[39] The interaction between melatonin and antioxidant enzymes ultimately leads to reduced oxidative stress and helps minimize the contribution of free radical damage to the progression of NCDs. Another antioxidant-enzyme interaction between phenolic compounds and GPx has been beneficial in managing fatty liver and atherosclerosis.

Antioxidant-superoxide dismutase interactions

The interaction between plant antioxidants (flavonoids), the antioxidant enzyme SOD, and inflammatory enzymes such as nitric oxide synthase and cyclooxygenase-2 (COX-2) has been shown to prevent inflammation. Ji *et al*. reported that SOD reduced the production of inducible nitric oxide synthase (iNOS) and COX-2 in a murine macrophage cell line.[22] iNOS catalyzes the production of nitric oxide (NO) in cells. Overproduction of NO has been linked to the initiation of inflammatory responses.[40] On the other hand, high concentrations of NO favor the formation of reactive nitrogen and oxygen species, which are implicated in stress and subsequent physiological effects. Similarly, Guerra *et al*. reported that all flavonoids inhibited the synthesis of iNOS and COX-2, a mechanism contributing to their anti-inflammatory properties.[40] Therefore, the interaction between antioxidants and iNOS/COX-2 presents a possible target for inflammation management.

SOD has also been shown to enhance insulin sensitivity through its influence on insulin receptor substrate 1 and protein kinase B. Overexpression of SOD ameliorated induced insulin resistance in experimental rats, and glucose uptake was increased by 50%.[41] The result demonstrated that increasing SOD activity offered protection against diet-induced diabetes. In their experiment, Song *et al*. demonstrated the use of terpenoids (a phytochemical with antioxidant activity) for the treatment of diabetes.[23] They administered a terpenoid-rich *Dillenia indica L* extract to streptozotocin-induced diabetic mice and explored the mechanism. The results indicated that the extract increased the production of insulin receptor substrate-1, inhibited phosphoinositol-dependent kinase-1 and protein kinase B, but enhanced glucose transporter 4 activity, thus increasing glucose absorption.

Similarly, Maksimenko and Vavaev demonstrated that extracellular SOD reduced the progression of atherosclerosis, hypertension, cardiac failure, and diabetes.[42] To formulate an antioxidant therapy, they developed various SOD isoenzyme-catalase conjugates for gene therapy and found that a covalent bi-enzyme SOD-CHS-CAT conjugate was the most effective and safest drug candidate.

Antioxidant-catalase interaction

The interaction between phenolic compounds and antioxidant enzymes, such as CAT and SOD, has been beneficial in the management of fatty liver and atherosclerosis.[43] Phenolics indirectly reduce fatty acid synthesis by inhibiting lipid-metabolizing enzymes such as fatty acid synthase and acetyl-CoA carboxylase, as well as lipogenic transcription factors.[24] There have been reports that phenolics also inhibit the expression of both HMG-CoA reductase, involved in the regulation of cholesterol biosynthesis, and sterol regulatory element-binding protein-2, which triggers HMG-CoA for cholesterol biosynthesis in the liver.[25] The inhibition of these two proteins leads to a reduction in cholesterol levels, potentially benefiting the treatment of atherosclerotic conditions. Ma *et al*. observed that melatonin enhances the production and activity of CAT by binding to nuclear receptors.[44] This interaction between melatonin and CAT ultimately reduces oxidative stress, helping to minimize free radical damage, which contributes to the progression of NCDs.

It is also important to note that free radical damage can lead to abnormal DNA, a condition that may contribute to the onset of NCDs. It has been reported that antioxidants can indirectly interact with poly (ADP-ribose) polymerase to restore damaged DNAs.[2,40] Natural antioxidant sources reduce DNA damage resulting from radiation.[45] Quercetin, a phytochemical compound with known antioxidant properties, has previously demonstrated anti-cancer effects.[46]

Available research shows that quercetin also binds to the telomerase sequence in humans, stabilizing DNA structures (G-quadru-

Table 2. Implications of dietary (non-enzymatic) and enzymatic antioxidants interactions in the management of NCDs

Non-enzymatic antioxidant	Enzymatic antioxidants	Effect of their interaction	Implication in the management of NCDs
Flavonoids[47]	SOD, COX-2 and iNOS	Enhanced production of SOD which suppresses the production of COX-2 and iNOS	Anti-inflammatory effect and reduced oxidative stress
Melatonin[1,36,38]	(SOD).CAT, GRd, GPx and SOD	Increase in the activity and expression of CAT, (GRd), GPx) and (SOD)	Regeneration of GSH from the GSSG which prevents free radical damage and reduces oxidative stress
(+)-Catechin[48]	GST and SOD	(+)-Catechin induces the production of glutathione S-transferases (GST) and SOD	Reduces free radical damage
Flavonoids[49]	SOD and CAT	Enhanced activities of Superoxide dismutase (SOD) and catalase (CAT)	Reduces the number of free radicals
Vitamin C[11]	SOD, CAT and GPX	Increase in the activities of SOD, CAT and GPX	Reduced oxidative stress
Vitamin E[11]	SOD	Reduced activity of SOD and decrease MDA level	Prevent lipid peroxidation, protect the brain cells during stress and reduce oxidative stress
Quercetin[24]	SOD, CAT and GSH	Quercetin enhances the activity of SOD, CAT and GSH	Reduced oxidative stress
Phenolics[24,43]	GPx, CAT and SOD	Increase in the activities of GPx, CAT and SOD and inhibition of HMGCoA reductase	Reduction in cholesterol level prevents atherosclerosis and reduces oxidative stress

COX, cyclooxygenase; GPx, glutathione peroxidase; GRd, glutathione reductase; GSH, glutathione; HMG-CoA, hydroxymethylglutaryl-coenzyme A; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; SOD, superoxide dismutase.

plex structure).[26] During this binding, a DNA duplex may form, further stabilizing and protecting it from oxidative damage. These interactions could protect DNA and promote DNA repair, thus reducing the accumulation of mutated genes and, in turn, decreasing the risk of NCDs. The management of NCDs can be influenced by the interaction between enzymatic and non-enzymatic antioxidants in food (Table 2).[1,11,24,36,38,43,47-49]

Antioxidant defense system

The protection of body cells and tissues from oxidative stress occurs through multiple mechanisms. These antioxidant defense systems are crucial in maintaining health and preventing oxidative damage. Antioxidants are either produced by the cell (endogenous) or obtained from dietary sources (exogenous). They are classified into enzymatic and non-enzymatic categories. Antioxidant defense systems can be broadly categorized into four types: preventive antioxidants, radical scavenging antioxidants, repair antioxidant systems, and cellular signalling antioxidant defense systems.[27]

The preventive antioxidant system comprises molecules that inhibit oxidative damage by suppressing the supply of ROS. Patekar *et al.* noted that antioxidant enzymes prevent oxidation by either preventing chain initiation or stabilizing metal ions that generate free radicals.[44] Proteins such as transferrin and caeruloplasmin chelate metals (iron and copper, respectively), preventing free radical formation. These antioxidants act rapidly to neutralize potential oxidants before they fully develop into reactive species.[28] They serve as the front-line defense against oxidants.

Radical scavenging antioxidants suppress the initiation and break oxidative chain reactions. These antioxidants scavenge ROS by transferring electrons to them, converting into radicals of lower oxidative potential. The newly formed radicals are then neutralized by other antioxidants. The antioxidants involved in this system include vitamin C, uric acid, albumin, bilirubin, and GSH, which are water-soluble. Others, such as vitamin E and ubiquinol, are lipid-soluble.[29] This category of antioxidants is also referred to as the second line of defense.[28]

The repair antioxidant system acts after oxidative damage has occurred. It comprises enzymes that repair damage caused by free radicals to biological molecules (DNA, proteins, and lipids) and mend cell membranes. These antioxidants recognize, degrade, and remove modified macromolecules, preventing their accumulation.[29] Popular antioxidants in this system include enzymes that repair damaged DNA (polymerases, glycosylases, and nucleases), along with proteolytic enzymes (proteinases, proteases, and peptidases). These are known as third-line antioxidants.

The fourth line of defense is the adaptation (cellular signalling antioxidant defense) system. These antioxidants are involved in adaptation processes that use signals generated by the formation and reaction of free radicals to prevent further oxidant production.[30] In this case, the signal generated by the presence of radicals stimulates the production and transportation of specific antioxidants to the site of damage.[28] All of these antioxidant defense systems work together to minimize the negative impact of oxidative damage.

Non-communicable diseases and antioxidant-enzyme interaction

Medical conditions that are not generally transmissible and are caused by non-infectious agents are referred to as NCDs.[31] Examples include cardiovascular diseases, cancer, neurodegenerative diseases, diabetes, and chronic hepatic diseases. The accumulation of free radicals in the body overwhelms the natural antioxidant mechanisms, causing oxidative stress, which is linked to the development and progression of NCDs.[32] Enzymes play a significant role in maintaining a balance between antioxidants and free radicals by either generating or breaking down ROS.[1]

Antioxidant-enzyme interaction in cardiovascular diseases

The interactions between antioxidants and enzymes are crucial

for maintaining the antioxidant defense system of the body and protecting it against oxidative stress.[33] Oxidative stress is associated with the pathophysiology of cardiovascular diseases (CVDs), while antioxidants are involved in neutralizing ROS and protecting against oxidative stress.[34] Enzymes such as CAT, SOD, and GPx are important components of the body's antioxidant defense system. Supplementation with antioxidants can enhance enzyme activity and reduce oxidative stress in patients with CVDs.

Many studies have investigated the interactions between antioxidants and enzymes in CVDs.[1,35,47] SOD catalyzes the dismutation of highly reactive superoxide radicals. Hypertension and atherosclerosis have been associated with an increased risk of CVDs.[48,49] Supplementation with antioxidants can increase the activity of SOD and decrease oxidative stress in patients with CVDs. Decreased catalase activity can lead to the development of atherosclerosis.[30] Catalase catalyzes the disintegration of hydrogen peroxide.[48] Vitamins C and E can enhance catalase activity and decrease oxidative stress.[35] Reduction of hydrogen peroxide and organic hydroperoxides is catalyzed by GPx. Supplementation with antioxidants enhances GPx activity and decreases oxidative stress in patients with CVDs.[50–52]

Numerous studies have shown that different antioxidants, including enzymatic and non-enzymatic antioxidants, enhance the bioactivity of ROS and/or decrease the severity of atherosclerosis.[53–55] It has been determined that vitamin A is a helpful supplement that may lower vascular oxidative stress in diabetic patients with ischemic heart disease.[35] In both male and female patients undergoing coronary artery bypass, melatonin administration may lessen myocardial ischemic-reperfusion injury.[56] Additionally, blood pressure is lowered in male hypertension patients by vitamins E, A, and C.[48,49]

Antioxidant-enzyme interaction in neurodegenerative diseases

Antioxidant-enzyme interactions are important for guarding against oxidative stress and preventing neurodegeneration. PD, AD, and Huntington's disease, which are neurodegenerative diseases, are characterized by the progressive loss of neurons in the brain and nervous system.[57] Oxidative stress causes the development and progression of these diseases. Antioxidant enzymes such as catalase, SOD, and GPx have the potential to protect neurons from oxidative damage and neurodegeneration.[58] Deficiency of these enzymes results in elevated levels of neurodegenerative diseases. The role of GPx as a crucial antioxidant enzyme has been further supported by many studies exploring the therapeutic potential of antioxidant compounds in neurodegenerative diseases.[59–61] These studies have demonstrated that these compounds, in addition to other mechanisms, act by upregulating GPx levels. Some naturally occurring antioxidants employed to regulate GPx include tomato seed extract, imperatorin, and the dietary flavonoid rutin.[60]

Beta-carotene and vitamins C and E neutralize free radicals and decrease oxidative stress in the brain.[62] There are suggestions that a combination of antioxidants and enzymes may be more effective in protecting against neuronal damage in PD.[63] For instance, a combination of SOD and vitamin E protects against neurodegeneration in PD. Since they can fight free radicals, antioxidants have a substantial impact on human health by potentially delaying the aging process. In particular, vitamin C serves as a potent antioxidant in reducing the consequences of oxidative damage brought on by, among other factors, pollution, anxiety, and poor diets.[64] As a result, there is a decreased long-term risk of neurodegenerative disorders. Polyphenols, a type of naturally occurring antioxidant, have been shown to have neuroprotective properties.[65] This protection is achieved through a variety of biological processes, including interactions with transition metals, neutralization of free radicals, modification of the activity of different enzymes, and impacts on intracellular signaling pathways and gene expression. Since antioxidants have been shown to lower oxidative stress markers, it can be assumed that they will be helpful in the prevention and treatment of these disorders.

Due to the important role oxidative stress plays in the etiology of AD, antioxidant therapy has received significant research attention and is effective in the treatment and prevention of AD.[66] The neurotoxic effects of peroxyl radicals can be slowed down by vitamin E, which has been proven to be highly effective against them. Vitamin E appears to impact peroxidation activity through both physical contact with a polyunsaturated lipid substrate and a mechanism for scavenging free radicals, such as hydrogen atom donor activity.[35]

Numerous clinical trials are being conducted to determine whether vitamin E has significant therapeutic advantages in AD. Lipid peroxidation and total glutathione in the central nervous system increased in response to vitamin E deficiency, serving as histological and molecular markers of oxidative stress.[50,63,60] Vitamin E considerably lowers oxidative and nitrosative damage in AD. Vitamin E and *Ginkgo biloba* extracts have been demonstrated to enhance cognitive performance.[67] Vitamins D and E supplements, in combination or alone, may slow down neuronal morphological changes and enhance learning and memory in AD patients.[64] In rats exhibiting symptoms of post-traumatic stress disorder, vitamin E prevented memory loss.[68]

Antioxidant dietary sources have also been demonstrated to have favorable effects in AD. It has been demonstrated that apple cider increases the activity of GPx, SOD, and CAT with a corresponding decrease in lipid peroxidation.[50] Vitamin C, E, carotenoids, flavonoids, and polyphenol-rich diets have been shown to support standard therapy for AD.[60] Rutin, myricetin, and hesperidin are dietary flavonoids that have positive effects on the treatment of Huntington's disease.[63] Typically, these effects are achieved by activating the nuclear erythroid 2-related factor 2 (Nrf2) neuroprotective and cytoprotective pathways.

Antioxidant-enzyme interaction in cancer

Antioxidant-enzyme interactions are important in cancer progression and development. Cancer cells produce high levels of ROS as by-products of their metabolism.[32,69] ROS cause DNA damage and promote cell proliferation and survival. To cushion the effects of ROS, cancer cells activate antioxidant pathways.

Many studies have illustrated the interactions between antioxidants and enzymes in the growth and development of cancer. Elevated levels of exogenous antioxidants have been demonstrated to inhibit the types of free radicals linked to the emergence of cancer in laboratory and animal studies.[47] Reduced GPx activity is linked to elevated cancer risk and progression in breast, lung, and prostate cancer. Overexpression of SOD in cancer cells can promote tumor growth by decreasing the levels of ROS. The expression of catalase is also altered in cancer cells, most likely to promote cell proliferation by causing genomic instability and oncogene activation.[70] Increased levels of catalase are associated with elevated metastasis of cancer cells. Despite the possibility that additional mechanisms are also at play, the regulation of catalase expression seems to be primarily controlled at the transcriptional level.

Targeting antioxidant enzymes can be an effective strategy for cancer treatment.[1] For instance, modulating the expression of catalase by targeting the reduction of cancer cells. Inhibition of GPx

has been shown to sensitize cancer cells to chemotherapy and radiation therapy by increasing the levels of ROS and inducing cell death.[58]

Antioxidant-enzyme interaction in diabetes

Diabetes, as a metabolic disorder, is associated with an imbalance between the generation of ROS and the antioxidant defense system.[71,72] Several interactions between antioxidants and enzymes occur in diabetes. SOD activity in diabetes is reduced due to the glycation of the enzyme, which leads to an accumulation of superoxide radicals and oxidative stress.[73] The activity of GPx is also reduced in diabetes due to a decrease in the availability of its cofactor, selenium.[73] In pregnant diabetic women, the activity of the GPx/SOD ratio may serve as a measure of glycemic management.

Vitamins C and E, flavonoids, and carotenoids are also effective in reducing oxidative stress in diabetes.[70] They neutralize free radicals directly and regenerate other antioxidants. They also modulate the action of antioxidant enzymes. The reduction in the action of antioxidant enzymes may contribute to oxidative stress in diabetes.

Supplementation with antioxidants or increasing their intake through diets can help to reduce the damage caused by ROS. Exogenous antioxidants can be balanced in the diet by primarily consuming medicinal herbs and phytoconstituents. Using medicinal plants has the benefit of having little to no adverse effects.[74,75] Given that the majority of tissues and organs in diabetic patients are affected by hyperglycemia-induced oxidative stress, using natural products with anti-diabetic and antioxidant abilities may have several positive impacts.[72] Studies on the anti-diabetic and antioxidant characteristics of plants that have been traditionally used to treat diabetes symptoms have shown that they can improve oxidative stress-induced dysfunction of endothelial cells and a reduction in insulin production.[76]

Several studies have shown that the presence of antioxidants in a variety of plants, including lycopene, retinol, α- and γ-tocopherol, β-cryptoxanthin, α- and β-carotene, lutein, and zeaxanthin, significantly lowers the risk of diabetes complications.[72,77] Other studies have validated and thoroughly described the benefits of antioxidant phytochemicals in reducing the problems of chronic illnesses like diabetes, heart disease, and obesity.[78] Due to their antioxidant qualities, phytochemicals control the activity of α-glucosidase and lipase, lower blood sugar levels, enhance pancreatic function, and work in conjunction with hypoglycemic agents to treat diabetes.

Antioxidant-enzyme interaction in hepatic diseases

Some hepatic diseases, such as cirrhosis and hepatitis, are associated with oxidative stress, particularly those involving inflammation.[79] Research on antioxidant therapy has generated interest due to its potential in mitigating these conditions. Various interactions between antioxidants and enzymes have been observed in hepatic diseases. SOD activity in hepatic diseases is reduced due to the generation of cytokines and other inflammatory mediators that impair its activity.[51] This leads to the accumulation of superoxide radicals and oxidative stress. The activity of GPx in hepatic diseases may be decreased due to a decrease in the availability of its cofactor, selenium. The reduction in the activity of GPx may predispose the body to accumulate hydrogen peroxide and lipid peroxides, as GPx activity reduces both hydrogen peroxide and lipid peroxides. The accumulation of hydrogen and lipid peroxides can damage liver cells and exacerbate the disease.

Vitamins C and E, carotenoids, and flavonoids are also effective in reducing oxidative stress in hepatic diseases.[80,81] They neutralize ROS, modulate antioxidant-enzyme activity, and regenerate other antioxidants. The reduction in the activity of antioxidant enzymes may lead to oxidative stress and liver damage. Increasing intake of antioxidants through diet or supplementation can help reduce the damage caused by ROS and improve liver function in hepatic diseases.

Antioxidant-enzyme effectiveness has been demonstrated in a wide range of diseases, such as chronic liver diseases including hemochromatosis, Wilson's disease, non-alcoholic steatohepatitis, chronic viral hepatitis, and alcoholic liver disease. Many components found in natural products or plants have anti-inflammatory and antioxidant properties, making them excellent options for managing chronic liver disease. Enhancing antioxidant products and decreasing malondialdehyde and ROS formation in the fatty liver can also lessen liver oxidative stress.

Antioxidant-enzyme interaction in kidney diseases

Chronic kidney disease (CKD) involves a progressive impairment of renal function that lasts for more than three months.[76] Since oxidative stress and inflammation have been suggested to play a role in the pathology and progression of CKD and its comorbidities (such as diabetes), antioxidants are being utilized in managing kidney diseases. It has been demonstrated that antioxidant therapy reduces the progression of CKD.[76] The ability of antioxidants to prevent or slow the progression of CKD by targeting oxidative stress and inflammation has been studied with promising outcomes. Pentoxifylline, a compound with antioxidant effects, reduces proteinuria and albuminuria in diabetic kidney disease in advanced stages of CKD through non-specific inhibition of phosphodiesterases, enzymes that have been widely implicated in the progression of kidney diseases.[77,78] Pentoxifylline has been shown to decrease malondialdehyde concentration, increase the GSH:GSSG ratio, and enhance the expression of Nrf2, a key regulator of cellular oxidative stress, further validating its antioxidant properties.[79] Quercetin, a known natural antioxidant, has been demonstrated to inhibit kidney fibrosis in a mouse model. This is achieved by the combined inhibition of mechanistic targets of rapamycin complexes 1 and 2 and β-catenin by quercetin.[80] These protein complexes play an important role in fibroblast activation in the kidney, and their inhibition reduces or prevents the progression of CKD.

Antioxidant-enzyme interaction in reproductive disorders

Natural antioxidants, alone or in combination with other antioxidants, are effective in managing stress-induced infertility problems. This is achieved by enhancing the activity of endogenous antioxidant enzymes (SOD, CAT, GR, GPx, and GSH) or by inhibiting oxidative stress-induced damage in the reproductive system.[81] In females, Vitamin A, carotenoids, resveratrol, and quercetin have been demonstrated to enhance the activity of endogenous antioxidant enzymes (SOD, CAT, GPx, and GR) in the ovary by stimulating the Nrf2 signaling pathway to increase the expression of these enzymes.[82] Vitamins C and E also inhibit oxidative stress-mediated damage in the ovaries, fallopian tubes, and uterine tissues by inhibiting TNF-α and caspase proteins (Casp3 and Casp8) expression, thus reducing apoptosis.[81] Additionally, quercetin increases the activity of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone. These interactions improve folliculogenesis, ovulation, and menstruation, leading to enhanced fertility. In males, oxidative stress has been implicated in sperm dysfunction and damage caused by ROS.[83] Antioxidant therapies involving carnitine, selenium, and vitamin B-12 have been proven to improve sperm count and motility, while vitamins C and E, glutathione, and coenzyme Q10 are beneficial in managing male

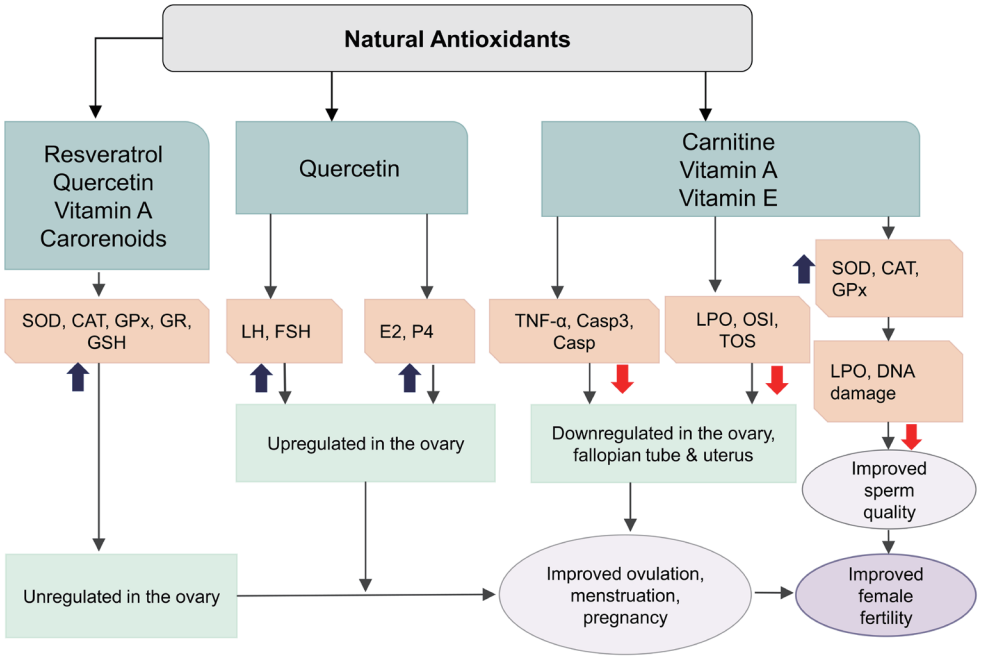

Fig. 2. Schematic representation of the interactions between natural antioxidants and the reproductive tract. Catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GRd), glutathione (GSH), oxidized glutathione (GSSG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), progesterone (P4), tumor necrosis factor-alpha (TNF-α), caspases (casp), lactoperoxidase (LPO), oxysuccinimide (OSI), total oxidant status (TOS), deoxyribonucleic acid (DNA).

infertility.[84] For instance, L-carnitine improves the activity of endogenous antioxidant enzymes by interacting with Nrf2 to increase their expression.[85] It also helps transport long-chain fatty acids for energy metabolism into the mitochondrial membrane, thus providing the energy necessary for sperm motility.[85] This enhances sperm parameters such as morphology, motility, and concentration. Coenzyme Q10, along with vitamins C and E, functions by scavenging ROS and reducing oxidative stress and DNA damage in the testis. Figure 2 illustrates the interaction between natural antioxidants and diseases affecting the reproductive system. Antioxidants improve fertility by enhancing the activities of endogenous antioxidants (SOD, CAT, GPx, and GSH) or gonadotropins (luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone) and by inhibiting oxidative stress, lipid peroxidation, total oxidative stress, tumor necrosis factor-α, and caspase proteins (Casp3 and Casp8).

Antioxidant-enzyme interaction in non-degenerative neurological diseases (brain cancer)

One of the major factors that disrupts normal brain homeostasis and contributes to the onset of cancers is oxidative stress. Therefore, antioxidants may prevent oxidative stress induced by oncogenic agents, thereby inhibiting carcinogenesis.[86] Recent data shows that excessive free radicals in the brain enhance oncogenesis by encouraging initiation, proliferation, angiogenesis, invasion, and cell arrest, regulating numerous processes that support oncogenesis. This underscores the role of antioxidants in managing cancers, including brain cancer.[87] Studies have shown that the development of pediatric brain tumors is less likely in pregnant women who regularly take vitamins C and E. Vitamin C has anticancer properties and prevents tumorigenesis. It reduces DNA damage by scavenging ROS, thus preventing carcinogenesis. In cancer cells, vitamin C interrupts cancer progression by suppressing HIF-1α, which is essential for the survival of cancer cells in hypoxic conditions.[86] Vitamin C also activates ten-eleven translocation proteins and inhibits pluripotency, eliminating the epigenetic and metabolomic profile of cancer cells.[88] Vitamin E, mainly γ- and δ-tocopherols, is effective against various cancers, including brain cancer. γ-Tocopherol is more effective in activating peroxisome proliferator-activated receptor gamma than δ-tocopherol.[89] It also induces a cytostatic effect on the cell cycle by deregulating extracellular signal-regulated protein kinases and subsequently suppressing cyclin E and cyclin-dependent kinase.[90] Resveratrol, a known natural antioxidant, has been shown to have chemotherapeutic effects on brain cancer. It crosses the blood-brain barrier, making it an effective agent against brain cancer.[86] Its anticancer properties stem from its interference with the initiation, proliferation, and metastasis of cancer cells.[91] It regulates many pathways, such as deregulating the signal transducer and activator of transcription by inhibiting Janus kinase activation, thus leading to antiproliferation and apoptosis.[92] Resveratrol also inhibits circulating oncogenic microRNAs (miRs) such as miR-19, miR-21, and miR-30a-5p, thereby suppressing the expression of genes that code for epidermal growth factor receptor, signal transducer and activator of transcription, COX-2, and downregulating the mTOR signaling pathway.[93] Endogenous antioxidant enzymes such as SOD have been shown to protect the brain by reducing apoptosis in mouse models by suppressing the activation of extracellular signal-regulated kinases 1 and 2.[94]

Antioxidant-enzyme interaction in psychiatric and neurodevelopmental disorders

An imbalance in redox homeostasis has been implicated in psychiatric disorders. There have been reports of increased oxidative stress and a decline in antioxidative defenses in psychiatric

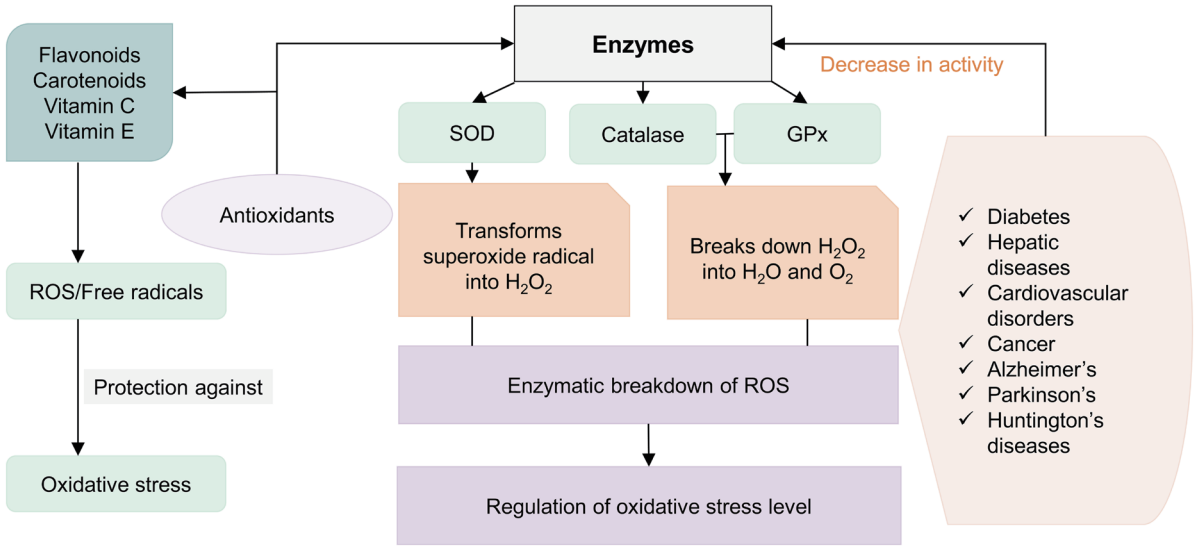

Fig. 3. Interactions between antioxidants and enzymes in non-communicable diseases. Reactive oxygen species (ROS), superoxide dismutase (SOD), glutathione peroxidase (GPx).

patients.[95] Therefore, antioxidants may serve as a treatment option for neuropsychiatric disorders. There is limited information on the molecular mechanisms involving antioxidants in treating psychiatric disorders. However, researchers have proposed that the activation of Nrf2 plays a major role in the antioxidant mechanism for counteracting oxidative stress in neuropsychiatric conditions, mediated by both exogenous and endogenous antioxidants (85). In a rat model, sulforaphane, a known antioxidant, has been demonstrated to activate the cellular antioxidant pathway through the glutamate-cysteine ligase catalytic subunit and Nrf2, resulting in a reduction in memory impairment.[96] Nadeem *et al.* reported that sulforaphane increased the expression of antioxidant enzymes (SOD, GPx, and GR) in an autistic rat model.[97]

Clinical implications of antioxidant-enzyme interaction in non-communicable diseases

Antioxidant-enzyme interaction in diagnosis and prognosis

Antioxidant enzymes and antioxidants are studied and used as biomarkers in the diagnosis and prognosis of several diseases. Interactions between antioxidants and enzymes can provide insight into the status of oxidative stress in the body, which is a hallmark of several pathological conditions (Fig. 3). Antioxidant-enzyme interactions can be investigated to evaluate oxidative stress levels and an individual's overall health status.[82,98] Glutathione, vitamin C, vitamin E, and other enzymes such as SOD and catalase are antioxidants that help neutralize ROS and prevent cellular damage. By scavenging free radicals and transforming them into less dangerous molecules, these antioxidants lower oxidative stress.[33] ROS are broken down and eliminated using enzymes like SOD and catalase. While catalase breaks down hydrogen peroxide into water and oxygen, SOD transforms the superoxide radical into hydrogen peroxide. These enzymatic processes assist in controlling ROS levels and preserving cellular homeostasis.

Monitoring the interaction between antioxidants and enzymes can reveal information about the body's overall oxidative stress levels. Increased oxidative stress has been associated with several disorders, including cancer, cardiovascular diseases, and neurological illnesses.[60,52] This increased oxidative stress results from an imbalance between ROS generation and antioxidant defense mechanisms. Clinicians can learn more about a patient's oxidative status and make predictions about the prognosis of specific illnesses by measuring the activity levels of antioxidants and enzymes. In some cases, the evaluation of antioxidant-enzyme interactions might be used as a diagnostic technique. For instance, assessing the levels of activity of particular antioxidant enzymes or markers of oxidative damage (such as lipid peroxidation or protein oxidation) can help determine disease progression, treatment response, or even identify specific pathological conditions linked to oxidative stress.

In CVDs, a reduction in the activity of SOD and GPx has been observed in patients, which has been associated with an elevated risk of cardiovascular issues.[52] A decrease in the activity of SOD and GPx has also been observed in patients with AD and PD. This reduction has been linked to cognitive decline and disease progression.[60] Additionally, a decrease in the activity of SOD and GPx has been reported in patients with various types of cancer, and this reduction has been implicated in an increased risk of cancer and poor prognosis.[32]

In general, the interactions between antioxidants and enzymes can provide valuable information for the diagnosis and prognosis of various diseases. However, further research is needed to fully understand the relationship between oxidative stress and disease, and to develop reliable biomarkers for diagnosing and prognosing these conditions.

Therapeutic strategies involving antioxidant-enzyme interaction

Therapeutic strategies involving antioxidant-enzyme interactions aim to harness the body's natural defense mechanisms to counter oxidative stress and mitigate the damage caused by ROS. These therapies can be specifically targeted to NCDs such as diabetes, neurodegenerative diseases, cancer, and inflammatory disorders.

Diabetes

In diabetic conditions, hyperglycemic-induced oxidative damage has been proven to be one of the leading causes of complications

such as diabetic retinopathy and diabetic neuropathy. Studies have revealed that polyphenols can prevent diabetes complications (diabetic retinopathy (DR) and diabetic neuropathy (DN)), due to their capacity to regulate endogenous antioxidant enzymes.[83,99] The expression of antioxidant enzymes (SOD, CAT, and GPx) is largely controlled by the interaction of Nrf2 with the antioxidant response element.[84] Reduction in Nrf2 activity and a corresponding decrease in these enzymatic antioxidants have been observed in the retina of diabetic patients.[100,101] This serves as a potential biomarker for DR. Upregulation of the activity of Nrf2 and, subsequently, the antioxidant enzymes, could prevent the onset of DR complications in diabetic patients. In the kidneys, CAT, SOD, and GPx are responsible for defending against oxidative damage, with SOD being the primary front-line antioxidant defense. Kwong-Han *et al*. reported the therapeutic advantage of targeting SOD as a treatment for type-2 DN through the renal AMPK-PGC-1-Nrf2 and AMPK-FoxO signaling pathways (AMP-activated protein kinase-peroxisome proliferator-activated receptor coactivator 1 (PGC-1)-nuclear factor erythroid 2-related factor 2 and AMPK-forkhead box O transcriptional factors).[102] The extracellular SOD enhances Nrf2, leading to a high level of NADPH dehydrogenase 1 expression and subsequent prevention of oxidative damage in the kidneys. The upregulation of SOD through Nrf2 can be targeted in the management of DN by the administration of polyphenols.[103]

Neurodegenerative diseases

The onset of neurodegenerative disorders has been linked to oxidative stress. Cell damage resulting from oxidative stress initiates degenerative processes through mitochondrial dysfunction, neuroinflammation, and apoptosis.[104,105] Antioxidant therapy can prevent mitochondrial malfunction and reduce the progression of degenerative events. Various kinds of antioxidants are constantly being evaluated for the management of neurodegenerative disorders, either individually or in combination.

Antioxidant treatments have produced positive therapeutic effects in the management of AD. Yang *et al*. observed that treatment with coenzyme Q10 (CoQ10) or lipoic acid upregulated ATP and SOD levels, while decreasing apolipoprotein E and A in AD models.[106] Lipoic acid treatment was also observed to decrease the levels of phosphorylated tau proteins and neuroinflammation markers, as well as improve synaptic transmission.[107] Similarly, carotenoids, polyphenolics such as anthocyanins, and resveratrol inhibited AD biomarker proteins, enhanced memory, and prevented inflammatory reactions.[107,108] Combination therapy using ubiquinol and ascorbic acid, lycopene with vitamin E, CoQ10 with omega-3 fatty acids, and resveratrol with curcumin have been demonstrated to diminish tau hyperphosphorylation and limit amyloid protein formation in AD animal models.[109,110]

Additionally, antioxidants including vitamins A and C, CoQ10, and α-lipoic acid have been suggested to improve behavioral parameters and reduce oxidative stress, mitochondrial dysfunction, and glutamate-induced toxicity in PD.[111,112] This was achieved through the activation of the Nrf2 pathway, increased GSH levels, decreased inflammatory factors, and subsequently enhanced recovery.[113]

Inflammation

In inflammatory disorders, oxidative damage has been implicated, making it rational to include antioxidants in therapeutic strategies for managing these conditions. Peroxynitrite (ONOO-) is one of the major oxidants involved in inflammation. Peroxynitrite can initiate DNA damage, leading to the stimulation of a nuclear enzyme, poly (ADP-ribose) synthase (PARS), which causes a decrease in cellular energy levels and leads to cell death.[114] Some antioxidant therapeutic strategies target either the inhibition of peroxynitrite formation and the increase of SOD activity or the inhibition of PARS activation. Inhibiting peroxynitrite formation or increasing SOD activity has been shown to delay tissue damage *in vivo* and reduce cellular failure associated with inflammation.[115] Antioxidants can also inhibit PARS activation, thus preventing organ damage resulting from inflammation. The therapeutic strategies targeting peroxynitrite involve three approaches: inhibiting its formation by reducing the concentrations of NO and O^{2-} or increasing superoxide dismutation by SOD; trapping peroxynitrite; or converting peroxynitrite to a less toxic product through isomerization to nitrate.[1–3,116]

Polyphenols, plant-based antioxidants, have demonstrated anti-inflammatory properties. This action is possible due to their capacity to inhibit pathways that trigger oxidative stress, and the synthesis and release of cytokines and chemokines, which are pro-inflammatory chemicals.[117] Research has shown that polyphenols exert their anti-inflammatory effects by affecting the expression of genes responsible for proinflammatory cytokines, lipoxygenase, nitric oxide synthase, and cyclo-oxygenase.[118]

Cancer

Elevated levels of ROS resulting from homeostasis imbalance are among the leading causes of the transformation of normal cells into cancerous cells. ROS also enhance their proliferation via two mechanisms: either by damaging biological molecules, leading to gene mutation and inflammation, or through abnormal oxidative stress redox signaling, which distorts signaling pathways and drives cancer progression.[119] Given the important role that ROS plays in cancer, they are therefore a target for anticancer therapy. The therapeutic strategies involving the use of antioxidants in cancer treatment can be executed through two main approaches: targeting ROS with non-enzymatic antioxidants and Nrf2 activators[120] or using SOD mimics, NAC, and GSH esters, including NOX inhibitors.[121] Nrf2 activation is crucial in cancer management due to its function in controlling various genes linked to oxidative stress regulation, protein degradation, and DNA repair. Nrf2 plays a critical role in maintaining cellular function and viability, particularly during stress.[120] Upon activation, Nrf2 is shuttled into the nucleus, where it binds to the antioxidant response element and enhances the expression of antioxidant genes.[122] Therefore, Nrf2 activation is an important therapeutic target in cancer management.

Additionally, the activity of nicotinamide adenine dinucleotide phosphate oxidase (NOXs), a major source of ROS, contributes to oxidative stress. Increased activity of this enzyme family can promote oxidative stress. Consequently, any agent that targets NOXs would be a promising therapeutic approach for cancer.[123]

Future perspectives

There is a clear link between oxidative stress and NCDs such as AD, PD, CVDs, cancer, and diabetes. Available evidence points to the negative effects of free radical damage in the pathogenesis of NCDs. While there are reports on the antioxidant activities of various compounds, both endogenous and exogenous, used for the prevention and management of these diseases, there is a paucity of information on how these compounds interact with other molecules to perform their functions. This gap encourages further discussion and presents opportunities for the next stage in the development of antioxidant therapies.

Conclusions

Therapeutic strategies targeting antioxidant-enzyme interactions in the body's natural defense mechanism against oxidative stress can offer targeted benefits for the management of various NCDs. Since endogenous antioxidant enzymes or antioxidants are responsible for most of the body's antioxidant capacity, strategies to enhance antioxidant-enzyme interactions for disease management involve increasing antioxidant activity or inhibiting ROS release to mitigate oxidative stress. We have discussed antioxidant mechanisms such as scavenging antioxidant enzyme activities and antioxidant interactions with other biological molecules. The protective and inhibitive effects of antioxidants on protein modification, lipid peroxidation, and DNA damage due to ROS have also been highlighted. Although this review explored multiple antioxidant-enzyme interaction strategies, some of these approaches are still undergoing trials, and their efficacy has not been fully established. The underlying biological processes require further investigation. A complete understanding of their mechanisms of action will facilitate the development of novel and effective therapeutic strategies for managing NCDs. Clarifying the specific interactions and signaling pathways that control antioxidant enzymes should be a primary goal of future studies.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Study concept and design (TOA, BOE, CNE, CON), acquisition of data (TOA), drafting of the manuscript (TOA, CON), critical revision of the manuscript for important intellectual content (TOA, BOE, CNE, CON), administrative, technical, or material support (BOE, CNE), and study supervision (CON). All authors have made significant contributions to this study and have approved the final manuscript.

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