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Role and Impact of Dietary Antioxidants on Aging and Lifespan: A Review

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Abstract

The effect of an antioxidant-rich diet on aging and lifespan has attracted significant scientific attention, primarily through the lens of the free radical theory of aging (FRTA). This theory suggests that oxidative stress is caused by an accumulation of reactive oxygen species (ROS), accelerates aging and contributes to cellular damage. The accumulation of free radicals and the oxidative damage that is induced significantly contribute to the aging process. This imbalance plays a key role in the development of chronic and degenerative diseases, such as cancer, autoimmune disorders, aging, cataracts, rheumatoid arthritis, cardiovascular disease, and neurodegenerative conditions. Antioxidants, such as vitamins C and E, polyphenols, and flavonoids – commonly found in fruits, vegetables, and plant-based foods are believed to mitigate oxidative damage, potentially enhancing health span and extending lifespan. While many studies report promising outcomes, including reduced oxidative damage and improved metabolic health, contradictory findings reveal negligible or even harmful effects in certain organisms. The complexity of aging involves multiple factors, including genome damage, telomere shortening, and mitochondrial dysfunction, emphasizing the need for a multifaceted approach that integrates biological, psychological and sociological perspectives. Research into dietary antioxidants highlights the value of a balanced diet rich in diverse food sources, which may offer protection against oxidative stress. Continued exploration is crucial to unravel the nuanced relationships between antioxidant intake, oxidative stress, and longevity, paving the way for potential dietary interventions to promote healthy aging and improve lifespan. Aging is a complex process involving multiple biological mechanisms, such as genome damage, telomere shortening, and mitochondrial dysfunction, which require a holistic approach to fully understand. Although, the role of antioxidants in preventing age-related diseases is well-documented but their definitive impact on lifespan and aging remains unclear and requires further study.

Keywords: Antioxidants, oxidative stress, free radical, ROS, aging, lifespan

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INTRODUCTION

An antioxidant is a substance that neutralizes the harmful effects of free radicals in the human body. It can be defined as a material that inhibits the oxidation of other molecules, even at very low concentrations [1]. Free radicals are by-products of the normal metabolic processes that occur within cells. During cellular respiration, when cells utilize oxygen, the redox (reduction–oxidation) reactions lead to the generation of free radicals, primarily in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [2]. Reactive oxygen species (ROS) are highly reactive oxygen derivatives, consisting of free radicals, such as superoxide anion ($O_2^{\bullet -}$) and hydroxyl radical ($HO^{\bullet}$), along with non-radical molecules like hydrogen peroxide (H_2O_2). Free radicals are molecules or fragments that can exist independently, meaning they are “free” from other molecules. Their high reactivity comes from having one or more unpaired electrons in their outer orbitals, making them “radicals.” These unpaired electrons seek stability by interacting with nearby molecules, often triggering a chain reaction that damages cellular components like proteins, lipids, and DNA [3]. The buildup of free radicals and the oxidative damage plays a major role in the aging process. The accumulation of free radicals and the oxidative damage that is induce significantly contribute to the aging process. This imbalance plays a key role in the development of chronic and degenerative diseases, such as cancer, autoimmune disorders, aging, cataracts, rheumatoid arthritis, cardiovascular disease, and neurodegenerative conditions. As the body ages, its antioxidant defense mechanisms gradually decline, reducing their effectiveness in neutralizing free radicals [4]. Incorporating a variety of antioxidant-rich foods into the daily diet can significantly reduce the harmful effects of oxidative stress, which is a major factor in aging and many chronic diseases. Fruits, such as berries, dark chocolate, and citrus, are well-known for their high content of polyphenols and vitamins C and E. These compounds act as antioxidants, neutralizing free radicals and supporting cellular health. The findings related to antioxidants emphasize the benefits of plant-based antioxidants, such as those found in grains like millet. Millet has a low glycemic index and high fiber content, providing metabolic benefits and antioxidant properties that may help in managing diabetes [5].

MECHANISM OF AGING AND OXIDATIVE STRESS

Aging is a complex process and a significant risk factor in the onset and progression of numerous disorders. As the global population continues to age, the prevalence of age-related chronic diseases will rise, greatly affecting quality of life. Oxygen is abundantly present within cells and readily accepts free electrons produced during normal oxidative metabolism due to its unique molecular structure. This process generates reactive oxygen species (ROS) that lead to disruptions in electron transport which can increase ROS production in mitochondria. Other cellular components, including endoplasmic reticulum-bound enzymes, cytoplasmic enzyme systems, and the plasma membrane surface, also contribute to ROS generation. Enzyme systems like cytochrome P450 monooxygenase, xanthine oxidoreductase, nitric oxide synthases, and enzymes involved in inflammatory processes (e.g., cyclooxygenase and lipoxygenase) further enhance ROS production. Oxidative free radicals are harmful byproducts of normal cellular metabolism [6]. Within our cells, natural substances called antioxidants neutralize and eliminate these dangerous free radicals. However, any free radicals that evade this process can cause damage to DNA, proteins, and mitochondria, leading to what is known as oxidative damage. Damage accumulates over time, and research on fruit flies suggests that oxidative damage may be a direct cause of aging. Supporters of the free-radical theory of aging argue that free radicals can lead to DNA damage, protein cross-linking, and the formation of age-related pigments. Oxidative damage is also linked to many age-associated diseases, such as cancer, heart disease, diabetes, and Alzheimer’s disease. While mitochondria do have some capacity to repair their DNA, these repair mechanisms are likely less efficient than those responsible for repairing nuclear DNA [7]. Additionally, research suggests that the ability of mitochondria to repair DNA damage declines with age, although the reasons for this are still unclear. Over time, the damaged mitochondria become so inefficient that they can no longer produce enough energy to meet the needs of the cell. As a result, mitochondria in older individuals are generally less efficient than those in younger people. Oxidative stress, marked by the buildup of reactive oxygen species (ROS), is a key factor in cell death mechanisms. Elevated ROS levels can harm essential cellular macromolecules, initiating apoptosis through mitochondrial pathways. ROS facilitate the release of cytochrome c from the mitochondria, which activates caspases and leads to cell death. Furthermore, ROS are involved in ferroptosis, an iron dependent form of cell death associated with lipid peroxidation and inflammation, playing a crucial role in various diseases [8]. While moderate ROS levels aid in cellular signaling, their excessive production becomes harmful, ultimately causing cell death. Mitochondrial dysfunction is a key factor in the development of age-related diseases, including neurodegenerative disorders, cancer, and metabolic syndromes. This dysfunction arises from several factors, such as mitochondrial DNA mutations, oxidative stress, and impaired mitochondrial dynamics, which contribute to reduced ATP production and increased reactive oxygen species (ROS) levels. The interaction between mitochondrial dysfunction and cellular

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senescence accelerates the aging process, highlighting mitochondria as a potential target for therapeutic strategies aimed at delaying aging. Enhancing mitochondrial function may support healthy aging and reduce the incidence of age-related diseases [9].

Current theories of aging integrate diverse biological, psychological, and sociological perspectives. Prominent biological theories include,

- *Genome Damage:* The progressive accumulation of DNA damage over time.
- *Telomere Shortening:* The gradual loss of protective chromosome caps, leading to cellular senescence.
- *Epigenetic Changes:* Modifications in gene expression that occur without alterations to the underlying DNA sequence.
- *Cellular Senescence:* The phenomenon where aging cells cease to divide but remain metabolically active.
- *Mitochondrial Dysfunction:* The decline in energy production that negatively impacts cellular health.

These theories underscore that aging results from a complex interaction of genetic, environmental and lifestyle factors, rather than a single isolated process [10, 11].

ANTIOXIDANT AND THEIR BIOLOGICAL EFFECTS

Antioxidants can be categorized into endogenous and exogenous types, particularly concerning the aging process.

Endogenous antioxidants are produced naturally by the body and include,

- *Enzymatic Antioxidants:* Enzymatic antioxidants, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are enzymes that work together to detoxify reactive oxygen species (ROS). SODs catalyze the conversion of superoxide radicals into hydrogen peroxide (H_2O_2) and oxygen. CATs and GPx then convert hydrogen peroxide into water, preventing its harmful buildup. GPx uses glutathione (GSH) as a reducing agent to detoxify hydrogen peroxide and organic hydroperoxides [12].
- *Non-Enzymatic Antioxidants:* Non-enzymatic antioxidants are molecules, like ascorbate, glutathione, carotenoids, and anthocyanins, that eliminate, counteract, and scavenge ROS. They can diffuse free radicals, which leads to a limited risk of oxidative stress. They can also chelate metal ions responsible for the generation of ROS, working in both aqueous and membrane domains.

Examples of non-enzymatic antioxidants include ascorbate, fibrin, glutathione, melatonin, mycothiol, phenolics, and serum albumin [13].

Exogenous Antioxidants [14] are sourced externally, primarily through diet, and consist of,

These are obtained through diet, particularly from plant-based foods.

- *Fruits*: Such as berries, oranges, kiwi, and pomegranates.
- *Vegetables*: including spinach, kale, broccoli, and carrots.
- *Nuts and Seed*: examples include walnuts, almonds, and sunflower seeds.
- *Herbs and Spices*: Such as turmeric, ginger, and cinnamon.
- *Green Tea and Red Wine* [15].

Incorporating a diverse range of food sources into the diet can significantly enhance antioxidant intake, promoting cellular health and overall well-being (Figure 1).

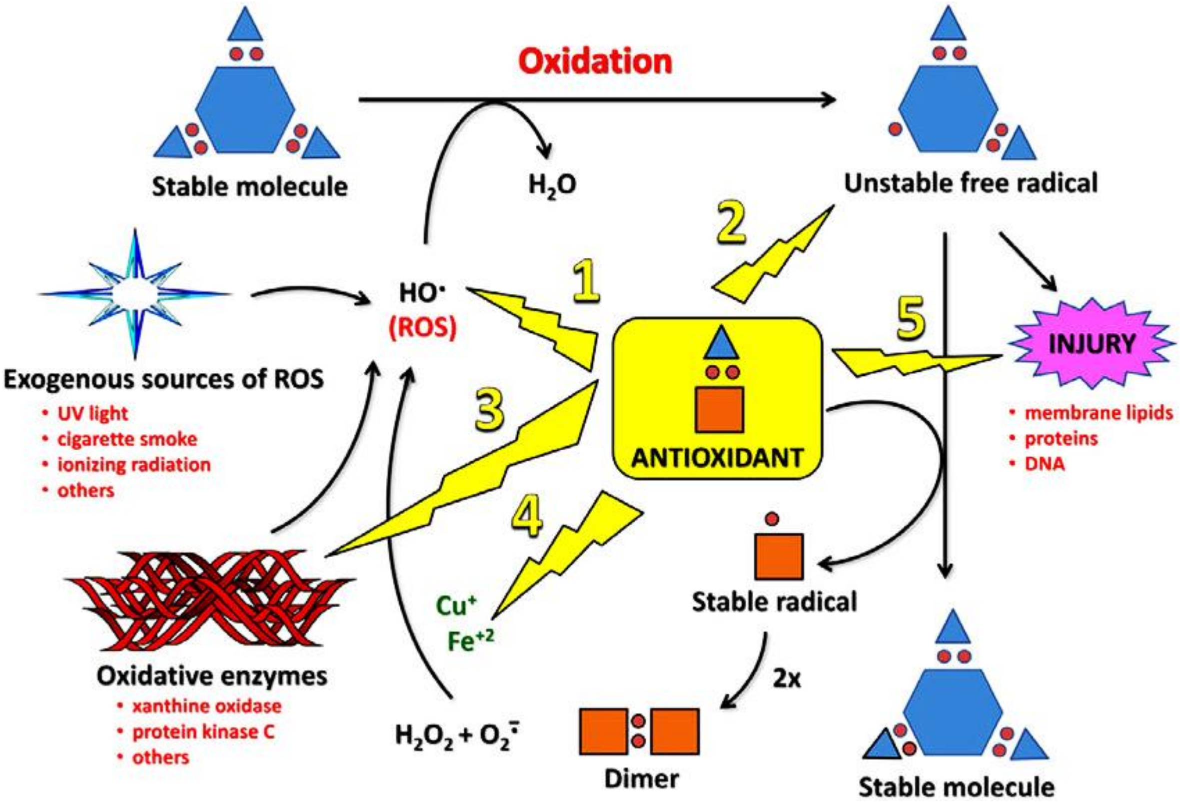

Figure 1. Five main mechanisms of antioxidant action.

- Radical scavenging (quenching ROS).
- Donation of H• atoms.
- Inhibition of oxidative enzymes.
- Chelation of transition metals (preventing ROS formation).
- Repair of damaged cellular components [16].

Mechanism of Action

Antioxidants play a crucial role in neutralizing free radicals – unstable molecules that can induce cellular damage. By donating electrons to these free radicals, antioxidants stabilize them, preventing further cellular harm. This mechanism halts chain reactions that would otherwise lead to oxidative stress, a condition associated with various diseases, including cancer and cardiovascular disorders [17].

- *Synergistic Effects:* occur when two or more antioxidants work in concert, enhancing their collective ability to neutralize free radicals and mitigate oxidative stress.

Mechanisms of Synergy

- *Regeneration:* Certain antioxidants regenerate others, boosting their overall activity. For instance, vitamin C can regenerate vitamin E after it has neutralized a free radical.
- *Complementary Actions:* Different antioxidants may act on distinct types of free radicals or oxidative pathways, offering more comprehensive protection [18].

Examples of Synergistic Combinations

- *Green Tea Polyphenols and Vitamin E:* This combination has demonstrated superior antioxidant activity compared to the individual compounds [19].
- *Curcumin and Ascorbic Acid:* Together, these compounds have shown enhanced efficacy in reducing oxidative damage in cellular models.

Leveraging synergistic antioxidant combinations may optimize therapeutic effects, improve health outcomes and potentially reduce the side effects associated with high doses of single agents [20].

Scientific Studies on Antioxidants and Lifespan

Research on the impact of antioxidants on lifespan has yielded mixed findings. While some studies suggest that antioxidants may delay aging and extend lifespan, particularly in model organisms, such as fruit flies and worms, other research shows no significant benefits and even potential risks associated with supplementation. The free radical theory of aging proposes that oxidative damage accelerates aging. However, results from randomized trials often contradict this, with many showing neutral or even adverse effects of antioxidant supplementation on longevity. Thus, the role of antioxidants in influencing lifespan remains complex and not entirely understood [21].

IN VITRO AND IN VIVO STUDIES: INSIGHTS FROM CELLULAR, ANIMAL, AND HUMAN MODELS

In vitro and in vivo studies play a crucial role in elucidating biological processes and evaluating the safety and efficacy of potential treatments.

In Vitro Studies

Performed in controlled laboratory settings, such as petri dishes, to investigate cellular mechanisms and responses without the complexities of an entire organism. Effective for initial screening of drug toxicity and efficacy, though their findings may not always directly translate to in vivo outcomes due to the absence of systemic interactions [22].

In Vivo Studies

Conducted on living organisms, these studies provide valuable insights into the overall biological effects and safety of substances. More reflective of human physiology but are typically more expensive and raise ethical concerns when compared to in vitro studies.

Together, these approaches offer complementary perspectives, enriching our understanding of therapeutic interventions and their implications for health [23].

EPIDEMIOLOGICAL STUDIES

Links Between Antioxidant-Rich Diets and Reduced Incidence of Aging-Related Diseases

Epidemiological studies have consistently demonstrated a strong association between diets rich in antioxidants and a lower incidence of aging-related diseases. The Mediterranean diet, abundant in fruits, vegetables, and healthy fats, is linked to reduced mortality and a lower risk of chronic conditions, including cancer and cardiovascular diseases. Antioxidants derived from natural food sources, such as berries and nuts, may help alleviate oxidative stress and inflammation, which are key drivers of the aging process. However, while dietary antioxidants show potential, clinical trials evaluating antioxidant supplements have yielded less conclusive results, often showing no significant impact on longevity [24].

Intervention studies investigating the effects of antioxidants, such as resveratrol, coenzyme Q10, and polyphenols, have produced mixed results regarding their influence on lifespan and aging biomarkers.

- *Resveratrol:* Some studies suggest that resveratrol may mimic the effects of caloric restriction, potentially extending lifespan in model organisms. However, human trials have shown inconsistent results, with no definitive evidence supporting longevity benefits.
- *Coenzyme Q10:* While coenzyme Q10 has demonstrated potential in enhancing mitochondrial function and reducing oxidative stress, clinical trials have not consistently shown significant effects on extending lifespan [25].
- *Polyphenols:* These compounds are associated with reduced oxidative stress and inflammation. However, human studies often lack sufficient statistical power or fail to establish a clear causal relationship with longevity [26].

Overall, although antioxidants show promise in laboratory settings, their efficacy in promoting human longevity remains inconclusive.

Limitations of Existing Studies and Conflicting Evidence on Antioxidant Supplementation vs. Dietary Sources

Research comparing antioxidant supplementation to dietary sources highlights significant limitations and conflicting findings.

- *Lack of Efficacy:* Numerous clinical trials have failed to demonstrate a positive association between antioxidant supplements and improvements in lifespan or mortality, suggesting that antioxidants from dietary sources may be more beneficial than from supplements.
- *Methodological Challenges:* Variations in trial design, potential biases, and confounding factors hinder the accurate interpretation of findings, making it difficult to draw firm conclusions regarding the effectiveness of supplementation.
- *Potential Risks:* Certain antioxidants, such as beta-carotene and vitamin E, have been associated with increased mortality in specific populations, raising concerns about the safety of their supplementation.
- *Complex Biological Interactions:* Antioxidants can behave differently within the body, with some potentially acting as pro-oxidants under conditions, complicating their overall impact on health [27].

Impact of Diet on Longevity Impact of Diet on Longevity: Evidence from Dietary Patterns

Diet plays a pivotal role in influencing longevity, with research showing that healthier dietary patterns can significantly extend life expectancy. For example, adherence to the U.K.'s Eatwell Guide diet at age 40 is estimated to increase life expectancy by approximately 8.9 years for men and 8.6 years for women. Broader analyses indicate that adopting an optimized diet could extend life expectancy by over 10 years for both sexes if implemented early in life. Key dietary modifications include increasing the intake of whole grains and nuts while reducing the consumption of red meat and sugar-sweetened beverages, which are strongly correlated with reduced mortality risk [28].

Comparison of Antioxidant-Rich Diets and Their Association with Increased Lifespan

Antioxidant-rich diets, such as the Mediterranean diet and the DASH diet, have been linked to increased lifespan and a lower risk of chronic diseases. The Mediterranean diet, characterized by a high intake of fruits, vegetables, whole grains, and healthy fats, offers protection against oxidative damage, contributing to improved longevity. Similarly, the DASH diet, which prioritizes nutrient-dense foods that reduce blood pressure and support heart health, is associated with enhanced lifespan. Studies suggest that antioxidants from these diets help mitigate oxidative stress, potentially extending lifespan through various biological pathways [29].

The combination of caloric restriction (CR) and elevated antioxidant intake plays a crucial role in modulating the aging process by reducing oxidative stress and boosting cellular defense mechanisms. CR is known to lower metabolic rates and the production of reactive oxygen species (ROS), both of which are implicated in aging and the development of age-related disorders. Antioxidants, such as vitamins C and E, counteract the damaging effects of ROS, thereby supporting longevity. The synergistic effects of CR and antioxidants activate key protective pathways, such as the Nrf2/antioxidant response element, leading to improved mitochondrial function and reduced inflammation. Together, these mechanisms can delay the onset of age-related diseases and potentially extend lifespan across multiple species [30].

Caloric Restriction and Antioxidants

Caloric restriction (CR) combined with high antioxidant intake influences aging by reducing oxidative stress and enhancing mitochondrial function. CR lowers reactive oxygen species (ROS) production, which is linked to age-related diseases, thereby extending lifespan in various organisms. Antioxidants, such as vitamins C and E, help scavenge ROS, further mitigating oxidative damage and promoting longevity. Together, CR and antioxidants create a synergistic effect that enhances cellular health and resilience, contributing to improved health span and lifespan. This dual approach is seen as a promising strategy for combating the aging process [31].

POTENTIAL SIDE EFFECTS AND CONTROVERSIES

The potential side effects and controversies surrounding antioxidant supplementation are notable. Research indicates that antioxidant supplements, such as vitamin E and beta carotene, may increase lung cancer risk in smokers, contradicting the assumption that they universally protect against oxidative damage. Additionally, studies on athletes show mixed results regarding antioxidant supplementation's effectiveness in reducing oxidative stress during exercise, with some suggesting it may impair performance. Furthermore, the benefits attributed to antioxidant-rich foods might stem from other compounds rather than their antioxidant properties alone. This complexity emphasizes the need for cautious interpretation of antioxidant supplementation in dietary practices [32].

Overconsumption of Antioxidants: Potential Risks, Including the Pro-Oxidant Effect When Taken in Excess

Overconsumption of antioxidants can lead to potential risks, including pro-oxidant effects. High doses of certain antioxidants, like vitamin E and beta-carotene, may paradoxically increase oxidative stress, particularly in smokers, potentially leading to adverse health outcomes. Flavonoids, while generally beneficial, can exhibit pro-oxidant activity under specific conditions, such as in the presence of transition metals, which can enhance free radical formation. This dual behavior underscores the complexity of antioxidant supplementation and highlights the importance of moderation to avoid unintended consequences on health and aging [33].

Controversies in Supplementation: Debate Over Whether High-Dose Supplements Provide the Same Benefits as Antioxidants from Whole Foods

The debate over the efficacy of high-dose antioxidant supplements compared to antioxidants from whole foods is contentious. Research suggests that whole foods provide a complex array of nutrients that work synergistically, enhancing absorption and health benefits, which isolated supplements often lack. High-dose supplements can lead to adverse effects, such as increased cancer risk in smokers and diminished exercise performance. Additionally, the body may not respond to synthetic antioxidants in the same way, it does to those from natural sources, making whole foods the preferred option for optimal health [34].

Lack of Consensus: Scientific Disagreements Regarding the Role of Antioxidant Supplements in Human Longevity

Scientific disagreements regarding the role of antioxidant supplements in human longevity highlight a lack of consensus in the field. While some studies suggest that antioxidants can combat oxidative stress and potentially extend lifespan, others indicate that high-dose supplements may increase risks, such as lung cancer in smokers and overall mortality rates. Additionally, evidence shows that antioxidants from whole foods are associated with lower disease risks, but similar benefits from supplements remain unproven. This ongoing debate underscores the complexity of antioxidant effects and the need for further research to clarify their role in aging and health [35].

FUTURE RESEARCH DIRECTION

Antioxidants in Gene Expression and Longevity

Recent research emphasizes the critical roles of antioxidants in regulating gene expression, epigenetics, and longevity pathways, particularly through mechanisms involving sirtuins and AMPK. Antioxidants play a vital role in mitigating oxidative stress, supporting DNA repair, and influencing cellular stress responses, all of which are essential for promoting longevity and preventing age-related diseases [36].

Sirtuins, often referred to as "longevity proteins," are key regulators of metabolism and oxidative stress, while AMPK helps maintain energy homeostasis and stimulates autophagy, enhancing cellular resistance to aging. These interconnected pathways highlight promising therapeutic opportunities for aging interventions by targeting antioxidant activity and modulating gene expression [37].

What Role Do AMPK and Sirtuins Play in Aging and Longevity

AMPK and sirtuins are essential metabolic sensors that play interconnected roles in aging and longevity. They regulate cellular energy metabolism, maintain intracellular energy balance, and support mitochondrial function and biogenesis. Beyond metabolism, they protect cells by facilitating DNA repair, promoting autophagy, and preventing cellular senescence, thereby mitigating age-related physiological decline. Sirtuins are particularly notable for addressing key hallmarks of aging, including neurodegeneration, chronic inflammation, metabolic dysfunction, DNA damage, genomic instability, and increased cancer risk. AMPK and sirtuins work synergistically, responding to shared stimuli such as caloric restriction, exercise, and oxidative stress, and acting through complementary signaling pathways to promote lifespan extension. However, their responsiveness declines with age, potentially contributing to the progression of age-related diseases [38].

How Can Genetic Profiles Be Used to Personalize Antioxidant Therapies

Genetic profiles can be utilized to personalize antioxidant therapies through redox phenotyping, an innovative method that categorizes individuals based on their unique antioxidant status. This approach involves genetic assessments to identify specific single nucleotide polymorphisms (SNPs) in prooxidant and antioxidant genes and evaluate variations that influence susceptibility to oxidative stress [39]. By distinguishing individuals with antioxidant deficiencies, researchers can develop analytical tools to rapidly screen antioxidant profiles and customize supplementation according to genetic and metabolic characteristics. Such personalization enables early identification of those at higher risk of oxidative stress, facilitates tailored nutritional interventions, and prevents unnecessary or potentially harmful supplementation. Genetic variations play a critical role in influencing protein expression, enzymatic activity, and the regulation of redox processes, ultimately affecting an individual's vulnerability to oxidative stress-related conditions. The overarching goal is to create precise, individualized therapies that enhance antioxidant balance and support overall cellular health [40].

The potential of personalized antioxidant-based therapies lies in their ability to improve health outcomes by customizing interventions to an individual's genetic and metabolic profiles. Studies suggest that tailoring antioxidant supplementation based on specific antioxidant status can enhance metabolic efficiency and mitigate oxidative stress [41].

Furthermore, genetic variations significantly influence detoxification pathways, highlighting the importance of personalized strategies in addressing individual needs for managing oxidative stress and associated health conditions. By identifying those who are most likely to benefit from targeted therapies, this approach has the potential to transform treatment paradigms in nutrition and health.

ADVANCING ANTIOXIDANT THERAPIES

Importance of Long-Term Human Studies

Further investigation into antioxidant therapies is crucial, particularly through long-term human studies, to evaluate their efficacy and safety. Research is needed to determine the optimal balance of antioxidants in the diet, tailored to individual metabolic profiles, as current findings remain inconsistent and lack consensus regarding their benefits versus risks. Longitudinal studies are essential to clarify the long-term effects of antioxidant supplementation, especially in relation to interactions with cancer treatments and overall health outcomes [42]. Additionally, the development of personalized redox profiling methods could help identify individuals who would benefit most from specific antioxidants, thereby improving treatment precision.

CONCLUSIONS

The impact of an antioxidant-rich diet on aging and lifespan has become a prominent area of interest in scientific research, particularly through the framework of the free radical theory of aging (FRTA).

This theory suggests that oxidative stress, caused by the buildup of reactive oxygen species (ROS), accelerates aging and leads to cellular damage. Antioxidants – such as vitamins C and E, polyphenols, and flavonoids found in fruits, vegetables, and other plant-based foods – are thought to counteract oxidative damage, potentially improving health span and extending lifespan. While many studies show promising effects, including reduced oxidative damage and better metabolic health, others report minimal or even adverse effects in certain organisms or contexts.

Although the health benefits of antioxidants, particularly in relation to age-related diseases, are well-established, their exact influence on lifespan remains unclear and warrants further exploration. Aging is a complex process involving multiple biological mechanisms, such as genome damage, telomere shortening, and mitochondrial dysfunction which require a holistic approach to fully understand. The study of dietary antioxidants highlights the value of a diverse, balanced diet in providing protection against oxidative stress. Continued research is critical to unravel the intricate relationships between antioxidant consumption, oxidative stress and longevity, offering insights into potential dietary strategies for promoting healthy aging and extending lifespan.

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