



## Antioxidants and their Role against Free Radicals-Mediated Metabolic Disorders: A Review

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### Abstract

Maintaining biological equilibrium and ensuring optimal physiological performance requires a precise balance between the production of free radicals and available antioxidant concentrations. This balance is typically sustained when endogenous defense mechanisms specifically glutathione, catalase, and superoxide dismutase regulate cellular free radicals below a critical threshold. However, should radical generation surpass the capacity of this internal scavenging network, the integration of natural exogenous antioxidants via dietary intake becomes vital for mitigating and forestalling oxidative damage. Persistent oxidative stress leads to cellular degradation, playing a fundamental role in the clinical development of various chronic-degenerative and metabolic diseases. Because oxidative stress stems from a disparity between pro-oxidant forces and the body's antioxidant defense systems, utilizing supplemental antioxidants to reinforce endogenous antioxidant defenses is a recognized therapeutic approach. This strategy is particularly effective in addressing metabolic disorders such as inflammatory states, atherosclerosis, type 2 diabetes, and metabolic syndrome, as well as the biological progression of aging.

**Keywords:** Antioxidant; Atherosclerosis; Free Radical; Metabolic Syndrome; Oxidative Stress

### Introduction

Within living organisms, antioxidants possess the capacity to neutralize or stabilize free radicals generated through internal oxidation, thereby managing their proliferation. When the body's

regulatory systems are bypassed by an overabundance of these radicals, the resulting state is defined as oxidative stress [1]. This condition arises when the balance between radical creation and the antioxidant defense network shifts toward elevated radical

levels, ultimately impairing cellular integrity. Free radicals induce damage in cellular macromolecules, triggering lipid peroxidation and structural modifications in protein and nucleic acid sequences. These biochemical processes are integral to the initiation and advancement of diverse degenerative and metabolic pathologies, including atherosclerosis, ischemic heart disease, diabetes, liver diseases, and carcinogenesis [2].

The stability of biological systems is widely considered dependent on the parity between oxidation and antioxidant activity. Under healthy physiological parameters, the human antioxidant defense network which includes glutathione (GSH), glutathione peroxidase, catalase, and superoxide dismutase facilitates the removal of surplus radicals like peroxyradicals (ROO<sup>•</sup>), alkoxy radicals (RO<sup>•</sup>), hydroxyl radicals (OH<sup>•</sup>), and superoxide anions (O<sub>2</sub><sup>•-</sup>). Nevertheless, the human endogenous antioxidant defense system is frequently unable to fully counteract oxidative stress during disease conditions without assistance from exogenous antioxidant agents [3]. Compounds such as carotenoids, vitamin E, vitamin C, and various phenolics play indispensable roles in the diverse antioxidant pathways of living beings [4,5].

Metabolic dysfunction occurs when standard biochemical pathways are interrupted. Acquired forms of these disorders often stem from environmental influences, including sedentary behavior and imbalanced caloric consumption. Nutrition is a pivotal factor in these conditions; diet-related metabolic issues, such as type 2 diabetes, obesity, and metabolic syndrome, serve as primary risk factors for the onset of further degenerative diseases [6,7]. By obstructing the pathogenesis of these diseases, antioxidants function as a core therapeutic method for preventing and treating manageable metabolic conditions [7].

The primary purpose of this article is to provide a contemporary perspective on how the synergistic relationship between endogenous and exogenous antioxidant can mitigate disease. It specifically aims to explain how an overabundance of free radicals triggers oxidative stress, which facilitates the onset of metabolic disorders, highlights the vital role of dietary exogenous antioxidants as essential partners to the body's internal defenses, and finally offers evidence-based insights to assist in the development of nutritional and medical interventions aimed at forestalling the clinical development of chronic diseases.

The significance of this article lies in its exploration of redox homeostasis. While the human body possesses a sophisticated internal network (endogenous enzymes like GSH and SOD), modern environmental factors and sedentary lifestyles often create a "pro-oxidant" environment that exceeds the body's natural capacity for repair. By identifying oxidative stress not as a singular cause, but as a critical biochemical mediator, this review underscores the necessity of interdisciplinary approaches combining nutrition, biochemistry, and medicine to mitigate the onset and progression of free radicals mediated metabolic disorders.

## Materials and Methods

An exhaustive search of scientific literature was performed to gather credible data regarding antioxidants and their role against free radicals-mediated metabolic disorders. Relevant academic works were systematically identified and extracted from several prominent databases, including African Journal Online, Biosis Previews, Web of Science, PubMed, Google Scholar, and Scopus. A comprehensive collection of more than 150 studies underwent critical evaluation; from this pool, only the most methodologically sound and pertinent publications were selected as references in this review.

## Free radical

Free radicals are defined as ions, molecules, or atoms containing unpaired electrons, a characteristic that renders them exceptionally reactive when interacting with other compounds. The oxidation reactions that produce these radicals can trigger cascading chain reactions, leading to further systemic oxidation. Typically, these entities arise from environmental stressors such as atmospheric pollution or tobacco smoke or through internal cellular metabolism when the body's free radical neutralizing systems are bypassed [8].

Within physiological matrix, these radicals frequently originate from oxygen, nitrogen, and sulfur molecules. They are classified into broader categories known as reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS). For instance, the reactive oxygen species group includes free radicals like the hydroxyl radical (OH<sup>•</sup>), perhydroxyl radical (HO<sub>2</sub><sup>•</sup>), and superoxide anion (O<sub>2</sub><sup>•-</sup>), alongside non-radical species such as hypochlorous acid (HOCl), singlet oxygen (<sup>1</sup>O<sub>2</sub>), and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). This group of radicals are generated during normal

metabolic functions and play vital roles in physiological processes, including ion transport, gene expression, programmed cell death (apoptosis), and intracellular signaling [9,10]. Nevertheless, an overabundance of these species can exert catastrophic effects on various biological molecules, such as DNA, RNA, lipids, and proteins, due to their minute size and extreme reactivity. When these radicals target these vital macromolecules, they frequently trigger the state known as oxidative stress [11].

Antioxidants are present in both extracellular and intracellular environments and are classified through various frameworks. Based on their functional mechanism, they are divided into non-enzymatic and enzymatic categories. Enzymatic antioxidants, including peroxidases, glutathione peroxidase, catalase, and superoxide dismutase, operate by decomposing and eliminating free radicals. In a multi-stage sequence requiring cofactors like iron, manganese, zinc, and copper, they transform hazardous oxidative byproducts into water and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Conversely, non-enzymatic antioxidants such as glutathione, carotenoids, plant polyphenols, vitamin E, and vitamin C function by disrupting the progression of free radical chain reactions [13].

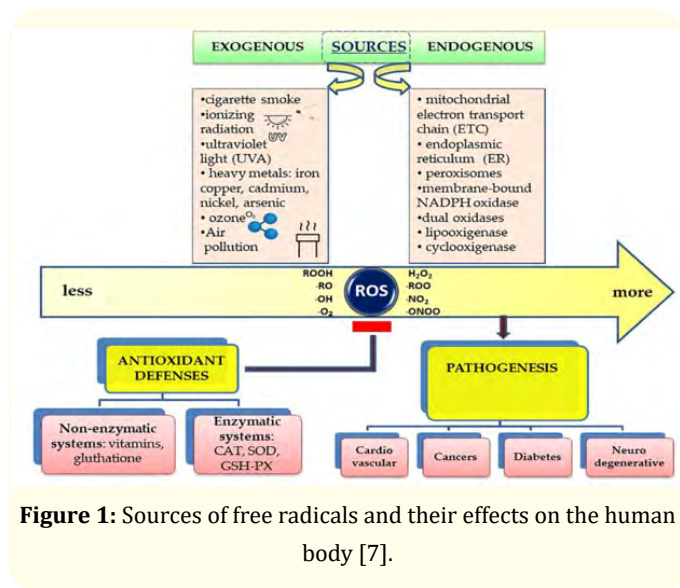


Figure 1: Sources of free radicals and their effects on the human body [7].

**Antioxidant**

An antioxidant is a molecular entity capable of impeding or delaying the oxidation of other molecules. While oxidative reactions are fundamental to cellular operations, they also carry destructive potential; consequently, antioxidants function to mitigate or halt oxidative cascades by neutralizing free radicals or obstructing their synthesis. As a result, antioxidants such as thiols or phenolic substances are frequently characterized as reducing agents [12].

The most potent antioxidants are those that terminate the free radical chain sequence, often referred to as primary antioxidants. These molecules typically possess phenolic or aromatic rings and donate a hydrogen radical to the oxidation-induced free radicals, transitioning into a radical state themselves. These resulting radical intermediates achieve stability through the formation of quinone structures and the resonance delocalization of electrons across the aromatic ring [14]. Over the last ten years, both the scientific community and the general public have shown significant interest in phenolic compounds and their radical-scavenging properties. This interest is driven by epidemiological research connecting diets abundant in natural antioxidants to a reduced incidence of diseases of the cardiovascular system and cancer linked to oxidative stress [6].

The human network of antioxidant defenses is comprised of exogenous antioxidants, primarily obtained through nutritional intake, and endogenous antioxidants, which include both non-enzymatic and enzymatic varieties (Table 1).

Endogenous antioxidants	Exogenous antioxidants
<b>Enzymatic antioxidants</b>	<b>Principal dietary antioxidants from fruits, vegetables and grains</b>
Superoxide dismutase (SOD)	Vitamins (vitamin C, vitamin E)
Catalase	Trace elements (zinc, selenium)
Glutathione peroxidase and reductase	Carotenoids (b-carotene, lycopene, lutein, zeaxanthin)
Thioredoxin reductase (protect against protein oxidation)	Phenolic acids (chlorogenic acids, gallic acid, caffeic acid, etc.)

Glucose-6-phosphate dehydrogenase (NADPH regeneration)	Flavonols (quercetin, kaempferol, myricetin)
<b>Non-enzymatic antioxidants (principal intracellular reducing agents)</b>	Flavanols (proanthocyanidins and catechins)
Glutathione (GSH), NADPH	Anthocyanidins (cyanidin and pelagonidin)
Coenzyme Q, uric acid, lipoic acid	Isoflavones (genistein, daidzein and glycitein)
Albumin, bilirubin	Flavanones (naringenin, eriodictyol and hesperetin)

**Table 1:** Classifications of antioxidants defence systems.

Source [4].

### Antioxidant action hierarchy in biological systems

The molecular components that form the antioxidant defense network in living organisms operate through multiple functional tiers. These stages include the prevention of radical formation, the scavenging of existing radicals, and the restoration of oxidative damage. According to their defensive priority, antioxidants are classified into the first, second, third, and fourth lines of defense [15].

- **First Line of Defense:** These antioxidants act by suppressing or entirely blocking the generation of free radicals within cellular environments. They neutralize precursor molecules that could evolve into radicals or deactivate radicals capable of triggering further oxidative cascades. Primary examples include glutathione peroxidase, catalase, and superoxide dismutase.
- **Second Line of Defense:** Often identified as scavenging antioxidants, these molecules neutralize active free radicals to prevent the start of a chain reaction and interrupt propagation by providing electrons. This group contains phenolic compounds and hydrophilic substances like glutathione, uric acid, and ascorbic acid, alongside lipophilic agents such as ubiquinol and alpha-tocopherol (vitamin E).
- **Third Line of Defense:** This tier is activated after oxidative harm has already been sustained. These consist of *de-novo* enzymes tasked with repairing biomolecular damage caused by radicals and restoring the integrity of cell membranes. This category includes DNA repair systems (such as nucleases, glycosylases, and polymerases) and proteolytic enzymes (including peptidases, proteases, and proteinases) found within both the mitochondria and cytosol of mammalian cells.

- **Fourth Line of Defense:** This level involves an adaptive response mechanism. It utilizes the specific signals generated by free radical production and reactions to preemptively inhibit further radical formation. The metabolic signal triggered by the radical induces the synthesis and localized transport of the necessary antioxidant to the site of stress [Ighodaro and Akinloye, 2018].

### Mechanisms of antioxidant activity

Antioxidant functionality is primarily defined by two overarching mechanisms. The first is a chain-breaking process where the primary antioxidant provides either a single electron (Single Electron Transfer, SET) or a hydrogen atom (Hydrogen Atom Transfer, HAT) to stabilize the radical. The second involves the elimination of radical initiators by neutralizing catalysts that trigger the oxidative chain [15].

HAT-based techniques evaluate the traditional capacity of an antioxidant to neutralize free radicals through the donation of hydrogen. Many researchers consider these methods the most biologically relevant, as they mirror the typical behavior of antioxidants *in-vivo*. However, the presence of various reducing agents, such as metals, can complicate HAT assays, potentially leading to inflated results regarding reactivity [16]. A classic demonstration of HAT is the reduction of 2,2-diphenyl-1-picrylhydrazyl (DPPH), which occurs when antioxidants donate hydrogen atoms to stabilize the molecule [13].

SET-oriented techniques identify the capacity of antioxidant to donate a single electron, thereby reducing diverse substances such as radicals, carbonyl groups, and metal ions. While SET

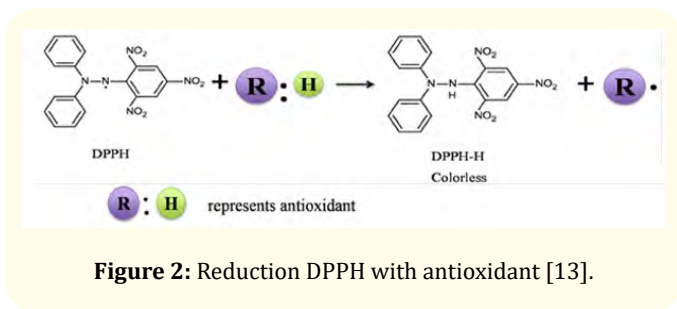


Figure 2: Reduction DPPH with antioxidant [13].

and HAT pathways virtually always take place simultaneously across all biological samples, their relative prevalence is dictated by the specific molecular architecture of the antioxidant and the surrounding pH levels [16]. A prominent illustration of the SET mechanism is the Ferric Reducing Antioxidant Power (FRAP) reaction. In this process, a transparent ferric-tripyridyltriazine complex is transformed into a deep blue ferrous state through the donation of an electron in the presence of an antioxidant [15].

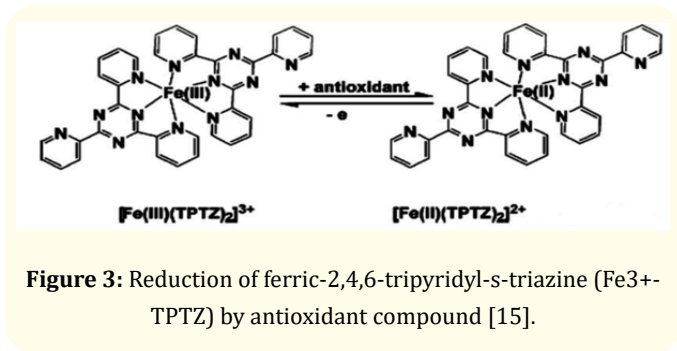


Figure 3: Reduction of ferric-2,4,6-tripyridyl-s-triazine (Fe<sup>3+</sup>-TPTZ) by antioxidant compound [15].

### Primary and secondary enzymatic defense

Primary endogenous enzymatic antioxidants serve as the first line of defense by directly neutralizing free radicals. These enzymes obstruct the formation of free radicals by scavenging superoxide anions (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), which typically arise from the incomplete reduction of molecular oxygen. Complementing this, secondary enzymes like glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PD) facilitate these processes. Their primary role involves the regeneration of reduced glutathione (GSH) and the production of NADPH, both of which are critical for sustained primary enzymatic activity [7,17].

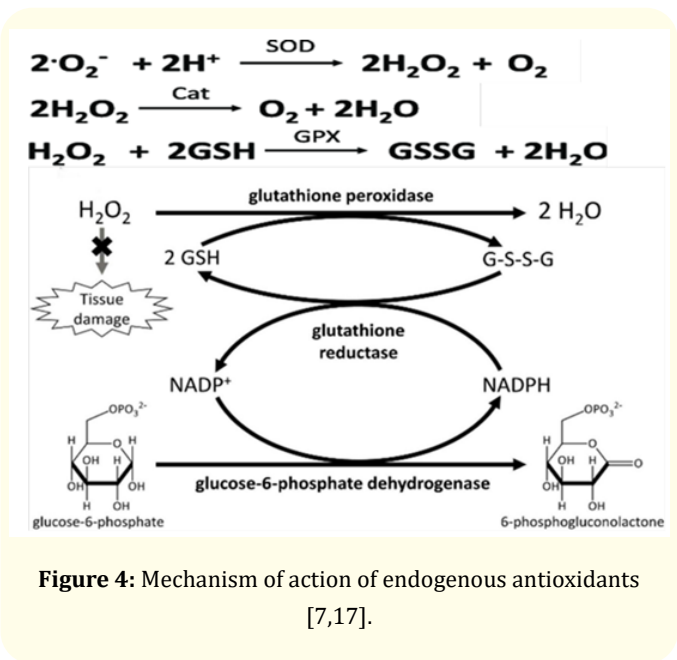


Figure 4: Mechanism of action of endogenous antioxidants [7,17].

The functionality of the antioxidant network hinges on the continuous restoration of reductants. Reductases such as thioredoxin reductase and glutathione reductase perform this task in an NADPH-dependent manner. Consequently, enzymes fueling the NADPH supply are categorized as secondary antioxidants; any impairment in their function disrupts the cellular redox equilibrium. The pentose phosphate pathway serves as the major metabolic reservoir for NADPH, driven by 6-phosphogluconate dehydrogenase and G6PD. Additional contributions are provided by the malic enzyme and specific folate-dependent pathways [17].

### Endogenous non-enzymatic antioxidants

These categories of antioxidants work together with enzymatic antioxidants to prevent free radical accumulation, and include glutathione, lipoic acid, melatonin and ubiquinone.

- Glutathione (GSH):** Glutathione possesses an active thiol (-SH) group, allowing it to independently scavenge hydroxyl radicals (OH<sup>·</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and peroxynitrite (ONOO<sup>-</sup>). GSH participates in a redox cycle where it dimerizes into glutathione disulfide (GSSG). The GSH/GSSG ratio is maintained through a synchronized reaction involving glutathione peroxidase and glutathione reductase (Figure 4) [7].

- **Lipoic acid:** Alpha lipoic acid is a disulfide molecule that undergoes a redox cycle analogous to GSH. It is proficient in scavenging radicals and restoring vitamins E and C, as well as GSH, to their functional states. Furthermore, it acts as a metal chelator, thereby inhibiting Fenton-type radical reactions [18]
- **Melatonin:** Synthesized from tryptophan, this neurohormone regulates circadian rhythms while serving as a robust antioxidant. It is particularly effective in shielding cellular membranes from lipid peroxidation [18].
- **Coenzyme Q10 (Ubiquinone):** As a lipid-soluble isoprenoid located in cell membranes, ubiquinone is vital for the electron transport chain. In its reduced form (quinol), it neutralizes reactive species and regenerates other oxidized antioxidants. The resulting quinone form is subsequently reduced back via NADPH-dependent systems [1,18].

**Natural Exogenous Antioxidants and Dietary Phenolics**

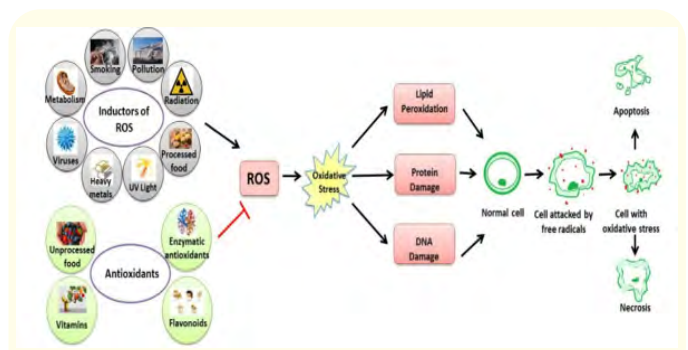
Exogenous antioxidants must be acquired through nutrition, as their synthesis is largely restricted to botanical or microbial organisms. This group includes phenolic compounds, tocopherols, vitamin C, and carotenoids. Phenolics, such as quercetin, resveratrol, and various phenolic acids, function as terminators of free radical chain reactions (Brewer, 2011).

- **Phenolic Compounds:** These diverse plant metabolites are characterized by aromatic rings with attached hydroxyl groups. They are categorized into flavonoids (e.g., rutin) and non-flavonoids (e.g., gallic acid). Their antioxidant capacity manifests through direct radical scavenging, the chelation of pro-oxidant metals like copper and iron, and the up-regulation of endogenous antioxidant enzymes [19,20].
- The efficacy of polyphenols is generally linked to the density of hydroxyl groups on their aromatic structures. They readily donate hydrogen ions (H<sup>+</sup>) to neutralize radicals. This process converts the antioxidant into a phenoxy radical, which remains stable due to resonance delocalization within the aromatic ring. This stability prevents the antioxidant radical from initiating further chain reactions [12,22].
- **Essential Vitamins and Carotenoids:** Vitamin C; a water-soluble electron donor that exists as ascorbic acid or ascorbate. It can undergo two-electron oxidation to form

dehydroascorbic acid, which is then recycled back to its active state via GSH-dependent pathways while Vitamin E; a fat-soluble antioxidant, primarily α-tocopherol, protects cell membranes. It is regenerated through interactions with vitamin C or other reducing equivalents [23]. Carotenoids; tetraterpenes include carotenes (like β-carotene, a vitamin A precursor) and xanthophylls are highly effective at quenching free radicals within various biological tissues [23].

**Interplay of oxidative stress and human pathology**

Oxidative stress stems from an overproduction of free radicals, a decline in the efficiency of antioxidant systems, or a combination of both. When this state persists, it triggers oxidative damage the chemical modification of lipids, proteins, and DNA, which fundamentally impairs cellular architecture and biological signaling [24,25]. Consequently, oxidative stress is a critical driver in the development of various chronic and metabolic conditions. It is heavily implicated in the progression of type 2 diabetes, atherosclerosis, systemic inflammation, numerous malignancies, metabolic syndrome, and the physiological decline associated with aging. Current research suggests that oxidative stress contributes significantly to inflammatory ailments (such as lupus, arthritis, and respiratory distress syndromes), cardiovascular diseases, stroke, neurological decline (Alzheimer’s and Parkinson’s), and complications arising from chronic habits like smoking and alcohol consumption [26,27].



**Figure 5:** Link between reactive oxygen species, oxidative stress and their effects on human body [7].

**Effect of antioxidants on metabolic disorders**

- **Type 2 diabetes:** Oxidation is a central pathogenic link in type 2 diabetes, a condition defined by insulin resistance

and compensatory insulin overproduction. Antioxidants offer therapeutic benefits by shielding pancreatic beta-cells from radicals induced programmed cell death (apoptosis). Evidence indicates a strong correlation between high dietary antioxidant intake, enhanced insulin sensitivity, and a reduction in diabetic complications [28]. Free radicals can disrupt the communication between insulin receptors and glucose transporters, fueling resistance. Conversely, hyperglycemia itself accelerates oxidative stress by inducing superoxide production within mitochondrial endothelial cells. This decoupling of oxidative phosphorylation leads to inefficient energy production and further radical generation. Thus, mitigating oxidative damage via antioxidants is a primary therapeutic goal [27].

- Furthermore, polyphenolic compounds can modulate glucose levels by inhibiting digestive enzymes like  $\alpha$ -amylase and  $\alpha$ -glucosidase, thereby slowing glucose absorption and preventing the formation of advanced glycation end-products. They also regulate hepatic glucose release and improve peripheral tissue uptake through intracellular signaling modulation [29]. Vitamin C has been shown to reduce microalbuminuria and improve insulin resistance, while alpha-lipoic acid enhances glucose metabolism by activating specific kinases that trigger glucose uptake. Alpha-lipoic acid also promotes the movement of glucose transporters (GLUT1 and GLUT4) to cell membranes in muscle and fat tissues [28].

- **Atherosclerosis versus antioxidant:** This progressive condition involves the buildup of fibrous materials and lipids within arterial walls. Low-density lipoprotein (LDL) penetrates the vascular intima, where ROS transform it into oxidized LDL (ox-LDL), a key driver of plaque formation. Antioxidants are vital in preventing atherosclerosis by neutralizing radicals and blocking the oxidation of LDL particles [30].

- **Metabolic syndrome versus antioxidant:** Characterized by abdominal obesity, hypertension, insulin resistance, and dyslipidemia, metabolic syndrome is fundamentally linked to oxidative stress and chronic low-grade inflammation. Excessive reactive oxygen species generation and mitochondrial dysfunction are hallmark features. Phenolic compounds are highly effective dietary interventions due to their dual antioxidant and anti-inflammatory properties, which help stabilize blood pressure, weight, and lipid profiles [30,31].

**Natural exogenous antioxidants in metabolic disorder management**

- **Quercetin:** This flavonoid targets mitochondrial pathways to influence fat breakdown and obesity. Studies show it can reduce waist circumference and postprandial glucose levels, particularly in specific genetic profiles [33].
- **Resveratrol:** By activating the sirtuin pathway, resveratrol regulates metabolic functions and aging. It promotes energy homeostasis by inhibiting fat formation and increasing lipolysis. Clinical models demonstrate its ability to improve body mass index (BMI) and insulin sensitivity [34,35].
- **Gallic Acid:** Gallic acid derived from sources like garlic, it prevents the inflammatory cascade that leads to metabolic syndrome. Meta-analyses suggest garlic intake significantly lowers triglycerides and total cholesterol [36].
- **Vitamin C:** Beyond preventing scurvy, Vitamin C regulates blood pressure by neutralizing free radicals and enhancing nitric oxide synthesis. It improves arterial dilation, reduces stiffness, and lowers lipid peroxides. At moderate doses, it reduces systemic inflammation in obese individuals and supports healthy glucose levels [37].

Cardiovascular system	Lipid metabolism	Obesity	Glucose metabolism	Blood pressure
Flavonoids				
↓ Blood pressure	↓ Total cholesterol	↓ Body weight	↓ Prandial glucose	↓ blood pressure
↓ Liver dysfunction	↓ LDL and oxidized LDL	↓ BMI	↓ Post-prandial glucose	
↓ Myocardial fibrosis	↓ Triacylglycerol	↑ Adiponectin	↓ Glucose intolerance	
↓ Endothelial dysfunction		↓ Visfatin	↓ Serum insulin	
↑ nitric oxide production			↑ Insulin sensitivity	
Resveratrol				

↓ Blood pressure ↑ NO production ↑ Na <sup>+</sup> excretion (renal)	↓ Total cholesterol ↓ Triacylglycerol ↓ PAI-1	↓ Visceral and sub-cutaneous fat	↑ Insulin production	
Vitamin C (ascorbic acid)				
↑ Blood pressure control ↑ nitric oxide activity	—	Modulate lipolysis	↑ Insulin sensitivity ↑ Insulin production	↓ Arterial stiffness ↑ blood flow
Vitamin E (tocopherol)				
↓ ox-LDL	↓ Total cholesterol	Peroxisome proliferator-activated receptors α and γ modulation Adipocyte differentiation	↓ inflammation,	
Carotenoids				
↓ Blood pressure ↓ Endothelial dysfunction	↓ LDL ↓ Triacylglycerol ↓ PAI-1	↓ Body weight ↓ Visceral fat ↑ Adiponectin	↑ Insulin sensitivity	

**Table 2:** Effects of some natural exogenous antioxidants on metabolic syndrome and cardiovascular risk factors.

Source [6,38]. PAI-1= Plasminogen activator inhibitor-1, ox-LDL = Oxidized low density lipoprotein.

**Safety and toxicity**

While the antioxidants discussed such as Vitamin E and C, β-carotene, and various phenolic compounds are essential for mitigating oxidative stress, their safety profile is non-linear. At supraphysiologic doses, these molecules can bypass their protective roles and exhibit significant toxicity or pro-oxidant behavior [39], as the resulting radical may not be efficiently recycled by the antioxidant defense mechanism earlier described in this review.

For instance, if the GSH-dependent or Vitamin C recycling pathways are overwhelmed, the antioxidant radical itself can initiate lipid peroxidation or damage cellular proteins. High doses of Vitamin C or phenolic compounds can reduce transition metals like Fe<sup>3+</sup> to Fe<sup>2+</sup>. This promotes the Fenton reaction, paradoxically increasing the production of highly reactive hydroxyl radicals [40].

- **Vitamin E (α-tocopherol):** Although α-tocopherol play a significant role in membrane protection, high-dose supplementation (typically > 400 IU/day) has been linked to adverse clinical conditions [41]. Excessive intake of Vitamin E has been linked to potential renal inflammation, and can also antagonize Vitamin K metabolism, leading to inhibition of platelet aggregation and an increased risk of hemorrhagic stroke [42].
- **Beta-Carotene:** Beta-carotene are highly effective at quenching free radicals within various biological tissues, but exhibits a distinct “U-shaped” safety curve at high dose. In high-dose interventions, β-carotene supplementation significantly increased the risk of lung cancer in smokers and asbestos-exposed individuals. In the highly oxidative environment of a smoker’s lungs, β-carotene can break down into eccentric cleavage products that impair Vitamin A signaling and promote DNA damage [43].

- **Phenolic compounds:** It is important to note that quercetin and resveratrol are essential in the management of metabolic disorders. However, they are not exempt from toxicity. At extreme concentrations, quercetin can inhibit mitochondrial ATP synthesis and topoisomerase enzymes, potentially leading to genotoxicity. Because these compounds have low bioavailability, users often take massive oral doses to achieve therapeutic effects, which can lead to gastrointestinal distress and potential interference with cytochrome P<sub>450</sub> enzymes, altering the metabolism of concurrent medications [39,41]. As a result, moderate doses are highly recommended in the application and uses of natural exogenous antioxidants.

## Conclusion

Oxidative stress, fueled by the accumulation of free radicals, is a significant contributor to the onset and exacerbation of metabolic and degenerative diseases. It creates a biochemical environment where chronic conditions like cancer, diabetes and heart disease are more likely to progress, especially when endogenous antioxidant defenses such as superoxide dismutase and glutathione peroxidase are compromised. Consequently, exogenous antioxidants from diet (polyphenols, vitamins, and carotenoids) are essential partners in maintaining redox homeostasis. Hence, understanding the synergy between natural exogenous and endogenous antioxidant systems is paramount for creating effective nutritional and medical strategies to alleviate the global impact of oxidative-related pathologies.

## Conflicts of Interest

Authors declared no conflicts of interest.

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