BIOCELL

Tech Science Press

http://doi.org/10.32604/biocell.2026.077286

REVIEW

Polyphenols in mtDNA Repair, Mitochondrial Biogenesis, and Mitophagy: An Integrative Review

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Received: 05 December 2025; Accepted: 20 January 2026; Published: 09 June 2026

ABSTRACT: Mitochondrial dysfunction is a central hallmark of metabolic, hepatic, cardiovascular, and neurodegenerative diseases. Dietary polyphenols modulate mitochondrial pathways, but their integrated effects remain poorly appreciated. This narrative review synthesizes preclinical and clinical evidence on four polyphenols (resveratrol, epigallocatechin-3-gallate, quercetin, and oleuropein) and examines their mechanisms in mitochondrial biogenesis, mtDNA protection, and mitophagy. Experimental studies indicate that these compounds activate conserved adaptive pathways, including sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), AMP-activated protein kinase (AMPK), and PTEN-induced kinase 1 (PINK1) with Parkin, therapy enhancing mitochondrial biogenesis, reducing oxidative stress, and promoting selective removal of damaged mitochondria. Evidence from human studies suggests improvements in endothelial function and metabolic flexibility, although direct human mitochondrial assessments remain scarce. Overall, dietary polyphenols appear to support mitochondrial quality control across multiple organs through coordinated signaling mechanisms. Critical limitations include bioavailability constraints and a lack of mitochondrial biomarkers in most clinical studies. Future investigations should incorporate advanced phenotyping and improved formulations to clarify the therapeutic potential of polyphenols as targeted modulators of mitochondrial health.

KEYWORDS: Mitophagy; mitochondrial biogenesis; polyphenols; oleuropein; bioactive compounds

1 Introduction

Mitochondria are highly dynamic and multifunctional organelles that play a central role in cellular energy production through oxidative phosphorylation (OXPHOS), while also regulating calcium homeostasis, redox signaling, apoptosis, innate immunity, and metabolic integration across tissues [1,2]. To meet fluctuating cellular demands, mitochondrial populations are continuously remodeled through coordinated processes of mitochondrial biogenesis, fusion and fission dynamics, and selective removal of dysfunctional organelles via mitophagy, collectively referred to as mitochondrial quality control [3]. Disruption of these processes compromises bioenergetic efficiency and promotes oxidative stress, thereby contributing to the development of metabolic, cardiovascular, and neurodegenerative diseases. In addition, emerging evidence indicates that mitochondria can participate in intercellular communication through the transfer of mitochondrial components or whole organelles, influencing tissue repair, inflammatory responses, and metabolic resilience under stress conditions [4,5]. An overview of mitochondrial structure and its core bioenergetic and regulatory functions is illustrated in Fig. 1.

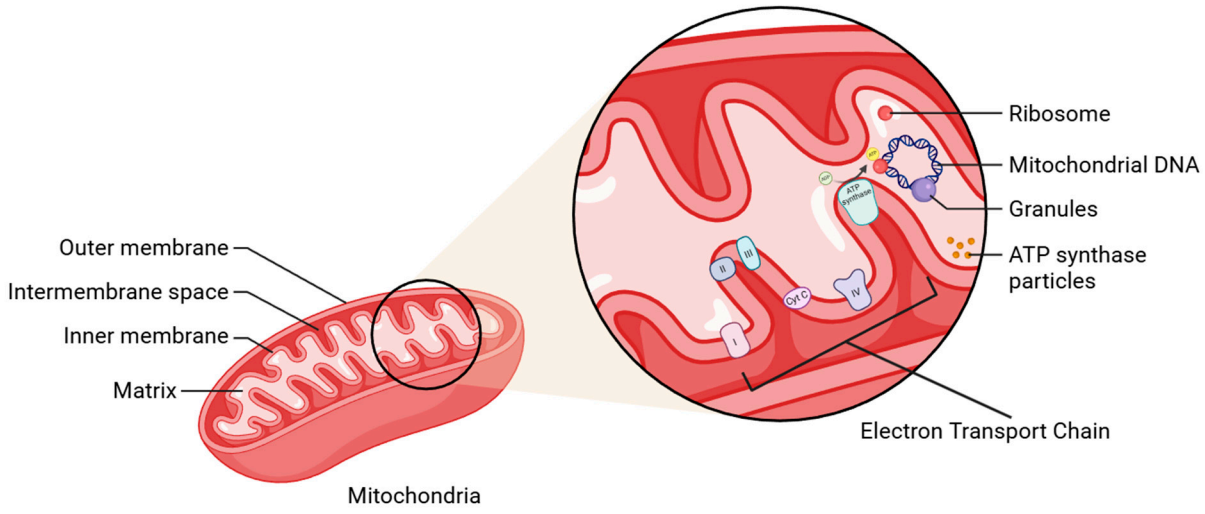

Figure 1: Mitochondrial structure and core cellular functions. Schematic representation of mitochondrial ultrastructure, highlighting the outer mitochondrial membrane, intermembrane space, inner mitochondrial membrane, and matrix. The inner membrane forms cristae that increase the surface area available for oxidative phosphorylation. The magnified inset illustrates the spatial organization of core mitochondrial components, including the electron transport chain embedded in the inner membrane, ATP synthase particles responsible for adenosine triphosphate (ATP) production, mitochondrial DNA organized in nucleoids, mitochondrial ribosomes, and matrix granules. Together, these structural and functional elements support mitochondrial energy metabolism, redox homeostasis, and the regulation of cellular bioenergetic capacity. This figure was created by the authors using Microsoft PowerPoint for Microsoft 365 (Version 2409; Microsoft Corporation, Redmond, WA, USA) and graphical elements from BioRender.com.

Mitochondrial dysfunction and the progressive accumulation of mitochondrial DNA (mtDNA) mutations have emerged as central mechanisms in aging and age-related chronic diseases [1,6]. Recent studies further support this concept by demonstrating that alterations in mitochondrial dynamics, impaired mitophagy, and diminished respiratory chain efficiency contribute to cellular senescence beyond the classical oxidative damage paradigm [2,7]. The modern reinterpretation of the mitochondrial theory of aging suggests that persistent mtDNA injury, altered turnover, and defective repair progressively impair OXPHOS, leading to decreased ATP output and sustained reactive oxygen species (ROS) production in a self-amplifying cycle of mitochondrial decline [2,8,9].

The human mitochondrial genome is a compact circular molecule of 16,569 base pairs encoding 37 essential genes for OXPHOS and mitochondrial protein synthesis [10]. Unlike nuclear DNA, mtDNA lacks protective histones and possesses a limited repertoire of repair pathways, relying primarily on base excision repair (BER), which makes it more susceptible to oxidative lesions [11,12]. Its physical proximity to the electron transport chain, which is the main intracellular source of ROS, further increases its vulnerability and results in mutation rates that are up to 10–50 times higher than those of nuclear DNA [10,12,13]. Accumulation of mtDNA damage with age has been consistently observed in multiple tissues, including brain, muscle, and cardiac tissue [14,15].

In addition to oxidative stress, multiple factors contribute to mitochondrial DNA damage, including replication errors mediated by DNA polymerase gamma, exposure to inflammatory mediators, impaired antioxidant defenses, altered mitochondrial dynamics, and an age-related decline in mitophagy efficiency [16,17]. Together, these mechanisms promote the accumulation of point mutations, deletions, and copy number alterations in mtDNA, particularly in post-mitotic tissues with limited regenerative capacity.

Guanine oxidation producing 8-oxo-7,8-dihydroguanine (8-oxoG) is one of the most abundant oxidative lesions and frequently leads to G to T transversions during replication [10,18]. When mtDNA heteroplasmy for deleterious variants exceeds approximately 60–80%, mitochondrial function becomes critically impaired, promoting increased electron leakage and elevated ROS formation [2,10]. Recent neuropathological evidence reinforces this mechanism: high burdens of somatic mtDNA deletions and point mutations have been found in substantia nigra neurons in Parkinson's disease [15], as well as increased mtDNA oxidation and reduced copy number in Alzheimer's disease brains [19]. These findings highlight mtDNA instability as a key contributor to neurodegeneration.

Polyphenols, natural bioactive molecules widely distributed in plant-based foods, have emerged as potent modulators of mitochondrial function capable of enhancing mtDNA protection [20]. Rather than acting solely as direct antioxidants, polyphenols function as metabolic and redox-signaling molecules that activate adaptive stress-response pathways such as sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), driving mitochondrial biogenesis and AMP-activated protein kinase (AMPK) activation. Through these mechanisms, polyphenols not only attenuate mitochondrial ROS production but also limit biomolecular damage to DNA, lipids, and proteins, enhance mitochondrial turnover, and promote coordinated mitochondrial biogenesis and mitophagy, thereby preserving mitochondrial genomic integrity and cellular resilience [20–22]. Their pleiotropic ability to modulate redox homeostasis and mitochondrial quality control places them among the most promising nutritional strategies to mitigate age-related mitochondrial deterioration.

Despite increasing evidence linking polyphenols to mitochondrial protection, their integrated effects on mtDNA stability, mitochondrial biogenesis, and mitophagy remain fragmented across preclinical and clinical studies [3,13]. Therefore, the aim of this integrative review is to critically synthesise current evidence on the role of selected dietary polyphenols, namely resveratrol, epigallocatechin-3-gallate, quercetin, and oleuropein, in modulating mtDNA damage and repair, mitochondrial biogenesis, and mitophagy. By integrating mechanistic insights with translational and clinical data, this review seeks to identify convergent pathways, highlight current limitations, and outline future directions for mitochondria-targeted nutritional strategies in aging and chronic disease.

Review Scope and Literature Identification

This narrative integrative review adopts a state-of-the-art approach to contextualise current knowledge on mitochondrial DNA damage and repair, mitochondrial biogenesis, and mitophagy, with a particular focus on the modulatory role of major dietary polyphenols. Rather than aiming for an exhaustive or systematic synthesis, the objective was to integrate mechanistic, preclinical, and clinical evidence into a coherent conceptual framework.

Relevant literature was identified through targeted searches of PubMed, Scopus, Web of Science Core Collection, and Google Scholar, using combinations of terms related to polyphenols and mitochondrial quality control processes. The search strategy was designed to capture foundational mechanistic studies as well as representative preclinical and clinical investigations with relevance to mitochondrial function. Reference lists of key articles were also screened to ensure coverage of seminal and recent contributions.

2 Mitochondrial DNA Damage, Oxidative Stress, and Age-Related Disease

mtDNA is particularly vulnerable to oxidative damage due to its proximity to the electron transport chain (ETC) and the continuous generation of reactive oxygen species (ROS), mainly superoxide anions produced at Complexes I and III during oxidative phosphorylation [10]. Estimates suggest that 1–2% of

cellular oxygen consumption leads to ROS formation, making the mitochondrial matrix a major site of oxidative stress [1]. Because guanine has the lowest oxidation potential among DNA bases, it is preferentially oxidized to 8-oxoG, one of the most abundant oxidative lesions in mtDNA [23]. This chemical selectivity means that even moderate increases in mitochondrial ROS production can disproportionately damage mtDNA, accelerating mutation accumulation.

The primary pathway responsible for repairing oxidative lesions in mtDNA is the base excision repair (BER) system, coordinated by mitochondrial glycosylases such as 8-oxoguanine DNA glycosylase 1 (OGG1), mutY DNA glycosylase homolog (MUTYH), and endonuclease VIII-like 1 (NEIL1). This process is followed by apurinic/apyrimidinic endonuclease 1 (APE1) processing, gap filling by DNA polymerase γ (POLG), and strand sealing by DNA ligase III [16,18]. Age-associated decline in BER enzyme expression contributes to progressive mtDNA instability and increased mutation load in tissues such as muscle, brain, and heart [14]. This age-dependent reduction in repair capacity means that even if ROS production remains constant, the balance shifts toward net accumulation of mtDNA damage over time.

Importantly, oxidative stress can also modify POLG itself, reducing its proofreading fidelity and impairing mtDNA replication accuracy [17,18]. This creates a reinforcing loop in which ROS damage mtDNA and simultaneously limits its accurate repair, a mechanism particularly relevant to understanding why aging tissues accumulate progressively more mtDNA mutations despite the presence of repair machinery. Thus, maintaining both the activity and structural integrity of POLG represents a critical target for interventions aimed at preserving mtDNA fidelity across the lifespan.

Mitochondrial transcription factor A (TFAM) plays essential roles in packaging mtDNA, maintaining nucleoid structure, and regulating transcription and replication [24]. Emerging evidence indicates that TFAM also participates in mtDNA quality control by binding damaged DNA and promoting degradation of severely compromised genomes through exonuclease-mediated pathways, preventing propagation of irreparable mutations [4]. These functions represent the canonical roles of TFAM in mtDNA maintenance. Beyond these canonical functions, TFAM regulates mtDNA copy number, influences nucleoid structure, and maintains the fidelity of mtDNA packaging. Changes in TFAM expression are associated with altered mitochondrial biogenesis and energy production capacity, making TFAM upregulation a key therapeutic objective in conditions characterized by mtDNA damage and impaired mitochondrial function [4,24]. Given its central role in coordinating multiple aspects of mtDNA homeostasis, TFAM has emerged as a key molecular target for nutritional and pharmacological interventions, as will be discussed in subsequent sections.

The accumulation of mtDNA damage across the lifespan has been proposed as a fundamental driver of aging and age-related pathologies [25]. In tissues with high metabolic demands (brain, heart, and skeletal muscle), mtDNA mutation burdens increase with age and correlate with declining mitochondrial function [26]. This is particularly evident in neurodegenerative diseases where elevated mtDNA damage, mutations, and deletions have been associated with neuronal loss and cognitive decline [27]. These tissue-specific patterns of mtDNA damage accumulation refer to differences in both the type and burden of lesions across organs. For example, post-mitotic tissues such as neurons and cardiomyocytes tend to accumulate higher levels of mtDNA deletions and oxidative lesions, whereas tissues with more active mitochondrial turnover exhibit distinct mutation spectra [3,4]. Such differences reflect not only local ROS production rates but also tissue-specific variation in mitochondrial repair capacity, mitophagy efficiency, and mtDNA turnover [3]. These mechanisms are schematically summarized in Fig. 2.

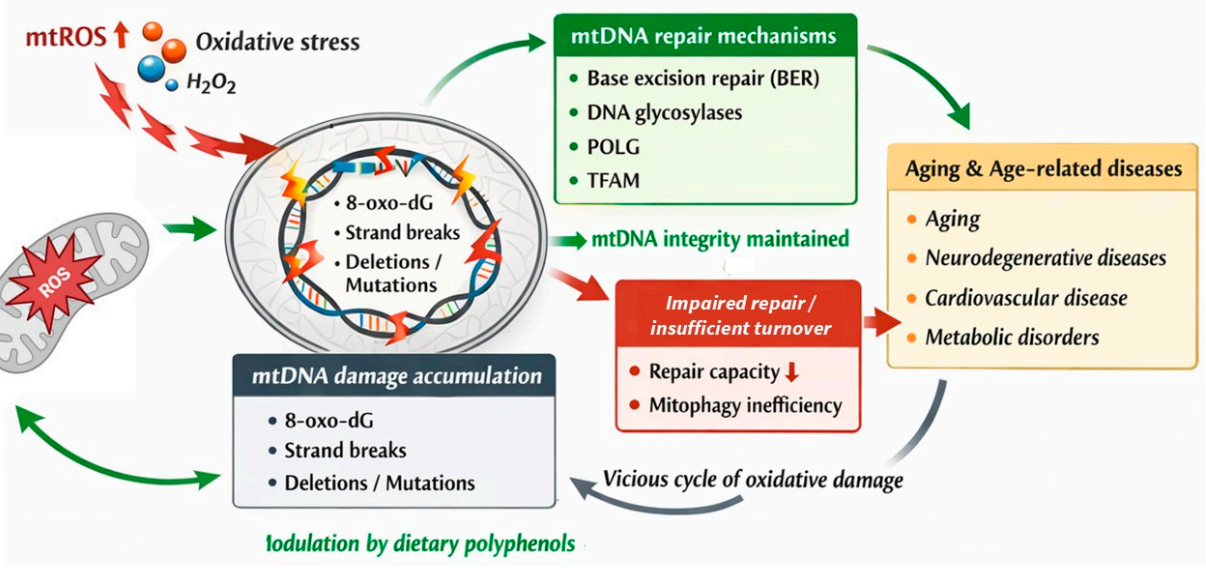

Figure 2: Mitochondrial reactive oxygen species-induced mtDNA damage and its contribution to aging and age-related diseases. Schematic overview illustrating how mitochondrial reactive oxygen species (mtROS), including hydrogen peroxide (H_2O_2), promote oxidative stress and induce mitochondrial DNA (mtDNA) damage. Accumulation of oxidative lesions such as 8-oxo-2′-deoxyguanosine (8-oxo-dG), strand breaks, deletions, and point mutations compromises mtDNA integrity and mitochondrial function. Under physiological conditions, mtDNA damage is counteracted by mitochondrial repair and maintenance mechanisms, including base excision repair (BER), DNA glycosylases, DNA polymerase γ (POLG), and mitochondrial transcription factor A (TFAM), which together preserve genome stability and support mitochondrial turnover. When repair capacity and mitophagy are insufficient, mtDNA damage accumulates, establishing a vicious cycle of oxidative stress and mitochondrial dysfunction. This progressive impairment contributes to aging and the development of age-related disorders, including neurodegenerative diseases, cardiovascular disease, and metabolic disorders. This figure was created by the authors using Microsoft PowerPoint for Microsoft 365 (Version 2409; Microsoft Corporation, Redmond, WA, USA) and graphical elements from BioRender.com.

The relationship between mtDNA integrity and metabolic homeostasis is equally compelling: tissues manifesting insulin resistance and impaired glucose tolerance frequently display reduced mtDNA copy number, increased heteroplasmy for pathogenic mtDNA variants, and decreased OXPHOS capacity [28]. These observations suggest that therapeutic interventions targeting mtDNA stability could yield benefits across multiple age-related conditions characterized by both mitochondrial dysfunction and metabolic decline. Against this backdrop of progressive mitochondrial genomic deterioration, polyphenolic compounds have emerged as promising agents capable of preserving mtDNA integrity through multiple complementary mechanisms, which we explore in the following sections. These interconnected mechanisms are schematically summarized in Fig. 3.

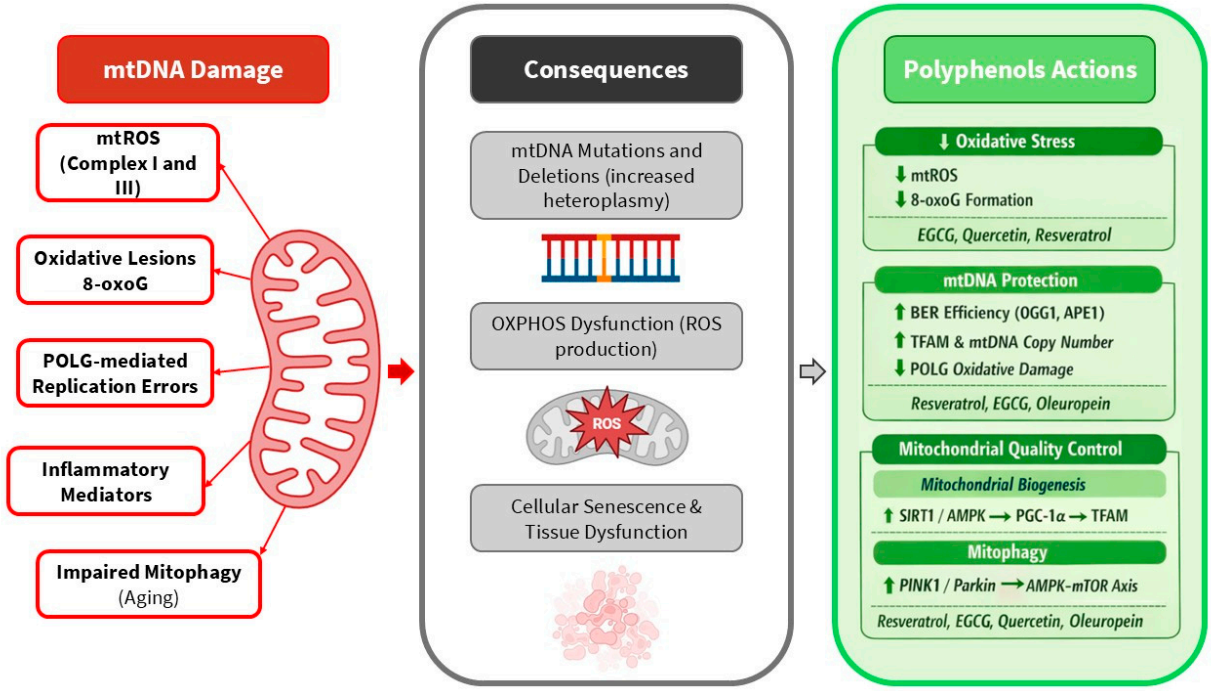

Figure 3: Causes and consequences of mitochondrial DNA damage and protective sites of action of dietary polyphenols. Schematic representation summarizing the main sources of mitochondrial DNA (mtDNA) damage, their downstream cellular consequences, and the protective mechanisms modulated by dietary polyphenols. Mitochondrial reactive oxygen species (mtROS) generated primarily at respiratory complexes I and III induce oxidative lesions such as 8-oxo-2′-deoxyguanosine (8-oxo-dG), replication errors mediated by DNA polymerase γ (POLG), and inflammatory signaling, which together contribute to mtDNA instability and impaired mitophagy during aging. Accumulation of mtDNA mutations and deletions increases heteroplasmy, leading to oxidative phosphorylation (OXPHOS) dysfunction, enhanced reactive oxygen species (ROS) production, cellular senescence, and tissue dysfunction. The right panel highlights the multi-level actions of dietary polyphenols, including epigallocatechin-3-gallate (EGCG), quercetin, resveratrol, and oleuropein. These compounds reduce oxidative stress by lowering mtROS levels and limiting oxidative base damage, enhance mtDNA protection through activation of base excision repair (BER) components and maintenance of mitochondrial DNA copy number, and support mitochondrial quality control by promoting mitochondrial biogenesis via sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK) signaling converging on peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) and mitochondrial transcription factor A (TFAM), as well as mitophagy through the PTEN-induced kinase 1 (PINK1)/Parkin axis. This figure was created by the authors using Microsoft PowerPoint for Microsoft 365 (Version 2409; Microsoft Corporation, Redmond, WA, USA) and graphical elements from BioRender.com.

3 Polyphenol-Mediated Protection of Mitochondrial DNA: Molecular Mechanisms

3.1 Direct ROS Scavenging at the Mitochondrial Level

Polyphenols exert protective effects partially through direct scavenging of ROS. Their phenolic hydroxyl groups participate in hydrogen atom transfer and electron transfer reactions that neutralize free radicals [22]. While this antioxidant activity represents only one facet of polyphenol bioactivity, it provides an important first line of defense against oxidative damage to mtDNA and mitochondrial proteins.

Epigallocatechin gallate (EGCG), the primary catechin in green tea, effectively reduces mitochondrial ROS in multiple *in vitro* models. In neuroblastoma and dopaminergic cell lines exposed to oxidative stress,

EGCG significantly decreased mitochondrial superoxide production and reduced accumulation of 8-oxoG in mtDNA [29]. Its multiple hydroxyl groups and gallate moiety confer both potent antioxidant activity and reported mitochondrial localization, understood as preferential activity within the mitochondrial microenvironment, allowing it to efficiently attenuate mitochondrial reactive oxygen species (mtROS) and support mitochondrial function under stress [30]. The structural features that enable EGCG's potent antioxidant activity, particularly the catechol moiety and the trihydroxyl arrangement on the B ring, provide a reference point for understanding structure-activity relationships among polyphenolic compounds [31].

Building upon these observations with EGCG, another well-characterized polyphenol, resveratrol, has demonstrated complementary mitochondrial antioxidant effects through somewhat different mechanisms. This stilbene, found in grapes and red wine, has demonstrated mitochondrial antioxidant effects by reducing superoxide formation and lipid peroxidation in neuronal and endothelial cell models subjected to oxidative injury [32,33]. These effects are partly attributed to improved mitochondrial membrane stability and enhanced ETC efficiency. Despite its simpler structure compared to EGCG, resveratrol's lipophilic character and capacity to activate SIRT1 enable significant mitochondrial effects that extend beyond simple radical scavenging [34,35]. The contrast between EGCG's multi-hydroxyl, hydrophilic structure and resveratrol's more lipophilic stilbene backbone illustrates how diverse chemical scaffolds can converge on similar protective outcomes through distinct molecular mechanisms.

Similarly, quercetin, a flavonol abundant in onions, apples, and berries, has been shown to suppress mitochondrial ROS formation and preserve mitochondrial membrane potential in endothelial and cardiac cells exposed to hydrogen peroxide, combining direct scavenging with activation of endogenous antioxidant pathways [36]. Quercetin's activity profile bridges the characteristics of both EGCG and resveratrol: like EGCG, it possesses multiple hydroxyl groups enabling robust radical scavenging; like resveratrol, it exhibits moderate lipophilicity, facilitating membrane penetration and interactions with lipid-soluble mitochondrial components.

Despite these documented antioxidant actions, direct scavenging is unlikely to account for the full range of mitochondrial benefits because polyphenols must overcome substantial barriers, including cellular uptake, mitochondrial transport, and competition with metabolic conjugation, before reaching mitochondrial ROS generation sites [22]. This limitation underscores the importance of understanding the non-antioxidant, signaling-based mechanisms through which polyphenols exert their mitochondrial protective effects, which we explore in the following subsections.

The chemical structures of the polyphenols discussed in this review are shown in Fig. 4.

3.2 Enhancement of mtDNA Repair: TFAM, BER Enzymes, and POLG Protection

Beyond direct ROS scavenging, polyphenols also modulate mtDNA repair processes by enhancing BER enzyme expression, promoting TFAM function, and supporting mtDNA maintenance pathways. These effects represent a more fundamental level of mitochondrial protection by addressing the repair and replication machinery itself rather than merely neutralizing oxidative damage.

Resveratrol has been shown to increase TFAM expression through SIRT1-PGC-1α activation, resulting in improved mtDNA copy number and reduced oxidative damage in skeletal muscle and neuronal tissues [37]. In aged rodents, resveratrol supplementation restored TFAM levels and enhanced expression of POLG and mitochondrial ribosomal proteins, contributing to improved mitochondrial integrity [37,38]. This multi-target effect highlights why resveratrol has emerged as a lead compound in mitochondrial-targeted nutrition research: rather than acting on a single pathway, it coordinates upregulation of multiple components of the mtDNA maintenance machinery. The downstream consequences of SIRT1 activation extend well beyond TFAM

upregulation alone, encompassing enhanced expression of nuclear-encoded mitochondrial proteins, improved mitochondrial biogenesis, and coordinated enhancement of antioxidant defenses [2].

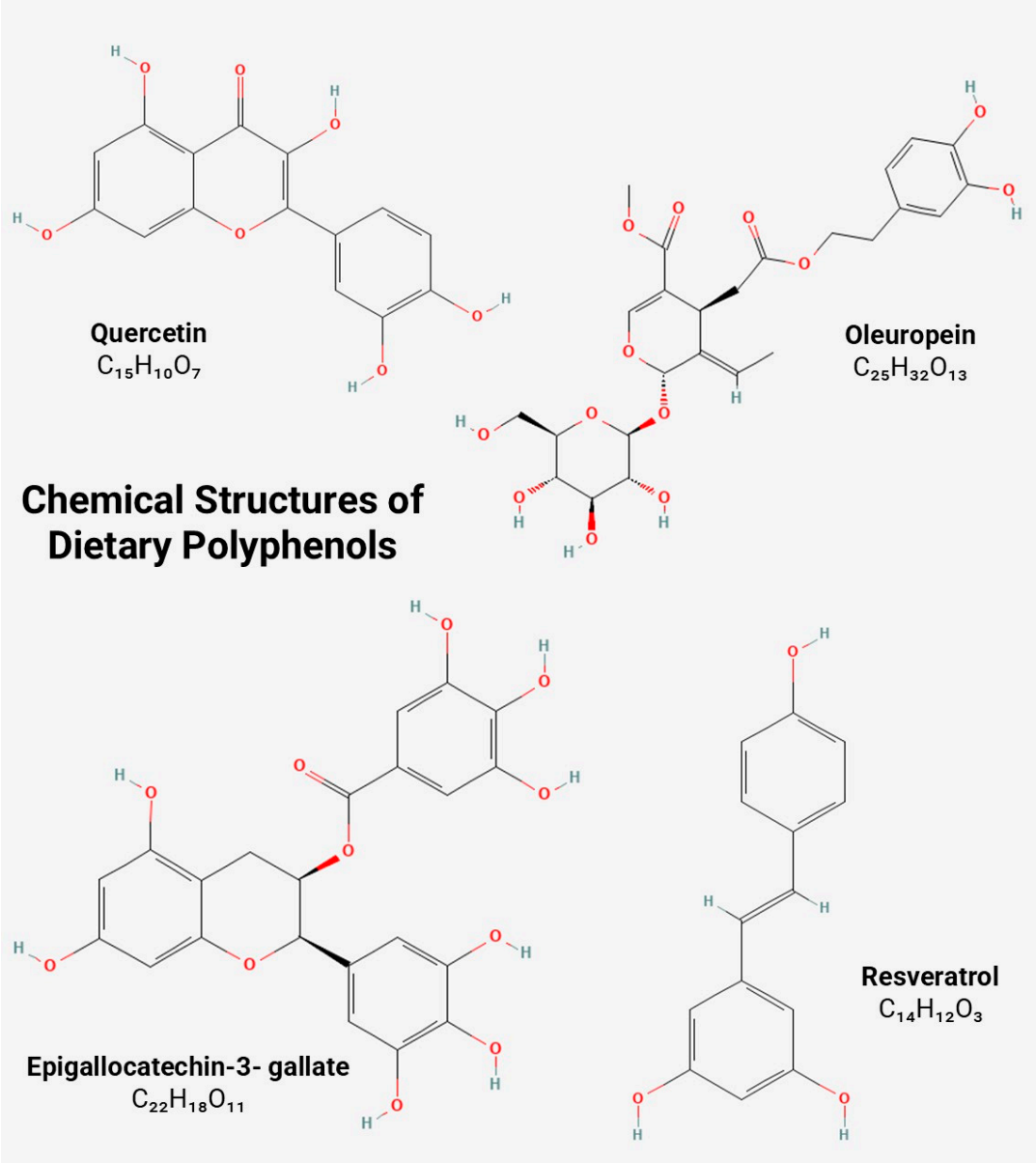

Figure 4: Chemical structures of dietary polyphenols. Chemical structures and molecular formulas of epigallocatechin-3-gallate, resveratrol, quercetin, and oleuropein. Structures were created by the authors using BioRender, based on standard chemical information from PubChem.

Complementing resveratrol's SIRT1-mediated effects, green tea catechins, including EGCG, have been reported to preserve nucleoid architecture and stabilize TFAM-mtDNA interactions under oxidative stress conditions, thereby reducing mtDNA fragmentation and maintaining replication fidelity [39]. By stabilizing the TFAM-mtDNA complex, EGCG preserves the structural organization essential for accurate mtDNA replication and transcription [40]. This stabilization effect is mechanistically distinct from resveratrol's transcriptional upregulation of TFAM: whereas resveratrol increases TFAM protein abundance, EGCG

enhances the functional interactions between existing TFAM molecules and mtDNA [40]. Together, these complementary mechanisms suggest potential synergistic benefits from combined polyphenol interventions targeting both TFAM expression and TFAM-mtDNA binding stability.

Another Mediterranean dietary polyphenol, oleuropein, the principal polyphenol in olive leaves and extra virgin olive oil, has demonstrated protective effects on mitochondrial biogenesis and mtDNA maintenance in experimental models of aging and metabolic stress. Oleuropein upregulated PGC-1α, Nuclear factor erythroid 2-related factor 1 (NRF1), and TFAM expression in cardiac and skeletal muscle cells, leading to increased mtDNA content and improved mitochondrial function [41–43]. Mediterranean dietary patterns, rich in oleuropein-containing olive products, have been epidemiologically associated with improved aging outcomes, suggesting that this polyphenol may contribute to these population-level health benefits [44,45]. The convergence of mechanistic data (showing oleuropein's effects on mtDNA maintenance) with epidemiological observations (linking Mediterranean diet adherence to healthy aging) provides compelling translational evidence for the clinical relevance of these molecular mechanisms.

Although direct protection of POLG by polyphenols has not been clearly demonstrated in purified enzyme assays, polyphenol-enhanced antioxidant capacity indirectly reduces oxidative modifications of POLG and supports more accurate mtDNA replication [46,47]. This indirect mechanism underscores an important principle: polyphenol effects on mitochondrial health often arise from systemic improvements in redox balance and cellular energetics rather than direct protein-polyphenol interactions. Consequently, the clinical benefits of polyphenol supplementation may manifest gradually as improved redox homeostasis enables more faithful mtDNA replication over multiple mitochondrial generations.

3.3 Activation of Mitochondrial Biogenesis Pathways: PGC-1α, SIRT1, AMPK

Beyond repair of existing mtDNA damage, polyphenols are potent activators of mitochondrial biogenesis, the coordinated synthesis of new mitochondrial components, including mtDNA, respiratory chain proteins, and membrane lipids. This represents a complementary strategy to direct mtDNA repair: by expanding the population of newly synthesized, undamaged mitochondria, biogenesis can effectively dilute the proportion of mitochondria harboring damaged mtDNA.

Resveratrol is widely recognized as a potent activator of SIRT1, a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase. SIRT1 activation by resveratrol leads to the deacetylation and activation of PGC-1α, a master regulator of mitochondrial biogenesis. Activated PGC-1α upregulates downstream transcription factors, including nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 (NRF2), and TFAM, which are essential for mitochondrial DNA replication, transcription, and overall mitochondrial function [48–50]. Evidence from experimental models and human studies suggests that resveratrol supplementation may enhance mitochondrial content and function [51–53]. In cellular and preclinical settings, resveratrol has been shown to improve mitochondrial density and respiratory capacity, partly through the preservation of mitochondrial integrity under oxidative stress conditions [51]. In humans, resveratrol supplementation has been associated with increased mitochondrial number and improvements in mitochondrial-related metabolic parameters, although effects on functional outcomes appear to be context-dependent [52,53]. The mechanistic elegance of this pathway lies in its coordination: a single upstream signal (SIRT1 activation) triggers a coordinated transcriptional program that simultaneously increases mtDNA replication capacity (via TFAM) [54], nuclear-encoded mitochondrial protein synthesis (via NRF1/2) [55], and mitochondrial import machinery, ensuring that all components necessary for functional mitochondria are upregulated in concert [2].

While resveratrol primarily signals through SIRT1, EGCG activates mitochondrial biogenesis primarily through AMPK phosphorylation, which increases NAD^+ levels and indirectly stimulates SIRT1-PGC-1α signaling [56–58]. In skeletal muscle and cardiac models, EGCG upregulated oxidative phosphorylation genes and improved mitochondrial respiration [59,60]. AMPK serves as a cellular energy sensor, and its activation by polyphenols links improved energy availability to mitochondrial expansion and mtDNA replication [61]. This creates a positive feedback loop: AMPK activation promotes mitochondrial biogenesis, which enhances ATP production capacity [62], which in turn supports the energy-demanding processes of mitochondrial quality control and cellular repair. The mechanistic overlap between EGCG's AMPK activation and resveratrol's SIRT1 activation, both converging on PGC-1α, suggests that these polyphenols might exhibit synergistic effects when co-administered.

Complementing the SIRT1 and AMPK pathways discussed above, quercetin induces mitochondrial biogenesis partly through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling [63], which upregulates antioxidant enzymes and enhances mitochondrial gene expression. In endurance-trained humans, quercetin supplementation increased mitochondrial biogenesis markers, although functional benefits were modest [63,64]. The relatively modest effects observed in human studies may reflect quercetin's lower bioavailability compared to resveratrol or EGCG, or may indicate that Nrf2-mediated biogenesis is less robust than SIRT1/AMPK-mediated pathways in driving quantitative mitochondrial expansion. Nevertheless, quercetin's ability to enhance endogenous antioxidant capacity through Nrf2 activation complements the biogenesis-promoting effects of other polyphenols, suggesting potential value in multi-polyphenol combinations.

The strategic importance of polyphenol-induced mitochondrial biogenesis is that it supports mtDNA integrity by generating a population of newly synthesized, undamaged mtDNA copies, diluting the relative proportion of mutated genomes. In cells with existing high heteroplasmy for deleterious mtDNA variants, enhanced biogenesis can shift the balance toward functional mitochondrial populations, partially compensating for pre-existing mtDNA damage as increasing mtDNA copy number and mitochondrial turnover have been associated with buffering against heteroplasmy-driven dysfunction [8] and potentially lowering the proportion of deleterious genomes below pathogenic thresholds [13,65]. This mechanism is particularly relevant in aging tissues where repair capacity may be compromised, but biosynthetic capacity remains partially intact, allowing biogenesis-promoting interventions to restore mitochondrial function even when repair pathways are impaired.

3.4 Polyphenols and Mitophagy: Selective Removal of Damaged Mitochondria

While the preceding sections have focused on preventing mtDNA damage and promoting repair or dilution through biogenesis, mitophagy represents a complementary quality control mechanism: the selective removal of dysfunctional or depolarized mitochondria, particularly those harbouring extensive mtDNA damage [3]. This process prevents the accumulation of defective organelles capable of generating excessive ROS, propagating mutant mtDNA, or impairing oxidative phosphorylation [3]. In recent years, an increasing number of studies have demonstrated that dietary polyphenols act as potent modulators of mitophagy, stimulating the turnover of damaged mitochondria through well-defined molecular pathways.

Extending its effects on biogenesis described above, resveratrol has also been widely studied for its ability to enhance mitophagic clearance of damaged mitochondria [66]. Resveratrol increases the expression of PTEN-induced kinase 1 (PINK1) and Parkin [67], two key regulators of the canonical mitophagy pathway, in neuronal [68], hepatic [69], and cardiac [70] models. By enhancing the stabilization of PINK1 on the outer mitochondrial membrane and promoting Parkin-mediated ubiquitination of damaged mitochondria [71],

resveratrol facilitates their recognition and engulfment by autophagosomes, leading to efficient clearance and replacement with newly generated organelles [72]. This mechanism is particularly important in tissues accumulating mtDNA-deficient mitochondria with age. The dual capacity of resveratrol to both promote mitochondrial biogenesis (via SIRT1-PGC-1α) [73] and enhance mitophagy (via PINK1/Parkin) [72] creates a coordinated quality control system: damaged mitochondria are removed while new, functional mitochondria are synthesized, ensuring maintenance of a healthy mitochondrial pool.

Similar to its role in promoting biogenesis, EGCG exerts pronounced effects on autophagy-mitophagy flux primarily through activation of AMPK [74] and inhibition of the mammalian target of rapamycin pathway [75], two master regulators of cellular energy sensing and autophagic induction. Through AMPK activation, EGCG increases the recruitment of autophagy-related proteins to damaged mitochondria, promotes autophagosome formation, and enhances lysosomal degradation, ultimately reducing the burden of dysfunctional mitochondria and lowering cellular oxidative stress [76]. These effects have been documented in cardiac [77], skeletal muscle [78], and neuronal cells [79] exposed to various oxidative stressors, indicating that EGCG acts across several tissues with metabolic or oxidative vulnerability. The mechanistic parallel between EGCG's effects on biogenesis and mitophagy, both mediated through AMPK, illustrates how a single upstream signaling node can coordinate multiple aspects of mitochondrial quality control.

Consistent with its effects on repair and biogenesis pathways discussed earlier, oleuropein also contributes to mitochondrial quality control by activating both AMPK and SIRT1 pathways [41], thereby promoting the elimination of mitochondria with impaired membrane potential or extensive mtDNA lesions. The stimulation of SIRT1-mediated deacetylation pathways not only enhances autophagic competence but also improves mitochondrial turnover, especially in conditions associated with aging or chronic oxidative stress [80]. Through these combined actions, oleuropein helps to maintain a healthy mitochondrial population capable of sustaining cellular energy requirements and preventing mtDNA mutant propagation. The convergence of multiple polyphenols (resveratrol, EGCG, oleuropein) on overlapping mitophagy pathways suggests that dietary patterns incorporating diverse polyphenol sources may provide more comprehensive mitochondrial protection than single-compound supplementation.

Altogether, by activating multiple signaling pathways that converge on mitophagy, polyphenols ensure that cells retain a functional mitochondrial pool and limit propagation of mtDNA defects across generations of mitochondria. This mechanism aligns with and complements the repair and biogenesis effects described in previous sections, illustrating how polyphenols coordinate multiple facets of mitochondrial quality control to preserve mtDNA integrity.

These interconnected mechanisms are summarized in Fig. 5, which provides an integrative overview of the effects of polyphenols on mtDNA repair, mitochondrial biogenesis, and mitophagy.

Integrative Comparison of Polyphenol-Mediated Mechanisms Regulating Mitochondrial Quality Control

The mechanistic evidence summarized in the preceding sections indicates that major dietary polyphenols, including resveratrol, EGCG, quercetin, and oleuropein, converge on a conserved set of regulatory pathways governing mitochondrial quality control, while differing in their relative emphasis on mitochondrial biogenesis, redox modulation, and mitophagy. A shared mechanistic core involves activation of upstream metabolic sensors such as SIRT1 and AMPK, which subsequently converge on PGC-1α to promote mitochondrial biogenesis and support mtDNA transcription and replication through downstream TFAM [24,54]. This coordinated regulation of mitochondrial gene expression and turnover underlies many of the protective effects of polyphenols on mitochondrial homeostasis across tissues [3,55]. An integrative comparison of these compound-specific mechanisms is provided in Table 1.

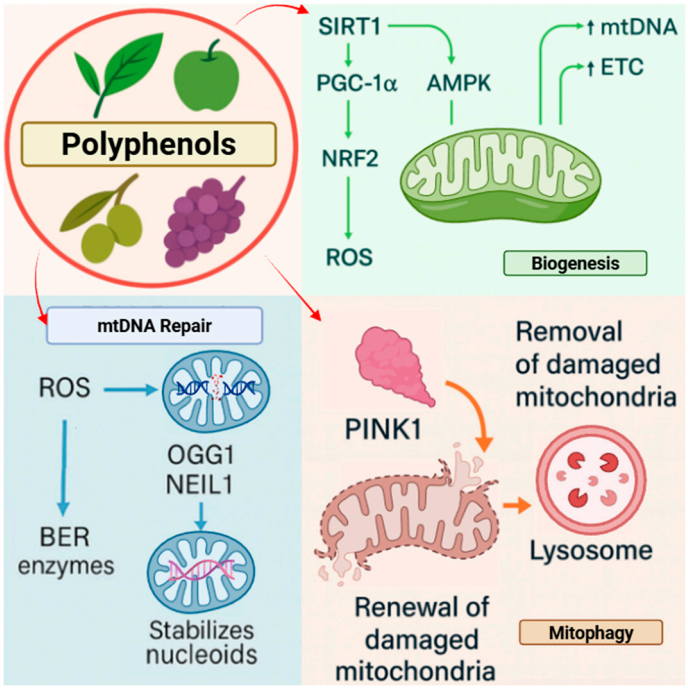

Figure 5: Overview of the mitochondrial pathways modulated by dietary polyphenols. Schematic overview illustrating the main mitochondrial pathways targeted by dietary polyphenols and their coordinated role in maintaining mitochondrial quality control. Polyphenols activate key metabolic and stress-responsive signaling pathways, including sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK), which converge on peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) to promote mitochondrial biogenesis, increase mitochondrial DNA (mtDNA) copy number, and enhance electron transport chain (ETC) capacity. In parallel, polyphenols modulate redox homeostasis through nuclear factor erythroid 2-related factor 2 (NRF2) signaling, contributing to the reduction of reactive oxygen species (ROS). The figure also depicts the contribution of polyphenols to mtDNA maintenance by supporting base excision repair (BER) pathways, including the activity of DNA glycosylases such as 8-oxoguanine DNA glycosylase (OGG1) and Nei-like DNA glycosylase 1 (NEIL1), thereby limiting oxidative lesions and stabilizing mitochondrial nucleoids. Additionally, polyphenols facilitate mitochondrial turnover by promoting mitophagy through the PTEN-induced kinase 1 (PINK1)-dependent pathway, enabling the selective removal of damaged mitochondria and renewal of the mitochondrial network. This figure was created by the authors using Microsoft PowerPoint for Microsoft 365 (Version 2409; Microsoft Corporation, Redmond, WA, USA) and graphical elements from BioRender.com.

Within this shared framework, compound-specific differences are evident. Resveratrol predominantly activates the SIRT1-PGC-1α axis, thereby linking NAD^+-dependent deacetylation to transcriptional programs supporting mitochondrial biogenesis and oxidative metabolism [48–50]. In parallel, resveratrol has been consistently shown to enhance PINK1/Parkin-dependent mitophagy, effectively coupling mitochondrial renewal with selective removal of dysfunctional organelles in neuronal, hepatic, and cardiac models [67,72].

EGCG primarily signals through AMPK activation, connecting improvements in mitochondrial redox balance with stimulation of mitochondrial biogenesis and autophagy-mitophagy pathways in a dose- and context-dependent manner [56,58]. Its pronounced antioxidant capacity further contributes to the reduction of mitochondrial oxidative damage and preservation of mitochondrial membrane potential, reinforcing mitochondrial functional stability under stress conditions [39,40].

Quercetin exhibits a broader mechanistic profile, combining activation of PGC-1α-dependent mitochondrial biogenesis with engagement of endogenous antioxidant pathways, including Nrf2-associated

signaling [36,81]. In hepatic and neurodegenerative models, quercetin robustly activates PINK1/Parkin-mediated mitophagy, highlighting a prominent role for mitochondrial clearance in its protective effects on mitochondrial quality control [82,83].

Oleuropein and related olive phenolics activate both AMPK- and SIRT1-associated pathways, promoting mitochondrial biogenesis, improving mitochondrial calcium handling, and reducing mitochondrial reactive oxygen species accumulation [43,84,85]. Although direct evidence for PINK1/Parkin-dependent mitophagy remains more limited for oleuropein compared with resveratrol or quercetin, available data support its role in enhancing mitochondrial turnover and resilience under metabolic and age-related stress [41,45].

Collectively, these findings indicate that dietary polyphenols do not operate through a single uniform mechanism but instead engage overlapping yet hierarchically distinct signaling pathways integrating mitochondrial biogenesis, redox homeostasis, and mitophagy. This mechanistic integration provides a coherent framework to explain how structurally diverse polyphenols exert convergent protective effects on mtDNA integrity and mitochondrial function.

Table 1: Comparative mechanisms of action of major dietary polyphenols on mitochondrial quality control pathways.

Polyphenol	Main Molecular Targets	Effects on Mitochondrial Biogenesis	Evidence on Mitophagy	Antioxidant/Redox Effects	References
Resveratrol	SIRT1, AMPK, PGC-1α	Induces mitochondrial biogenesis via SIRT1-PGC-1α-TFAM signaling	Consistent activation of PINK1/Parkin-mediated mitophagy in neuronal, hepatic and cardiac models	Reduces mtROS and improves ETC efficiency	[34,50,66,67]
EGCG	AMPK, redox-sensitive pathways	Stimulates mitochondrial biogenesis primarily through AMPK-dependent mechanisms	Indirect induction of autophagy-mitophagy, highly context- and dose-dependent	Potent direct ROS scavenging and preservation of mitochondrial membrane potential	[30,39,56,86]
Quercetin	PGC-1α, Nrf2, PPARγ	Promotes mitochondrial biogenesis in brain, liver and skeletal muscle models	Robust PINK1/Parkin activation, including frataxin-dependent mechanisms	Activates endogenous antioxidant defense systems	[36,82,83,87]
Oleuropein	AMPK, SIRT1, Ca^{2+} handling pathways	Enhances mitochondrial biogenesis and metabolic flexibility	Limited direct evidence supports mitochondrial turnover indirectly	Reduces mitochondrial ROS and improves calcium uptake	[41,43,84,85]

Note: AMPK, AMP-activated protein kinase; ETC, electron transport chain; EGCG, epigallocatechin gallate; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin-1; TFAM, mitochondrial transcription factor A.

To address the translational relevance of these compounds, Table 2 summarizes the main dietary sources and biological applications of the polyphenols discussed, complementing the mechanistic comparison presented above.

Table 2: Dietary sources and biological applications of major polyphenols involved in mitochondrial quality control.

Polyphenol	Main Dietary Sources	Primary Target Tissues/Systems	Main Biological and Clinical Applications	References
Resveratrol	Grapes, red wine, berries, peanuts	Vascular endothelium, liver, skeletal muscle, brain	Cardiometabolic health, endothelial dysfunction, NAFLD, neurodegenerative disorders, aging-related mitochondrial decline	[48–50,73,88–93]

Table 2: *Cont.*

Polyphenol	Main Dietary Sources	Primary Target Tissues/Systems	Main Biological and Clinical Applications	References
Epigallocatechin-3-gallate	Green tea	Liver, cardiovascular system, adipose tissue, brain	NAFLD, dyslipidaemia, endothelial dysfunction, metabolic disorders associated with oxidative stress	[39,56–58,94–97]
Quercetin	Onions, apples, berries, tea	Liver, vascular endothelium, brain, skeletal muscle	NAFLD, hypertension, vascular dysfunction, neurodegenerative diseases	[81–83,87,98–101]
Oleuropein	Olive leaves, extra virgin olive oil	Cardiovascular system, skeletal muscle, metabolic tissues	Hypertension, cardiometabolic risk reduction, metabolic aging	[41,43,45,84,102–104]

Note: NAFLD, non-alcoholic fatty liver disease.

3.5 Polyphenols as Mitochondrial Uncoupling Agents

Beyond their established roles in antioxidant defense, mitochondrial biogenesis, and mitophagy, an additional mechanism through which dietary polyphenols may modulate mitochondrial function is mild mitochondrial uncoupling. Mitochondrial uncoupling refers to a partial dissipation of the proton gradient across the inner mitochondrial membrane, leading to reduced coupling efficiency between electron transport and ATP synthesis and to a lower mitochondrial membrane potential ($\Delta\Psi m$) [105].

Importantly, while excessive uncoupling is energetically detrimental, a modest or regulated increase in proton leak has been proposed as an adaptive mechanism that reduces mtROS formation by limiting electron backpressure at the respiratory chain [21]. This concept is consistent with the framework of mitohormesis, whereby mild mitochondrial stress triggers adaptive responses that ultimately improve mitochondrial resilience and cellular homeostasis [21].

From a mechanistic perspective, several dietary polyphenols possess physicochemical properties that allow them to interact with the inner mitochondrial membrane and modulate proton conductance, acting as weak uncouplers rather than classical protonophores [22,105]. These compounds can facilitate proton cycling or alter membrane fluidity and redox state, resulting in small reductions in $\Delta\Psi m$ that are sufficient to lower mtROS generation without collapsing ATP production [105,106].

In the case of resveratrol, evidence supporting uncoupling-like bioenergetic modulation includes reports of mitochondrial membrane potential depolarization in human cellular models, alongside mitochondrial functional adaptations [107]. In parallel, mechanistic work shows that resveratrol can directly modulate mitochondrial respiratory chain function (e.g., via complex I/NADH oxidation), which provides a plausible bioenergetic basis for shifts in $\Delta\Psi m$ and redox pressure, even when not framed as "uncoupling" per se [108].

Similarly, for EGCG, experimental literature supports mitochondrial modulation through pathways that intersect with uncoupling biology, including regulation of uncoupling protein-2 (UCP2) in liver-injury models [109]. Because UCPs can contribute to proton leak and $\Delta\Psi m$ modulation, these observations provide mechanistic support for the view that EGCG may influence coupling efficiency under stress conditions, although the magnitude and direction of effect are context-dependent [109]. Consistent with mitochondria-centric syntheses, catechins are frequently discussed as modulators of OXPHOS/$\Delta\Psi m$ with potential downstream implications for mtROS [106].

In contrast, for quercetin, mitochondrial effects are predominantly discussed in the context of redox signaling and regulation of mitochondrial apoptosis pathways. The literature reports preservation of mitochondrial membrane potential under stress conditions, linked to inhibition of mPTP opening

and reduced oxidative burden, rather than direct bioenergetic uncoupling. Accordingly, quercetin may be discussed cautiously in relation to membrane-potential-associated mitochondrial regulation, while emphasizing that classification as a mitochondrial uncoupler would require dedicated proton-leak and respiratory measurements [110].

A comparable level of caution applies to olive-derived phenolics. Experimental evidence shows that oleuropein suppresses mitochondrial ROS generation in cell models through signaling pathways involving TRPV1, SIRT1, and upregulation of uncoupling protein expression, thereby limiting conditions that favor excessive mitochondrial superoxide formation under high membrane potential states [111]. Related review on olive polyphenols consistently describes mitochondrial protective effects, including redox regulation, preservation of mitochondrial function, and stabilization of membrane potential under stress [112]. These actions can therefore be discussed as compatible with preventing excessive ΔΨm-driven mtROS generation, while avoiding classification as direct mitochondrial uncoupling in the absence of dedicated proton-leak measurements.

Taken together, current evidence supports the inclusion of mild uncoupling-like bioenergetic modulation as a complementary mechanism in polyphenol-mediated mitochondrial quality control, particularly through regulated ΔΨm changes and mtROS reduction [106]. However, the strength of evidence differs among compounds, and claims of "uncoupling" should be framed conservatively unless proton-leak assays and coupling-efficiency measurements are explicitly reported [105].

3.6 Preclinical Evidence for Polyphenol-Mediated Mitochondrial Protection

A growing number of preclinical studies [81,113] and systematic reviews [20,114,115] converge on the conclusion that polyphenols exert mitochondrial protection through a complex interplay of mechanisms that go well beyond simple antioxidant effects. These mechanisms include attenuation of ROS production, enhancement of mtDNA repair pathways, upregulation of key regulatory proteins such as TFAM and POLG, stimulation of mitochondrial biogenesis, and activation of mitophagy to remove damaged organelles. Such coordinated engagement of multiple mitochondrial defense systems is particularly relevant in conditions of chronic oxidative stress, where preserving mtDNA integrity is essential for maintaining respiratory capacity and preventing accumulation of mutations.

3.6.1 Resveratrol

Resveratrol is one of the best-characterized polyphenols in terms of mitochondrial regulation. Preclinical evidence indicates that dietary resveratrol supplementation enhances aerobic capacity and promotes a shift toward oxidative muscle fiber composition, together with the up-regulation of genes involved in oxidative phosphorylation and mitochondrial biogenesis in skeletal muscle [73]. In parallel, resveratrol has been reported to increase mitochondrial oxidative capacity and activate metabolically active tissues such as brown adipose tissue, further supporting its role in promoting systemic oxidative metabolism [116]. These mitochondrial adaptations were associated with protection against diet-induced obesity and insulin resistance, and mechanistically linked to activation of SIRT1 and deacetylation of the transcriptional coactivator PGC-1α, which in turn induced downstream nuclear respiratory factors and TFAM. The study provided direct *in vivo* evidence that resveratrol can drive a coordinated mitochondrial biogenesis program and improve whole-body metabolic health.

Recent work corroborates these findings: resveratrol has been shown to improve mitochondrial biogenesis and function by activating PGC-1α via SIRT1/PGC-1α signaling in rodent models of metabolic injury [49]. In addition, resveratrol supplementation enhances mitochondrial energy metabolism and

increases the activity of mitochondrial enzymes such as succinate dehydrogenase and citrate synthase in skeletal muscle, consistent with improved oxidative capacity [117]. Complementary work by Price et al. in mice and cultured cells confirmed that SIRT1 is required for the ability of moderate doses of resveratrol to activate AMPK, increase mitochondrial content, and improve mitochondrial respiration, thus placing AMPK upstream or in parallel with SIRT1 in the control of mitochondrial function by resveratrol [73].

Beyond biogenesis, resveratrol also modulates mitochondrial quality control through mitophagy. In a long-term study in mdx mice, a model of Duchenne muscular dystrophy–associated cardiomyopathy, Kuno et al. [88] administered resveratrol chronically (0.4 g/kg food for 56 weeks) and observed a marked improvement in cardiac function, accompanied by reduced mitochondrial DNA deletions, lower mitochondrial ROS levels, and a decrease in the number of mitochondria-containing autophagosomes. Resveratrol induced nuclear accumulation of FoxO3a and up-regulated several autophagy- and mitophagy-related genes, indicating restoration of impaired mitophagy and autophagic flux in dystrophic hearts. Together, these preclinical studies support the view that resveratrol coordinates mitochondrial biogenesis (via SIRT1/AMPK-PGC-1α-NRF1/TFAM signaling) with mitophagy-mediated clearance of damaged mitochondria, thereby improving mitochondrial network quality under metabolic and myopathic stress.

3.6.2 Epigallocatechin-3-Gallate (EGCG)

EGCG, the major catechin in green tea, also exerts consistent mitochondrial effects. In a diet-induced obesity model, Lee et al. [58] fed C57BL/6 mice a high-fat diet with or without 0.2% (w/w) EGCG for 8 weeks. EGCG supplementation reduced body-weight gain and plasma triglycerides, increased core body temperature, and significantly elevated mitochondrial DNA content and the expression of genes related to thermogenesis and mitochondrial biogenesis in brown adipose tissue, including PGC-1α, nuclear respiratory factors, and uncoupling protein-1. These changes were accompanied by increased AMPK phosphorylation, suggesting that EGCG activates an AMPK-PGC-1α axis to stimulate mitochondrial biogenesis and thermogenic capacity *in vivo*.

In a complementary *in vitro* study, the same group [118] investigated whether EGCG directly regulates PGC-1α gene expression in hepatocytes (HepG2) and 3T3-L1 adipocytes. Treatment with EGCG for 24 h increased PGC-1α mRNA levels in a dose-dependent manner, with 10 μM EGCG producing a significant up-regulation. Using a luciferase reporter containing the −970/+412 bp region of the PGC-1α promoter, they demonstrated that EGCG also enhanced promoter activity at similar concentrations, indicating transcriptional activation of PGC-1α. These data suggest that EGCG can promote mitochondrial biogenesis by directly inducing PGC-1α transcription in metabolic tissues.

Although fewer mechanistic studies explicitly quantify mitophagy, the AMPK activation consistently observed in EGCG-treated cells and tissues is tightly linked to autophagy and mitophagy pathways in other contexts. Reviews of flavonoid actions highlight that EGCG accumulates in mitochondria, modulates mitochondrial ROS production, and may trigger mitophagy under certain stress conditions, thereby contributing to mitochondrial quality control [119]. Overall, preclinical evidence indicates that EGCG acts as a mitochondrial biogenesis enhancer via AMPK- and PGC-1α-dependent signaling, while its impact on mitophagy appears context- and dose-dependent and is still less systematically quantified than that of resveratrol.

3.6.3 Quercetin

Quercetin displays a broad spectrum of mitochondrial actions, supported by both biogenesis-focused and mitophagy-focused preclinical studies. In a pivotal experiment, Davis et al. [87] administered quercetin

orally to mice (12.5 or 25 mg/kg/day for 7 days) and showed that supplementation increased markers of mitochondrial biogenesis in both skeletal muscle and brain, including PGC-1α and cytochrome c, and elevated citrate synthase activity. These mitochondrial changes were accompanied by a significant improvement in endurance exercise tolerance, demonstrating a functional impact of quercetin-induced mitochondrial biogenesis.

In a traumatic brain injury model (TBI), Li et al. [81] treated mice with quercetin after experimental TBI and evaluated mitochondrial outcomes in the injured brain. Quercetin administration up-regulated PGC-1α expression, restored cytochrome c levels, improved mitochondrial respiratory chain function, reduced malondialdehyde, and increased superoxide dismutase activity, indicating reduced oxidative damage and enhanced mitochondrial antioxidant defense. The authors concluded that quercetin protects against mitochondrial dysfunction after TBI by stimulating mitochondrial biogenesis through the PGC-1α pathway and alleviating oxidative stress.

Quercetin also has one of the clearest preclinical datasets linking a dietary polyphenol to mitophagy. In a high-fat diet-induced non-alcoholic fatty liver disease model, Liu et al. [82] fed mice a high-fat diet for 10 weeks with or without quercetin. Quercetin alleviated hepatic steatosis, improved liver histology, and reduced triglyceride accumulation. Mechanistically, quercetin increased frataxin expression and activated PINK1/Parkin-dependent mitophagy, as shown by elevated PINK1 and Parkin levels, increased LC3-II and autophagosome formation, and enhanced co-localization of mitochondria with autophagosomes. Inhibition of frataxin or mitophagy blunted these protective effects, demonstrating that quercetin counteracts steatosis by promoting frataxin-mediated mitophagy and improving mitochondrial quality control in hepatocytes.

Further support comes from models of Parkinson's disease and acute liver injury. In a 6-hydroxydopamine-induced Parkinson's disease model, Wang et al. [83] showed that quercetin improved motor behavior, reduced dopaminergic neuron loss, and restored mitochondrial structure, while increasing PINK1 and Parkin expression and normalizing mitophagy flux, effects that were interpreted as an improvement in mitochondrial quality control in the nigrostriatal system. In acute liver failure, Wu et al. [120] reported that quercetin targeted the PPARγ/PGC-1α/NF-κB axis, modulated excessive mitophagy, reduced hepatocyte apoptosis, and dampened inflammatory responses, suggesting that fine-tuning mitophagy is essential to balance cytoprotection and cell death in hepatic injury.

Collectively, these studies indicate that quercetin not only induces mitochondrial biogenesis (PGC-1α-dependent) but also recalibrates mitophagy (PINK1/Parkin and related pathways) in liver, brain, and other organs, thereby supporting mitochondrial quality control in diverse stress settings.

3.6.4 Oleuropein

Oleuropein, a major secoiridoid derivative abundant in olive leaves and extra virgin olive oil, has been less extensively studied than resveratrol or quercetin, but available preclinical data support a meaningful impact on mitochondrial quality. Kikusato et al. [43] examined the effects of oleuropein on cultured avian muscle cells, focusing on mitochondrial genes and ROS production. Cells treated with oleuropein showed increased expression of avian uncoupling protein and manganese superoxide dismutase, along with up-regulation of PGC-1α. Functionally, oleuropein suppressed superoxide generation per mitochondrion, indicating improved mitochondrial efficiency and enhanced antioxidant capacity at the organelle level. The authors concluded that oleuropein induces mitochondrial biogenesis and decreases ROS generation in muscle cells, possibly via PGC-1α-mediated signaling.

A recent review of olive phenolic compounds summarizes additional preclinical work showing that oleuropein-rich extracts preserve mitochondrial membrane potential, improve oxidative phosphorylation,

and reduce oxidative stress in models of cardiometabolic and neurodegenerative disease [84]. The studies included in this review often report activation of AMPK and SIRT1, increased PGC-1α expression, and improvements in mitochondrial respiration and ATP production, consistent with stimulation of mitochondrial biogenesis and enhanced resistance to oxidative injury [84]. Although direct measurements of mitophagy with oleuropein are relatively scarce, experimental data indicate modulation of autophagy/mitophagy markers and improved mitochondrial turnover in liver and muscle, suggesting that oleuropein may coordinate AMPK/SIRT1-PGC-1α-driven mitochondrial biogenesis with reduced mitochondrial ROS and improved turnover in metabolically challenged tissues.

3.7 Clinical Evidence for Polyphenol-Mediated Mitochondrial Protection

Although most mechanistic insights into polyphenol effects on mtDNA, mitochondrial biogenesis, and mitophagy come from experimental models, an increasing number of clinical trials have examined resveratrol [121], EGCG [86], quercetin [122], and olive-derived phenolics [123] in cardiometabolic and neurodegenerative settings. These studies typically use organ-level or systemic endpoints such as flow-mediated dilation (FMD), liver fat content, serum transaminases, or cognitive scores, which can be interpreted as functional readouts of mitochondrial health, even though direct measures of mitochondrial function in human tissues are rarely available.

3.7.1 Resveratrol

In the cardiovascular system, several randomized controlled trials (RCTs) have evaluated whether resveratrol can recapitulate the endothelial and mitochondrial benefits seen in preclinical models. In overweight/obese adults with mildly elevated blood pressure, acute supplementation with 270 mg resveratrol significantly improved brachial artery FMD within a few hours compared with placebo, without major changes in blood pressure or lipids, suggesting a rapid enhancement of endothelial nitric oxide bioavailability and reduced oxidative stress at the vascular wall [89]. More recently, a crossover trial in individuals with chronic kidney disease and type 2 diabetes has shown that several weeks of resveratrol supplementation improve endothelial function and circulating markers of vascular health, again interpreted as a consequence of improved mitochondrial redox balance and reduced ROS generation in endothelial cells [90]. Meta-analyses of RCTs broadly support a modest but significant benefit of resveratrol on endothelial function, particularly in populations with established cardiometabolic disease, although heterogeneity in dose, formulation and duration is substantial [91–93].

Clinical data in non-alcoholic fatty liver disease (NAFLD) show a more nuanced picture. An early trial in patients with biopsy-proven NAFLD using high-dose resveratrol (3 g/day for 8 weeks) did not improve liver fat, aminotransferases or insulin sensitivity, despite favorable effects on some inflammatory markers [124]. In contrast, a randomized controlled trial using a micronized trans-resveratrol formulation (at doses of 50 mg or 200 mg daily for 6 months) reported statistically significant reductions in liver fat grade and serum alanine aminotransferase (ALT), as well as improvements in other hepatic enzymes and insulin resistance [125]. A systematic review and meta-analyses conclude that resveratrol does not consistently improve core NAFLD outcomes (liver fat content, fibrosis scores) but may ameliorate inflammatory and oxidative stress parameters, which are tightly linked to mitochondrial dysfunction in this disease [126].

Neurodegenerative disorders provide a third clinical arena to examine potential mitochondrial effects of resveratrol. In a phase II RCT in patients with mild-to-moderate Alzheimer's disease (AD), oral resveratrol (up to 1 g twice daily for 52 weeks) was safe, penetrated the central nervous system, and altered trajectories of cerebrospinal fluid amyloid-β42 and neuroinflammatory markers compared with placebo, although

no clear cognitive benefit was demonstrated over 1 year [127]. Subsequent imaging analyses suggested that resveratrol-treated patients showed patterns of brain volume loss compatible with "normalization" of disease-related neuroinflammation rather than overt neurotoxicity, again consistent with a hormetic mitochondrial mechanism [128]. Other small studies in mild cognitive impairment and AD populations report improvements in hippocampal connectivity or glucose metabolism, but results are inconsistent and often underpowered [129]. Overall, clinical data indicate that resveratrol can modulate vascular and hepatic function and central biomarkers in ways that are compatible with the mitochondrial biogenesis and mitophagy effects described preclinically, but robust organ-level benefits (e.g., hard cardiovascular or cognitive outcomes) remain to be conclusively demonstrated.

3.7.2 Epigallocatechin-3-Gallate (EGCG)

EGCG, the main catechin in green tea, has likewise been tested clinically in cardiovascular and hepatic settings. In patients with coronary artery disease, a single oral dose of 300 mg EGCG acutely improved brachial artery FMD compared with placebo, indicating reversal of endothelial dysfunction within hours [130]. This effect was interpreted as a reduction in oxidative stress and restoration of nitric oxide bioavailability in the vascular endothelium, processes tightly regulated by mitochondrial ROS. However, a more recent trial that compared green tea, a catechin-enriched drink, and pure EGCG found that only whole green tea (but not isolated EGCG) improved FMD, suggesting that other tea constituents or metabolite interactions may be required to achieve sustained vascular benefits *in vivo* [131]. Interventional data in patients with type 2 diabetes and dyslipidaemia also show modest improvements in triglycerides, high-density lipoprotein (HDL) cholesterol levels with green tea or EGCG supplementation, which may indirectly reflect enhanced mitochondrial fatty-acid oxidation and improved metabolic flexibility [132,133].

In NAFLD, several RCTs have examined green tea or EGCG-rich preparations. A double-blind study in NAFLD patients consuming a green tea beverage with high-density catechins (200–1080 mg/day; predominantly EGCG) for 12 weeks reported reductions in liver fat on imaging, improved ALT and aspartate aminotransferase, and favorable changes in oxidative stress markers compared with catechin-free control tea [94]. More recently, a randomized controlled trial using purified EGCG in NAFLD patients showed significant improvements in hepatic steatosis indices and liver enzymes over several months, supporting a direct hepatoprotective effect of EGCG in humans [95]. Reviews synthesizing these data conclude that EGCG-based interventions can ameliorate liver fat and oxidative stress in a subset of NAFLD patients, in line with preclinical evidence that EGCG enhances mitochondrial β-oxidation, activates AMPK, and reduces mitochondrial ROS in the liver [96,97].

For the nervous system, EGCG has been evaluated as an adjunctive therapy in several neurodevelopmental and neurodegenerative conditions. In the phase Ib PERSEUS trial, children with Down syndrome received EGCG (up to 9 mg/kg/day) or placebo combined with cognitive training for 6 months; the intervention was safe but did not significantly improve global cognition or adaptive behaviour compared with placebo in this age group [134]. In Fragile X syndrome, a similar design combining EGCG with cognitive training produced modest improvements in specific cognitive domains and daily living skills, suggesting that EGCG can modulate synaptic plasticity under certain conditions [135]. Ongoing and recently reported trials in older adults with subjective cognitive decline and apolipoprotein E ε4 allele carriers, such as the PENSA study, indicate that EGCG added to an intensive multidomain lifestyle intervention may enhance composite cognitive scores, although disentangling the isolated effect of EGCG from the lifestyle package is challenging [136]. Overall, the clinical evidence suggests that EGCG is cardiovascularly and neurologically safe and can improve some cardiometabolic and hepatic endpoints; its direct impact

on human mitochondrial function remains inferential, but consistent with AMPK-PGC-1α activation and mitochondrial quality-control pathways described in experimental models.

3.7.3 Quercetin

Quercetin, a flavonol abundant in onions and apples, has been primarily studied clinically for its vascular and hepatic effects. In a randomized, double-blind, placebo-controlled crossover trial in overweight-to-obese adults with pre-hypertension or stage 1 hypertension, supplementation with 162 mg/day quercetin from onion skin extract for 6 weeks significantly reduced 24-h ambulatory blood pressure compared with placebo, while effects on FMD and lipid profile were modest [98]. A meta-analysis of RCTs confirms that quercetin supplementation lowers systolic blood pressure by a few mmHg and reduces vascular cell adhesion molecule-1, consistent with improved endothelial function and reduced vascular inflammation [99]. However, in post-myocardial infarction patients, 8 weeks of 500 mg/day quercetin did not significantly improve classical cardiometabolic risk markers, highlighting that background cardiovascular damage and medication use may modulate responsiveness [100]. From a mitochondrial perspective, these vascular benefits probably reflect reduced mitochondrial ROS and improved nitric oxide signaling in the endothelium, in agreement with preclinical data, but direct mitochondrial measurements in human vessels are lacking.

Emerging clinical data suggest that quercetin may also influence hepatic steatosis in NAFLD. A randomized double-blind trial in NAFLD patients using quercetin 500 mg twice daily for 12 weeks reported significant reductions in body fat mass and intrahepatic lipid contents, but no clear changes in aminotransferases compared with placebo [101]. Similarly, a more recent RCT using MRI-proton density fat fraction as a quantitative endpoint showed that 12 weeks of quercetin supplementation led to a statistically significant reduction in intrahepatic lipid content versus placebo, with a trend towards greater weight loss in the quercetin arm that may have contributed to the hepatic effect [101]. These findings are consistent with experimental models in which quercetin enhances hepatic mitophagy via the frataxin-PINK1/Parkin axis and restores mitochondrial function, but again, human trials have not directly quantified mitochondrial biogenesis or mitophagy in liver tissue.

Clinical evidence for quercetin in neurodegenerative diseases is more limited. Small trials in community samples and specific patient groups have examined high-dose quercetin (up to 1000 mg/day) on cognitive performance, with mixed results and no consistent improvement across domains [137] Most of the support for quercetin's neuroprotective and mitochondria-targeted actions still derives from preclinical models of Alzheimer's disease, Parkinson's disease and Huntington's disease, where quercetin attenuates mitochondrial dysfunction, oxidative stress and protein aggregation [138–140]. Translating these mitochondrial effects into robust clinical benefits in humans will require larger, longer trials with more sensitive mitochondrial and cognitive endpoints.

3.7.4 Oleuropein and Olive Leaf Extract

Oleuropein and its derivatives, including hydroxytyrosol, are key phenolic constituents of olive leaves and extra virgin olive oil and have been clinically tested mostly in the form of olive leaf extract (OLE). In patients with stage 1 hypertension, a head-to-head RCT comparing OLE (500 mg twice daily) with the angiotensin-converting enzyme inhibitor captopril found that 8 weeks of OLE reduced systolic and diastolic blood pressure to a similar extent as captopril, while additionally improving some lipid parameters [102]. Another randomized, placebo-controlled trial in overweight/obese adults with mildly elevated cholesterol showed that 8 weeks of phenolic-rich OLE significantly lowered daytime diastolic blood pressure and improved triglycerides, supporting a cardioprotective effect of olive phenolics [103]. Another trial in

prehypertensive patients confirmed that OLE can reduce 24-h blood pressure variability, improve lipid profile, and attenuate systemic inflammation [104], all of which are processes closely linked to vascular mitochondrial function and oxidative stress.

Direct human data on hepatic or neuronal outcomes with oleuropein-rich preparations are scarce. However, the consistent cardiometabolic benefits observed across RCTs, together with strong preclinical evidence that oleuropein enhances mitochondrial biogenesis, preserves mitochondrial membrane potential, and reduces mitochondrial ROS in cardiomyocytes, skeletal muscle, and brain, suggest that improvements in mitochondrial quality control underlie at least part of the clinical effect [45,84,85]. The absence of direct measurements of mtDNA copy number, respiratory chain activity, or mitophagy markers in human tissues remains an important gap, but the convergence between experimental and clinical findings supports the inclusion of olive phenolics as candidate mitochondria-targeted nutraceuticals in cardiometabolic prevention strategies.

4 Translational Perspectives, Limitations, and Future Directions

This section integrates the main translational implications of the reviewed evidence, highlights the conceptual novelty of a mitochondria-centered framework for polyphenol action, and discusses the key methodological and biological limitations that currently constrain clinical translation.

As summarized in the preceding sections, growing evidence indicates that dietary polyphenols do not act primarily through direct antioxidant effects but through activation of conserved mitochondrial stress-adaptation pathways, including SIRT1-PGC-1α, AMPK, Nrf2, and PINK1/Parkin signaling. Resveratrol is the clearest example, as multiple studies show its ability to activate SIRT1 and promote PGC-1α deacetylation, enhance mitochondrial biogenesis, and stimulate mitophagy across metabolic and myopathic models [73,88]. EGCG activates AMPK and up-regulates PGC-1α transcription in hepatocytes and adipocytes, supporting an AMPK-driven mitochondrial biogenesis program with downstream effects on β-oxidation and thermogenesis [58,118]. Quercetin exhibits a dual action: it enhances PGC-1α-mediated mitochondrial biogenesis in muscle and brain [87], and it also stimulates frataxin-dependent PINK1/Parkin mitophagy in hepatocytes, improving mitochondrial clearance and organellar turnover in steatotic liver [120]. Oleuropein and related olive phenolics improve mitochondrial membrane potential, reduce ROS production, and activate AMPK/SIRT1 pathways, contributing to mitochondrial resilience in metabolic and neurodegenerative models [43,84].

Despite this emerging mechanistic integration, important knowledge gaps remain. First, bioavailability and mitochondrial targeting of most polyphenols are limited, as they undergo rapid conjugation and reach low intracellular concentrations, raising questions about the physiological relevance of some *in vitro* effects. Second, direct human evidence of changes in mtDNA stability, mitochondrial biogenesis, or mitophagy remains scarce. Even in well-designed clinical studies, endpoints are typically vascular or hepatic rather than mitochondrial in nature, such as flow-mediated dilation in cardiometabolic populations [89–91] or hepatic outcomes including liver fat content and serum transaminases in NAFLD [94,124,126], making mechanistic translation difficult. Third, the relative contribution of biogenesis versus mitophagy in different tissues is unknown and likely context-dependent, as excessive mitophagy may be maladaptive in certain pathological states. Fourth, substantial heterogeneity exists across preclinical studies in terms of cell models, animal strains, doses, treatment durations, and methods used to quantify mitochondrial outcomes, complicating cross-study comparisons. Fifth, mitochondrial biomarkers are not standardized, with studies variably assessing mtDNA copy number, respiratory chain activity, ROS production, TFAM expression, or PINK1/Parkin signaling, which limits the ability to draw unified conclusions. Sixth, most clinical trials rely

on non-optimised formulations, and virtually none compare free polyphenols with nanoencapsulated or mitochondria-targeted preparations, preventing robust dose-response interpretation. Finally, this review is limited by the variability and methodological inconsistency of available evidence, and by the inability to perform quantitative synthesis due to heterogeneity in experimental approaches and endpoints.

Beyond pathway-level descriptions, future research would benefit from incorporating methodologies that directly quantify mitochondrial damage, turnover, and functional heterogeneity. In this regard, long-range PCR-based lesion frequency assays provide a direct estimate of oxidative mtDNA damage across the mitochondrial genome, while ultra-deep sequencing approaches allow detection of low-frequency mtDNA mutations and early heteroplasmy shifts that may precede overt mitochondrial dysfunction. These methodologies have been highlighted as critical for accurately assessing mitochondrial genomic stability by Fontana and Gahlon [141], and by Stewart and Chinnery [13], particularly in the context of aging and neurodegenerative disease. At the functional level, mitochondrial phenotyping techniques such as high-resolution respirometry and Seahorse extracellular flux analysis enable integrated assessment of oxidative phosphorylation, coupling efficiency, and respiratory reserve capacity [142]. Unlike transcriptomic or protein-level readouts, these approaches capture dynamic mitochondrial performance under physiological and stress conditions [143].

Importantly, emerging evidence supports the use of circulating mitochondrial biomarkers as clinically accessible indicators of mitochondrial stress and quality control. Circulating cell-free mtDNA, oxidized mtDNA fragments, and mitochondrial-derived vesicles have been proposed as surrogate markers of mitochondrial damage and turnover in cardiometabolic and neurodegenerative disorders. This concept has been developed in recent work by Liu et al. [4] and Ye et al. [3], who highlight their potential value in human intervention studies where tissue biopsies are not feasible. Finally, integrative multi-omics strategies, including metabolomics and single-cell transcriptomics, are increasingly recommended to capture interindividual variability in mitochondrial responses to polyphenols. A recent review by Guan et al. [20] suggests that these approaches are essential to distinguish adaptive mitochondrial remodelling from maladaptive stress responses and to explain the heterogeneous outcomes reported across clinical trials.

In addition to these mechanistic and methodological gaps, safety considerations are essential to contextualize the translational potential of polyphenols. Overall, polyphenols consumed as part of foods are considered safe, but concentrated supplements can produce dose and context dependent adverse effects. For green tea catechins, hepatotoxicity is the most consistent safety signal. The European Food Safety Authority concluded that supplemental catechin intakes at or above 800 mg per day, expressed as epigallocatechin gallate equivalents, may raise safety concerns, particularly when administered as bolus doses or under fasting conditions [144]. Resveratrol is generally well tolerated in clinical trials; however, higher doses are more frequently associated with gastrointestinal symptoms such as nausea, abdominal discomfort, and diarrhea, and given its biological activity, caution is warranted in individuals receiving anticoagulant or antiplatelet therapies or multiple cardiometabolic drugs where additive effects or interactions are plausible [121]. Quercetin supplementation has shown good tolerability in most randomized trials, but uncertainties persist regarding long-term high-dose use. Recent safety evaluations for food supplement scenarios emphasize the importance of considering dose, formulation, and vulnerable populations such as individuals with renal or hepatic impairment when extrapolating beyond typical dietary exposure [145,146]. Olive phenolics, including oleuropein and hydroxytyrosol, appear well tolerated across randomized controlled trials, with adverse events generally mild and infrequent. Nonetheless, their potential hypotensive or glucose-lowering effects may theoretically add to antihypertensive or antidiabetic treatments, supporting a prudent and medication-aware approach in clinical translation [45]. Taken together, future research should focus on: (i) advanced mitochondrial phenotyping in

humans, including circulating mitophagy markers, cell-free mtDNA profiling and patient-derived cell models; (ii) optimising polyphenol formulations to improve mitochondrial delivery (e.g., nanoformulations, synergistic polyphenol combinations); (iii) organ-specific evaluation of mitochondrial pathways in heart, liver, brain and skeletal muscle; and (iv) long-term clinical trials that include mitochondrial biomarkers along with standard clinical outcomes. Addressing these gaps will be essential to determine whether polyphenols can be validated as effective, mitochondria-targeted nutraceuticals.

5 Conclusions

Experimental and clinical evidence indicate that dietary polyphenols exert biologically relevant effects on mitochondrial quality control rather than acting primarily as direct antioxidants. Across tissues, these compounds converge on conserved pathways regulating mitochondrial biogenesis, mtDNA stability, redox balance, and mitophagy, notably through SIRT1–PGC-1α, AMPK, Nrf2, and PINK1/Parkin signaling.

While these mechanisms provide a coherent framework to explain reported benefits in cardiometabolic, hepatic, and neurodegenerative contexts, clinical outcomes remain heterogeneous, and direct evidence of mitochondrial remodeling in human tissues is limited. Future studies integrating mitochondrial-specific biomarkers, optimized formulations, and targeted population stratification will be essential to define the translational relevance of polyphenols as mitochondria-oriented nutritional interventions.

Acknowledgement: Not applicable.

Funding Statement: The authors received no specific funding for this study.

Author Contributions: The authors confirm contribution to the paper as follows: Conceptualization, Desirée Victoria-Montesinos, Pablo Barcina-Pérez and Ana María García-Muñoz; Methodology, Desirée Victoria-Montesinos and Pablo Barcina-Pérez; Investigation, Desirée Victoria-Montesinos and Ana María García-Muñoz; Resources, Desirée Victoria-Montesinos and Pablo Barcina-Pérez; Writing—original draft preparation, Desirée Victoria-Montesinos; Writing—review and editing, Desirée Victoria-Montesinos, Pablo Barcina-Pérez and Ana María García-Muñoz; Visualization, Desirée Victoria-Montesinos and Ana María García-Muñoz; Supervision, Desirée Victoria-Montesinos and Pablo Barcina-Pérez; Project administration, Desirée Victoria-Montesinos and Pablo Barcina-Pérez; Funding acquisition, Desirée Victoria-Montesinos. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

Term	Interpretation
8-oxoG	8-oxo-guanine
AD	Alzheimer's disease
ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
BER	Base excision repair
EGCG	Epigallocatechin-3-gallate
ETC	Electron transport chain
FMD	Flow-mediated dilation
HDL	High-density lipoprotein

mtDNA	Mitochondrial DNA
NAD	Nicotinamide adenine dinucleotide
NAFLD	Non-alcoholic fatty liver disease
NRF1	Nuclear respiratory factor 1
NRF2	Nuclear respiratory factor 2
Nrf2	Nuclear factor erythroid 2-related factor 2
OLE	Olive leaf extract
OXPHOS	Oxidative phosphorylation
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PINK1	PTEN-induced kinase 1
POLG	DNA polymerase gamma
RCTs	Randomized controlled trials
ROS	Reactive oxygen species
SIRT-1	Sirtuin 1
TBI	Traumatic brain injury
TFAM	Mitochondrial transcription factor A

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