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Review Article

A Comprehensive Review of Free Radicals, Oxidative Stress, and Antioxidants: Overview, Clinical Applications, Global Perspectives, Future Directions, and Mechanisms of Antioxidant Activity of Flavonoid Compounds

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Absorption of free radicals in the body cannot be done by antioxidant compounds originating from the human body, so exogenous antioxidants are required to help in their natural antioxidant action. Oxidative stress can be caused by an imbalance of free radical inhibitors and the accumulation of free radicals that enter cellular structures. Synthetic antioxidants found in external antioxidants are not the primary choice because they are harmful and carcinogenic. Therefore, using natural ingredients provides a necessary alternative to constructing novel natural antioxidants. Recent studies have highlighted critical analysis and evaluation that flavonoids are a unique class of secondary metabolites found in plants and used in communities as traditional therapeutics with proven bioactivity. This could support new discoveries based on various herbal medicines and in addition, the functional effectiveness of flavonoids as antioxidants against free radicals. In this review, there are several strengths in the discussion. First, the study takes a comprehensive approach by covering various aspects, including the properties and sources of free radicals, oxidative stress in relation to different diseases, antioxidant defense mechanisms, and the specific antioxidant mechanisms of flavonoids. Second, the focus on natural antioxidants, especially flavonoids, and also discussion about clinical applications and human studies, limitations, global perspectives, and future research directions of flavonoids compounds become references in the selection of natural medicines. But, several constraints should be considered when interpreting the findings of this review. First, the discussion about the mechanism of antioxidant compounds is only discussed in general and only takes one example of a compound (flavonoid) that has the potential as an antioxidant. Second, the lack of findings regarding the relationship between several diseases discussed with free radicals. Third, a limited number of studies investigated regarding clinical applications and human studies of some of the diseases discussed.

1. Introduction

Radicals, also known as free radicals in chemistry, are molecules or ions that have unpaired electrons in their atomic orbitals. Radicals are generated by various pathways but the most common routes involve redox processes. Electrolysis, heat, and ionizing radiation are all known to produce radicals. An imbalance in the production of these unpaired electrons and antioxidants causes oxidative stress, which leads to diseases such as cancer, dermatitis, cataracts, stroke, and asthma [1, 2]. Increased oxidative stress can have serious implications for DNA damage (to proteins, nucleic acids, and lipids), which can have a negative influence on health [3, 4].

Antioxidants are substances that prevent, inhibit, or reduce oxidation processes [5–7]. Historically, antioxidants have been used industrially to prevent rubber vulcanization and metal corrosion, scavenge-free radicals [8], and more

recently as stabilizers, lubricants, and food preservatives [9]. In 2015, according to market research data, the market value of synthetic and natural antioxidants was over USD 2 billion and is projected more than 50% to approximately USD 4.5 billion by 2022 [10].

Given the many harmful effects caused by the oxidative stress on human biological systems, further research on new leads of antioxidants activity derived from natural products is required. Flavonoids are well-studied bioactive antioxidant molecules found in plants. Albert Szent-Gyorgi, a Nobel prize winner from Hungary, first investigated flavonoids in 1936 and found an unusual interaction between vitamin C and an unknown chemical he called vitamin P in lemon peel [11]. The main feature of flavonoids is there are two benzene rings with a low weight. Flavonoids are classified into several compounds such as flavonols, isoflavones, flavones, flavanols, and flavanonols. These flavonoid compounds are distinguished by saturation and oxidation of the C-ring structure [12]. In this review, we describe about sources of free radicals, oxidative stress, and types of antioxidants. We also explain the antioxidant reaction mechanisms of flavonoid compounds to counter free radicals that invade structure cells.

2. Properties and Sources of Free Radicals

Radicals are atoms containing unpaired or free electrons that exist in the free form [13]. Free radicals can be produced from normal cellular metabolism. Due to their unstable property and high reactivity, free radicals readily interact with other molecules to achieve stability. In addition, free radicals usually have short lives because they have an odd number of electrons [14]. Free radicals or pro-oxidants are classified into two types, namely, reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS oxidants are classified into superoxide anions ($O_2\bullet^-$), peroxyl radicals (ROO•), hydroxyls (OH•), and hydrogen peroxide (H_2O_2). Representative RNS oxidants are nitrogen oxide (NO•) and peroxynitrite (NO3•) (Table 1) [22, 23].

Free radical reactions have the following three main stages: initiation, propagation, and termination. In the initiation stage, molecules start a chain reaction and undergo homolysis to form free radical molecules. Free radicals are formed from neutral molecules by the energy from UV light, heating, or free radical initiators [24]. In the propagation stage, free radical molecules react with other neutral molecules to form new free radical molecules [25]. The free radical reaction ends in a termination stage in which two free radicals combine into a neutral molecule [26].

The principal sources of free radicals come from outside the body such as x-rays, ozone, industrial chemicals, environmental air pollution, pesticides, radiation, and smoking [29]. Superoxides, organic radicals, and hydroxyl radicals are all converted to hydrogen peroxide by ionizing radiation. At the cellular level, this peroxide participates in secondary oxidative activity or undergoes redox reactions with metal ions such as copper and iron. Numerous studies have demonstrated that fibroblasts exposed to alpha particles produce more peroxide more rapidly at this level with increased intracellular oxygen [30]. Synthesis of 8-hydroxyguanine is a major outcome of UV radiation (UVA)-induced oxidative reactions, which also causes a decrease in intracellular glutathione (GSH) levels, which return to normalcy following exposure ends [31]. Arsenic hampers the activity of antioxidant enzymes such as glutathione reductase, glutathione peroxidase, and glutathione transferase by binding to the sulfhydryl group. This interaction prompts the enzyme to generate peroxide, superoxide, and nitric oxide. Cytosine, guanine, and thymine (several DNA bases) can be substituted by the free radicals produced by these processes, which can damage DNA [32, 33] (Figure 1).

Formation of free radicals is the result of nonenzymatic and enzymatic reactions in tissues involved in the respiratory chain, prostaglandin production, adrenalin autoxidation, phagocytic cells, riboflavin depletion, ischemia, aging, cancer, infections, and mental stress [14]. However, other sources of free radicals can originate within the human body (endogenous) such as the endoplasmic reticulum, mitochondria, and peroxisomes.

Mitochondria are the major organelles in the production of adenosine triphosphate (ATP). The major end product of ROS generation in mitochondria is the superoxide anion radical. Both carbohydrate and fatty acid oxidation pathways are in mitochondria [34]. The process of ATP or energy formation in mitochondria involves the process of electron transport with the help of four enzyme complexes, consisting of complex I, complex II, complex III, and complex IV. Complex III (cytochrome c reductase or ubiquinone) and complex I (NADH dehydrogenase) are the major sites in the electron transport chain where superoxide radical is generated [35–38]. The antimycin inhibitor A can be used to detect most of the ROS production in complex III. Reduced ubiquinone is generated by electron transfer from NADH dehydrogenase to coenzyme Q. Consequently, the reduced ubiquinone regenerates coenzyme Q with the semiquinone anion as an intermediate to generate the superoxide anion radical [39]. MAO, cytochrome b5 reductase, NADPH oxidase 4, and dihydroorotate dehydrogenase are part of the mitochondria that may contribute to ROS generation. ROS can lead to the formation of other highly reactive radicals such as singlet oxygen, nitrogen species, and carbonate radicals [40, 41]. The main factor contributing to ROS production in mitochondria lies in the respiratory process [42].

The circulatory pathway on the peroxisome utilizes electron transfer to generate H_2O_2. H_2O_2, $O_2\bullet^-$, OH•, and NO• are some of the additional free radicals generated in peroxisomes (Figure 1). The main metabolic mechanism of peroxisomes to produce H_2O_2 is produced by the oxidation of fatty acids. Several peroxisomal enzymes have been shown to create ROS, including acyl CoA oxidases, D-amino acid oxidases, L-hydroxy oxidases, urate oxidases, xanthine oxidases, and D-aspartate oxidases [43]. Endoplasmic reticulum enzymes such as diamine oxidase, cytochrome p-450, and b5 enzymes enhance ROS generation [44]. Erop1p is a key thiol oxidase enzyme that catalyzes the electron exchange from a dithiol to molecular oxygen to produce H_2O_2 [45].

Table 1: Description of the radicals generated during metabolism.

Free radicals	Sign	Description	References
Superoxide anion	$O_2\bullet^-$	(1) Formed by auto-oxidation reaction, enzymatic process, and nonenzymatic electron transfer reactions (2) Also formed by the reduced state of one electron from O_2 (3) Generated with the help of enzymes such as cyclooxygenase, lipoxygenase, xanthine oxidase, and NADPH oxidase (4) Mainly produced in mitochondria	[15–18]
Hydroxyl	OH•	(1) Produced by the Fenton reaction and decomposition of peroxynitrite $Fe^{+2} + H_2O_2 \longrightarrow Fe^{+3} + OH\bullet + OH^-$ (fenton reaction) (2) Also produced by a radical reaction of superoxide and hydrogen peroxide or Haber–Weiss reaction $O_2\bullet^- + H_2O_2 \longrightarrow O_2 + OH\bullet + OH^-$ (Haber–Weiss reaction) (3) Formed from the neutral form of hydroxide ions (4) Reacts strongly with inorganic molecules such as carbohydrates, lipids, and proteins and can cause serious harm	[19–21]
Peroxyl radical	ROO•	(1) Formed by radical interactions with two cellular constituents: lipids and nucleobases (2) Perhydroxyl radical (HOO•) is produced when superoxide is protonated and is the most basic type of peroxyl radical (3) Contains as 0.3% of the total $O2\bullet^-$ in the protonated state in cytoplasm of a typical cell (4) Initiate fatty acid peroxidation and potentially promote tumor growth	[46–48]
Hydrogen peroxide	H_2O_2	(1) Formed by enzyme superoxide dismutase (SOD) catalyzed dismutation reaction (2) Harmful to cells even at a 10 μM level (3) Readily diffuses across the membranes (4) Indirectly damages by producing hydroxyl radical (OH•) with transition metal ions	[49, 50]
Nitrogen monoxide	NO•	(1) Produced by enzymatic nitric oxide synthesis (NOS) (2) Assists conversion of L-arginine into L-citrulline (3) There are isoforms involved in this radical deformation, namely, neuronal (nNOS), endothelial (eNOS), and inducible (iNOS) (4) Easily diffuses through cytoplasm and plasma membrane because of the aqueous and lipid solubility (5) Controls enzymatic activity and play a significant role in cellular redox regulation by nitrosylating the proteins (6) Stimulating protein kinases and guanylate cyclase in blood vessels	[51–53]
Peroxynitrite	$OONO^-$	(1) Formed by immediate O^- to NO reaction (2) Shows similar reactivity to hypochlorous acid and lipid solubility (3) Generates highly reactive and toxic nitroso-peroxo-carboxylates ($ONOOCO_2^-$) (4) Shows similar reactivity to hypochlorous acid and lipid solubility	[51, 54]

3. Oxidative Stress

The imparity between cellular antioxidant and produced reactive-free radicals such as RNS or ROS and is known as oxidative stress [55]. Excess ROS/RNS cause oxidative stress because cellular antioxidant mechanisms cannot neutralize them [56]. Increased oxidative stress can adversely affects human health, including molecular damage to proteins, lipids, and nucleic acids, and can have adverse health effects [57–59]. Cell death (apoptosis or necrosis) is the result of damage to biological systems or the formation of numerous reactive chemical species by oxidative stress. Oxidative stress is associated with more than fifty diseases such as diabetes, hypertension, cancer, cardiovascular disease, and neurodegenerative diseases [60, 61].

Proteins can also undergo conformational changes that affect their function when proteins are damaged by oxidative stress [62]. The occurrence of oxidative stress increases the likelihood of DNA damage. The most prominent example is the formation of 8-oxo-2′-deoxyguanosine (8-OHdG) as a major marker in DNA mutagenesis [63]. Epigenetic information can be lost by DNA damage, most likely due to defective methylation of CpG islands in gene promoters [64].

3.1. Cancers and Oxidative Stress. Human cancer development involves external and internal factors that are complex to cause changes in cellular and molecular structures [65–67]. Oxidative damage to DNA has been demonstrated to be a crucial component of the process leading to carcinogenesis [68]. Cancer develops rapidly due to the activation of oncogene by radicals and chromosome abnormalities [69]. Numerous model systems have implicated these free radical species in each step of carcinogenesis. A high abundance of these free radicals can damage cells and cause apoptosis. DNA reactions and radical species are thought to be responsible for

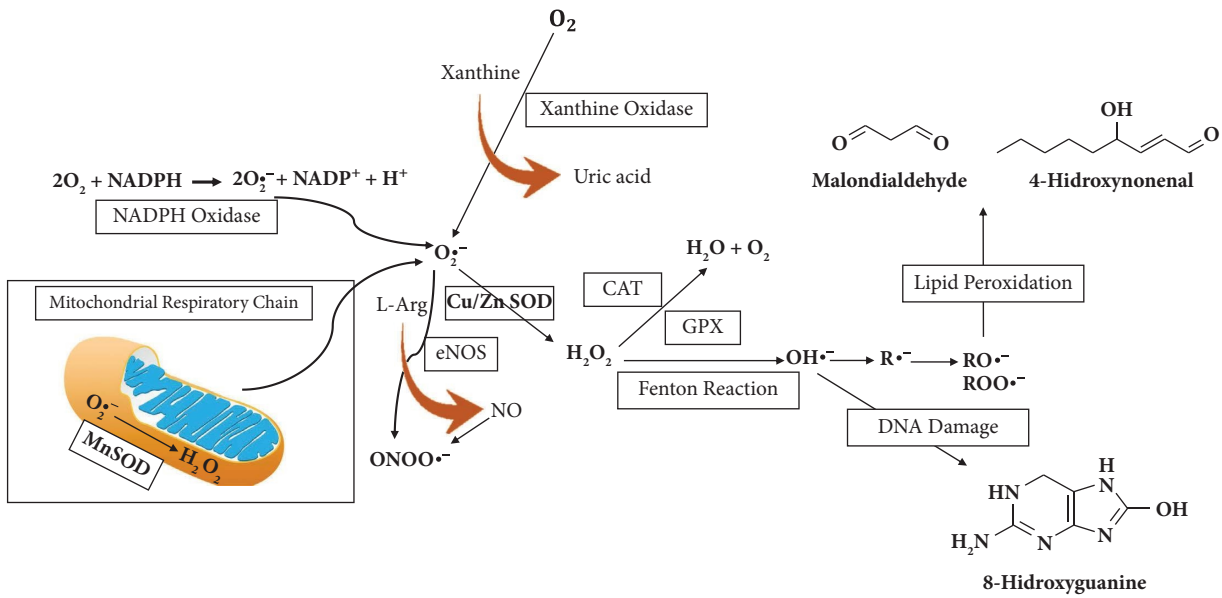

Figure 1: A general overview of free radical sources and their health impacts [27, 28].

many types of cancer and can induce mutations that alter the cell cycle and lead to neoplasia [60]. Overproduction of ROS affects the ability of cancer cells to spread and proliferate [70]. ROS influences cancer cell migration in a variety of ways, including infiltrating pod formation, regulation of gene expression, cytoskeleton remodeling, cell-cell interaction, and matrix degradation [71].

Cancer cells are subject to chronic oxidative stress caused by mitochondrial dysfunction and metabolic abnormalities. Indeed, elevated ROS levels normally promote cell death, but cancer cells circumvent this by driving several oncogenes that subsequently express nuclear factor erythroid 2-related factor 2 (NRF2). The main function of NRF2 is to protect the growing cancer growth from DNA damage and reactive radical species [72]. ROS play a role in cancer development by promoting cyclin D1 production, ERK and JNK phosphorylation, and MAPK activation [73]. However, despite profound mutagenesis, cancer cells prevent ROS-induced death while promoting proliferation. ROS promote lipid peroxidation and protein oxidation in neoplastic diseases. In addition, ROS cause deleterious protein carbonylation and have profound effects on other proteins or lipids [74]. Lipid peroxidation causes cancer cells to accumulate chemicals, including 4-hydroxy-2-nonenal, one of the most studied phospholipid peroxidation products due to its reactivity and cytotoxicity. Hydroxyl radicals can bind deoxyribonucleic acid to form 8-OHdG that increases the likelihood of denaturation. By converting DNA strands pairs (GC to TA) during deoxyribonucleic acid replication, 8-OHdG can also initiate cancer causing mutagenesis [75]. The 8-OHdG molecules may be utilized as a marker to identify free radicals during DNA mutagenesis [76]. Furthermore, high ATP levels are required for increased proliferation of cancer cells, resulting ROS accumulation, especially during the early stages of cancer development.

3.2. Diabetes and Oxidative Stress. A fundamental component of diabetes is insulin resistance that is associated with compensatory insulin hypersecretion. Insulin resistance may result from inhibition of the signature process between the glucose transport system and the insulin enzyme triggered by reactive oxygen species [77]. Conversely, diabetes itself causes oxidative stress, resulting in thermogenetic effects. In endothelial cells, hyperglycemia produces superoxide ions at the mitochondrial level. Electron transfer and oxidative phosphorylation are decoupled in diabetes, resulting in superoxide anions generation and insufficient ATP generation. Diabetes treatment regimens, therefore, include avoiding the harm posed by oxidation. Previously, increased free fatty acids levels and accumulation of intramuscular lipids were thought to be responsible for β-pancreatic cell death and insulin resistance [78].

Macroangiopathy is one of the many consequences of diabetes that develops over time and is of great important. Correlations with coronary atherosclerosis, dyslipidemia, hypertension, and diabetes can be used to explain why diabetic patients are at increased risk of cardiovascular disease. However, fatty acids and glucose in cardiac cells and the effect of hyperglycemias on blood vessels are also involved in this process [79, 80].

Impaired myocardial microvascular function is the underlying cause of diabetic cardiovascular problems. Diabetic cardiomyopathy also undergoes functional and anatomical alterations that result from pharmacologically targeted processes. Sodium/glucose cotransporter-2 inhibitors are first-class antidiabetic drugs that reduce mortality diabetic patients [80]. There is evidence that empagliflozin may reduce the risk of heart failure in atherosclerotic and diabetic patients. Empagliflozin positively affects diabetic cardiac microvascular injury and protects mitochondria from oxidative stress [81]. Another recent

study showed that aminoguanidine was effective in treating heart problems caused by diabetes. Aminoguanidine prevents cardiac remodeling caused by diabetes and contractile dysfunction [82].

3.3. Neurological Disease and Oxidative Stress. Many neurological conditions such as memory loss, multiple sclerosis, depression, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and Parkinson's disease (PD) are associated with oxidative stress [83, 84]. Numerous experimental and clinical studies on AD have demonstrated that accumulation of free radicals in the body is a key factor in the development of dementia and neuronal loss [85]. A common source of toxic peptides found in the brains of AD patients is known to be due to degeneration of brain neurons seen during the AD process. Amyloid is formed by free radical action [83].

Monoamine oxidase (MAO) is an important source of ROS, especially in PD. Poly (ADP-ribose) polymerase (PARP), mitochondrial permeability transition pore (MPTP), and mtDNA are the main targets of mitochondrial generated ROS [86]. While NOS inhibition has been demonstrated to be effective in protecting neurons, other oxidative sources include NADPH oxidase found in astrocytes, microglia, and neurons [87].

Several mechanisms are involved in the pathogenesis of degeneration by neuron cells, including impaired synaptic transmission, irregular calcium levels in neurons, abnormal kinase signaling pathways, and protein misfolding [86]. Accumulation of active free radicals or oxidative stress in the human body is closely associated with ion imbalance and protein aggregation in the brain's morphological system, resulting in degenerative disorders of the neurons themselves [88].

3.4. Kidney Diseases and Oxidative Stress. Accumulation of active free radicals and oxidative stress also causes uremia, proteinuria, and diseases that affect the kidneys, glomeruli, interstitial tubules, and the entire renal system [89]. The synthesis of proinflammatory cytokines and recruitment of inflammatory cells during the early stages of the inflammation occurring in the kidney can be predicted by the accumulation of free radicals or oxidative stress in the body. Key transcription factors in the inflammatory process are governed by IL-1b, NF-β, and TNF-α. These three cytokines are proinflammatory mediators. Increased transcription production of TGF-β is the final step in disease formation [90]. Therefore, renal failure may be caused by repeated effects of oxidative stimuli that act chronically on the smallest cells within the kidney, resulting in excessive fibrotic tissue formation and impaired kidney function. Some drugs, such as bleomycin, gentamycin, tacrolimus, and cyclosporine, have a reputation for being nephrotoxic because they increase free radical levels and promote the free radical accumulation through lipid peroxidation [91]. Several types of nephropathy are caused by heavy metals (arsenic, lead, hydrargyrum, and cadmium) and transitional metals (chromium, cobalt, copper, and iron) that act as potent oxidative stressor in humans [90].

3.5. SARS-CoV-2 and Oxidative Stress. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that can interact with the angiotensin-converting enzyme II (ACE2) receptor on host cells. Generally, this virus can affect the digestive system, central nervous system, heart, and kidneys and lead to organ failure, posing a significant threat to the human body [92]. A majority of these therapeutic interventions aim to address essential proteins of SARS-CoV-2, which include the main protease (M^{Pro}), spike glycoprotein (S), papain-like protease (PL^{Pro}), RNA-dependent RNA polymerase (RdRNA polymerase), and helicase [93]. The development of the virus in the body is closely related to the proliferation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the body. ROS and RNS play a crucial role in signal transduction. The activation of pattern recognition receptors by viral proteins or nucleic acids initiates the interferon response via the involvement of TIR-domain-containing adapter-inducing interferon (TRIF) and interferon regulatory factors (IRFs). Simultaneously, it leads to an upregulation in the expression and activity of inducible nitric oxide synthase (iNOS) through the adapter protein myeloid differentiation primary response-88 (MyD-88) [94]. Excessive generation of harmful reactive oxygen species (ROS) and heightened inflammation pose risks to tissues, potentially leading to damage. An uncontrolled inflammatory response gives rise to oxidative stress, characterized by an imbalance between oxidants and antioxidants. This imbalance stimulates inflammatory cells to continuously produce cytokines, creating a detrimental "vicious circle" [95]. Hesperidin, saffron, vitamin, α-lipoic acid and rosemary are examples of compounds that can counteract free radicals that enter the body [96].

Vitamin A plays a crucial role in boosting the immune system and controlling both cellular and humoral immune reactions. The generation of antibodies, referred to as immunoglobulins (Ig), is essential for sustaining humoral immune responses. A study on animals demonstrated that vitamin A can enhance humoral immunity by elevating the serum concentrations of IgG, IgM, and IgA [97]. Vitamin A might hinder inflammatory reactions triggered by SARS-CoV-2 by controlling various essential genes such as epidermal growth factor receptor, mitogen-activated protein kinase 1 and 14, interleukin-10, protein kinase C beta type, intercellular adhesion molecule 1, and catalase [98]. Moreover, the findings of this systematic review suggested that vitamin C could have beneficial impacts on the clinical outcomes of SARS-CoV-2 patients. Vitamin C serves as a potent antioxidant, particularly for lung epithelial cells. It seems to eliminate reactive oxygen species (ROS) and impede pathways associated with neutrophil extracellular trap formation and cytokine storms [99]. Vitamin C has the potential to inhibit lactate production, which holds significant importance since lactate levels in the serum and tissues are elevated in critically ill SARS-CoV-2 patients. Elevated lactate levels weaken the host immune system by reducing the production of type I interferon and limiting viral clearance [100]. New research explains how vitamin D contributes to increasing LL-37 levels (cathelicidin with antimicrobial properties and a promoter of respiratory pathogen clearance), thereby providing protection against SARS-CoV-2

infection. Consequently, it has been suggested that this vitamin could be beneficial in treating SARS-CoV-2. Surface plasmon resonance assays have demonstrated that LL-37 binds to the SARS-CoV-2 spike protein, thereby inhibiting its attachment to the hACE2 receptor, which is essential for viral entry into the cell [101]. Vitamin E is a fat-soluble antioxidant known for its ability to shield cells from damage caused by reactive oxygen species (ROS), particularly during respiratory infections. In addition, it plays a role in various aspects of immune response, including antibody production, phagocytosis, and T cell function. Vitamin E influences T cell function by impacting membrane integrity, cell division, signal transduction, and several inflammatory mediators such as prostaglandin E2 and proinflammatory cytokines [102]. Moreover, it appears that vitamin E can trigger gene expression signals that counteract those associated with SARS-CoV-2.

α-Lipoic acid has the capability to alleviate oxidative stress by replenishing other antioxidants and binding to metal ions [103]. Moreover, this compound can inhibit the activation of NF-κB, an inflammatory transcription factor. In addition, alpha-lipoic acid might lower the activity of a disintegrin and metalloprotease 17 (ADAM17), also known as tumor necrosis factor-α-converting enzyme. Decreased ADAM17 activity could potentially reduce the shedding of ACE2 and lessen the severity of SARS-CoV-2 infection [104].

As previously mentioned, SARS-CoV-2 elevates reactive oxygen species (ROS) production in host cells, potentially leading to oxidative stress if not countered by the antioxidant defense system. Glutathione peroxidase-1 (GPx1), a cytosolic selenoenzyme with antiviral properties, plays a vital role as an antioxidant defense against ROS [105]. This selenoprotein facilitates the detoxification of hydrogen peroxide into water molecules and is particularly involved in safeguarding against viral respiratory infections. There is evidence suggesting an interaction between GPx1 and the main protease of SARS-CoV-2, the 3-chymotrypsin-like protease, which is crucial for viral replication [106]. This interaction relies on the host's selenium status to counteract SARS-CoV-2 virulence. Consequently, selenium supplementation may enhance the clinical outcomes of SARS-CoV-2 patients.

Zinc, on the other hand, may improve mucociliary clearance by enhancing cilia morphology and increasing cilia beat frequency. It can also enhance the integrity and barrier function of the respiratory epithelium by boosting antioxidant activity and increasing the expression of tight junction proteins such as claudin-1 and zonula occludens-1. In addition, zinc may exhibit antiviral effects by disrupting viral replication cycles [107]. Furthermore, zinc could be advantageous for bacterial coinfection in viral pneumonia, as it might hinder the growth of *Streptococcus pneumoniae* by regulating bacterial manganese homeostasis. Moreover, zinc has the potential to reduce the production of proinflammatory cytokines by inhibiting IκB kinase activity and nuclear factor-κB (NF-κB) signaling [108].

3.6. Advantages of Free Radicals. The function, location, and abundance of ROS/RNS can have positive rather than negative effects on health. Similar to superoxide ($O_2\bullet^-$) and nitric oxide (NO•) radicals, it plays a role in signaling pathways and participates in physiological responses when present in low or moderate amounts [10]. These radicals can play a role in altering the redox homeostasis of cells and tissues and detect mitochondrial dysfunction when these radicals interact with each other [51]. H_2O_2, produced by various oxidative enzymes, can be used as an important signaling molecule and serves as a substrate for the generation of further reactive species such as HOCl [23, 109]. ROS plays a role not only in immune response but also in the phagocytosis mediated degradation of xenobiotics and organisms. ROS are oxygen containing molecules with a wide range of chemical properties, including diffusion within living cells and chemical interactions with biomolecules. Normal amounts of free radicals are beneficial to health, such as fighting inflammation, killing bacteria, and controlling the smooth muscle tone of blood vessels and organs in the body [110].

4. Antioxidant Defenses

Antioxidants are substances enough to donate an electron to unquenched free radicals to neutralize them and reduce their potential for harm [111]. Cellular damage is mostly delayed or prevented by these antioxidants' ability to scavenge free radicals. Due to their low molecular weight, these antioxidants can easily interact with some free radicals to stop a series of reactions [112, 113].

Antioxidants can be divided into several major categories, including water soluble and liposoluble, biological, and synthetic (Figure 2) [114]. Water-soluble antioxidants are found in vegetables and fruits and are best absorbed by the body. On the other hand, the body quickly removes them through urine. Both vitamin C and polyphenols are examples of water-soluble antioxidants. Antioxidants that are absorbed in the presence of lipids are known as liposoluble or fat-soluble antioxidants. Therefore, without lipids, the body is unable to absorb and utilize these antioxidants. However, note that they are difficult to remove from cells and tissues and can build up over time, preventing you from getting adequate amounts. A prime example of a fat-soluble antioxidant is vitamin E [115].

There are two categories of antioxidants, namely, biological antioxidants and synthetic antioxidants [116]. Enzymatic and nonenzymatic biological antioxidants are further classified into two categories. Antioxidants-involved enzymes can break down ROS, thus protecting the body from free radical damage. Superoxide dismutase, catalase, and glutathione peroxidase are the main classes of enzymatic antioxidants. On the other hand, glutathione reductase and thioredoxin reductase are the secondary enzymes of antioxidants [117, 118].

4.1. Primary Enzymatic Antioxidants. In human biological systems, superoxide dismutase (SOD) contains external body fluids and aerobic cells [119, 120]. This enzyme accelerates the radical conversion of superoxide anions into hydrogen peroxide and oxygen [121, 122]. There are three main types of SOD (all bound to metal cofactors). SOD

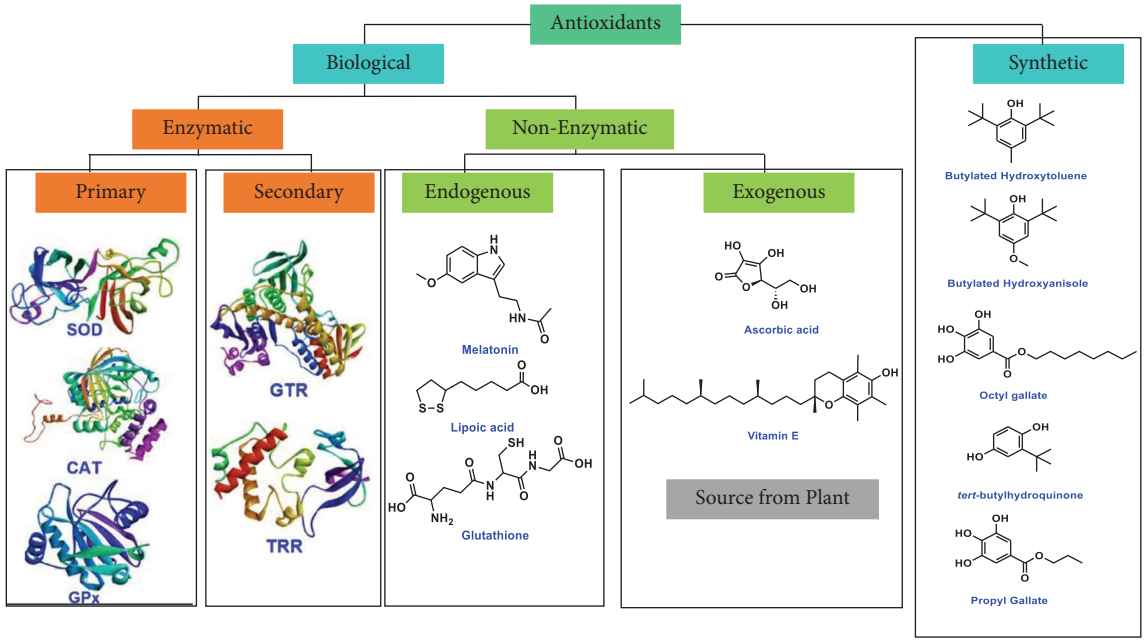

Figure 2: Schematic approaches for the classification of antioxidants [114].

bound to zinc or copper and SOD bound to manganese, iron, and nickel [123]. In high altitude plants, copper- and zinc-bound SODs are commonly found on apoplasts, peroxisomes, chloroplast, and cytosols. Manganese-bound SOD is also present in peroxisomes and mitochondria. Iron-bound SOD is normally found in chloroplasts and peroxisomes [124]. The classification of SOD in humans can also be divided into zinc-bound SOD type 1 and manganese-bound SOD type 2. Both enzymes are in the cytoplasm. The last is SOD type 3 that binds zinc extracellularly [125–127].

Almost all living organisms involved in oxygen processes in life contain a common catalase that is used to catalyze the breakdown of H_2O_2 into H_2O and O_2 [128]. In the human biological system, there are primary or byproducts of metabolic activity that highly toxic H_2O_2. This molecule must be converted into other compounds so as not to damage the cellular structure. These gaseous, less harmful water and oxygen molecules are produced by the rapid conversion of hydrogen peroxide in the body by the catalases (CAT) [129]. CAT have a Kcat value greater than 106/sec, and this allows to quickly change molecules. Although there has been significant debate regarding the function of CAT peroxynitrite, the current study revealed that CAT may be able to scavenge $ONOO^-$ [130].

Glutathione peroxidase (GPx) has four selenium cofactors that act as a catalyst for the breakdown of hydroperoxide radicals. At least four different glutathione peroxidase isozymes exist in mammals. GPx 1 is the most prevalent and highly efficient hydrogen peroxide scavenger, while GPx 4 is particularly active against lipid hydroperoxides [131].

4.2. Secondary Enzymatic Antioxidants. Classes of reductase enzymes such as glutathione reductase (GTR) and thioredoxin reductase (TRR) are enzymes that play a role in the secondary antioxidant system as they are responsible for the constant generation of NADPH to balance ROS production. NADPH can neutralize the effects of toxic molecules entering the human body [132]. Another source of NADPH metabolism can also be through the pentose phosphate pathway with the help of enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase [117].

4.3. Nonenzymatic Antioxidants. Nonenzymatic antioxidants are compounds that can counteract free radicals without the intervention of enzymes. Normally, this action does not occur catalytically and is found in low molecular weight chemicals. Therefore, nonenzymatic antioxidants consist of either endogenous (eukaryotic cells can produce them by themselves) or exogenous (antioxidants must be taken outside the body).

4.3.1. Endogenous Nonenzymatic Antioxidants. Melatonin, known as *N*-acetyl-5-methoxytryptamine, is one of the antioxidants that can easily penetrate cell membranes and the blood-brain barrier, thus protecting cell membranes from lipid peroxidation [133]. The amino acid tryptophan is the source of this hormone melatonin. Melatonin is called a terminal antioxidant because it does not enter the redox cycle. A redox cycle is a cycle of molecules that are repeats oxidation and reduction [134]. Melatonin can be oxidized to form free radicals end products but cannot go back to its original state [135].

1,2-dithiolane-3-pentanoic acid or α-lipoic acid is a disulfide compound that participate in metal chelation and undergoes redox cycles to scavenge active ROS. α-Lipoic acid can prevent the Fenton reactions on radicals and regenerate both vitamins such as C and E in a viable form [136]. This compound can also act as a thiol antioxidant such as the glutaredoxin protein [137].

Glutathione has thiol groups' antioxidant characteristics because it can be oxidized and reduced reversibly and has a thiol group in its system [138]. Glutathione is a cellular antioxidant because of its importance in maintaining the cell's redox state and its high concentration. Glutathione is a peptide that is produced in cells from amino acids. Glutathione can directly react with oxidants in cells and diminish other metabolites [139].

Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-polyisoprene parabenzoquinone) or often called ubiquinone is generated via isoprenoid oligomerization and the mevalonate pathway that begins with isopentenyl pyrophosphate and dimethylallyl pyrophosphate [140]. Ubiquinone is an antioxidant molecule that is fat soluble and protects the body from lipid peroxidation and oxidative damage. It can scavenge certain ROS and regenerate other oxidized antioxidants [141].

4.3.2. Exogenous Nonenzymatic Antioxidants. Extracorporeal or exogeneous antioxidants must be taken regularly because their synthetic pathways are usually in plant cells or microorganisms. Vitamins, flavonoids, and carotenoids are examples of extracorporeal molecules that exhibit antioxidant activity. Dehydroascorbic acid (DHA) can be produced by two electron oxidation of vitamin C or ascorbic acid (AA). AA is found in tomatoes, pineapples, watermelons, and all citrus fruits (Figure 3). The main function of AA is to scavenge ROS in the form of O_2, H_2O_2, organic peroxides, HClO, or OH [142]. On the other hand, other vitamins such as vitamin E can be defined as highly bioavailable water-soluble vitamins with antioxidant properties [143]. α-Tocopherol protects membranes from oxidation by interacting with radicals in the peroxidation reaction chain. This can prevent continued propagation and remove free radical intermediates [144]. Flavonoids can be classified as compounds with high oxidant activity because they are highly effective in reducing ROS such as superoxide anions and peroxyl radicals through the mechanism of hydrogen atom transfer (HAT) [145, 146]. Flavonoids also can chelate some metal ions and block the formation of free radicals such as quercetin, an example of a flavonoid that can be an iron chelator and iron stabilizer [147]. Catechol derivatives can also block the Fenton reaction in the formation of other free radicals [12, 148]. Carotenoids have the biological activity of scavenging of ROS. β-Carotene, one of the most abundant carotenoids found in carrots, pumpkins, and mangoes, has been proposed as a cancer chemopreventive agent [149, 150].

4.4. Synthetic Antioxidants. Synthetic antioxidants interact with free radical species through metal ion binding, oxygen deactivation, radical to nonradical species conversion, and UV radiation saturation [151]. Examples of synthetic antioxidants include propyl gallate (PG), octyl gallate (OG), *tert*-butylhydroquinone (TBHQ), butylhydroxytoluene (BHT), and butylhydroxyanisole (BHA) (Figure 3) [111, 152]. BHT is less effective than BHA due to the two sterically hindered *tert*-butyl groups. BHA is very effective in controlling the oxidation of short-chain lipids. BHA and BHT are less effective in inhibiting ROS activity when compared to TBHQ [153, 154]. This is due to the two *para*-hydroxyl groups responsible for the antioxidation activity of TBHQ [155]. PG is known as a safe antioxidant because it can preserve oils and foods from spoilage caused by peroxide formation [154]. In addition, PG stabilizes foods and cosmetics. OG can be defined as a food preservative composed of gallic acid and 1-octanol ester. BHT and BHA are very commonly used antioxidants in the diet industry [156].

5. Overview and Bioavailability of Flavonoids

Flavonoids, characterized by the presence of two benzene rings (A and B) linked by three central carbon chains, comprise a diverse group of compounds sharing a C6-C3-C6 basic carbon skeleton. Their classification is based on variations in the oxidation level of the central carbon chain (C3) and differences in the linkage sites of the B-ring. Flavonoids encompass various subclasses including flavones, flavonols, isoflavones, anthocyanins, chalcones, neoflavonoids, and flavanones. Indeed, the C ring serves as a distinguishing feature for each subfamily of flavonoids. Within these subfamilies, individual monomers vary in the type, position, and quantity of substituents such as hydroxyl groups, and certain flavonoids have the capacity to form oligomers as well [157, 158].

Anthocyanin, a prevalent flavonoid, is abundantly found in various food items, particularly in vegetables, berries, and grains with vibrant colors. The primary site of anthocyanin absorption is the stomach. Despite its short retention time following oral administration, anthocyanin can be rapidly absorbed in the stomach through an *in situ* fluorescence reaction. The overall absorption rate of pelargonidin administered orally was observed to be 18% after 2 hours in the stomach. However, due to the acidic environment and limited absorption area of the gastric mucosa, the absorption efficiency of anthocyanins in the stomach is relatively low. Anthocyanins, known for their hydrophobic nature, are primarily absorbed in the small intestine through passive diffusion [159].

In natural functional foods, glycosides typically exhibit low bioavailability, with only a small portion being absorbed into the bloodstream. However, they still demonstrate efficacy, potentially attributed to their metabolites, such as secondary glycosides or aglycones, which enter the body and play significant roles. Following oral administration, some flavonoids can be directly absorbed, while others undergo metabolism and transformation facilitated by intestinal flora and liver metabolizing enzymes, yielding active metabolites [160].

The liver serves as a crucial metabolic site for flavonoids upon absorption into the body. O-methylated glutathione and sulfate are recognized as some of the most active structural configurations. Glutathione and sulfonate conjugates of flavonoids are predominantly found in the small intestine and liver, while the *O*-methylated form is specific to β-cyclocatechol flavonoids. Flavonoids undergo two primary metabolic processes in the liver, i.e., oxidation reactions and conjugation reactions. Oxidation reactions involve the metabolism of flavonoids by cytochrome P450

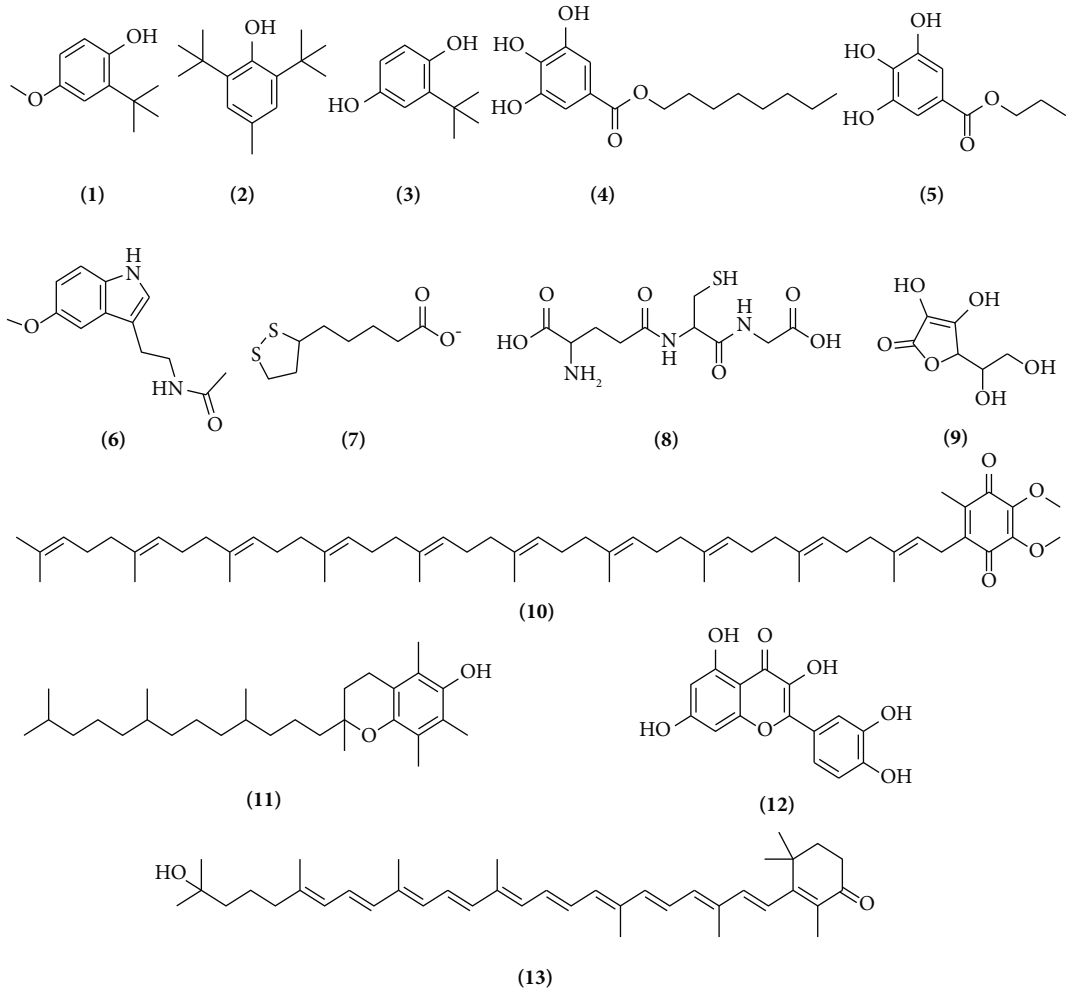

Figure 3: Structures presenting natural and synthetic antioxidants: (**1**) butylhydroxyanisole (BHA), (**2**) butylhydroxytoluene (BHT), (**3**) *tert*-butylhydroquinone (TBHQ), (**4**) octyl gallate (OG), (**5**) propyl gallate (PG), (**6**) melatonin, (**7**) α-lipoic acid, (**8**) glutathione, (**9**) vitamin C, (**10**) coenzyme Q10, (**11**) vitamin E (**12**) quercetin, and (**13**) carotenoid K.

enzymes predominantly found in the liver [161]. Lipinski proposed a set of five fundamental criteria for screening potential drug molecules as follows: (1) the compound's structure should contain no more than 5 hydrogen bond donors, including hydroxyl and amino groups, (2) the compound should not possess more than 10 rotatable bonds, (3) the logarithm of the compound's fat-water partition coefficient (log P) should fall within the range of 2–5, (4) the compound should have no more than 10 hydrogen bond acceptors, and (5) the molecular weight of the compound should be below 500 daltons. These guidelines serve as a framework for evaluating the potential suitability of molecules for drug development [162].

Nevertheless, when applying these five rules to assess flavonoids, it becomes apparent that flavonoids typically possess higher molecular weights and larger dosage forms, leading to poorer solubility. Consequently, their absorption in the gastrointestinal tract is often limited. However, by employing modifications to both the dosage form and chemical structure, it is possible to enhance their absorption and bioavailability [163].

6. Clinical Applications and Human Studies of Flavonoids Compounds

Aging in biology is a multifaceted phenomenon characterized by the gradual decline of cells over time, primarily caused by the cumulative buildup of damage across various cell types. This process is partly attributed to the diminishing capacity of cells to repair and maintain themselves as they age, heightened stress levels, DNA damage, mitochondrial dysfunction, and inflammation [164]. Prominent diseases such as eye disorders (macular degeneration), joint degeneration, skin conditions, vascular disease, atherosclerosis, metabolic disorders (obesity and diabetes), circulatory issues (hypertension and coronary artery disease), and neurodegenerative diseases (Alzheimer's, dementia, and declining cognitive function) are significantly influenced by age [164]. Several human studies have examined the impact of flavonoid or polyphenolic intake on mortality as a response dependent on age [165, 166]. A recent study conducted on the Danish Diet Cancer and Health Cohort, involving more than 50,000 participants, revealed that

consuming approximately 500 mg/day of total flavonoids in the diet was associated with a reduction in overall mortality. Interestingly, higher intakes of up to 2000 mg/day did not lead to further decreases in mortality. The study also found similar effects on reduced mortality associated with the consumption of specific subclasses of flavonoids, including flavonols, flavanols, flavanones, flavones, and anthocyanins. In addition, there was evidence suggesting that dietary flavonoids might mitigate the increased mortality rates associated with alcohol and smoking consumption. Notably, some variations in mortality outcomes were observed across different cohorts in the studies [167]. A notable rise in mortality was observed among women in the group with high grapefruit consumption compared to those with low consumption. Conversely, selected flavonoid and polyphenol-rich foods such as tea, peppers, blueberries, red wine, and strawberries were linked to reduced mortality rates. The general agreement from numerous studies is that dietary flavonoids substantially decrease mortality rates and may offer some defense against factors contributing to elevated mortality rates. Many reports on dietary flavonoids and mortality also explore the potential association with mortality from cardiovascular diseases [168, 169].

Obesity-induced dietary habits have led to a notable rise in the prevalence of diabetes, an age-related condition, across various countries in recent years. A recent meta-analysis encompassing 18 distinct prospective cohort studies on polyphenol consumption and the risk of type 2 diabetes revealed an inverse relationship when comparing the highest and lowest quintiles of intake. This association was observed for flavonoids, flavonols, flavan-3-ols, catechins, anthocyanidins, and isoflavones [170].

Flavonoids have been extensively studied for their potential as anticancer agents, primarily due to their ability to inhibit several pro-oncogenic pathways and genes within cancer cells. In addition, they have been found to induce responses and genes similar to tumor suppressors, albeit to a lesser extent [171–173]. At this time, clinical trials evaluating the therapeutic effects of genistein on prostate and colorectal cancer are currently ongoing. In addition, studies investigating the combination of isoflavones with other agents showed no significant impact on advanced pancreatic cancer, but there may be an influence on PSA levels in patients with prostate cancer [174, 175].

Flavonoids and polyphenolics are compounds with immunomodulatory properties, impacting various types of immune cells. The effects can vary significantly depending on the specific compound, animal model, and immune component being studied. Reviews examining the effects of flavonoids and related compounds on immune cell responses highlight their diverse effects on immune cells and immune responses [176, 177]. These effects include influencing β cell and antibody production, boosting NK cell cytotoxicity, suppressing Th17-dependent differentiation and NLRP3 inflammation, and stimulating CD^{8+} cell induction. However, human intervention studies on the effects of flavonoids on immune responses yield mixed results, and these compounds are not commonly utilized in immune therapies [178, 179].

7. Antioxidant Mechanism of Flavonoids Compounds

Antioxidants generally exhibit activity based on hydrogen atom transfer (HAT), single electron transfer via proton transfer (SET-PT), and transition metal chelation (TMC) mechanisms [180, 181]. Antioxidants exhibit their activity by (i) preventing the formation and derivatization of free radicals, (ii) interfering with radical oxidation process, and (iii) generating inert free radical derivatization reactions [114].

7.1. Hydrogen Atom Transfer (HAT). Hydrogen atom transfer (HAT) or hydrogen atom abstraction is a basic reaction in aerobic combustion, and oxidation processes involving hydrogen atoms. Basically, this reaction involves the transfer of two elementary particles, namely, a proton and an electron [182]. Here is the general process of HAT: $A\bullet + B - OH \longrightarrow A - H + B\bullet$. In this case, bond dissociation energy (BDE) of B-OH is lower than BDE A-OH [183]. BDE is energy to break down chemical compounds into several parts [184].

Antioxidant HAT, symbolized by AH, interacts with free radicals. Antifree radical species are converted to antioxidant free radical (A•), while the radicals are stabilized to generate impaired species [185]. We give examples of flavonoids as antioxidants. Flavonoid antioxidants donate hydrogen atoms to free radical molecules, resulting in the formation of nonradical species (ROOH, ROH, or RH) and antioxidant free radical (A•). Any molecule with lower reduction potential than the radical species can donate an H atom to its free radical (except for infeasible kinetic reactions) [154]. The ability and efficacy of flavonoids as antioxidants is determined by their conformation, especially the number and position of OH groups and the aromatic ring [186]. The aromatic ring is important for the stability of antioxidants when they react with free radicals. Numerous *in vitro* and *in vivo* studies have been conducted with natural flavonoids to confirm the relationship between flavonoid structure and antioxidant activity. The hydroxyl cluster (red dotted circle in Figure 4), the *ortho*-dihydroxy arrangement in the B ring (green dotted circle in Figure 4); the C2-C3 unsaturated bond paired with the C4 carbonyl cluster in the C compartment (blue dotted circle in Figure 4) can contribute to increased antioxidant activity of a compound [187].

Free radical stabilization is carried out by the free hydroxyl group that can donate H atoms to form more stable phenoxy flavonoid radicals [188]. The hydroxyl groups on the B skeleton are the most effective free radical scavenger for both oxygen and nitrogen. These internal hydroxyl groups donate electrons and hydrogen to peroxyl, hydroxyl, and peroxynitrite radicals, neutralizing them to produce relatively stable flavonoid radicals as shown in Figure 5 [190]. Hydroxyl clusters are effective ROS and RNS scavengers. The antioxidant capacity of flavonoids appears to be dominated by hydroxyl groups [189]. The presence of hydroxyl cluster in compartment B and the total number of hydroxyl groups correlated with stronger antioxidant

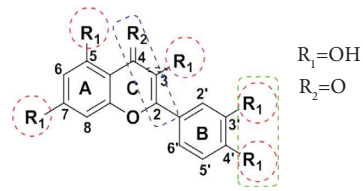

Figure 4: Summary of the flavonoid antioxidant.

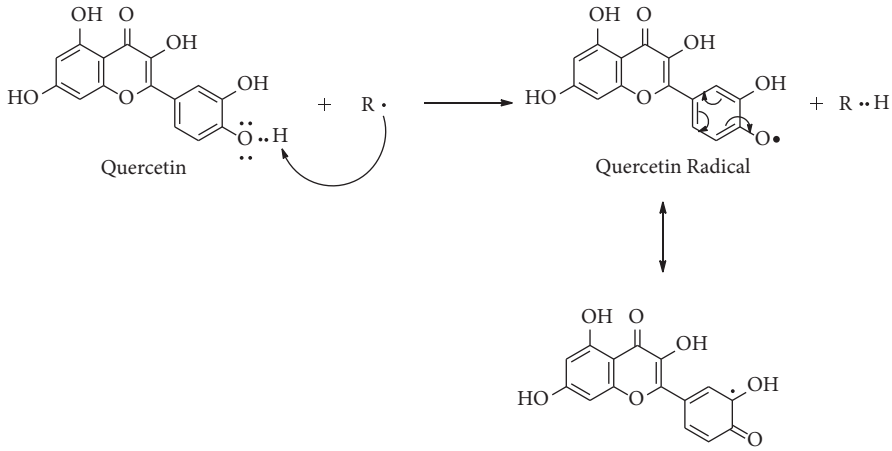

Figure 5: Reaction of quercetin with radical species and stabilization of quercetin-free radicals [188–190].

activity [191]. They found that the antioxidant activity of quercetin and its derivatives is very high compared to other substances. Flavonols with five hydroxyl groups, such as quercetin, have higher antioxidant activity than those without free radical neutralization because aromatic ring resonance stabilizes the radical [192]. However, the presence of alkyl chain or branched alkyl groups at the para position reduces antioxidant activity. The two bulky groups of BHT at *ortho* positions improve the stability of the aromatic ring radicals. Sterically hindered groups on the aromatic rings can form a barrier to the radical area and slow down the growth rate of free radicals. The number of hydroxyl groups on the aromatic ring also affects antiradical ability. Flavonoids have stronger antioxidant activity than phenolic acids [136].

7.2. Single Electron Transfer via Proton Transfer (SET-PT). Single electron transfer is one of the mechanisms of action of antioxidants in counteracting free radicals. The mechanism of single electron transfer (SET) is the provision of one electron to the free radical compound so that the free radical becomes its less reactive anion form. After that, the anion of the free radical will react with hydrogen ions to form a stable compound [193]. In this mechanism, the antioxidant donates one electron to the free radical so that the antioxidant becomes radicalized; therefore, the ability to donate electrons is crucial to the antioxidant activity. Here is the general process of SET: $A-OH + B\bullet \longrightarrow A-OH\bullet^{+} + B^{-}$ [194]

Anions are an energetically stable species with an odd number of electrons resulting from electron transfer mechanisms. Radical cations ($A-OH^{+}$) are relatively stable and difficult to react with other chemical species [195]. Aromatic ring structures produced by the reaction with radicals in $A-OH\bullet^{+}$ can be dispersed throughout the molecule [196]. As shown in Figure 6, antioxidant species can cause to stabilize radicals. The most important limitation in determining radical irrigation in single electron transfer process comes from the ionization potential (IP). Lower IP value makes it easier to withdraw electrons and react with radicals, resulting in increased antioxidant activity [198].

7.3. Transition Metal Chelation (TMC). Transition metal chelation is an antioxidant mechanism to chelate metals that form multiple coordination bonds between organic molecules. It involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central metal atom. This process often occurs in the human body [199].

Flavonoids utilize the transition metal chelation (TMC) mechanism to exert their antioxidant activity [200]. Such processes are catalyzed by switchover metals such as iron (Fe), cobalt (Co), manganese (Mg), and copper (Cu). Chelation, on the other hand, is susceptible to specific conditions, such as metal ions not attaching to proteins or other chelator molecules. As shown in Figure 7, the formation of OH-free radicals in the Fenton reaction can be reduced by adding metals or metal chelators. This can suppress the reduction of Fe^{+3} [201]. Flavonoids contain chelating properties that bind to metal ions within structural cells and prevent oxidation. Some flavonoids have the opportunity to bind heavy or transitional metal ions such as iron and copper that are important in free radical generation

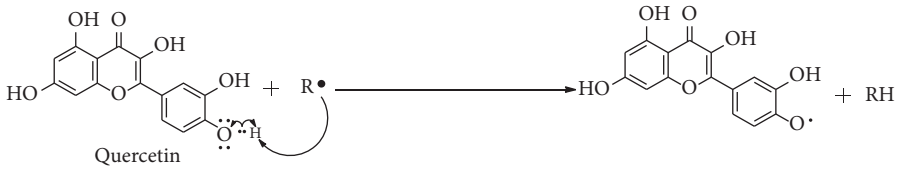

Figure 6: Single electron transfer abstraction mechanism of quercetin [195, 197, 198].

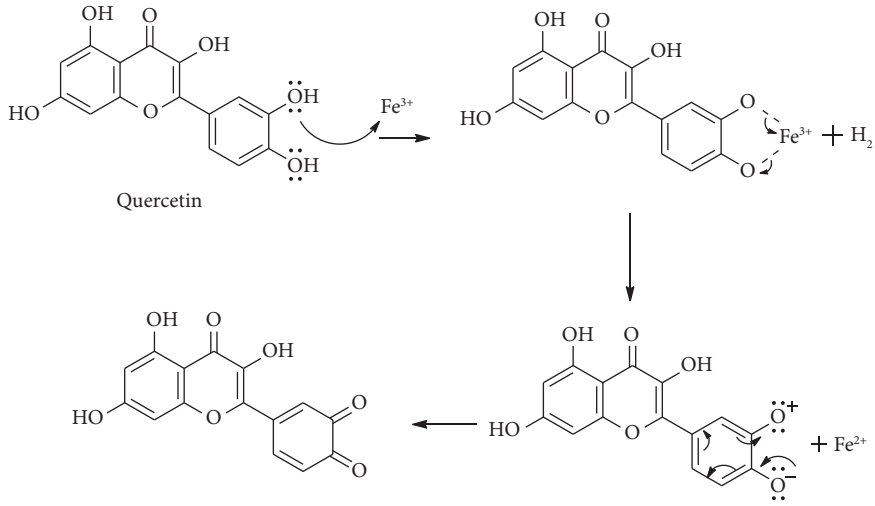

Figure 7: Transition metal chelation mechanism of quercetin [200–202].

and oxidation processes [202]. Flavonoids have the adequate ability to combat incoming free radicals. Nevertheless, the nature of the flavonoid structure can be an important consideration in the reducing power and chelating potential of metals. For example, the metal chelating and free radical scavenging properties of catechol depend on the influence of two hydroxyl groups, two conjugated bonds on the active carboxylic group, and the B ring [203].

8. Actual Limitations of Flavonoids

The current limitations on the utilization of flavonoids in medical, pharmaceutical, food, and cosmetic sectors are primarily influenced by the following two key factors: (i) chemical and biophysical attributes, encompassing issues like poor solubility, chemical stability, bioavailability, and metabolic stability (including hepatic, intestinal, and intestinal microflora metabolism) and (ii) challenges associated with plant production, including the low yield of these secondary metabolites relative to biomass and complexities involved in enhancing biosynthesis, as well as intricate methods for isolation, extraction, and purification [204].

A primary issue concerning flavonoids is their limited bioavailability. Following oral intake, only a small fraction of flavonoids is absorbed in the upper gastrointestinal tract, including the oral cavity, while a considerable portion reaches the small intestine and can interact with the intestinal microbiota in the colon. Some flavonoids may undergo metabolism by liver enzymes, such as cytochrome P450, leading to the formation of active metabolites [158, 205]. The absorption of flavonoids in the human body varies depending on the molecular structure conformation and pH levels. Once absorbed by the intestinal epithelium, flavonoids undergo transformation into conjugated metabolites, such as glucuronides, sulfates, and methylated metabolites. These transformations occur initially in the intestine and subsequently in the liver [206].

The aglycones of flavonoids, characterized by their small molecular size and high hydrophobicity, enter the liver through the hepatic portal vein, where two primary metabolic reactions occur, i.e., oxidation reactions facilitated by cytochrome P450 enzymes (phase I) and conjugation reactions (phase II). Flavonoid glycosides, on the other hand, have higher hydrophilicity and molecular weight and can only be absorbed after undergoing hydrolysis into aglycones or phenolic acids by the intestinal microbiota. The rapid metabolic elimination of flavonoids underscores the importance of developing innovative approaches to enhance their delivery [207, 208].

9. Global Perspective of Usage Flavonoids

Europe has been the focal point for numerous studies investigating the consumption of total flavonoids, allowing for a relatively accurate depiction of their intake across the continent. Notably, initiatives like the European Prospective Investigation into Cancer and Nutrition (EPIC) have facilitated comparisons across 10 European nations using consistent methodologies. Generally, there is an observed trend of increasing intake from south to north in Europe [209]. Interestingly, despite the Mediterranean (MED) countries' reputation for high consumption of fruits,

vegetables, and red wine, their total flavonoid intake (ranging from 250 to 400 mg/day) tends to be lower compared to non-MED countries (ranging from 350 to 600 mg/day), particularly due to the significantly higher tea consumption in non-MED countries. If thearubigins were factored in, these differences would likely be more pronounced [210]. The United Kingdom stands out in Europe for its notably high total flavonoid intake, attributed to its entrenched tea culture. Eastern European nations, such as Poland, also exhibit high total flavonoid intake (approximately 600 mg/day), largely influenced by their substantial tea consumption [211]. France serves as an interesting case, with southern regions classified as MED and northern regions as non-MED. Consequently, France demonstrates an intermediate total flavonoid intake, with key sources including fruit, tea, and red wine—a blend of dietary patterns from MED to non-MED regions [212]. Conversely, Scandinavian countries like Finland, where tea consumption is lower, exhibit lower total flavonoid intake (ranging from 200 to 250 mg/day) compared to MED countries, reflecting their relatively lower fruit consumption as well.

In Asian countries, comprehensive data on total flavonoid intake are scarce, with only information available for East Asian nations such as China and South Korea. In China, total flavonoid intake ranges from 65 mg/day without proanthocyanidins to 225 mg/day with proanthocyanidins [213]. Notably, thearubigins, formed during the fermentation of green tea to black tea, are not included in these studies, despite the prevalent consumption of green tea in China rather than black tea. South Korea exhibits a slightly higher total flavonoid intake compared to China, estimated at 320 mg/day [214]. In East Asian countries, soy and its derivatives, serving as primary sources of isoflavones, significantly contribute to total flavonoid intake. However, in South Korea and China, proanthocyanidins and flavan-3-ol monomers emerge as the most abundant flavonoids, respectively [215]. Japan, China, and South Korea have focused extensively on isoflavones due to their potential phytoestrogenic effects, but research specifically targeting total flavonoids is limited in these regions. Conversely, in the Middle East, a recent study conducted in Iran revealed a remarkably high mean intake of 1650 mg/day, marking the highest worldwide total flavonoid intake. This substantial intake is attributed to the widespread consumption of black tea among Middle Eastern populations [209].

In the Americas, particularly in the United States, numerous studies have been conducted to estimate total flavonoid intake, leveraging the development of USDA databases. The mean intake of total flavonoids in the US ranges from 250 to 400 mg/day, encompassing proanthocyanidins and thearubigins. Despite relatively modest tea consumption, it remains a primary source of total flavonoids in the US, possibly due to lower intake of fruits and vegetables [216]. Significant variations in total flavonoid intake among ethnicities have been noted in the US. Non-Hispanic whites exhibit the highest intake (>300 mg/day), while non-Hispanic blacks, Mexican Americans, and other ethnicities consume around 200 mg/day [217]. Data on total flavonoid intake in other American countries are limited. To date, Brazil and Mexico are the only countries with available data. Total flavonoid intake is approximately 150 mg/day in Mexico and 50 mg/day in Brazil, representing the lowest reported intake globally. Notably, thearubigins are not accounted for in these studies, but their contribution is minimal as tea consumption is rare among Brazilians and Mexicans [218]. In these Latin-American nations, citrus juices emerge as the primary source of total flavonoids, followed by fruit in Mexico and beans in Brazil. However, it is important to acknowledge a potential underestimation of total flavonoids due to missing food composition data on certain tropical foods commonly consumed in their diets, which could serve as significant sources of flavonoids. Examples include jicama, guava, prickly pears, papaya, mamey, zapote, sweet potato, and nopal [212].

Australia has been the focus of several studies examining total flavonoid intake. Being a nation with a strong tea-drinking culture, Australia exhibits a high intake of total flavonoids, estimated between 650 and 700 mg/day, which include thearubigins. Across the documented Australian populations, black tea stands out as a significant contributor, accounting for at least 75% of the total polyphenol intake [219].

10. Future Directions of Flavonoids Compounds

Flavonoids, vital secondary metabolites synthesized by plants and microorganisms, boast a multitude of biological activities. The recognition of these properties has sparked a growing interest in leveraging flavonoids across various industries including medical, pharmaceutical, cosmetic, food, and nutraceutical sectors. Current research and development endeavors surrounding flavonoids primarily focus on their identification, extraction techniques, exploration of novel functionalities, and applications for promoting health. Techniques such as molecular docking, advanced extraction methodologies, and integration into diverse delivery systems are being employed to enhance flavonoid yield, solubility, and stability. These innovations pave the way for the advancement of new industrial manufacturing technologies aimed at harnessing the potential benefits of flavonoids [220].

One prospective solution to tackle the limitations associated with flavonoids involves the extensive adoption and advancement of nanotechnology. Nanotechnology presents promising prospects across various scientific domains including medicinal chemistry, healthcare, and pharmaceutical science. The unique characteristics of nanoparticles, such as their minute size and large surface area, render them particularly suitable for applications in the medical and pharmaceutical sectors. Their capability to enhance the efficacy of plant-derived products, augment the production of secondary plant metabolites compared to biomass, mitigate adverse effects, and boost bioavailability makes them an ideal avenue for addressing flavonoid challenges [221].

Nanovesicle systems such as liposomes and ethosomes, along with cyclodextrins and dendrimers, micro- and nanoparticles, nanostructured lipid carriers, solid lipid nanoparticles, and nanomicelles represent prevalent

examples of biocompatible and biodegradable nanoparticles [222]. Another research investigation delves into the distinctive attributes of nanomicelles, which facilitate efficient delivery and enhanced bioavailability of diverse nutrients, including flavonoids. Nanomicelles offer numerous advantages stemming from their size and structural makeup. They bolster drug stability, shield them from elimination by the mononuclear phagocyte system, and result in extended blood circulation [223].

There is undeniable evidence supporting the use of nanotechnology for precisely targeting the delivery of flavonoids to enhance their bioavailability. Nonetheless, thus far, these delivery systems for flavonoids have mainly been replicated in laboratory settings (*in vitro*), with limited application in human models. In the foreseeable future, conducting clinical trials holds the potential to significantly enhance both the efficacy and safety profiles of utilizing flavonoids as novel therapeutic approaches for human diseases [224].

11. Conclusion

Free radicals can be produced by normal metabolism in the body and affect human biological systems. When the balance of pro-oxidant and antioxidants is disturbed, oxidative stress accumulates and causes severe damage to structural cells and tissues such as lipids, protein, and nucleic acids. This causes tissue damage in a variety of illness situations, including diabetes, neurological diseases, cancer, and others, hastening disease development. Flavonoids hold promise as natural compounds with potential health benefits, but their clinical applications require rigorous investigation to overcome existing limitations. Global perspectives from various continents provide valuable insights into dietary patterns and their associations with health outcomes. Future research should focus on addressing challenges in study design, enhancing bioavailability, and elucidating mechanisms of action to unlock the full potential of flavonoids in promoting human health. In this review, we focused on flavonoids as potent antioxidant because flavonoids as secondary metabolites sourced from plants can prevent the development of free radicals. The presence of hydroxyl groups on the flavonoids structure becomes a determining factor in the scavenging of free radicals. In fact, the position of the hydroxyl group on the B ring can be a metal chelation agent that makes the flavonoids molecular structure a good antioxidant.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

[1] K. Chen, J. Zhang, N. M. Beeraka et al., "Advances in the prevention and treatment of obesity-driven effects in breast cancers," *Frontiers in Oncology*, vol. 12, pp. 1–22, 2022.

[2] G. Martemucci, C. Costagliola, M. Mariano, L. D'andrea, P. Napolitano, and A. D'Alessandro, "Free radical properties, source and targets, antioxidant consumption and health," *Oxygen*, vol. 2, pp. 48–78, 2022.

[3] Y. Yu, Y. Cui, L. Niedernhofer, and Y. Wang, "Occurrence, biological consequences, and human health relevance of oxidative stress-induced DNA damage," *Chemical Research in Toxicology*, vol. 29, no. 12, pp. 2008–2039, 2016.

[4] B. Salehi, Z. Selamoglu, M. Sevindik et al., "*Achillea* spp.: a comprehensive review on its ethnobotany, phytochemistry, phytopharmacology and industrial Applications," *Cellular & Molecular Biology*, vol. 66, no. 4, pp. 78–103, 2020.

[5] T. Ayoka, B. Ezema, C. Eze, and C. Nnadi, "Antioxidants for the prevention and treatment of non-communicable diseases," *Journal of Exploratory Research in Pharmacology*, vol. 7, pp. 178–188, 2022.

[6] D. Granato, F. Shahidi, R. Wrolstad et al., "Antioxidant activity, total phenolics and flavonoids contents: should we ban *in vitro* screening methods?" *Food Chemistry*, vol. 264, pp. 471–475, 2018.

[7] E. Atta, N. Mohamed, and A. Abdelgawad, "Antioxidants: an overview on the natural and synthetic types," *European Chemical Bulletin*, vol. 6, no. 8, pp. 365–375, 2017.

[8] E. D. Cömert and V. Gökmen, "Evolution of food antioxidants as a core topic of food science for a century," *Food Research International*, vol. 105, pp. 76–93, 2018.

[9] G. A. El-Chaghaby, A. F. Ahmad, and E. S. Ramis, "Evaluation of the antioxidant and antibacterial properties of various solvents extracts of Annona squamosa L. leaves," *Arabian Journal of Chemistry*, vol. 7, no. 2, pp. 227–233, 2014.

[10] R. R. Kotha, F. S. Tareq, E. Yildiz, and D. L. Luthria, "Oxidative stress and antioxidants-A critical review on *in vitro* antioxidant assays," *Antioxidants*, vol. 11, no. 12, pp. 2388–2430, 2022.

[11] S. Khandker, A. Kabir, M. Hasan et al., "Elachi lemon (*Citrus limon*) peel and pulp: antioxidant, antimicrobial, anticoagulant activities, bioactive compounds, minerals, and heavy metals," *Current Bioactive Compounds*, vol. 17, no. 6, pp. 47–58, 2021.

[12] J. Treml and K. Smejkal, "Flavonoids as potent scavengers of hydroxyl radicals," *Comprehensive Reviews in Food Science and Food Safety*, vol. 15, no. 4, pp. 720–738, 2016.

[13] E. Sisein, "Biochemistry of free radicals and antioxidants," *Scholars Academic Journal of Biosciences*, vol. 2, pp. 110–118, 2014.

[14] A. Phaniendra, D. B. Jestadi, and L. Periyasamy, "Free radicals: properties, sources, targets, and their implication in various diseases," *Indian Journal of Clinical Biochemistry*, vol. 30, no. 1, pp. 11–26, 2015.

[15] C. M. C. Andrés, J. M. Pérez De La Lastra, C. Andrés Juan, F. J. Plou, and E. Pérez-Lebeña, "Superoxide anion chemistry—its role at the core of the innate immunity,"

International Journal of Molecular Sciences, vol. 24, no. 3, pp. 1841–1844, 2023.

[16] M. Rinnerthaler, J. Bischof, M. Streubel, A. Trost, and K. Richter, "Oxidative stress in aging human skin," *Biomolecules*, vol. 5, no. 2, pp. 545–589, 2015.

[17] Y. Sheng, I. A. Abreu, D. E. Cabelli et al., "Superoxide dismutases and superoxide reductases," *Chemical Reviews*, vol. 114, no. 7, pp. 3854–3918, 2014.

[18] M. Hayyan, M. A. Hashim, and I. M. Alnashef, "Superoxide ion: generation and chemical implications," *Chemical Reviews*, vol. 116, no. 5, pp. 3029–3085, 2016.

[19] T. Kanti Das, M. Wati, and K. Fatima-Shad, "Oxidative stress gated by fenton and Haber Weiss reactions and its association with alzheimer's disease," *Archives of Neuroscience*, vol. 2, no. 3, pp. 1–8, 2014.

[20] Y. Nosaka and A. Nosaka, "Understanding hydroxyl radical (OH•) generation processes in photocatalysis," *ACS Energy Letters*, vol. 1, no. 2, pp. 356–359, 2016.

[21] R. Hopkins, "Superoxide in biology and medicine: an overview," *Reactive Oxygen Species*, vol. 1, pp. 99–109, 2016.

[22] R. Apak, A. Calokerinos, S. Gorinstein et al., "Methods to evaluate the scavenging activity of antioxidants toward reactive oxygen and nitrogen species (IUPAC Technical Report)," *Pure and Applied Chemistry*, vol. 94, no. 1, pp. 87–144, 2022.

[23] H. Sies, V. V. Belousov, N. S. Chandel et al., "Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology," *Nature Reviews Molecular Cell Biology*, vol. 23, no. 7, pp. 499–515, 2022.

[24] A. Zeb, "Concept, mechanism, and applications of phenolic antioxidants in foods," *Journal of Food Biochemistry*, vol. 44, no. 9, pp. 4–e13420, 2020.

[25] F. Ahmadinejad, S. Geir Møller, M. Hashemzadeh-Chaleshtori, G. Bidkhori, and M.-S. Jami, "Molecular mechanisms behind free radical scavengers function against oxidative stress," *Antioxidants*, vol. 6, no. 3, pp. 51–15, 2017.

[26] A. Zeb, "Ellagic acid in suppressing *in vivo* and *in vitro* oxidative stresses," *Molecular and Cellular Biochemistry*, vol. 448, no. 1-2, pp. 27–41, 2018.

[27] A. Hansa, A. Devi, M. Upadhyay et al., "Toxicological implications of industrial effluents on plants: a review focusing on phytoremediation techniques," *International journal of Environmental Science and Technology*, vol. 21, no. 2, pp. 2209–2224, 2024.

[28] P. Poprac, K. Jomova, M. Simunkova, V. Kollar, C. J. Rhodes, and M. Valko, "Targeting free radicals in oxidative stress-related human diseases," *Trends in Pharmacological Sciences*, vol. 38, no. 7, pp. 592–607, 2017.

[29] A. Aranda-Rivera, A. Cruz-Gregorio, Y. Arancibia-Hernández, E. Hernández-Cruz, and J. Pedraza-Chaverri, "RONS and oxidative stress: an overview of basic concepts," *Oxygen*, vol. 2, no. 4, pp. 437–478, 2022.

[30] R. Nilsson and N. Liu, "Nuclear DNA damages generated by reactive oxygen molecules (ROS) under oxidative stress and their relevance to human cancers, including ionizing radiation-induced neoplasia part I: physical, chemical and molecular biology aspects," *Radiation Medicine and Protection*, vol. 1, no. 3, pp. 140–152, 2020.

[31] A. Kammeyer and R. Luiten, "Oxidation events and skin aging," *Ageing Research Reviews*, vol. 21, pp. 16–29, 2015.

[32] A. T. Jan, M. Azam, K. Siddiqui, A. Ali, I. Choi, and Q. M. R. Haq, "Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants," *International Journal of Molecular Sciences*, vol. 16, no. 12, pp. 29592–29630, 2015.

[33] S. S. Singhal, S. P. Singh, P. Singhal, D. Horne, J. Singhal, and S. Awasthi, "Antioxidant role of glutathione S-transferases: 4-Hydroxynonenal, a key molecule in stress-mediated signaling," *Toxicology and Applied Pharmacology*, vol. 289, no. 3, pp. 361–370, 2015.

[34] B. Morant-Ferrando, D. Jimenez-Blasco, P. Alonso-Batan et al., "Fatty acid oxidation organizes mitochondrial supercomplexes to sustain astrocytic ROS and cognition," *Nature Metabolism*, vol. 5, no. 8, pp. 1290–1302, 2023.

[35] H. Wong, P. A. Dighe, V. Mezera, P. Monternier, and M. D. Brand, "Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions," *Journal of Biological Chemistry*, vol. 292, no. 41, pp. 16804–16809, 2017.

[36] S. Kausar, F. Wang, and H. Cui, "The role of mitochondria in reactive oxygen species generation and its implications for neurodegenerative diseases," *Cells*, vol. 7, no. 12, pp. 274–319, 2018.

[37] Q. Duong, Y. Levitsky, M. Dessinger, J. O. Strubbe-Rivera, and J. N. Bazil, "Identifying site-specific superoxide and hydrogen peroxide production rates from the mitochondrial electron transport system using a computational strategy," *Function*, vol. 2, no. 6, pp. zqab050–21, 2021.

[38] T. Ohnishi, S. Ohnishi, and J. C. Salerno, "Five decades of research on mitochondrial NADH-quinone oxidoreductase (complex I)," *Biological Chemistry*, vol. 399, no. 11, pp. 1249–1264, 2018.

[39] N. Klimova, A. Fearnow, and T. Kristian, "Role of NAD^+-Modulated mitochondrial free radical generation in mechanisms of acute brain injury," *Brain Sciences*, vol. 10, no. 7, pp. 449–512, 2020.

[40] Q. Kanwal, M. Ahmed, A. Ur-Rehman et al., "Hypolipidemic effect of chloroform extract of *Lagenaria siceraria*: potential inhibitory activity of phytochemicals targeting the HMG-CoA reductase revealed by molecular docking and simulation studies," *Journal of Chemistry*, vol. 2023, pp. 1–15, 2023.

[41] A. Hunyadi, "The mechanism(s) of action of antioxidants: from scavenging reactive oxygen/nitrogen species to redox signaling and the generation of bioactive secondary metabolites," *Medicinal Research Reviews*, vol. 39, no. 6, pp. 2505–2533, 2019.

[42] R. Mailloux, "An update on mitochondrial reactive oxygen species production," *Antioxidants*, vol. 9, no. 6, pp. 472–514, 2020.

[43] S. Dogan, G. Giacchin, E. Zito, and C. Viscomi, "Redox signaling and stress in inherited myopathies," *Antioxidants and Redox Signaling*, vol. 37, no. 4-6, pp. 301–323, 2022.

[44] S. S. Cao and R. J. Kaufman, "Endoplasmic reticulum stress and oxidative stress in cell fate decision and human disease," *Antioxidants and Redox Signaling*, vol. 21, no. 3, pp. 396–413, 2014.

[45] E. Ponnampalam, A. Kiani, S. Santhiravel, B. Holman, C. Lauridsen, and F. Dunshea, "The importance of dietary antioxidants on oxidative stress, meat and milk production, and their preservative aspects in farm animals: antioxidant action, animal health, and product quality- invited review," *Animals*, vol. 12, no. 23, pp. 3279–3345, 2022.

[46] A. Said and S. M. Mekelleche, "Investigation of reaction mechanisms and kinetics of the radical scavenging ability of 5-*tert*-butylbenzene-1,2,3-triol and 3,5-di-*tert*-butylbenzene-1,2-diol compounds towards OOH radical,"

Progress in Reaction Kinetics and Mechanism, vol. 43, no. 2, pp. 101–111, 2018.

[47] A. Panov, "Perhydroxyl Radical (OH_2•) as Inducer of the isoprostane lipid peroxidation in mitochondria," *Molecular Biology*, vol. 52, no. 3, pp. 295–305, 2018.

[48] A. Baschieri, Z. Jin, and R. Amorati, "Hydroperoxyl radical (HOO•) as a reducing agent: unexpected synergy with antioxidants. A review," *Free Radical Research*, vol. 57, no. 2, pp. 115–129, 2023.

[49] G. Fang, J. Gao, C. Liu, D. D. Dionysiou, Y. Wang, and D. Zhou, "Key role of persistent free radicals in hydrogen peroxide activation by biochar: implications to organic contaminant degradation," *Environmental Science & Technology*, vol. 48, no. 3, pp. 1902–1910, 2014.

[50] M. Zheng, Y. Liu, G. Zhang, Z. Yang, W. Xu, and Q. Chen, "The applications and mechanisms of superoxide dismutase in medicine, food, and cosmetics," *Antioxidants*, vol. 12, no. 9, pp. 1675–1720, 2023.

[51] R. Radi, "Oxygen radicals, nitric oxide, and peroxynitrite: redox pathways in molecular medicine," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 115, no. 23, pp. 5839–5848, 2018.

[52] S. A. Adebayo, M. Ondua, L. J. Shai, and S. L. Lebelo, "Inhibition of nitric oxide production and free radical scavenging activities of four South African medicinal plants," *Journal of Inflammation Research*, vol. 12, pp. 195–203, 2019.

[53] N. Moldogazieva, I. Mokhosoev, N. Feldman, and S. Lutsenko, "ROS and RNS signaling: adaptive redox switches through oxidative/nitrosative protein modifications," *Free Radical Research*, vol. 1, pp. 1–65, 2018.

[54] S. Debnath, R. Ghosh, R. Nair, D. Pradhan, and P. Chatterjee, "Advancesin the development of water-soluble fluorogenic probes for bioimaging of hypochlorite/hypochlorous acid in cells and organisms," *ACS Omega*, vol. 7, no. 43, pp. 38122–38149, 2022.

[55] T. Oliveira, N. Gusmão, L. Silva, and L. Coelho, "Free radicals and actinobacteria as a misexplored goldmine of antioxidant compounds," *Anais da Academia Brasileira de Ciências*, vol. 93, no. suppl 3, pp. 5–e20202024, 2021.

[56] A. B. Jena, R. R. Samal, N. K. Bhol, and A. K. Duttaroy, "Cellular Red-Ox system in health and disease: the latest update," *Biomedicine & Pharmacotherapy*, vol. 162, pp. 114606–114621, 2023.

[57] S. Briyal, A. Ranjan, and A. Gulati, "Oxidative stress: a target to treat Alzheimer's disease and stroke," *Neurochemistry International*, vol. 165, pp. 105509–105513, 2023.

[58] M. Kuntic, O. Hahad, T. Münzel, and A. Daiber, "Crosstalk between oxidative stress and inflammation caused by noise and air pollution-implications for neurodegenerative diseases," *Antioxidants*, vol. 13, no. 3, pp. 266–327, 2024.

[59] H. Forman and H. Zhang, "Targeting oxidative stress in disease: promise and limitations of antioxidant therapy," *Nature Reviews Drug Discovery*, vol. 20, no. 9, pp. 689–709, 2021.

[60] G. Pizzino, N. Irrera, M. Cucinotta et al., "Oxidative stress: harms and benefits for human health," *Oxidative Medicine and Cellular Longevity*, vol. 2017, pp. 1–13, 2017.

[61] D. Teleanu, A. Niculescu, I. Lungu et al., "An overview of oxidative stress, neuroinflammation and neurodegenerative diseases," *International Journal of Molecular Sciences*, vol. 23, no. 11, pp. 5938–6022, 2022.

[62] R. Mesika and D. Reichmann, "When safeguarding goes wrong: impact of oxidative stress on protein homeostasis in health and neurodegenerative disorders," *Advances in Protein Chemistry and Structural Biology*, vol. 114, pp. 221–264, 2019.

[63] A. Chiorcea-Paquim, "8-oxoguanine and 8-oxodeoxyguanosine biomarkers of oxidative DNA damage: a review on HPLC–ECD determination," *Molecules*, vol. 27, no. 5, pp. 1620–1718, 2022.

[64] M. Yasui, Y. Kanemaru, N. Kamoshita, T. Suzuki, T. Arakawa, and M. Honma, "Tracing the fates of site-specifically introduced DNA adducts in the human genome," *DNA Repair*, vol. 15, pp. 11–20, 2014.

[65] T. Tang, Z. Yang, D. Wang et al., "The role of lysosomes in cancer development and progression," *Cell & Bioscience*, vol. 10, pp. 131–218, 2020.

[66] A. P. Mishra, B. Salehi, M. Sharifi-Rad et al., "Programmed cell death, from a cancer perspective: an overview," *Molecular Diagnosis and Therapy*, vol. 22, no. 3, pp. 281–295, 2018.

[67] T. A. Sani, E. Mohammadpour, A. Mohammadi et al., "Cytotoxic and apoptogenic properties of Dracocephalum kotschyi aerial part different fractions on calu-6 and mehr-80 lung cancer cell lines," *Farmacia*, vol. 65, pp. 189–199, 2017.

[68] M. T. Smith, K. Z. Guyton, C. F. Gibbons et al., "Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis," *Environmental Health Perspectives*, vol. 124, no. 6, pp. 713–721, 2016.

[69] A. Glasauer and N. S. Chandel, "Targeting antioxidants for cancer therapy," *Biochemical Pharmacology*, vol. 92, no. 1, pp. 90–101, 2014.

[70] G.-Y. Liou, H. Döppler, K. E. Delgiorno et al., "Mutant KRas-induced mitochondrial oxidative stress in acinar cells upregulates EGFR signaling to drive formation of pancreatic precancerous lesions," *Cell Reports*, vol. 14, no. 10, pp. 2325–2336, 2016.

[71] G. Pizzino, A. Bitto, M. Interdonato et al., "Oxidative stress and DNA repair and detoxification gene expression in adolescents exposed to heavy metals living in the Milazzo-Valle del Mela area (Sicily, Italy)," *Redox Biology*, vol. 2, pp. 686–693, 2014.

[72] S. Wu, H. Lu, and Y. Bai, "Nrf2 in cancers: a double-edged sword," *Cancer Medicine*, vol. 8, no. 5, pp. 2252–2267, 2019.

[73] S. K. Saha, S. B. Lee, J. Won et al., "Correlation between oxidative stress, nutrition, and cancer initiation," *International Journal of Molecular Sciences*, vol. 18, no. 7, pp. 1544–1630, 2017.

[74] R. Benfeitas, M. Uhlen, J. Nielsen, and A. Mardinoglu, "New challenges to study heterogeneity in cancer redox metabolism," *Frontiers in Cell and Developmental Biology*, vol. 5, pp. 65–20, 2017.

[75] S. Urbaniak, K. Boguszewska, M. Szewczuk, J. Kazmierczak-Baranska, and B. Karwowski, "8-Oxo-7,8-Dihydro-20-Deoxyguanosine (8-oxodG) and 8-hydroxy-20-deoxyguanosine (8-OHdG) as a potential biomarker for gestational diabetes mellitus (GDM) development," *Molecules*, vol. 25, pp. 1–13, 2022.

[76] G. E. Forcados, D. B. James, A. B. Sallau, A. Muhammad, and P. Mabeta, "Oxidative stress and carcinogenesis: potential of phytochemicals in breast cancer therapy," *Nutrition and Cancer*, vol. 69, no. 3, pp. 365–374, 2017.

[77] X.-F. Chen, L. Wang, Y.-Z. Wu et al., "Effect of puerarin in promoting fatty acid oxidation by increasing mitochondrial oxidative capacity and biogenesis in skeletal muscle in diabetic rats," *Nutrition & Diabetes*, vol. 8, pp. 1–13, 2018.

[78] M. Sharifi-Rad, N. V. Anil Kumar, P. Zucca et al., "Lifestyle, oxidative stress, and antioxidants: back and forth in the

pathophysiology of chronic diseases," *Frontiers in Physiology*, vol. 11, pp. 694–721, 2020.

[79] X. Li, C. Li, W. Zhang, Y. Wang, P. Qian, and H. Huang, "Inflammation and aging: signaling pathways and intervention therapies," *Signal Transduction and Targeted Therapy*, vol. 8, pp. 239–329, 2023.

[80] B. S. Karam, A. Chavez-Moreno, W. Koh, J. G. Akar, and F. G. Akar, "Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes," *Cardiovascular Diabetology*, vol. 16, pp. 120–129, 2017.

[81] H. Zhou, S. Wang, P. Zhu, S. Hu, Y. Chen, and J. Ren, "Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission," *Redox Biology*, vol. 15, pp. 335–346, 2018.

[82] Z. Pei, Q. Deng, S. A. Babcock, E. Y. He, J. Ren, and Y. Zhang, "Inhibition of advanced glycation endproduct (AGE) rescues against streptozotocin-induced diabetic cardiomyopathy: role of autophagy and ER stress," *Toxicology Letters*, vol. 284, pp. 10–20, 2018.

[83] R. Pluta, J. Kis, S. Januszewski, M. Jabłoński, and S. J. Czuczwar, "Cross-talk between amyloid, tau protein and free radicals in post-ischemic brain neurodegeneration in the form of alzheimer's disease proteinopathy," *Antioxidants*, vol. 11, pp. 146–223, 2022.

[84] W. Hassan, H. Noreen, S. Rehman, M. Kamal, and J. B. T. da Rocha, "Association of oxidative stress with neurological disorders," *Current Neuropharmacology*, vol. 20, no. 6, pp. 1046–1072, 2022.

[85] Y. Zhang, H. Chen, R. Li, K. Sterling, and W. Song, "Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future," *Signal Transduction and Targeted Therapy*, vol. 8, pp. 248–326, 2023.

[86] T. Viel, M. Toricelli, A. R. Pereira et al., "Mechanisms of neuroplasticity and brain degeneration: strategies for protection during the aging process," *Neural Regeneration Research*, vol. 16, no. 1, pp. 58–67, 2021.

[87] A. Terzi and D. M. Suter, "The role of NADPH oxidases in neuronal development," *Free Radical Biology and Medicine*, vol. 154, pp. 33–47, 2020.

[88] T. S. Leyane, S. W. Jere, and N. N. Houreld, "Oxidative stress in ageing and chronic degenerative pathologies: molecular mechanisms involved in counteracting oxidative stress and chronic inflammation," *International Journal of Molecular Sciences*, vol. 23, no. 13, pp. 7273–7328, 2022.

[89] M. Gyurászová, R. Gurecká, J. Bábíčková, and Ľ. Tóthová, "Oxidative stress in the pathophysiology of kidney disease: implications for noninvasive monitoring and identification of biomarkers," *Oxidative Medicine and Cellular Longevity*, vol. 2020, pp. 1–11, 2020.

[90] L. Pérez, L. Muñoz-Durango, C. Riedel et al., "Endothelial-to-mesenchymal transition: cytokine-mediated pathways that determine endothelial fibrosis under inflammatory conditions," *Cytokine & Growth Factor Reviews*, vol. 1, pp. 1–14, 2016.

[91] D. Rotariu, E. Babes, D. Tit et al., "Oxidative stress-Complex pathological issues concerning the hallmark of cardiovascular and metabolic disorders," *Biomedicine & Pharmacotherapy*, vol. 152, pp. 113238–113315, 2022.

[92] I. Wessels, B. Rolles, A. Slusarenko, and L. Rink, "Zinc deficiency as a possible risk factor for increased susceptibility and severe progression of Corona Virus Disease 19," *British Journal of Nutrition*, vol. 127, no. 2, pp. 214–232, 2022.

[93] V. Alagarsamy, V. Solomon, B. Narendhar, M. Sulthana, P. Sundar, and A. Aishwarya, "Molecular docking, Molecular dynamics, and ADMET investigation of selected phytochemicals as promising inhibitors of SARS-CoV-19 targets," *Pharmakeftiki*, vol. 35, pp. 26–47, 2023.

[94] K. Ibrahim, S. Darwish, E. Mantawy, and E. El-demerdash, "Molecular mechanisms underlying cyclophosphamide-induced cognitive impairment and strategies for neuroprotection in preclinical models," *Molecular and Cellular Biochemistry*, vol. 1, pp. 1–21, 2023.

[95] X. Zhang, S. Yu, X. Li et al., "Research progress on the interaction between oxidative stress and platelets: another avenue for cancer?" *Pharmacological Research*, vol. 191, pp. 106777–106812, 2023.

[96] M. Daglia, A. Pasdaran, A. Ahandani, and Z. Selamoglu, "Medicinal plants as a hopeful therapeutic approach against COVID-19 infection," *Central Asian Journal of Medical and Pharmaceutical Sciences Innovation*, vol. 3, pp. 12–21, 2023.

[97] S. Foshati, F. Mirjalili, M. Rezazadegan, F. Fakoorziba, and R. Amani, "Antioxidants and clinical outcomes of patients with coronavirus disease 2019: a systematic review of observational and interventional studies," *Food Science and Nutrition*, vol. 10, no. 12, pp. 4112–4125, 2022.

[98] A. Pisoschi, A. Pop, F. Iordache et al., "Antioxidant, anti-inflammatory and immunomodulatory roles of vitamins in COVID-19 therapy," *European Journal of Medicinal Chemistry*, vol. 232, pp. 114175–114218, 2022.

[99] F. Bezerra, M. Lanzetti, R. Nesi et al., "Oxidative stress and inflammation in acute and chronic lung injuries," *Antioxidants*, vol. 12, no. 3, pp. 548–646, 2023.

[100] S. Genc, A. Taghizadehghalehjoughi, M. Naldan et al., "Evaluation of various blood biomarkers associated with the outcomes of patients with COVID-19 treated in intensive care units," *Experimental and Therapeutic Medicine*, vol. 27, no. 2, pp. 82–11, 2024.

[101] M. Vaghari-Tabari, I. Mohammadzadeh, D. Qujeq et al., "Vitamin D in respiratory viral infections: a key immune-modulator?" *Critical Reviews in Food Science and Nutrition*, vol. 63, no. 14, pp. 2231–2246, 2023.

[102] Y. Li, Y. Liu, S. Liu et al., "Diabetic vascular diseases: molecular mechanisms and therapeutic strategies," *Signal Transduction and Targeted Therapy*, vol. 8, pp. 152–229, 2023.

[103] A. Ashok, S. Andrabi, S. Mansoor, Y. Kuang, B. Kwon, and V. Labhasetwar, "Antioxidant therapy in oxidative stress-induced neurodegenerative diseases: role of nanoparticle-based drug delivery systems in clinical translation," *Antioxidants*, vol. 11, no. 2, pp. 408–436, 2022.

[104] S. Jiang, H. Yang, Z. Sun, Y. Zhang, Y. Li, and J. Li, "The basis of complications in the context of SARS-CoV-2 infection: pathological activation of ADAM17," *Biochemical and Biophysical Research Communications*, vol. 679, pp. 37–46, 2023.

[105] S. S. Sajjadi, S. Foshati, S. Haddadian-Khouzani, and M. H. Rouhani, "The role of selenium in depression: a systematic review and meta-analysis of human observational and interventional studies," *Scientific Reports*, vol. 12, pp. 1045–1113, 2022.

[106] J. Wang, M. Zhang, Y. Ding et al., "Coronaviral main protease induces LPCAT3 cleavage and endoplasmic reticulum (ER) stress," *Viruses*, vol. 15, no. 8, pp. 1696–1712, 2023.

[107] H. Lu, Y. Zhou, L. Yang et al., "Involvement and repair of epithelial barrier dysfunction in allergic diseases," *Frontiers in Immunology*, vol. 15, pp. 1348272–1348315, 2024.

[108] A. Chauhan, A. Islam, H. Prakash, and S. Singh, "Phytochemicals targeting NF-κB signaling: potential anti-cancer interventions," *Journal of Pharmaceutical Analysis*, vol. 12, no. 3, pp. 394–405, 2022.

[109] M. P. Murphy, H. Bayir, V. Belousov et al., "Guidelines for measuring reactive oxygen species and oxidative damage in cells and *in vivo*," *Nature Metabolism*, vol. 4, no. 6, pp. 651–662, 2022.

[110] G. Engwa, F. N. EnNwekegwa, and B. Nkeh-Chungag, "Free Radicals, oxidative stress-related diseases and antioxidant supplementation," *Alternative Therapies in Health & Medicine*, vol. 28, no. 1, pp. 114–128, 2022.

[111] İ. Gulcin, "Antioxidants and antioxidant methods: an updated overview," *Archives of Toxicology*, vol. 94, no. 3, pp. 651–715, 2020.

[112] E. Da Pozzo, M. De Leo, I. Faraone et al., "Antioxidant and antisenescence effects of bergamot juice," *Oxidative Medicine and Cellular Longevity*, vol. 2018, pp. 1–14, 2018.

[113] A. Elsayed Azab, . A Adwas, A. S. Ibrahim Elsayed, A. A Adwas, S. Ibrahim Elsayed, and F. A. Quwaydir, "Oxidative stress and antioxidant mechanisms in human body," *Journal of Applied Biotechnology & Bioengineering*, vol. 6, no. 1, pp. 43–47, 2019.

[114] I. Mirończuk-Chodakowska, A. M. Witkowska, and M. E. Zujko, "Endogenous non-enzymatic antioxidants in the human body," *Advances in Medical Sciences*, vol. 63, no. 1, pp. 68–78, 2018.

[115] G. Lazzarino, I. Listorti, G. Bilotta et al., "Water-and fat-soluble antioxidants in human seminal plasma and serum of fertile males," *Antioxidants*, vol. 8, no. 4, pp. 96–13, 2019.

[116] A. Yadav, R. Kumari, A. Yadav, J. Mishra, S. Srivatva, and S. Prabha, "Antioxidants and its functions in human body- A review," *Research in Environment and Life Sciences*, vol. 9, pp. 1328–1331, 2016.

[117] J. Fan, J. Ye, J. J. Kamphorst, T. Shlomi, C. B. Thompson, and J. D. Rabinowitz, "Quantitative flux analysis reveals folate-dependent NADPH production," *Nature*, vol. 510, no. 7504, pp. 298–302, 2014.

[118] M. Benhar, "Roles of mammalian glutathione peroxidase and thioredoxin reductase enzymes in the cellular response to nitrosative stress," *Free Radical Biology and Medicine*, vol. 127, pp. 160–164, 2018.

[119] C. D. Fernando and P. Soysa, "Optimized enzymatic colorimetric assay for determination of hydrogen peroxide (H_2O_2) scavenging activity of plant extracts," *MethodsX*, vol. 2, pp. 283–291, 2015.

[120] S. Bardaweel, M. Gul, M. Alzweiri, A. Ishaqat, H. Alsalamat, and R. Bashatwah, "Reactive oxygen species: the dual role in physiological and pathological conditions of the human body," *The Eurasian Journal of Medicine*, vol. 50, no. 3, pp. 193–201, 2018.

[121] C. Winterbourn, "Biological chemistry of superoxide radicals," *ChemTexts*, vol. 6, pp. 7–13, 2020.

[122] A. Khorobrykh, "Hydrogen peroxide and superoxide anion radical photoproduction in PSII preparations at various modifications of the water-oxidizing complex," *Plants*, vol. 8, no. 9, pp. 329–417, 2019.

[123] M. Islam, A. Rauf, F. Fahad et al., "Superoxide dismutase: an updated review on its health benefits and industrial applications," *Critical Reviews in Food Science and Nutrition*, vol. 62, no. 26, pp. 7282–7300, 2021.

[124] H. Abedi and A. Shahpiri, "Functional characterization of a manganese superoxide dismutase from *Avicennia marina*: insights into its role in salt, hydrogen peroxide, and heavy metal tolerance," *Scientific Reports*, vol. 14, pp. 406–414, 2024.

[125] T. Kambe, K. M. Taylor, and D. Fu, "Zinc transporters and their functional integration in mammalian cells," *Journal of Biological Chemistry*, vol. 296, pp. 100320–100327, 2021.

[126] B. Chen, P. Yu, W. Chan et al., "Cellular zinc metabolism and zinc signaling: from biological functions to diseases and therapeutic targets," *Signal Transduction and Targeted Therapy*, vol. 9, pp. 6–41, 2024.

[127] L. He, S. Eslamfam, X. Ma, and D. Li, "Autophagy and the nutritional signaling pathway," *Frontiers of Agricultural Science and Engineering*, vol. 3, pp. 222–230, 2016.

[128] A. Grigoras, "Catalase immobilization-A review," *Biochemical Engineering Journal*, vol. 117, pp. 1–20, 2017.

[129] C. M. C. Andrés, J. M. Pérez De La Lastra, C. A. Juan, F. J. Plou, and E. Pérez-Lebeña, "Chemistry of hydrogen peroxide formation and elimination in mammalian cells, and its role in various pathologies," *Stresses*, vol. 2, no. 3, pp. 256–274, 2022.

[130] J. Tejero, S. Shiva, and M. Gladwin, "Sources of vascular nitric oxide and reactive oxygen species and their regulation," *Physiological Reviews*, vol. 99, no. 1, pp. 311–379, 2019.

[131] B. R. Cardoso, D. J. Hare, A. I. Bush, and B. R. Roberts, "Glutathione peroxidase 4: a new player in neurodegeneration?" *Molecular Psychiatry*, vol. 22, no. 3, pp. 328–335, 2017.

[132] A. Tarafdar and G. Pula, "The role of NADPH oxidases and oxidative stress in neurodegenerative disorders," *International Journal of Molecular Sciences*, vol. 19, no. 12, pp. 3824–3919, 2018.

[133] D. Kopustinskiene and J. Bernatoniene, "Molecular mechanisms of melatonin-mediated cell protection and signaling in health and disease," *Pharmaceutics*, vol. 13, no. 2, pp. 129–219, 2021.

[134] V. Tretter, B. Hochreiter, M. L. Zach, K. Krenn, and K. U. Klein, "Understanding cellular redox homeostasis: a challenge for precision medicine," *International Journal of Molecular Sciences*, vol. 23, pp. 106–126, 2021.

[135] J. Boutin, M. Liberelle, S. Yous, G. Ferry, and F. Nepveu, "Melatonin facts: lack of evidence that melatonin is aradical scavenger in living systems," *Journal of Pineal Research*, vol. 76, pp. 6–e13012, 2024.

[136] H. Zhang and R. Tsao, "Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects," *Current Opinion in Food Science*, vol. 8, pp. 33–42, 2016.

[137] B. Amir Aslani and S. Ghobadi, "Studies on oxidants and antioxidants with a brief glance at their relevance to the immune system," *Life Sciences*, vol. 146, pp. 163–173, 2016.

[138] C. Gaucher, A. Boudier, J. Bonetti, I. Clarot, P. Leroy, and M. Parent, "Glutathione: antioxidant properties dedicated to nanotechnologies," *Antioxidants*, vol. 7, no. 5, pp. 62–21, 2018.

[139] K. Aquilano, S. Baldelli, and M. R. Ciriolo, "Glutathione: new roles in redox signaling for an old antioxidant," *Frontiers in Pharmacology*, vol. 5, pp. 196–212, 2014.

[140] A. Tafazoli, "Coenzyme Q10 in breast cancer care," *Future Oncology*, vol. 13, no. 11, pp. 1035–1041, 2017.

[141] S. Q. E. Lee, T. S. Tan, M. Kawamukai, and E. S. Chen, "Cellular factories for coenzyme Q 10 production," *Microbial Cell Factories*, vol. 16, pp. 39–16, 2017.

[142] J. Kocot, D. Luchowska-Kocot, M. Kiełczykowska, I. Musik, and J. Kurzepa, "Does vitamin C influence neurodegenerative diseases and psychiatric disorders?" *Nutrients*, vol. 9, no. 7, pp. 659–729, 2017.

[143] M. Yaman, J. Çatak, H. Ugur et al., "The bioaccessibility of water-soluble vitamins: a review," *Trends in Food Science & Technology*, vol. 109, pp. 552–563, 2021.

[144] B. Salehi, P. L. Jornet, E. P.-F. López et al., "Plant-derived bioactives in oral mucosal lesions: a key emphasis to curcumin, lycopene, chamomile, aloe vera, green tea and coffee properties," *Biomolecules*, vol. 9, pp. 1–23, 2019.

[145] A. Ivanova, E. Gerasimova, and E. Gazizullina, "Study of antioxidant properties of agents from the perspective of their action mechanisms," *Molecules*, vol. 25, no. 18, pp. 4251–4327, 2020.

[146] B. Salehi, D. Mnayer, B. Özçelik et al., "Plants of the genus *lavandula*: from farm to pharmacy," *Natural Product Communications*, vol. 13, no. 10, pp. 1934578X1801301–1402, 2018.

[147] D. Kurpios-Piec, M. Majewska-Wierzbicka, H. Czeczot, and M. Podsiad, "Flavonoids as hydroxyl radical scavengers, iron reductants and chelators: *In vitro* antioxidant action," *Acta Poloniae Pharmaceutica- Drug Research*, vol. 78, no. 5, pp. 635–648, 2022.

[148] F. Benítez, V. Melín, G. Perez-Gonzalez et al., "The ferryl generation by fenton reaction driven by catechol," *Chemosphere*, vol. 335, pp. 139155–155, 2023.

[149] R. Martí, S. Roselló, and J. Cebolla-Cornejo, "Tomato as a source of carotenoids and polyphenols targeted to cancer prevention," *Cancers*, vol. 8, no. 6, pp. 58–28, 2016.

[150] N. Kanwal, A. Rasul, G. Hussain et al., "Oleandrin: a bioactive phytochemical and potential cancer killer via multiple cellular signaling pathways," *Food and Chemical Toxicology*, vol. 143, 2020.

[151] N. Carsono, S. G. Tumilaar, D. Kurnia, D. Latipudin, and M. H. Satari, "A review of bioactive compounds and antioxidant activity properties of piper species," *Molecules*, vol. 27, no. 19, pp. 6774–6822, 2022.

[152] H. Moharram and M. Youssef, "Methods for determining the antioxidant activity: a review," *Alexandria Journal of Food Science and Technology*, vol. 11, pp. 31–42, 2014.

[153] M. Ahmed, A. Khaleeq, and S. Ahmad, "Antioxidant and antifungal activity of aqueous and organic extracts of liquorice," *World Applied Sciences Journal*, vol. 30, pp. 1664–1667, 2014.

[154] F. Shahidi and P. Ambigaipalan, "Phenolics and polyphenolics in foods, beverages and spices: antioxidant activity and health effects–A review," *Journal of Functional Foods*, vol. 18, pp. 820–897, 2015.

[155] A. Nath, W. Yehye, and M. Johan, "Butylated hydroxy benzylidene ring: an important moiety for antioxidant synergism of semicarbazones," *Journal of Thermal Analysis and Calorimetry*, vol. 146, no. 5, pp. 2101–2114, 2021.

[156] S. Koudelka, P. Turanek Knotigova, J. Masek et al., "Liposomal delivery systems for anti-cancer analogues of vitamin E," *Journal of Controlled Release*, vol. 207, pp. 59–69, 2015.

[157] L. Chen, X. Lin, X. Fan et al., "A self-emulsifying formulation of Sonchus oleraceus Linn for an improved anti-diabetic effect *in vivo*," *Food & Function*, vol. 11, no. 2, pp. 1225–1229, 2020.

[158] L. Chen, H. Cao, Q. Huang, J. Xiao, and H. Teng, "Absorption, metabolism and bioavailability of flavonoids: a review," *Critical Reviews in Food Science and Nutrition*, vol. 62, no. 28, pp. 7730–7742, 2022.

[159] S. Forester, Y. Choy, A. Waterhouse, and P. Oteiza, "The anthocyanin metabolites gallic acid, 3-*O*-methylgallic acid, and 2,4,6-trihydroxybenzaldehyde decrease human colon cancer cell viability by regulating pro-oncogenic signals," *Molecular Carcinogenesis*, vol. 53, no. 6, pp. 432–439, 2014.

[160] H. Teng and L. Chen, "Polyphenols and bioavailability: an update," *Critical Reviews in Food Science and Nutrition*, vol. 59, no. 13, pp. 2040–2051, 2019.

[161] A. Steed, G. Christophi, G. Kaiko et al., "The microbial metabolite desaminotyrosine protects from influenza through type I interferon," *Science*, vol. 357, no. 6350, pp. 498–502, 2017.

[162] Y. Fang, W. Cao, F. Liang, M. Xia, S. Pan, and X. Xu, "Structure affinity relationship and docking studies of flavonoids as substrates of multidrug-resistant associated protein 2 (MRP2) in MDCK/MRP2 cells," *Food Chemistry*, vol. 291, pp. 101–109, 2019.

[163] M. Deepika, R. Thangam, T. Sheena et al., "A novel rutin-fucoidan complex based phytotherapy for cervical cancer through achieving enhanced bioavailability and cancer cell apoptosis," *Biomedicine & Pharmacotherapy*, vol. 109, pp. 1181–1195, 2019.

[164] Y. Liu, W. Weng, R. Gao, and Y. Liu, "New insights for cellular and molecular mechanisms of aging and aging-related diseases: herbal medicine as potential therapeutic approach," *Oxidative Medicine and Cellular Longevity*, vol. 2019, pp. 1–25, 2019.

[165] N. Bondonno, F. Dalgaard, C. Kyro et al., "Flavonoid intake is associated with lower mortality in the Danish diet cancer and health cohort," *Nature Communications*, vol. 10, pp. 3651–3710, 2019.

[166] G. Pounis, S. Costanzo, M. Bonaccio et al., "Reduced mortality risk by a polyphenol-rich diet: an analysis from the Moli-sani study," *Nutrition*, vol. 48, pp. 87–95, 2018.

[167] S. Safe, A. Jayaraman, R. Chapkin, M. Howard, K. Mohankumar, and R. Shrestha, "Flavonoids: structure–function and mechanisms of action and opportunities for drug development," *Toxicological Research*, vol. 37, no. 2, pp. 147–162, 2021.

[168] Y. Kim and Y. Je, "Flavonoid intake and mortality from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies," *Clinical Nutrition ESPEN*, vol. 20, pp. 68–77, 2017.

[169] K. Ivey, M. Jensen, J. Hodgson, A. Eliassen, A. Cassidy, and E. Rimm, "Association of flavonoid-rich foods and flavonoids with risk of all-cause mortality," *British Journal of Nutrition*, vol. 117, no. 10, pp. 1470–1477, 2017.

[170] J. Rienks, J. Barbaresko, K. Oluwagbemigun, M. Schmid, and U. Nothlings, "Polyphenol exposure and risk of type 2 diabetes: dose-response meta-analyses and systematic review of prospective cohort studies," *The American Journal of Clinical Nutrition*, vol. 108, no. 1, pp. 49–61, 2018.

[171] H. Kikuchi, B. Yuan, X. Hu, and M. Okazaki, "Chemopreventive and anticancer activity of flavonoids and its possibility for clinical use by combining with conventional chemotherapeutic agents," *American Journal of Cancer Research*, vol. 9, no. 8, pp. 1517–1535, 2019.

[172] S. Alseekh, L. Perez de Souza, M. Benina, and A. Fernie, "The style and substance of plant flavonoid decoration; towards defning both structure and function," *Phytochemistry*, vol. 174, pp. 1–12, 2020.

[173] C. Rodriguez-Garcia, C. Sanchez-Quesada, and J. Gaforio, "Dietary flavonoids as cancer chemopreventive agents: an updated review of human studies," *Antioxidants*, vol. 8, no. 5, pp. 137–226, 2019.

[174] M. Khater, F. Greco, and H. Osborn, "Antiangiogenic activity of flavonoids: a systematic review and meta-analysis," *Molecules*, vol. 25, no. 20, pp. 4712–4731, 2020.

[175] A. Bisol, P. de Campos, and M. Lamers, "Flavonoids as anticancer therapies: a systematic review of clinical trials," *Phytotherapy Research*, vol. 34, no. 3, pp. 568–582, 2020.

[176] M. Farzaei, A. Singh, R. Kumar et al., "Targeting infammation by flavonoids: novel therapeutic strategy for metabolic disorders," *International Journal of Molecular Sciences*, vol. 20, pp. 1–39, 2019.

[177] G. Martinez, M. Mijares, and J. De Sanctis, "Effects of flavonoids and its derivatives on immune cell responses," *Recent Patents on Inflammation & Allergy Drug Discovery*, vol. 13, no. 2, pp. 84–104, 2019.

[178] S. Sharma and A. Naura, "Potential of phytochemicals as immune-regulatory compounds in atopic diseases: a review," *Biochemical Pharmacology*, vol. 173, pp. 113790–113828, 2020.

[179] D. Margina, A. Ungurianu, C. Purdel et al., "Analysis of the intricate efects of polyunsaturated fatty acids and polyphenols on inflammatory pathways in health and disease," *Food Chemistry Toxicology*, vol. 143, pp. 1–23, 2020.

[180] C. Y. Lee, A. Sharma, J. Semenya, C. Anamoah, K. Chapman, and V. Barone, "Computational study of *ortho*-substituent effects on antioxidant activities of phenolic dendritic antioxidants," *Antioxidants*, vol. 9, no. 3, pp. 189–214, 2020.

[181] J. Zhang and P. A. Mccullough, "Lipoic acid in the prevention of acute kidney injury," *Nephron*, vol. 134, no. 3, pp. 133–140, 2016.

[182] F. Meger and J. Murphy, "Recent advances in C–H functionalisation through indirect hydrogen atom transfer," *Molecules*, vol. 28, no. 16, pp. 6127–6178, 2023.

[183] J. Bell and J. Murphy, "Recent advances in visible light-activated radical coupling reactions triggered by (i) ruthenium, (ii) iridium and (iii) organic photoredox agents," *Chemical Society Reviews*, vol. 50, no. 17, pp. 9540–9685, 2021.

[184] M. Salamone, M. Galeotti, E. Romero-Montalvo et al., "Bimodal Evans-polanyi relationships in hydrogen atom transfer from C(sp^3)–H bonds to the cumyloxyl radical. A combined time-resolved kinetic and computational study," *Journal of the American Chemical Society*, vol. 143, no. 30, pp. 11759–11776, 2021.

[185] R. A. Apak, M. Özyürek, K. Güçlü, and E. Çapanoğlu, "Antioxidant activity/capacity measurement. 2. Hydrogen atom transfer (HAT)-based, mixed-mode (electron transfer (ET)/HAT), and lipid peroxidation assays," *Journal of Agricultural and Food Chemistry*, vol. 64, no. 5, pp. 1028–1045, 2016.

[186] M. Saleem, A. I. Durani, A. Asari et al., "Investigation of antioxidant and antibacterial effects of citrus fruits peels extracts using different extracting agents: phytochemical analysis with *in silico* studies," *Heliyon*, vol. 9, no. 4, pp. 3–e15514, 2023.

[187] L. Todorov, L. Saso, and I. Kostova, "Antioxidant activity of coumarins and their metal complexes," *Pharmaceuticals*, vol. 16, no. 5, pp. 651–726, 2023.

[188] E. M. Kamel, A. Bin-Ammar, A. A. El-Bassuony et al., "Molecular modeling and DFT studies on the antioxidant activity of *Centaurea scoparia* flavonoids and molecular dynamics simulation of their interaction with *β*-lactoglobulin," *RSC Advances*, vol. 13, no. 18, pp. 12361–12374, 2023.

[189] I. Górniak, R. Bartoszewski, and J. Króliczewski, "Comprehensive review of antimicrobial activities of plant flavonoids," *Phytochemistry Reviews*, vol. 21, pp. 2209–2224, 2019.

[190] M. Parcheta, R. Swisłocka, S. Orzechowska, M. Akimowicz, R. Choinska, and W. Lewandowski, "Recent developments in effective antioxidants: the structure and antioxidant properties," *Materials*, vol. 14, no. 8, pp. 1984–2024, 2021.

[191] W. Lewandowski, H. Lewandowska, A. Golonko, G. Świderski, R. Świsłocka, and M. Kalinowska, "Correlations between molecular structure and biological activity in logical series of dietary chromone derivatives," *PLoS One*, vol. 15, no. 8, pp. 7–e229526, 2020.

[192] S. A. de Souza Farias, K. S. da Costa, and J. Martins, "Analysis of conformational, structural, magnetic, and electronic properties related to antioxidant activity: revisiting flavan, anthocyanidin, flavanone, flavonol, isoflavone, flavone, and flavan-3-ol," *ACS Omega*, vol. 6, no. 13, pp. 8908–8918, 2021.

[193] E. Çakmak and D. Işın, "A theoretical evaluation on free radical scavenging activity of 3-styrylchromone derivatives: the DFT study," *Journal of Molecular Modeling*, vol. 26, pp. 1–11, 2020.

[194] P. Vinduja and K. Muraleedharan, "Theoretical studies on anti-oxidant activity of the phytochemical, coumestrol and its derivatives," *Functional Foods- Phytochemicals and Health Promoting Potential*, vol. 1, pp. 1–15, 2021.

[195] A. Bruix and K. Neyman, "Modeling ceria-based nanomaterials for catalysis and related applications," *Catalysis Letters*, vol. 146, no. 10, pp. 2053–2080, 2016.

[196] T. Shameera Ahamed, V. Rajan, K. Sabira, and K. Muraleedharan, "DFT and QTAIM based investigation on the structure and antioxidant behavior of lichen substances atranorin, evernic acid and diffractaic acid," *Computational Biology and Chemistry*, vol. 80, pp. 66–78, 2019.

[197] E. Heřmánková, M. Zatloukalová, M. Biler et al., "Redox properties of individual quercetin moieties," *Free Radical Biology and Medicine*, vol. 143, pp. 240–251, 2019.

[198] R. A. Apak, M. Özyürek, K. Güçlü, and E. Çapanoğlu, "Antioxidant activity/capacity measurement. 1. Classification, physicochemical principles, mechanisms, and electron transfer (ET)-based assays," *Journal of Agricultural and Food Chemistry*, vol. 64, no. 5, pp. 997–1027, 2016.

[199] V. Timoshnikov, O. Selyutina, N. Polyakov, V. Didichenko, and G. Kontoghiorghes, "Mechanistic insights of chelator complexes with essential transition metals: antioxidant/pro-oxidant activity and applications in medicine," *International Journal of Molecular Sciences*, vol. 23, no. 3, pp. 1247–1329, 2022.

[200] V. S. Shubina, V. I. Kozina, and Y. V. Shatalin, "Comparison of antioxidant properties of a conjugate of taxifolin with glyoxylic acid and selected flavonoids," *Antioxidants*, vol. 10, no. 8, pp. 1262–1321, 2021.

[201] A. Maldonado, E. Winkler, M. Raineri et al., "Free radical formation by the peroxidase-like catalytic activity of MFe_2O_4 (M = Fe, Ni and Mn) nanoparticles," *Journal of Physical Chemistry*, vol. 1, pp. 1–47, 2019.

[202] Z. Kejík, R. Kaplánek, M. Masarík et al., "Iron complexes of flavonoids-antioxidant capacity and beyond," *International Journal of Molecular Sciences*, vol. 22, no. 2, pp. 646–720, 2021.

[203] X. Wang, Y. Li, L. Han, J. Li, C. Liu, and C. Sun, "Role of flavonoids in the treatment of iron overload," *Frontiers in Cell and Developmental Biology*, vol. 9, pp. 685364–685412, 2021.

[204] S. Liga, C. Paul, and F. Péter, "Flavonoids: overview of biosynthesis, biological activity, and current extraction techniques," *Plants*, vol. 12, no. 14, pp. 2732–2825, 2023.

[205] M. Li, Y. Zheng, J. Zhao et al., "Polyphenol mechanisms against gastric cancer and their interactions with gut microbiota: a review," *Current Oncology*, vol. 29, no. 8, pp. 5247–5261, 2022.

[206] A. Cassidy and A. Minihane, "The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids," *The American Journal of Clinical Nutrition*, vol. 105, no. 1, pp. 10–22, 2017.

[207] R. Al-Ishaq, A. Liskova, P. Kubatka, and D. Büsselberg, "Enzymatic metabolism of flavonoids by gut microbiota and its impact on gastrointestinal cancer," *Cancers*, vol. 13, no. 16, pp. 3934–4020, 2021.

[208] K. Murota, Y. Nakamura, and M. Uehara, "Flavonoid metabolism: the interaction of metabolites and gut microbiota," *Bioscience, Biotechnology, and Biochemistry*, vol. 82, no. 4, pp. 600–610, 2018.

[209] R. Zamora-Ros, V. Knaze, J. Rothwell et al., "Dietary polyphenol intake in Europe: the European prospective investigation into cancer and nutrition (EPIC) study," *European Journal of Nutrition*, vol. 55, pp. 1359–1375, 2016.

[210] G. Grosso, U. Stepaniak, R. Topor-Mądry, K. Szafraniec, and A. Pająk, "Estimated dietary intake and major food sources of polyphenols in the Polish arm of the HAPIEE study," *Nutrition*, vol. 30, no. 11-12, pp. 1398–1403, 2014.

[211] A. Witkowska, M. Zujko, A. Waśkiewicz, K. Terlikowska, and W. Piotrowski, "Comparison of various databases for estimation of dietary polyphenol intake in the population of Polish adults," *Nutrients*, vol. 7, no. 11, pp. 9299–9308, 2015.

[212] R. Escobar-Cévoli, C. Castro-Espín, V. Béraud, G. Buckland, and R. Zamora-Ros, "An overview of global flavonoid intake and its food sources," *Flavonoids- From Biosynthesis to Human Health*, vol. 23, pp. 1–20, 2017.

[213] Y. Ma, W. Gao, K. Wu, and Y. Bao, "Flavonoid intake and the risk of age-related cataract in China's Heilongjiang Province," *Food & Nutrition Research*, vol. 59, no. 1, pp. 29564–30364, 2015.

[214] S. Jun, S. Shin, and H. Joung, "Estimation of dietary flavonoid intake and major food sources of Korean adults," *British Journal of Nutrition*, vol. 115, no. 3, pp. 480–489, 2016.

[215] Z. Zhang, L. He, Y. Liu, J. Liu, Y. Su, and Y. Chen, "Association between dietary intake of flavonoid and bone mineral density in middle aged and elderly Chinese women and men," *Osteoporosis International*, vol. 25, no. 10, pp. 2417–2425, 2014.

[216] Q. Xiao, Y. Park, A. Hollenbeck, and C. Kitahara, "Dietary flavonoid intake and thyroid cancer risk in the NIH-AARP diet and health study," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 23, no. 6, pp. 1102–1108, 2014.

[217] A. Miranda, J. Steluti, R. Fisberg, and D. Marchioni, "Dietary intake and food contributors of polyphenols in adults and elderly adults of Sao Paulo: a population-based study," *British Journal of Nutrition*, vol. 115, no. 6, pp. 1061–1070, 2016.

[218] K. Kim, T. Vance, and O. Chun, "Estimated intake and major food sources of flavonoids among US adults: changes between 1999-2002 and 2007-2010 in NHANES," *European Journal of Nutrition*, vol. 55, no. 2, pp. 833–843, 2016.

[219] K. Kent, K. Charlton, J. Russell, P. Mitchell, and V. Flood, "Estimation of flavonoid intake in older Australians: secondary data analysis of the blue mountains eye study," *Journal of Nutrition in Gerontology and Geriatrics*, vol. 34, no. 4, pp. 388–398, 2015.

[220] F. Shah, A. Ramzi, S. Baharum et al., "Recent advancement of engineering microbial hosts for the biotechnological production of flavonoids," *Molecular Biology Reports*, vol. 46, no. 6, pp. 6647–6659, 2019.

[221] S. Anjum, S. Ishaque, H. Fatima et al., "Emerging applications of nanotechnology in healthcare systems: grand challenges and perspectives," *Pharmaceuticals*, vol. 14, no. 8, pp. 707–727, 2021.

[222] M. Dobrzynska, M. Napierala, and E. Florek, "Flavonoid nanoparticles: a promising approach for cancer therapy," *Biomolecules*, vol. 10, no. 9, pp. 1268–1317, 2020.

[223] L. Li, Y. Zeng, M. Chen, and G. Liu, "Application of nanomicelles in enhancing bioavailability and biological efficacy of bioactive nutrients," *Polymers*, vol. 14, no. 16, pp. 3278–3319, 2022.

[224] S. Sysak, B. Czarczynska-Goslinska, P. Szyk et al., "Metal nanoparticle-flavonoid connections: synthesis, physicochemical and biological properties, as well as potential applications in medicine," *Nanomaterials*, vol. 13, no. 9, pp. 1531–1547, 2023.