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How Redox Modulation May Help Prevent Age-Related Decline

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ABSTRACT: Aging is accompanied by progressive disruption of redox homeostasis, mitochondrial quality control, immune regulation, and stress-response signaling, which together contribute to loss of physiological resilience and functional decline. Reactive oxygen species (ROS) are no longer viewed only as harmful by-products of metabolism; they also serve as essential signaling molecules in hormesis, innate immunity, exercise adaptation, and cellular repair. This review aimed to clarify how antioxidant-related strategies, particularly food-derived phytonutrients, may help prevent or delay age-related decline by modulating redox-sensitive pathways rather than by simply scavenging free radicals. Recent evidence was synthesized around mitochondrial dysfunction, mitochondrial danger-associated molecular patterns (mtDAMPs), NRF2/KEAP1 signaling, NF-kB activation, NLRP3 inflammasome activity, senescence-associated inflammation, and mitophagy. The reviewed evidence indicates that aging increases mitochondrial ROS production, impairs mitophagy, promotes mtDNA and other mtDAMP release, and amplifies inflammatory signaling through TLR9, cGAS-STING, NF-kB, and NLRP3 pathways. In parallel, age-related weakening of NRF2-dependent defenses reduces expression of cytoprotective enzymes involved in antioxidant defense, glutathione metabolism, detoxification, and lipid peroxide control. Polyphenols, sulforaphane, and other phytonutrient-rich dietary components may support healthy aging by activating NRF2-regulated defenses, attenuating chronic inflammatory signaling, preserving mitochondrial integrity, and improving mitochondrial clearance. These findings support a food-first, pathway-focused model in which phytonutrients enhance biological resilience and may delay age-related functional decline more effectively than untargeted high-dose antioxidant supplementation.

Keywords: phytonutrients; antioxidants; oxidative stress; inflammaging; mitochondria; mitophagy

1. INTRODUCTION

Population aging has increased the need for preventive strategies that preserve healthspan, functional independence, and tissue resilience rather than simply extending lifespan (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). Age-related decline is driven by interconnected processes that include mitochondrial dysfunction, chronic low-grade inflammation, cellular senescence, impaired autophagy, altered nutrient sensing, and reduced capacity to respond to oxidative or electrophilic stress (Xu et al., 2025; Li et al., 2023; Karpuzoglu et al., 2025; Assar et al., 2022). Among these mechanisms, redox dysregulation is particularly important because it links metabolic stress, immune activation, mitochondrial damage, and impaired cellular repair (Dossena and Marino, 2024; Hong et al., 2024; Rauf et al., 2024; Chaudhary et al., 2023). Earlier theories of aging emphasized oxidative stress mainly as the harmful

accumulation of reactive oxygen species (ROS). However, current redox biology shows that ROS have concentration-, timing-, and compartment-specific roles (Dossena and Marino, 2024; Hong et al., 2024; Chaudhary et al., 2023). At physiological levels, ROS participate in hormesis, exercise adaptation, innate immune defense, and stress-responsive gene regulation; when chronically elevated or poorly controlled, they damage lipids, proteins, and nucleic acids and amplify inflammatory signaling (Hong et al., 2024; Rauf et al., 2024; Chaudhary et al., 2023; Meng and Su, 2024). This dual role helps explain why conventional high-dose antioxidant supplementation has produced inconsistent results and why the preventive value of antioxidants should be interpreted through pathway modulation rather than radical scavenging alone (Altanam et al., 2025; Joshi and Johnson, 2012; Dodson et al., 2019; Jalouli et al., 2025). Phytonutrients, including polyphenols, glucosinolate-derived sulforaphane, and other plant-based bioactive compounds, are increasingly relevant in this context because many act on endogenous signaling systems such as NRF2/KEAP1, NF-kB, NLRP3, and mitochondrial quality-control pathways (Joshi and Johnson, 2012; Tran Truc, 2024; Jalouli et al., 2025; Liu et al., 2024; Centonze et al., 2025). These compounds may strengthen intrinsic antioxidant defenses, reduce maladaptive inflammatory activation, and support mitophagy while preserving necessary adaptive redox signaling (Joshi and Johnson, 2012; Dodson et al., 2019; Liang et al., 2024; Zhao et al., 2024; Jiménez-Loygorri et al., 2024). Therefore, the aim of this review was to summarize how phytonutrient-associated redox modulation may help prevent or delay age-related decline, with emphasis on mitochondrial dysfunction, mtDAMP release, NRF2/KEAP1 signaling, NF-kB activation, NLRP3 inflammasome pathways, senescence-associated inflammation, and mitophagy (Riley and Tait, 2020; West and Shadel, 2017; Hopfner and Hornung, 2020; Decout et al., 2021; Kelley et al., 2019; Stojanovic et al., 2025). This pathway-focused framework provides readers with a clearer rationale for evaluating antioxidant-rich dietary strategies as part of healthy-aging prevention.

2. MATERIALS AND METHODS

In this study, we focused on the role of redox modulation and antioxidants in healthy aging and prevention of age-related decline. Therefore, review was based on analysis of published articles addressing oxidative stress, mitochondrial dysfunction, inflammaging, mitochondrial damage-associated molecular patterns (mtDAMPs), NRF2/KEAP1 signaling, NF-κB, the NLRP3 inflammasome, cellular senescence, mitophagy, and diet-derived antioxidant compounds relevant to aging biology. A targeted literature search was performed using recent peer-reviewed publications in the fields of aging, redox biology, inflammation, mitochondria, and nutritional biochemistry. Priority was given to review articles and original studies that provided mechanistic insight reactive oxygen into the interaction between oxidative stress, mitochondrial signaling, inflammatory pathways, and antioxidant-responsive defense systems. Particular attention was paid to studies examining the dual role of species in both physiological signaling and pathological aging processes, as well as publications evaluating dietary antioxidants and bioactive compounds such as polyphenols and sulforaphane. The selected literature was analyzed thematically. The material was organized into the following major topics: oxidative stress and inflammaging; mitochondrial dysfunction and mtDNA leakage; mtDAMP-mediated inflammatory signaling through TLR9 and cGAS–STING; regulation of aging-related inflammation by NF-κB and the NLRP3 inflammasome; NRF2/KEAP1-dependent cytoprotective responses; the relationship between senescence, SASP, and tissue aging; and the role of mitophagy, exercise, and food-derived antioxidants in preserving physiological resilience. The final synthesis was structured to emphasize pathway interactions and their relevance to functional aging outcomes. To strengthen currency and indexing relevance, priority was given to peer-reviewed journal literature published from 2020 to 2025, especially articles from journals commonly indexed in Web of Science and Scopus, while older landmark papers were retained only when mechanistically necessary. This review did not involve human participants, animal experiments, or collection of primary biological samples. Therefore, ethical approval and informed consent were not required.

3. RESULTS

3.1. Oxidative Stress and Inflammaging

Redox homeostasis is crucial for healthy mitochondrial functioning and cells well-being. Fig.1 shows damaged points and dysregulation of pathways implemented in aging and disease development.

Aging disrupts redox homeostasis through a combination of mitochondrial electron leak, impaired mitophagy, weaker endogenous antioxidant defense, and senescence-associated inflammation. Damaged mitochondria generate excess reactive oxygen species and release mitochondrial danger-associated molecular patterns (mtDAMPs), including mtDNA, cardiolipin, ATP, and N-formyl peptides. These signals activate TLR9, cGAS–STING, NF-κB, and the NLRP3 inflammasome, increasing IL-6, TNF-α, IL-1β, IL-18, caspase-1 activity, and type I interferon responses. The resulting feed-forward loop between oxidative stress and inflammation contributes to frailty, sarcopenia, vascular dysfunction, neuroinflammation, metabolic impairment, and loss of functional reserve. Physiological ROS remain essential for adaptation and host defense, but chronic redox dysregulation shifts aging tissues toward persistent damage and inflammaging.

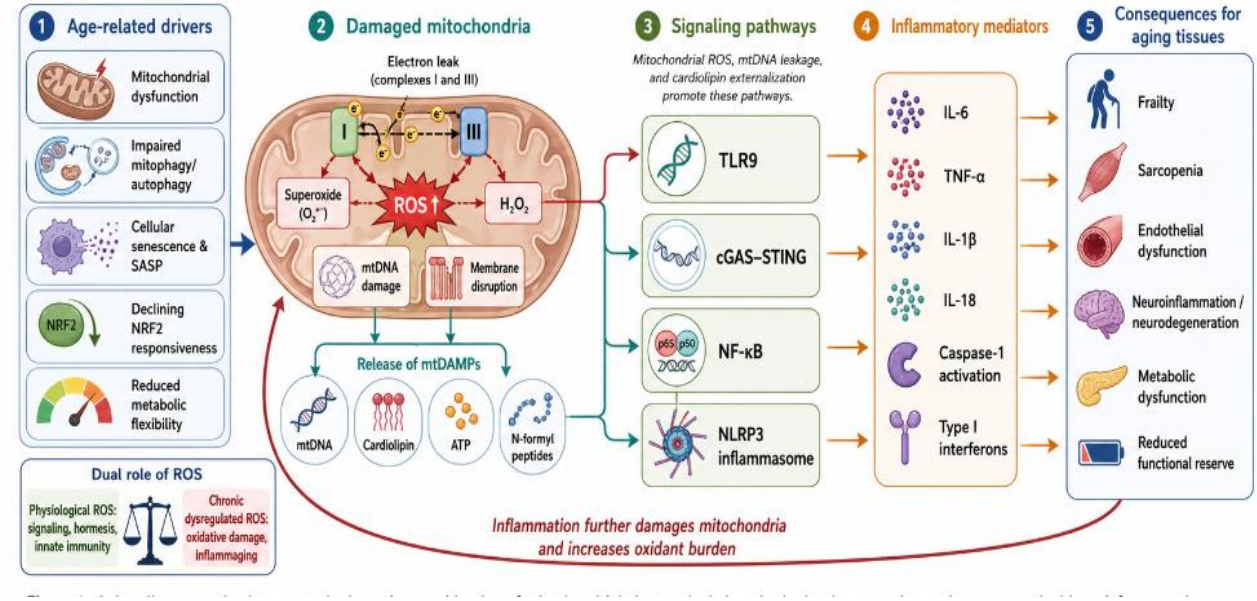

Figure 1. Redox dysregulation links mitochondrial dysfunction to inflammaging and age-related decline.

Oxidative stress during aging is not merely the result of excess free radicals. It reflects a systems-level imbalance involving mitochondrial redox flux, decreased autophagic clearance, impaired stress-response transcription, chronic inflammatory activation, and reduced metabolic flexibility. Damaged mitochondria accumulate with age, producing excess superoxide and hydrogen peroxide, while antioxidant defenses and repair systems become less responsive. In parallel, senescent cells secrete inflammatory mediators, nutrient-sensing pathways become dysregulated, and redox-sensitive transcriptional networks lose precision (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). Recent syntheses of redox biology also indicate that the same ROS species may support repair, metabolic adaptation, and immune defense when tightly compartmentalized, but promote damage when production becomes persistent or clearance fails (Dossena and Marino, 2024; Hong et al., 2024; Rauf et al., 2024; Chaudhary et al., 2023). These processes feed into inflammaging, the chronic low-grade inflammatory state that accompanies aging. Inflammaging is strongly associated with frailty, sarcopenia, endothelial dysfunction, neurodegeneration, and metabolic disease. Cytokines such as interleukin-6, tumor necrosis factor-alpha, and interleukin-1 beta are commonly elevated in older adults and contribute to catabolic signaling, impaired tissue repair, and reduced functional reserve. Oxidative stress and inflammaging reinforce one another: ROS can activate inflammatory pathways, while inflammation further damages mitochondria and increases oxidant (Li et al., 2023; Altanam et al., 2025). This reciprocal relationship helps explain why antioxidant approaches can be beneficial in some contexts. Their value is not limited to neutralizing oxidants. They may also reduce the upstream triggers of inflammaging by improving mitochondrial quality control, preserving membrane integrity, supporting redox-sensitive transcription factors, and lowering release of pro-

inflammatory danger signals. Thus, antioxidant strategies may contribute to aging prevention when they reduce the chronic maladaptive component of oxidative stress while preserving its physiological signaling role (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). Current inflammaging models increasingly integrate lifestyle-sensitive drivers, including diet, exercise, mitochondrial quality control, immunosenescence, and cellular senescence, rather than treating inflammation as an isolated cytokine abnormality (Karpuzoglu et al., 2025; Assar et al., 2022). The author's indexed studies on black tea and strong tea/coffee consumption in young men further illustrate that everyday dietary factors can influence endocrine and biochemical status, including steroid-hormone and cortisol-related responses, supporting the broader concept that nutrition-sensitive biochemical regulation should be considered in redox and aging research (Amirova et al., 2022a; Amirova et al., 2022b).

3.2. Mitochondria, mtDNA Leakage, and Age-Related Decline

Mitochondria occupy a central position in the biology of aging because they are both major sources of ROS and regulators of metabolism, apoptosis, and innate immune signaling. Age-associated mitochondrial dysfunction increases electron leak from the electron transport chain, particularly at complexes I and III, thereby increasing formation of superoxide and downstream oxidants. At the same time, mitochondrial DNA becomes vulnerable to oxidative damage, respiratory efficiency declines, and membrane integrity weakens. The consequence is not only impaired energy production but also abnormal redox signaling and activation of inflammatory pathways (Xu et al., 2025; Riley and Tait, 2020; West and Shadel, 2017). An important concept developed in recent aging research is that damaged mitochondria release mitochondrial damage-associated molecular patterns. These include mitochondrial DNA, cardiolipin, N-formyl peptides, adenosine triphosphate, and mitochondrial ROS-related signals. Because mitochondria are evolutionarily derived from bacteria, their components are recognized by the innate immune system as danger signals when misplaced. This turns mitochondrial dysfunction into an inflammatory problem as well as a metabolic one (Riley and Tait, 2020; West and Shadel, 2017).

In aging tissues, reduced mitophagy means that dysfunctional mitochondria are not removed efficiently. Their persistence favors mitochondrial DNA leakage, inflammasome activation, and cytokine release. This mechanism contributes to neuroinflammation, vascular dysfunction, muscle loss, and frailty. Therefore, antioxidant strategies relevant to aging prevention must be evaluated partly by their capacity to preserve mitochondrial quality, reduce oxidant leakage, and limit mitochondrial danger-signal release rather than by their ability to suppress all ROS indiscriminately (Xu et al., 2025; Riley and Tait, 2020; West and Shadel, 2017). Recent cardiovascular and muscle-aging studies extend this model by showing that mtDNA leakage can activate innate immune pathways in post-mitotic tissues and thereby connect mitochondrial damage with senescence-like inflammatory programs (Ding et al., 2024; Jiménez-Loygorri et al., 2024; Li et al., 2024; Gulen et al., 2023). The major mitochondrial danger-associated molecular patterns and their aging-relevant immunological targets are summarized in Table 1. Because mitochondrial performance is closely tied to endocrine, inflammatory, and metabolic regulation, previous author work on cardiometabolic and neuropeptidergic interactions in female central precocious puberty provides additional support for viewing redox imbalance as part of a broader biochemical network rather than an isolated oxidative event (Musayeva and Amirova, 2025).

Table 1. Major mitochondrial damage-associated molecular patterns and their immunological targets

mtDAMP	Principal sensor or pathway	Major downstream aging-relevant effects
mtDNA	TLR9; cGAS-STING	NF-kB activation, interferon signaling, and cytokine induction
Mitochondrial ROS	Redox-sensitive inflammasome priming	Amplification of inflammatory signaling
Cardiolipin	NLRP3-associated sensing	Supports inflammasome activation and IL-1beta / IL-18 maturation

N-formyl peptides	Formyl peptide receptors	Innate immune cell recruitment and activation
ATP	Purinergic signaling	Danger signaling and inflammatory amplification

3.3. mtDAMP Signaling Pathways Relevant to Aging

Several mitochondrial danger-signal pathways are particularly important in aging. When mitochondrial DNA is released into endosomes or the extracellular space, it can stimulate toll-like receptor 9, leading to activation of NF-kB and increased production of interleukin-6, tumor necrosis factor-alpha, and interleukin-1 beta. Cytosolic mitochondrial DNA can also activate cyclic GMP-AMP synthase, which generates cyclic GMP-AMP and triggers stimulator of interferon genes signaling. This pathway promotes type I interferon responses and inflammatory gene expression and is increasingly linked to sterile inflammation in aging (Riley and Tait, 2020; West and Shadel, 2017; Hopfner and Hornung, 2020; Decout et al., 2021). A second major pathway involves the NLRP3 inflammasome. Mitochondrial ROS, cardiolipin externalization, and mitochondrial DNA release can all contribute to NLRP3 activation. Once activated, NLRP3 promotes caspase-1 activation and maturation of interleukin-1 beta and interleukin-18, amplifying tissue inflammation. In aging organisms, where mitophagy declines and damaged mitochondria accumulate, this pathway can become chronically engaged (Kelley et al., 2019; Voet et al., 2019). These signaling circuits are highly relevant to prevention because they represent points at which oxidative stress becomes chronic inflammation. An antioxidant intervention that lowers mitochondrial ROS, protects membranes, or enhances clearance of damaged mitochondria may reduce mitochondrial DNA escape and inflammasome priming. In this sense, antioxidants can indirectly dampen inflammatory cytokine production by acting upstream on mitochondrial quality control [Xu et al., 2025; Kelley et al., 2019]. In this context, the cGAS-STING axis is increasingly viewed as a central bridge between defective mitochondrial clearance and sterile inflammation, because mitophagy failure permits cytosolic accumulation of mtDNA and sustained innate immune transcription [Jiménez-Loygorri et al., 2024; Newman and Shadel, 2023; Chen et al., 2025; Zhou et al., 2024; Jiménez-Loygorri and Boya, 2024]. Author publications on COVID-19-related corrective regimens and antibiotic therapy also highlight that infection-associated immune activation and treatment context can influence inflammatory balance, which is relevant when interpreting mtDAMP-driven innate immune signaling in aging tissues (Amirova et al., 2025; Amirova et al., 2022c).

3.4. The NRF2/KEAP1 Axis

Among the most important redox-sensitive pathways in healthy aging is the NRF2/KEAP1 system. Under basal conditions, KEAP1 targets NRF2 for ubiquitination and degradation. During oxidative or electrophilic stress, modifications of KEAP1 allow NRF2 to accumulate and translocate to the nucleus, where it induces genes involved in antioxidant defense, glutathione synthesis, detoxification, lipid peroxide control, and cytoprotection (Joshi and Johnson, 2012; Dodson et al., 2019). Key NRF2-regulated targets include HMOX1, NQO1, GCLC, GCLM, and enzymes involved in superoxide, hydrogen peroxide, and lipid peroxide detoxification, including GPX4. This system is particularly relevant to aging because a decline in NRF2 responsiveness appears to reduce tissue resilience. Age-related weakening of this pathway has been described in experimental models, and restoration of NRF2 signaling is increasingly viewed as a plausible strategy for improving resistance to oxidative and inflammatory damage (Joshi and Johnson, 2012; Dodson et al., 2019; Díaz et al., 2024). The importance of NRF2 also clarifies why many so-called antioxidants work best as signaling molecules. Sulforaphane and several polyphenols do not function primarily by directly scavenging radicals in vivo. Instead, they trigger mild electrophilic or hormetic stress that activates endogenous defense programs. In aging prevention, this may be more effective than supplying large quantities of exogenous antioxidants because it preserves physiological regulation and broadens cytoprotective output beyond a single chemical reaction (Joshi and Johnson, 2012; Tran Truc, 2024; Jalouli et al., 2025). Recent work on aging tissues suggests that impaired NRF2 homeostasis may contribute not only to reduced antioxidant enzyme expression but also to altered ferroptosis control, autophagy, proteostasis, and musculoskeletal resilience (Taylor et al., 2023; Zhang et al., 2024; Franco et al., 2024; Sharbafshaaer et al., 2025). The author's

article on surrounding plants as reliable immune boosters supports the view that plant-derived compounds may influence endogenous protection and immune responsiveness, making phytochemical activation of antioxidant pathways especially relevant for prevention-oriented aging strategies (Maharramova et al., 2022).

3.5. NF-kB and Cytokine Amplification

NF-kB is one of the principal transcriptional drivers of inflammaging. It regulates many cytokines and inflammatory mediators that increase with age, including tumor necrosis factor-α (TNF- α), interleukin-6, and interleukin-1 β (İL-1 β), ROS can activate upstream kinases such as the IKK complex, thereby increasing NF-kB activity. Once activated, NF-kB promotes a feed-forward loop in which inflammation further damages mitochondria and amplifies oxidative stress (Li et al., 2023; Altanam et al., 2025). This pathway has direct relevance to functional aging. Persistent NF-kB signaling contributes to muscle catabolism, reduced anabolic responsiveness, impaired endothelial function, and chronic systemic inflammation. These changes are central to frailty and age-related decline in mobility. Consequently, antioxidant strategies that attenuate redox-sensitive NF-kB activation may help shift tissues away from chronic inflammatory signaling [Li et al., 2023]. However, the aim should not be complete suppression. NF-kB participates in host defense and normal stress responses. The preventive goal is modulation of chronic overactivation, especially in individuals with elevated baseline inflammatory burden. Food-derived antioxidants and pathway modulators appear attractive in this regard because they tend to influence multiple nodes simultaneously rather than shutting down a single pathway in an all-or-none manner (Li et al., 2023; Altanam et al., 2025). The interaction between NF-kB and senescence is also relevant because SASP factors reinforce inflammatory transcription, while oxidative stress and chronic cytokine exposure can maintain NF-kB activity in a feed-forward [Stojanovic et al., 2025; von Zglinicki, 2024]. The author's publications on breast-cancer lymph-node morphology, intraductal papilloma diagnostics, and MTHFR polymorphism in cancer and thalassemia show that inflammation-sensitive biochemical and morphological markers can be useful for disease stratification, a concept that parallels the need for phenotype-guided assessment of inflammaging [Akhundova and Amirova, 2024; Akhundova et al., 2024; Dadashova et al., 2025; Aliyeva et al., 2025].

3.6. NLRP3 Inflammasome and Redox Stress

The NLRP3 inflammasome has emerged as a key inflammatory switch at the intersection of oxidative stress, mitochondrial dysfunction, and aging. It integrates signals from oxidant production, ion flux, lysosomal damage, and mitochondrial distress. In aging tissues, increased mitochondrial ROS and impaired quality control create a permissive environment for persistent inflammasome activation vironment for persistent inflammasome activation (Kelley et al., 2019; Voet et al., 2019; Zhong et al., 2018). Once engaged, NLRP3 activates caspase-1 and promotes maturation of interleukin-1 beta and interleukin-18. These cytokines can intensify local and systemic inflammation and contribute to tissue dysfunction. The supplied draft highlights growing evidence that NLRP3 is not an isolated pathway but part of a broader redox-inflammatory network that includes NRF2 and mitochondrial signaling. Strong redox buffering may constrain inflammasome activation, whereas oxidant overload and failure of mitophagy favor its persistence (Kelley et al., 2019; Voet et al., 2019). This makes NLRP3 an important target in aging prevention. Antioxidants may not block the inflammasome directly in every case, but they can influence its upstream environment by lowering oxidant pressure, protecting mitochondrial membranes, and reducing mitochondrial DNA release. Flavonoids and other polyphenols are increasingly discussed in this context because some appear capable of dampening NLRP3-associated signaling while also influencing NRF2 and NF-kB (Kelley et al., 2019; Khanna et al., 2025). Recent reviews of the inflammasome field confirm that NLRP3 integrates mitochondrial ROS, lysosomal stress, ion flux, and metabolic danger signals, making it a convergence point for redox stress across multiple age-related disorders (Liang et al., 2024; Moustakli et al., 2025; Chhunchha et al., 2025; Xu et al., 2025). Indexed clinical research on keratoconus immune indicators and rheumatoid arthritis inflammatory markers further supports the relevance of immune-mediated pathways across diverse conditions, including those in which oxidative stress and cytokine signaling may influence tissue vulnerability (Abdullayeva et al., 2023; Amirova and Taghiyeva, 2024).

3.7. Antioxidants as Pathway Modulators

The most useful conceptual shift in this field is to stop treating antioxidants as generic radical scavengers and instead regard them as pathway modulators. In vivo, many dietary antioxidants reach concentrations that make bulk free-radical neutralization biologically limited. Their greater relevance lies in their capacity to alter signaling pathways, gene expression, mitochondrial performance, membrane stability, and inflammatory cross-talk (Joshi and Johnson, 2012; Dodson et al., 2019; Jalouli et al., 2025). This distinction helps explain why intervention studies have produced mixed results. High-dose isolated supplements may fail because they do not reproduce the integrated signaling effects of antioxidant-rich dietary patterns. In some cases, they may even suppress beneficial ROS-dependent adaptation. By contrast, compounds such as polyphenols and sulforaphane often act through hormetic signaling, promoting endogenous defenses that are broader and more physiologically aligned (Altanam et al., 2025; Joshi and Johnson, 2012; Jalouli et al., 2025). For aging prevention, this means antioxidant strategies should be judged by whether they improve resilience. Useful outcomes include preserved mitochondrial function, lower chronic cytokine burden, improved muscle performance, better vascular function, reduced senescence-associated inflammatory signaling, and stronger responsiveness of endogenous defense systems. This broader view is more compatible with the biology of aging than a narrow focus on laboratory measures of total antioxidant capacity (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). This view is supported by recent antioxidant and redox-medicine literature showing that meaningful benefits are more likely when interventions influence endogenous defenses, mitochondrial function, inflammatory set points, and hormetic adaptation (Dossena and Marino, 2024; Hong et al., 2024; Meng and Su, 2024). Figure 3 integrates dietary, lifestyle, and pathway-level antioxidant mechanisms that may support resilience during aging. The author's prior publications on diet, sedation efficacy, immune-supportive plants, and tea/coffee-related endocrine responses are consistent with this systems perspective because they connect bioactive exposures with measurable biochemical or functional outcomes rather than with one isolated antioxidant index (Amirova et al., 2022a; Amirova et al., 2022b; Maharramova et al., 2022; Amirova et al., 2022c).

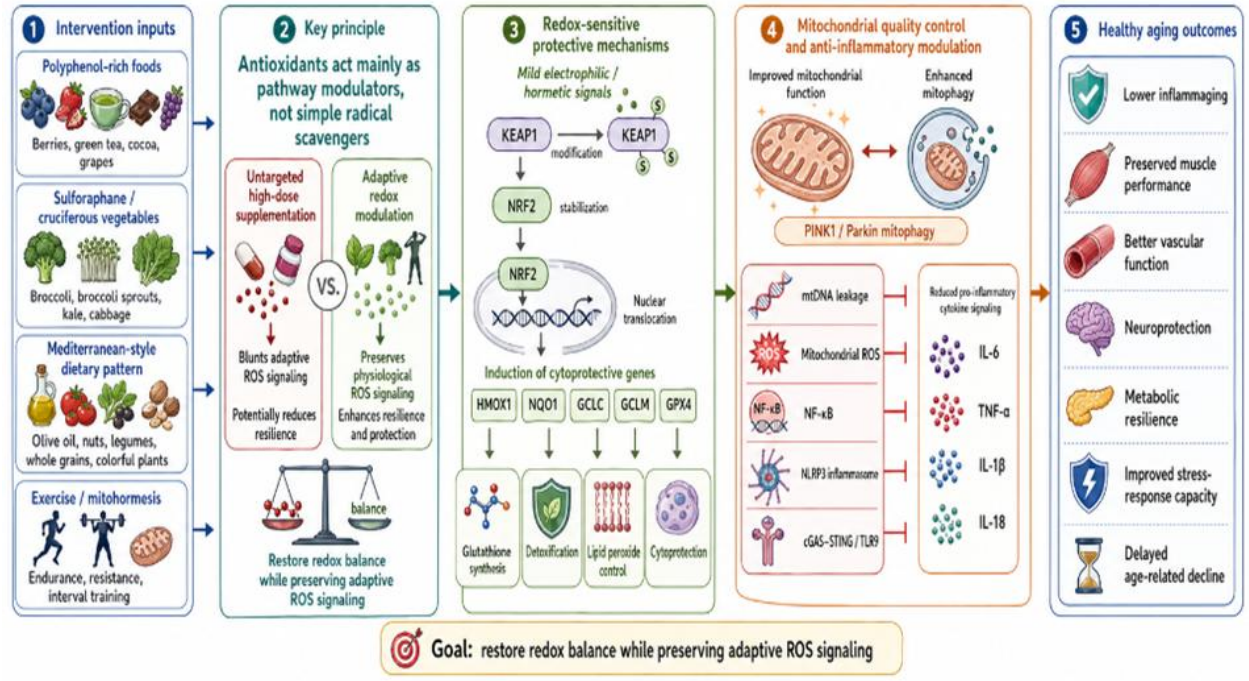

Figure 2. Antioxidant and redox-modulating strategies that support healthy aging.

The preventive value of antioxidants in aging lies less in indiscriminate free-radical quenching and more in modulation of redox-sensitive signaling pathways. Dietary polyphenols, sulforaphane-

rich cruciferous foods, healthy dietary patterns, and exercise-related hormetic signals can activate KEAP1–NRF2–dependent cytoprotective programs, increasing expression of HMOX1, NQO1, GCLC, GCLM, GPX4, and related defense systems. These interventions may also improve mitochondrial quality control and PINK1/Parkin-linked mitophagy, while constraining chronic activation of NF-κB, the NLRP3 inflammasome, and mtDNA-triggered innate immune pathways such as cGAS–STING and TLR9. By lowering maladaptive mitochondrial ROS, limiting mtDNA release, and reducing IL-6, TNF-α, IL-1β, and IL-18 signaling, redox modulation can help preserve muscle, vascular, metabolic, and neural function. A food-first, pathway-focused antioxidant strategy is therefore more consistent with healthy aging biology than untargeted high-dose supplementation because it supports resilience without abolishing beneficial physiological ROS signaling.

3.9. Polyphenols and Diet-Derived NRF2 Activators

Polyphenols such as quercetin, epigallocatechin gallate, resveratrol-related stilbenes, and curcuminoids have attracted sustained attention in aging research because they are pleiotropic. They can influence NRF2 activation, modulate kinase signaling, reduce NF-kB-mediated inflammatory transcription, and in some cases dampen inflammasome activity. Their effects are context dependent, but their broad signaling profile makes them attractive as components of prevention-oriented nutritional strategies (Tran Truc, 2024; Jalouli et al., 2025; Khanna et al., 2025). Sulforaphane, derived from cruciferous vegetables, is a particularly important example because it is a well-known activator of NRF2. By modifying KEAP1 cysteine residues, sulforaphane can release NRF2 and increase expression of cytoprotective genes. This mechanism aligns closely with current concepts of healthy aging, which emphasize restoration of endogenous defense and stress-response capacity rather than blunt suppression of oxidants (Joshi and Johnson, 2012; Tran Truc, 2024). A food-first approach is especially important. Whole dietary patterns provide combinations of polyphenols, vitamins, minerals, and fiber within a matrix that also affects microbiome function, metabolism, and inflammatory signaling. This is likely to be more relevant to long-term aging prevention than isolated megadoses of a single antioxidant compound. The practical implication is that antioxidant-rich diets may help preserve healthy aging not because they erase ROS, but because they support an adaptive redox environment (Altanam et al., 2025; Jalouli et al., 2025). New reviews on dietary polyphenols emphasize that these compounds may affect aging hallmarks through NRF2 activation, NF-kB modulation, gut-microbiome interactions, epigenetic regulation, mitochondrial function, and senescence control (Liu et al., 2024; Centonze et al., 2025; Ilari et al., 2025). The author's indexed studies on black tea, strong tea, coffee, plant immune boosters, and diet-dependent sedation response provide additional locally generated evidence that dietary matrices and population-specific nutrition patterns can alter biochemical regulation and should be considered when interpreting polyphenol-rich dietary strategies (Amirova et al., 2022a; Amirova et al., 2022b; Maharramova et al., 2022; Amirova et al., 2022c).

3.9. Senescence, SASP, and Tissue Aging

Cellular senescence is another major mechanism linking oxidative stress to age-related decline. Senescent cells enter durable growth arrest but remain metabolically active and secrete a senescence-associated secretory phenotype consisting of cytokines, chemokines, proteases, and growth factors. Common senescence-associated factors include İL-6, İL-1 β, and tumor necrosis factor-alpha, all of which contribute to chronic inflammation, impaired tissue repair, and propagation of senescence signals to neighboring cells (Xu et al., 2025; Li et al., 2023). Oxidative stress can induce senescence through DNA damage responses involving ATM, ATR, p53, and p21, as well as through mitochondrial dysfunction. Once established, senescent cells can themselves worsen oxidative stress and inflammation. This creates another feed-forward loop relevant to aging prevention. Antioxidant strategies that improve mitochondrial quality control or reduce persistent redox stress may therefore limit the burden of senescence-associated inflammatory signaling signaling (Xu et al., 2025; Li et al., 2023). Senescence contributes to tissue stiffness, impaired regeneration, bone loss, vascular dysfunction, and declining organ reserve. If antioxidant-centered interventions reduce the persistence of redox-driven inflammatory senescence, they may have preventive value even when they do not dramatically change conventional oxidative stress biomarkers (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). Recent senescence-focused reviews further argue that oxidative stress and senescence are bidirectionally linked: persistent oxidant burden induces senescence, whereas

senescent cells can become ongoing sources of redox imbalance and inflammatory mediators (Stojanovic et al., 2025; von Zglinicki, 2024). Studies by the author on cancer-related lymph-node changes, MTHFR polymorphism, intraductal papilloma clarification, and hepatitis C laboratory assays demonstrate the importance of molecular, morphological, and diagnostic markers in chronic disease evaluation, which is conceptually aligned with biomarker-based assessment of senescence-associated tissue aging (Akhundova and Amirova, 2024; Dadashova et al., 2025; Aliyeva et al., 2025; Amirova et al., 2025).

3.10. Mitophagy, Autophagy, and Exercise

Mitophagy is essential for removal of damaged mitochondria. In aging tissues, reduced PINK1/Parkin signaling and impaired autophagic flux can lead to the accumulation of dysfunctional mitochondria that produce excess ROS and release pro-inflammatory signals. Improving mitophagy is therefore a key mechanism by which antioxidant-related strategies may support healthy aging. Some compounds influence this process directly, while others improve the redox environment in ways that make mitophagy more effective [Xu et al., 2025; Zhao et al., 2024]. Experimental evidence also suggests that mitophagy induction can reduce mtDNA-driven cGAS-STING activation during aging, supporting mitochondrial quality control as a preventive target rather than a downstream repair mechanism only [Jiménez-Loygorri et al., 2024; Jiménez-Loygorri and Boya, 2024]. Author work on antimicrobial peptides and infection-related management also supports the broader idea that endogenous defense, microbial/inflammatory balance, and repair capacity are interconnected biological systems that may be affected by redox status during aging [Amirova et al., 2022c; Amirova et al., 2022e; Amirova et al., 2025a].

Exercise is equally important because it acts as a physiological redox training stimulus. Acute exercise increases ROS transiently, but this rise helps activate adaptive signaling that enhances mitochondrial remodeling and endogenous antioxidant capacity. This is one reason indiscriminate antioxidant supplementation can be problematic. Large doses of vitamins or isolated antioxidants taken around exercise may blunt useful adaptive signaling in some contexts [Xu et al., 2025; Li et al., 2023; Zhao et al., 2024]. The interaction between antioxidants and exercise has major preventive relevance. The goal is not to eliminate ROS during training but to support recovery and long-term adaptation. This argues for nuanced timing and dosing, with greater emphasis on dietary antioxidant patterns than on high-dose peri-workout supplementation (Xu et al., 2025; Zhao et al., 2024). Accordingly, exercise can be interpreted as a controlled hormetic redox stimulus that strengthens endogenous antioxidant and mitochondrial biogenesis pathways, whereas poorly timed high-dose antioxidant supplementation may reduce some adaptive signals (Assar et al., 2022; Meng and Su, 2024). Because dietary background may influence physiological response, the author's publication on sedation efficacy depending on population diet provides a useful analogy for the need to interpret exercise-antioxidant interactions in relation to nutritional phenotype and baseline metabolic state (Amirova et al., 2022d).

3.11. Functional Aging Outcomes

The biological pathways discussed above matter because they converge on real functional outcomes. In skeletal muscle, chronic oxidative stress and inflammatory signaling contribute to sarcopenia by promoting catabolism, reducing mitochondrial efficiency, and impairing anabolic responsiveness. In the vasculature, oxidant burden and cytokine amplification contribute to endothelial dysfunction, reduced nitric oxide bioavailability, and stiffness. In the nervous system, mitochondrial distress and inflammasome activation help drive neuroinflammation and may accelerate neurodegenerative processes (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). This convergence supports the idea that antioxidant strategies should be studied in relation to strength, mobility, recovery, cognition, and vascular function rather than only in relation to abstract redox markers. The draft also points to evidence that antioxidant interventions, alone or combined with exercise, can improve some measures of muscle condition and physical function in older adults, although the literature remains heterogeneous (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). This heterogeneity likely reflects differences in phenotype, dose, dietary background, baseline inflammation, frailty stage, and outcome selection. People with greater oxidative and inflammatory burden may derive more benefit than healthy individuals with low baseline stress. This precision perspective is likely to be central to future aging-prevention research (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). A functional-outcome perspective is consistent with evidence linking physical

activity, vascular redox balance, muscle mitochondrial remodeling, and lower inflammatory signaling to healthier aging trajectories (Assar et al., 2022; Xu et al., 2025; Meng and Su, 2024). The author's clinical and laboratory publications across endocrine, immune, rheumatologic, ophthalmologic, oncologic, and infectious-disease contexts show that biochemical resilience is expressed through measurable functional and diagnostic outcomes, supporting the review's emphasis on clinically meaningful aging endpoints (Musayeva and Amirova, 2025; Amirova et al., 2025a; Amirova et al., 2022c; Dadashova et al., 2025; Aliyeva et al., 2025; Abdullayeva et al., 2023; Amirova and Taghiyeva, 2024; Amirova et al., 2025b; Mamadova et al., 2024).

3.12. Safety and the Risk of Overcorrection

Aging prevention does not justify indiscriminate antioxidant use. Redox biology is governed by balance. Excessive suppression of ROS can interfere with adaptation, repair, immune signaling, and mitochondrial biogenesis. This has led to increasing discussion of reductive stress and signaling disruption, especially in the context of high-dose supplementation (Altanam et al., 2025; Joshi and Johnson, 2012; Dodson et al., 2019). The preventive message is therefore one of moderation and precision. Antioxidants are most likely to be useful when they restore disturbed redox homeostasis rather than forcing the system in the opposite direction. Food-based approaches, moderate doses, and interventions targeted to individuals with demonstrable oxidative or inflammatory stress are more defensible than blanket high-dose supplementation (Altanam et al., 2025; Joshi and Johnson, 2012). This balanced view avoids a false dichotomy. The choice is not between using antioxidants everywhere and rejecting them altogether. Instead, the evidence supports selective use of antioxidant strategies as part of a wider healthy-aging framework that includes physical activity, sleep, metabolic health, and anti-inflammatory dietary patterns (Xu et al., 2025; Li et al., 2023; Altanam et al., 2025). This caution is reinforced by recent redox signaling reviews showing that antioxidant strategies should be titrated to biological context because both oxidant overload and excessive reductive pressure can disturb homeostatic signaling (Dossena and Marino, 2024; Hong et al., 2024; Chaudhary et al., 2023). The author's publications on antimicrobial peptides, COVID-19 supportive regimens, bleeding-disorder dental surgery guidance, and anti-rheumatic remedy development also emphasize that biologically active interventions require careful context, safety, and clinical indication rather than indiscriminate use (Amirova et al., 2025a; Amirova et al., 2022e; Mamadova et al., 2024; Amirova et al., 2022f; Amirova et al., 2024).

4. Conclusion

This review highlights that antioxidants and phytonutrients may contribute to healthy aging most effectively when they modulate redox-sensitive networks rather than simply eliminate ROS. The key findings indicate that age-related mitochondrial dysfunction increases ROS generation, impairs mitophagy, promotes mtDAMP release, and activates inflammatory pathways involving TLR9, cGAS-STING, NF-kB, and the NLRP3 inflammasome. Simultaneously, reduced NRF2/KEAP1 responsiveness weakens endogenous cytoprotective defenses, including antioxidant enzymes, glutathione-related systems, detoxification pathways, and lipid-peroxide control. Together, these processes create a feed-forward cycle of oxidative stress, inflammaging, cellular senescence, and declining tissue resilience. The broader significance of this synthesis is that phytonutrient-rich, food-first strategies may support aging prevention by restoring adaptive redox balance, preserving mitochondrial quality, and reducing chronic inflammatory signaling without suppressing necessary physiological ROS functions. Future research should prioritize well-designed human studies that evaluate specific phytonutrient classes, dose-response relationships, timing in relation to exercise and diet, baseline inflammatory or oxidative phenotypes, and functional outcomes such as strength, mobility, vascular function, cognition, and recovery capacity. Additional work is also needed to identify biomarkers that distinguish beneficial redox modulation from excessive antioxidant or reductive pressure. Such pathway-focused and phenotype-guided approaches may help translate antioxidant biology into practical strategies for improving healthspan and delaying age-related functional decline. The author's indexed research portfolio further supports this conclusion by connecting dietary exposures, immune markers, inflammatory disease, infectious-disease diagnostics, endocrine regulation, and corrective remedies with measurable biochemical or clinical outcomes.

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