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Nutritional antioxidants: A strategic approach to chronic disease prevention

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Abstract
Chronic diseases, including cardiovascular disorders, diabetes, cancer and neurodegenerative conditions, are among the leading causes of morbidity and mortality globally. These diseases impose a significant burden on healthcare systems and public health. A key factor in their development is oxidative stress which occurs when there is an imbalance between the production of free radicals and the body's antioxidant defense systems. Free radicals are highly reactive molecules that can damage cells, tissues and DNA, contributing to the onset and progression of various chronic diseases. Antioxidants which are naturally occurring compounds in foods, play a critical role in mitigating oxidative stress by neutralizing free radicals and protecting cellular structures from oxidative damage. Dietary antioxidants, including vitamins C and E, carotenoids, polyphenols and flavonoids, have garnered attention for their potential in reducing oxidative damage and promoting health. These antioxidants are abundant in a wide variety of foods, including fruits, vegetables, nuts, seeds and whole grains. Research has shown that regular consumption of antioxidant-rich foods can support the body's defense systems, reduce inflammation and lower the risk of developing chronic conditions such as heart disease, diabetes and certain cancers. This review examines the current evidence on the health benefits of dietary antioxidants, including their mechanisms of action, food sources and the role they play in preventing oxidative stress. Furthermore, it explores the potential implications for public health strategies, such as the incorporation of antioxidant-rich foods into dietary guidelines and health policies aimed at reducing the global burden of chronic diseases.

Keywords: Chronic diseases, oxidative stress, dietary antioxidants, Vitamins C and E, health benefits, public health strategies

Introduction

Chronic non-communicable diseases (NCDs), such as cardiovascular disease, type 2 diabetes mellitus, malignancies and neurological illnesses, are the primary causes of death and disability globally. A prevalent underlying mechanism involved in their pathogenesis is oxidative stress, characterized by an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. Reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide and hydroxyl radicals, can inflict damage on cellular proteins, lipids and nucleic acids, resulting in compromised cellular function and the advancement of illness (Halliwell 2015) [18]. Antioxidants are substances that can stop ROS from doing damage which lowers oxidative damage. There are both enzymatic and non-enzymatic antioxidants in the body. Enzymatic antioxidants include superoxide dismutase, catalase and glutathione peroxidase. The non-enzymatic antioxidants include glutathione and uric acid. But dietary antioxidants from fruits, vegetables, nuts, cereals, drinks and spices are very important for keeping redox homeostasis (Gulcin 2020) [17].

Vitamins C and E, carotenoids, polyphenols, flavonoids and trace minerals like selenium and zinc are all examples of dietary antioxidants. These chemicals function as radical scavengers and furthermore control cellular signaling pathways, change gene expression and affect inflammatory and immunological responses (Scalbert 2005) [45]. There is more and more evidence that eating more foods high in antioxidants is linked to a lower risk of getting NCDs. However, it is still unclear if taking isolated antioxidants works (Miller 2005; Lippman 2009) [26, 34]. Antioxidants have become more important in diet and public health. Nonetheless, although encouraging observational evidence, randomized controlled studies have yielded inconclusive results, underscoring the intricacies of nutritional combinations, bioavailability and population-specific effects. This review seeks to objectively evaluate the function of dietary antioxidants in the prevention of chronic illnesses, synthesize current molecular understanding, examine data from clinical and epidemiological investigations and offer implications for dietary guidelines.

Biology of Oxidative Stress and Antioxidant Defense

Oxidative stress occurs when the production of ROS exceeds the body's natural antioxidant defenses. This imbalance damages lipids, proteins and DNA, contributing to atherosclerosis, insulin resistance, carcinogenesis and neuronal degeneration. Chronic exposure to oxidative stress is closely linked with diseases such as:

- **Cardiovascular disease:** Oxidation of low-density lipoprotein (LDL) accelerates plaque formation.
- **Type 2 diabetes:** ROS impair insulin signaling and pancreatic β-cell function.
- **Cancer:** DNA damage induced by free radicals promotes mutations and tumorigenesis.
- **Neurodegenerative diseases:** Oxidative stress is associated with Alzheimer's and Parkinson's pathology.

Oxidative Stress

Oxidative stress is characterized by an imbalance between the generation of reactive oxygen species (ROS) and the capacity of biological systems to detoxify these reactive

intermediates or to repair the consequent damage (Sies 2015) [48]. Reactive oxygen species (ROS) encompass free radicals, including superoxide anion (O_2^-) and hydroxyl radical (•OH), as well as non-radical derivatives such as hydrogen peroxide (H_2O_2).

Even while ROS are generated naturally during mitochondrial oxidative phosphorylation, too much of them can harm proteins, nucleic acids and lipids in cells which can lead to cell malfunction and the start of disease processes (Halliwell 2015) [18].

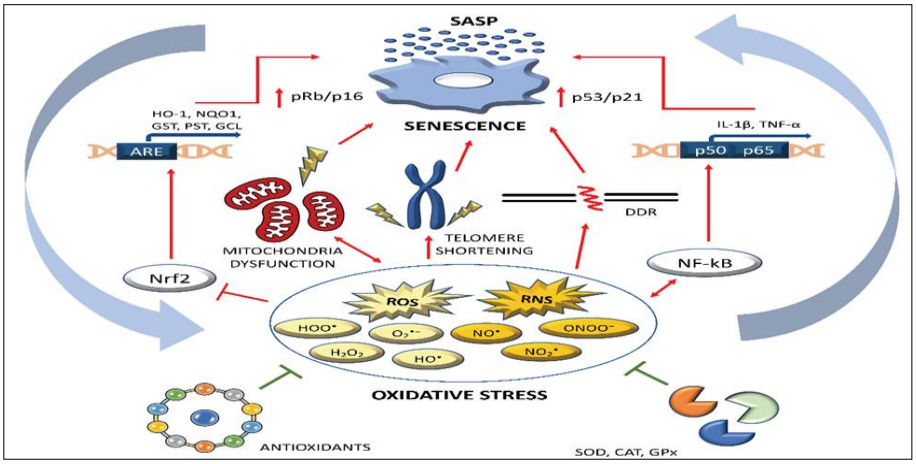

Fig 1: The interplay between oxidative stress (OS) and senescence (Varesi *et al*., 2022) [58]

Sources of ROS

There are two ways to make ROS: inside the body and outside of it. Endogenous sources including mitochondrial respiration, NADPH oxidase activity, cytochrome P450 metabolism and inflammatory cell activation (Finkel 2011) [15]. Environmental contaminants, cigarette smoke, UV radiation, ionizing radiation and certain medications and xenobiotic are all examples of exogenous sources (Lobo 2010) [27]. The total exposure to these factors affects oxidative load and the risk of getting sick.

The Physiological Function of ROS

At low to moderate levels, ROS act as signaling molecules that control processes like apoptosis, gene expression and the immunological response. They turn on transcription factors including nuclear factor erythroid 2–related factor 2 (Nrf2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). These factors regulate genes that are involved in inflammation and antioxidant defense (Sies 2017) [47]. In this way, ROS are like a "double-edged sword": they are good for you at normal levels but bad for you when there are too many of them.

Endogenous Antioxidant Defense Systems

The body has a complicated system of antioxidants that works against ROS.

The superoxide dismutase (SOD) turn superoxide into hydrogen peroxide, catalase and glutathione peroxidase turn hydrogen peroxide into water and peroxiredoxins work on peroxides (Birben 2012) [4].

Non-enzymatic antioxidants, including glutathione, uric acid, bilirubin and coenzyme Q10, neutralize free radicals and restore oxidized antioxidants (Gulcin 2020) [17]. These systems work together to keep the redox equilibrium in cells.

Interaction with Antioxidants in Food

The dietary antioxidants play an important function when the body's own systems are too much for them to handle. Vitamins C and E, carotenoids, polyphenols and trace elements can neutralize ROS, regenerate other antioxidants and change redox-sensitive signaling pathways (Scalbert 2005) [45]. This relationship underscores the significance of diet in preserving oxidative homeostasis.

Major classes of Dietary Antioxidants

The dietary antioxidants include a wide range of substances with different chemical structures and biological roles. You can get them mostly from plant-based meals, although some are also in animal products. There are four primary types: vitamins (C and E), carotenoids, polyphenols and trace minerals like selenium and zinc. Each category has its own distinct impact on the antioxidant defense system and on the body as a whole. The key groups include:

- **Vitamins:** Vitamin C (citrus fruits, strawberries) and Vitamin E (nuts, seeds).
- **Carotenoids:** β-carotene, lutein and lycopene (carrots, spinach, tomatoes).
- **Polyphenols:** Flavonoids and resveratrol (berries, red wine, cocoa).
- **Minerals with antioxidant roles:** Selenium and zinc (seafood, whole grains).

Vitamin C (Ascorbic Acid)

Vitamin C is an antioxidant that dissolves in water and is found in many fruits and vegetables, including citrus fruits, berries, kiwifruit, peppers and leafy greens. It serves as an electron donor, directly neutralizing reactive oxygen species and restoring oxidized vitamin E, glutathione and other antioxidants (Naidu 2003) [37]. Vitamin C is important for making collagen, keeping the immune system healthy and controlling gene expression (Carr 2017) [8]. Low levels of vitamin C in the blood are linked to a higher risk of heart disease and a weaker immune system. (Jacob 2002) [20]

Vitamin E (Tocopherols and Tocotrienols)

Vitamin E is a collection of fat-soluble chemicals that are found in whole grains, nuts, seeds and vegetable oils. In humans, α-tocopherol is the type that works best. Its main job as an antioxidant is to keep polyunsaturated fatty acids in cell membranes from lipid peroxidation (Brigelius-Flohé 2002) [6]. Vitamin E also affects how cells send signals, how

the immune system works and how inflammation works (Maret 2019) [33]. Epidemiological studies indicate a negative correlation between vitamin E consumption and cardiovascular disease risk; nevertheless, extensive supplementation experiments have shown conflicting findings (Miller 2005) [34].

Carotenoids

Plants make carotenoids which are pigments that give many fruits and vegetables their red, orange and yellow colors. The main carotenoids in food are β-carotene, lycopene, lutein and zeaxanthin. They have antioxidant benefits because they stop singlet oxygen from forming and remove peroxyl radicals (Krinsky 2005) [25].

Carotenoids do more than only protect cells from damage; they also help keep eyes healthy (especially lutein and zeaxanthin in the macula) and may lessen the risk of several malignancies and heart problems (Olson 1999) [38]. Nonetheless, high-dose β-carotene supplementation has demonstrated detrimental effects in smokers, elevating lung cancer incidence (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994).

Polyphenols

Flavonoids, phenolic acids, stilbenes and lignin's are all types of polyphenols. They constitute the biggest category of dietary antioxidants. There are a lot of them in fruits, vegetables, tea, coffee, chocolate, wine and spices. Polyphenols function as radical scavengers and as modulators of cellular signaling pathways associated with inflammation, apoptosis and metabolism (Scalbert 2005) [45]. The epidemiological studies regularly demonstrate inverse correlations between polyphenol-rich diets, such as the Mediterranean diet and the incidence of chronic illnesses (Pandey 2009) [40]. Quercetin, catechins and anthocyanins are examples of flavonoids that have been researched a lot for their heart and brain health advantages.

Table 1: Major Dietary Antioxidants and Food Sources

Antioxidant	Food Sources	Key Mechanisms	Reference
Vitamin C (Ascorbic acid)	Citrus fruits, berries, kiwi, bell peppers	Free radical scavenging, regenerates vitamin E, supports immune function	Carr 2017 [8]
Vitamin E (α-tocopherol)	Nuts, seeds, vegetable oils, spinach	Lipid peroxidation prevention, scavenges ROS in membranes	Brigelius-Flohé 2002 [6]
Carotenoids (β-carotene, lycopene, lutein, zeaxanthin)	Carrots, tomatoes, leafy greens, sweet potatoes	Free radical scavenging, photo protection, gene expression modulation	Giovannucci 2002 [16]
Polyphenols (Flavonoids, Catechins, Resveratrol)	Tea, cocoa, berries, grapes, wine	Nrf2 activation, NF-κB inhibition, anti-inflammatory, chelation	Pandey 2009 [40]; Del Rio 2013 [9]
Selenium	Brazil nuts, seafood, cereals	Cofactor for glutathione peroxidase, oxidative stress reduction	Rayman 2012 [42]
Zinc	Meat, legumes, nuts, whole grains	Cofactor for superoxide dismutase, immune support	Maares 2016 [28]
Coenzyme Q10	Meat, fish, whole grains	Electron transport chain stabilization, mitochondrial protection	Bjelakovic 2013 [5]

Selenium and Zinc as Trace Elements

Some trace elements are necessary cofactors for antioxidant enzymes. Selenium is a part of glutathione peroxidases and thioredoxin reductases which defend against oxidative damage (Rayman 2000) [43]. You may find selenium in nuts (particularly Brazil nuts), shellfish and cereals. Zinc which is found in meat, legumes, nuts and whole grains, helps stabilize cell membranes and is important for the function of superoxide dismutase (Prasad 2014) [41].

Lack of these nutrients weakens the body's defenses against free radicals, although adding them has been found to help protect some groups of people. But eating too much of it might be bad for you which shows how important it is to eat a balanced diet.

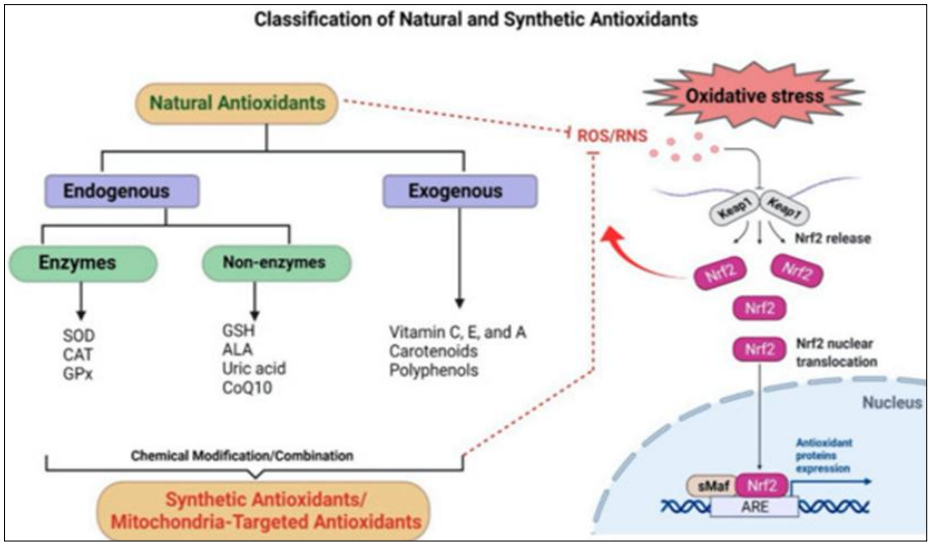

Fig 2: Classification of natural and synthetic antioxidants and the endogenous Nrf2 pathway which regulates the activation of ARE genes (Ashok *et al*., 2022) [59]

Role of Dietary Antioxidants in Specific Chronic Diseases (Cardiovascular, Cancer, Diabetes, Neurodegenerative Disorders)

The oxidative stress and inflammation are the same pathogenic mechanisms that cause chronic illnesses. Too much reactive oxygen species (ROS) can damage biomolecules, change signaling pathways and speed up the course of illness. Researchers have looked into dietary antioxidants a lot to see whether they may stop or slow down these processes (Faisal *et al*., 2024) [31].

Cardiovascular Diseases (CVD)

Oxidative stress is a major cause of atherosclerosis, high blood pressure and ischemic heart disease. ROS facilitate the oxidation of low-density lipoprotein (LDL), endothelial dysfunction, vascular inflammation and plaque instability (Stocker 2004) [49]. Vitamin C enhances endothelial function by augmenting nitric oxide bioavailability, whereas vitamin E inhibits lipid peroxidation of LDL particles (Carr 2017; Brigelius-Flohé 2002) [6, 8]. Polyphenols, especially flavonoids derived from tea, cocoa and berries, augment vascular responsiveness, diminish platelet aggregation and increase lipid profiles (Pandey 2009) [40]. Regular intake of polyphenol-rich foods, such as the Mediterranean diet, is associated with decreased cardiovascular morbidity and death (Estruch 2013) [12].

Nonetheless, intervention experiments utilizing high-dose vitamin E supplements have shown inconclusive outcomes. The Heart Outcomes Prevention Evaluation (HOPE) research revealed no advantage of vitamin E intake in diminishing cardiovascular events (Yusuf 2000) [57]. This difference shows that whole-food dietary sources may work better than single supplements.

Cancer

Reactive oxygen species (ROS) cause cancer by damaging DNA, changing genes and turning on cancer-causing signaling pathways (Valko 2006) [53]. Antioxidants may counteract these processes by neutralizing reactive oxygen species (ROS), improving DNA repair and influencing cell proliferation and death (Khalid *et al*., 2024) [46]. The epidemiological studies indicate that diets abundant in fruits and vegetables which include carotenoids and polyphenols, are negatively correlated with cancer risk (Key 2002) [24]. For example, eating tomatoes with lycopene has been connected to a decreased risk of prostate cancer and eating foods with flavonoids has been linked to a lower risk of breast and gastrointestinal cancers (Giovannucci 2002) [16]. Nevertheless, randomized controlled trials utilizing individual antioxidant supplements have yielded inconsistent or detrimental results. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) research shown that β-carotene supplementation elevated lung cancer risk among smokers (ATBC research Group 1994) [51]. The SELECT study likewise indicated that vitamin E administration elevated the risk of prostate cancer (Lippman 2009) [26]. These results highlight the intricacy of antioxidant interactions and the advantages of dietary sources compared to isolated supplementation (Maryam *et al*., 2024) [30].

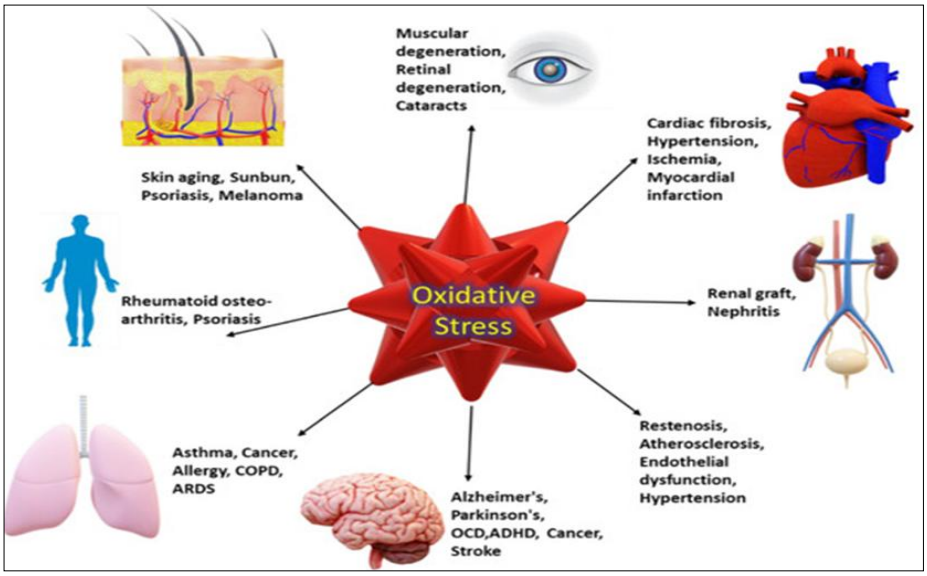

Fig 3: Oxidative stress Adverse Impacts on Human Health (Shah *et al*., 2022) [56]

Type 2 Diabetes Mellitus

Oxidative stress is a major cause of insulin resistance and pancreatic β-cell malfunction, both of which are problems that lead to type 2 diabetes. Reactive oxygen species (ROS) disrupt insulin signaling by stimulating stress-sensitive pathways, including JNK and NF-κB, resulting in decreased glucose absorption (Evans 2003) [13].

Antioxidants in food may help with insulin sensitivity and blood sugar management. Research has demonstrated that vitamin C can reduce fasting blood glucose and HbA1c levels in people with diabetes (Afkhami-Ardekani 2007) [1]. Polyphenols, particularly flavonoids such as quercetin and catechins, augment glucose absorption in muscle cells and safeguard β-cells from oxidative damage (Williamson 2017) [54]. Moreover, adherence to antioxidant-rich dietary patterns, such the Mediterranean diet or diets abundant in fruits and vegetables, has been correlated with a decreased risk of type 2 diabetes (Salas-Salvadó 2011) [44]. Supplementation trials, however, continue to provide inconsistent results, underscoring the significance of dietary interventions over pharmaceutical dosages of antioxidants.

Neurodegenerative Disorders

Alzheimer's disease (AD) and Parkinson's disease (PD) are two examples of neurodegenerative disorders that are closely associated to oxidative stress and mitochondrial

dysfunction. Neurons are especially susceptible owing to their elevated oxygen demand and lipid-dense membranes (Butterfield 2010) [7]. In Alzheimer's disease (AD), reactive oxygen species (ROS) help amyloid-β build up and in Parkinson's disease (PD), they cause the death of dopaminergic neurons.

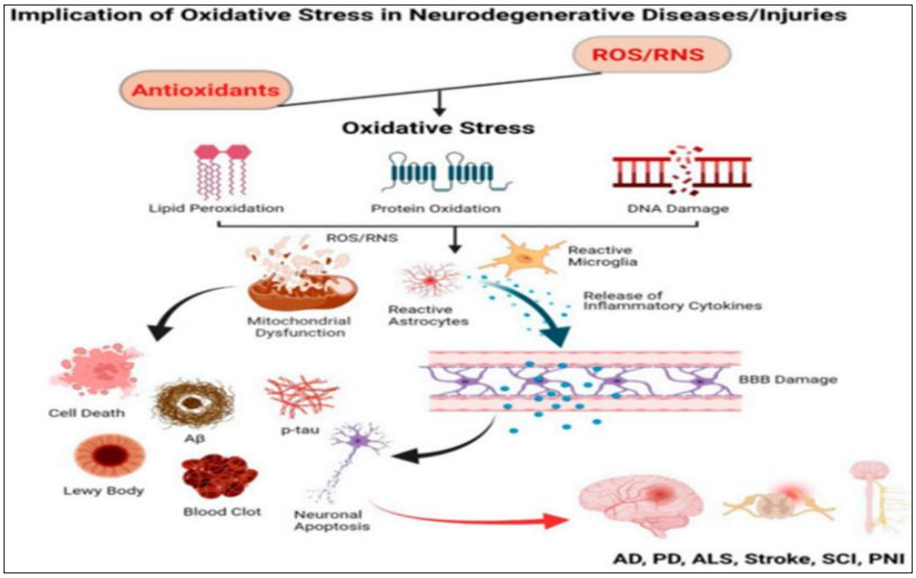

Fig 4: Schematic representing the effect of oxidative stress in neurodegenerative diseases. Imbalance in the level of ROS/RNS and antioxidants leads to an oxidative stress condition that causes damage to cellular biomolecules, i.e., lipids, proteins and DNA (Ashok *et al.*, 2022) [59]

The researchers have looked at whether vitamin E might slow down cognitive decline. Some research indicates that elevated dietary consumption of vitamin E correlates with a decreased risk of Alzheimer's disease, however supplementation trials have demonstrated little or no benefits (Morris 2002; Dysken 2014) [11, 35]. Polyphenols like resveratrol, catechins and curcumin protect neurons by penetrating the blood-brain barrier, stopping the production of amyloid plaques and improving neuronal survival pathways (Mandel 2008) [29]. The carotenoids such as lutein and zeaxanthin are associated with enhanced cognitive function in older persons, attributed to their antioxidant and anti-inflammatory properties in brain tissues (Johnson 2013) [22]. In aggregate, data indicates that antioxidant-rich diets may confer protection against neurodegeneration; nevertheless, further studies are required for validation.

Table 2: Effects of Antioxidants on Chronic Diseases

Chronic Disease	Antioxidant	Observed Effects	Strength of Evidence	Reference
Cardiovascular Disease	Vitamin C, Vitamin E, Polyphenols	Improved endothelial function, reduced LDL oxidation, anti-inflammatory	Moderate (epidemiological strong; supplementation mixed)	Carr 2017 [8]; Pandey 2009 [40]
Cancer	β-carotene, Lycopene, Polyphenols	DNA protection, apoptosis modulation, reduced incidence with dietary intake	Moderate (dietary sources strong; supplement trials inconsistent)	Giovannucci 2002 [16]; Lippman 2009 [26]
Type 2 Diabetes	Vitamin C, Flavonoids	Improved insulin sensitivity, reduced oxidative stress, better glycemic control	Moderate (diet-based evidence strong; supplementation limited)	Afkhami-Ardekani 2007 [1]; Williamson 2017 [54]
Neurodegenerative Disorders	Vitamin E, Polyphenols, Carotenoids	Reduced cognitive decline, neuroprotection, amyloid inhibition	Weak–Moderate (dietary patterns promising; supplement trials inconsistent)	Morris 2002 [35]; Mandel 2008 [29]

Evidence from Clinical and Epidemiological Studies

Epidemiological studies consistently indicate that diets abundant in fruits, vegetables and other antioxidant-rich foods correlate with a decreased risk of chronic illnesses. Randomized controlled trials (RCTs) and meta-analyses of standalone antioxidant supplements have shown inconclusive or detrimental outcomes, prompting significant enquiries over dosage, bioavailability and the intricacies of dietary matrices (Maryam *et al.*, 2024) [30].

Numerous studies support the beneficial role of antioxidants in disease prevention:

- High intake of fruits and vegetables reduces risk of cardiovascular disease and stroke.
- Vitamin C supplementation has shown protective effects against hypertension.
- Lycopene from tomatoes is linked to a reduced risk of prostate cancer.

Polyphenols in green tea are associated with improved cognitive function and lower risk of neurodegenerative diseases. However, results from supplementation trials are mixed, suggesting whole-food sources may be more effective than isolated supplements.

Vitamin C

Numerous clinical trials have evaluated the impact of vitamin C supplementation on cardiovascular outcomes, immunological function and diabetes. A meta-analysis conducted by Jenkins *et al.* (2007) [21] determined that

vitamin C supplementation results in a slight reduction in blood pressure and enhancement of endothelial function; nevertheless, its impact on significant cardiovascular outcomes remains indeterminate. A different comprehensive analysis showed that vitamin C lowered fasting blood glucose levels in those with type 2 diabetes, however the impact was only mild (Afkhami-Ardekani 2007) [1].

Vitamin E

Vitamin E supplementation has undergone substantial investigation about its role in the prevention of cardiovascular disease and cancer. Initial observational studies indicated potential preventive benefits; however, extensive randomized controlled trials yielded unsatisfactory outcomes.

- The HOPE research (Yusuf 2000) [57] showed that giving high-risk individuals vitamin E did not lower the number of cardiovascular events.
- A meta-analysis conducted by Miller *et al*. (2005) [34] indicated that high-dose vitamin E (>400 IU/day) may elevate all-cause mortality.
- The SELECT study (Lippman 2009) [26] showed that using vitamin E supplements can raise the risk of prostate cancer.

These results indicate that supplementation, especially at elevated levels, may disturb physiological redox equilibrium and produce pro-oxidant effects.

Carotenoids

Numerous extensive trials have evaluated β-Carotene supplementation. The ATBC research (1994) and the CARET trial (Omenn 1996) [39] both found that smokers who used β-carotene supplements had a higher chance of getting lung cancer. On the other hand, observational studies still show that eating foods high in carotenoids lowers the risk of cancer and eye problems. This contradiction emphasizes the necessity of ingesting carotenoids within a nutritional framework rather than as standalone pharmaceutical supplements (Iqbal *et al*., 2025) [32].

Table 3: Key Findings from Major Clinical Trials of Antioxidant Supplements

Trial	Antioxidant	Population	Intervention	Outcome	Reference
HOPE	Vitamin E	High-risk CVD patients	400 IU/day	No reduction in CV events	Yusuf 2000 [57]
SELECT	Vitamin E & Selenium	Healthy men	Vitamin E 400 IU/day, Selenium 200 µg/day	Increased prostate cancer risk	Lippman 2009 [26]
ATBC	β-Carotene	Male smokers	20 mg/day	Increased lung cancer incidence	ATBC Study Group 1994
Cocoa Meta-analysis	Flavonoids	Adults	Cocoa polyphenols (various doses)	Improved endothelial function, reduced BP	Hooper 2012 [19]
Green Tea	Catechins	Overweight adults	576 mg/day EGCG	Reduced body fat, improved insulin sensitivity	Nagao 2007 [36]

Polyphenols

The clinical investigations regarding polyphenols have shown more encouraging outcomes, especially for cardiovascular health. A meta-analysis of flavonoid-rich cocoa therapies showed that they enhanced endothelial function, lowered blood pressure and improved lipid profiles (Hooper 2012) [19]. Randomized experiments have demonstrated that catechins in green tea can help people lose weight and make their bodies more sensitive to insulin (Nagao 2007) [36]. Resveratrol has demonstrated efficacy in enhancing insulin sensitivity in small studies, although its outcomes have been contradictory in bigger randomized controlled trials (Timmers 2011) [52].

Trace Elements (Selenium and Zinc)

The researchers have looked at selenium as a way to stop cancer, but the findings have been mixed. The Nutritional Prevention of Cancer (NPC) study indicated decreased risks of certain malignancies with selenium supplementation; however, the SELECT trial could not corroborate these results (Lippman 2009; Rayman 2012) [26, 42]. Zinc supplementation enhances immune function and diminishes the duration of illnesses, including the common cold (Maares 2016) [28]. Nonetheless, research supporting long-term advantages in chronic illness prevention remains insufficient.

Meta-Analytical Evidence Regarding Antioxidant Supplements

Bjelakovic *et al*. (2013) [5] performed an extensive Cochrane review encompassing over 78 randomized controlled trials (RCTs) with nearly 300,000 participants, determining that antioxidant supplements (beta-carotene, vitamin A and vitamin E) were linked to elevated mortality rates, whereas vitamin C and selenium exhibited no consistent impact on survival. These results underscore the divergence between food-derived and supplement-derived antioxidant approaches.

Mechanisms of Action of Dietary Antioxidants

For a long time, people thought that the main health advantages of antioxidants came from their capacity to stop free radicals from doing damage. But new study shows that their functions are far more complicated than that; they include cell signaling, gene control and changing the body's own defense mechanisms.

Free Radical Scavenging

The classical process entails the direct donation of electrons or hydrogen atoms to neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS). Vitamins C and E are great examples:

- Vitamin C gives electrons to hydroxyl radicals and superoxide to make them less harmful.
- Vitamin E gives hydrogen atoms to lipid radicals which stops lipid peroxidation chains.

This step is very important for keeping the membrane strong and safe for big molecules like DNA and proteins.

Metal Chelation

Some antioxidants work by binding transition metals like iron and copper which speed up the Fenton process and create very reactive hydroxyl radicals. Flavonoids and

polyphenols have hydroxyl groups that bind to Fe^{2+} and Cu^{2+} which lowers oxidative stress.

Increasing the activity of Endogenous Antioxidant Enzymes

A lot of antioxidants in food turn on transcription factors that control antioxidant response elements (ARE). The Nuclear factor erythroid 2–related factor 2 (Nrf2): Curcumin, resveratrol and epigallocatechin gallate (EGCG) are polyphenols that turn on Nrf2. This makes superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) work harder. Instead of depending on direct scavenging, this method boosts the body's own antioxidant defense.

Table 4: Mechanisms of Action of Dietary Antioxidants

Antioxidant Type	Mechanism	Examples	Reference
Vitamins (C, E)	Free radical scavenging	Neutralize ROS, prevent lipid peroxidation	Halliwell 2015 [18]
Polyphenols	Nrf2 activation, NF-κB inhibition, chelation	Flavonoids, Resveratrol	Kensler 2007 [23]; Aggarwal 2006 [2]
Carotenoids	Gene expression modulation, photoprotection	Lycopene, β-carotene, lutein	Giovannucci 2002 [16]
Selenium & Zinc	Cofactor for antioxidant enzymes	GPx, SOD	Rayman 2012 [42]; Maares 2016 [28]
CoQ10 & Lipoic acid	Mitochondrial protection	Electron transport chain stabilization	Bjelakovic 2013 [5]
Polyphenols & Fiber	Gut microbiota modulation	Catechins, EGCG	Del Rio 2013 [9]

Anti-Inflammatory Signaling

Antioxidants also have an effect on pathways that cause inflammation:

- Polyphenols stop NF-κB, a transcription factor that controls pro-inflammatory cytokines like IL-6, TNF-α and COX-2.
- Omega-3 fatty acids, while not traditional antioxidants, regulate redox-sensitive inflammatory pathways.

This combined effect as an antioxidant and anti-inflammatory lowers the risk of heart disease and neurological disorders.

Modulation of Apoptosis and Cell Survival Pathways

Polyphenols and carotenoids affect signaling pathways such MAPK, PI3K/Akt and JNK which have an effect on apoptosis, cell growth and stress responses. The resveratrol stimulates Sirtuin 1 (SIRT1) which leads to the creation of new mitochondria and longer life.

Epigenetic Control

Some antioxidants affect epigenetic processes, including DNA methylation and histone acetylation. EGCG (green tea catechin) stops DNA methyl transferases which turns on tumor suppressor genes again. Butyrate, a short-chain fatty acid derived from dietary fiber fermentation, functions as a histone deacetylase (HDAC) inhibitor, increasing the expression of antioxidant and anti-inflammatory genes.

Protection of Mitochondria

Mitochondria are both where ROS comes from and where it goes. Antioxidants guard mitochondrial DNA, proteins and membranes:

The Lipoic acid and coenzyme Q10 help keep the electron transport chain stable.

The Polyphenols enhance mitochondrial biogenesis through the activation of PGC-1α.

Gut Microbiota Modulation

New data suggests that antioxidants, particularly polyphenols, influence their effects through the modification of gut flora.

- Gut bacteria convert polyphenols into beneficial chemicals.
- Antioxidants, on the other hand, encourage good bacteria (such Lactobacillus and Bifid bacterium) while keeping bad bacteria from growing.

This two-way interaction helps lower inflammation throughout the body and promote metabolic health.

Discussion

The evidence examined reveals a paradox in antioxidant research: observational and mechanistic studies robustly indicate the advantageous roles of antioxidant-rich diets in the prevention of chronic diseases, whereas randomized controlled trials (RCTs) of isolated antioxidant supplements frequently do not replicate these benefits and, in certain instances, indicate detrimental effects. Prospective cohort studies regularly demonstrate inverse correlations between the intake of fruits, vegetables, nuts and whole grains and the development of cardiovascular disease, type 2 diabetes and certain malignancies (Estruch 2013; Pandey 2009) [12, 40]. Mechanistic studies offer a robust justification, as antioxidants function not only through radical scavenging but also through metal chelation, enhancement of endogenous antioxidant enzymes, inhibition of pro-inflammatory signaling, mitochondrial protection and modulation of gut microbiota (Kensler 2007; Del Rio 2013) [9, 23].

There are a number of reasons why observational data and supplements experiments might not match up. First, entire meals have a lot of different antioxidants, fiber, minerals and phytochemicals that work together, but isolated supplements do not have this food matrix (Del Rio 2013) [9]. Second, supplements frequently provide supraphysiologic levels that might induce antioxidants to exhibit pro-oxidant behavior, so altering redox signaling; for instance, high-dose vitamin E and β-carotene supplementation in smokers elevated mortality and cancer risk (Miller 2005; ATBC Study Group 1994) [34]. Third, differences in baseline nutritional status, smoking, comorbidities, genetic polymorphisms and gut microbiome diversity across individuals have a big effect on how well antioxidants work which makes it hard to generalize supplementation (Lippman 2009) [26]. Fourth, numerous polyphenols have poor bioavailability and their advantageous metabolites rely on microbial conversion, underscoring the pivotal importance of host–microbe interactions (Williamson 2021)

[55]. Finally, several randomized controlled trials (RCTs) have been of limited length and utilized intermediate biomarkers which are insufficient for capturing the long-latency impacts of antioxidants on chronic disease outcomes.

These constraints give rise to several debates. Current data does not endorse routine antioxidant supplementation for the primary prevention of chronic illness in the general population; furthermore, some supplements may elevate risk in susceptible individuals (Miller 2005; Lippman 2009; Bjelakovic 2013) [5, 26, 34]. It is still hard to figure out what the best amount to eat is since the effects on the body rely on the pharmacokinetics of each molecule, the food matrix and the host's differences (Williamson 2021) [55]. The timing of exposure may be significant, since enduring dietary practices rather than late-life supplementation may elicit protective benefits. Moreover, the absence of standardized biomarkers for oxidative stress and antioxidant status hampers the evaluation of both exposure and outcomes, highlighting the necessity for validated instruments such as F_2-isoprostanes or particular polyphenol metabolites (Del Rio 2013) [9].

From a public health standpoint, research unequivocally supports a food-first strategy. Diets abundant in fruits, vegetables, nuts, legumes and whole grains exemplified by the Mediterranean diet are correlated with a decreased risk of cardiovascular disease and other chronic ailments (Estruch 2013; Pandey 2009) [12, 40]. Supplementation need to be confined to verified deficits or therapeutic applications within certain groups; its frequent usage among well-nourished persons is inadvisable (Lippman 2009) [26]. Doctors need to stress that "antioxidant" does not always equal good and that taking excessive dosages alone might be bad. Personalized nutrition methodologies that incorporate genetics, metabolomics and microbiome characterization may ultimately provide more precise treatments (Williamson 2021) [55].

The existing corpus of evidence possesses significant limitations. The diversity in trial designs, dependence on singular nutritional supplements, oversight of bioavailability and microbiome interactions and the lack of extensive long-term pragmatic studies hinder conclusive outcomes. Subsequent investigations ought to concentrate on extensive randomized controlled trials (RCTs) of whole-food therapies, categorized by initial nutritional status, genetic and microbial variables and underpinned by validated biomarkers. Longitudinal studies monitoring life-course exposures are essential to determine whether early or sustained antioxidant consumption provides the most significant advantage.

Limitations

Even though there has been a lot of study on dietary antioxidants, there are still several big problems that make it hard to grasp what we know and use it in real life. Most clinical trials have concentrated on individual isolated substances rather than comprehensive whole-food therapies, so neglecting the synergistic benefits inherent in natural diets. Trial designs exhibit significant variety, encompassing variations in dosages, chemical forms, participant demographics, baseline nutritional condition and research duration. This variability frequently results in contradictory outcomes and hinders meta-analytical synthesis. Additionally, several studies have employed short-term treatments or intermediate indicators instead of long-term definitive outcomes, such as cardiovascular events, cancer incidence, or death, so constraining the capacity to derive conclusive insights on chronic disease prevention. Bioavailability and metabolism of antioxidants provide significant problems, as several polyphenols and carotenoids need gut microbial conversion to active metabolites and variations in microbiota makeup among individuals affect systemic exposure and effectiveness. Furthermore, the absence of standardized, reliable biomarkers for evaluating antioxidant consumption and oxidative stress impedes accurate assessment of dose–response relationships and the elucidation of underlying mechanisms.

Future Directions

Consequently, further research should emphasize whole-diet intervention studies over separate supplements to more accurately represent real-world usage and synergistic effects. Stratified research designs that consider genetic variants, initial nutritional status, lifestyle variables and gut microbiome composition are crucial for personalized nutrition strategies. Longer research with strong clinical objectives will help us learn more about the long-term consequences on health. The establishment of validated biomarkers, including oxidative stress indicators, polyphenol metabolites and inflammatory mediators, will augment the accuracy of nutritional therapies and mechanistic investigations. Moreover, the integration of omics technologies, including metabolomics, transcriptomic and microbiome analysis, might elucidate precise pathways via which dietary antioxidants exert their effects, possibly uncovering novel intervention targets. Lastly, looking at how antioxidant-rich foods affect people across their whole lives, even when they were young, might help us find the best times to intervene and stop diseases from happening. Addressing these limitations will yield a more thorough and applicable comprehension of the role of dietary antioxidants in human health.

Conclusion

In conclusion, dietary antioxidants are essential for preserving human health and mitigating the risk of chronic diseases through various mechanisms, including direct free radical scavenging, metal chelation, activation of endogenous antioxidant enzymes, modulation of inflammatory pathways, mitochondrial protection and interactions with the gut microbiota. Epidemiological studies repeatedly demonstrate the beneficial effects of antioxidant-rich diets, especially those that priorities fruits, vegetables, nuts, whole grains and other plant-based foods. However, randomized controlled studies with separate antioxidant supplements have frequently had uneven or even detrimental results, underscoring the constraints of high-dose supplementation and the significance of the whole-food matrix. Current research clearly supports a food-first strategy, prioritizing dietary patterns abundant in natural antioxidants above regular supplementation for chronic disease prevention. Subsequent research must to concentrate on comprehensive dietary therapies, enduring effects, stratified trials that account for genetic and microbiome diversity and validated biomarkers to clarify specific pathways. In the end, the best way to stay healthy, avoid chronic illness and get the most out of dietary antioxidants is to eat a balanced diet that is full of natural sources of antioxidants.

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