NQO1 Variation, Coenzyme Q10 Activation, and the Genetic Basis of Cutaneous Oxidative Defense in Skin Aging

A Literature Review

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ABSTRACT

Background. NAD(P)H:quinone oxidoreductase 1 (*NQO1*) is a broadly expressed cytosolic redox enzyme that catalyzes the obligatory two-electron reduction of quinones to hydroquinones, thereby minimizing semiquinone formation and limiting the propagation of reactive oxygen species. Through this activity, *NQO1* contributes to cellular redox homeostasis, quinone detoxification, and the maintenance of antioxidant defense systems, including processes related to coenzyme Q10 redox balance. These functions are particularly relevant in tissues that are continuously exposed to environmental oxidative stress, such as skin. In this context, variation in *NQO1* expression or enzymatic activity influences cutaneous oxidative resilience and the biological response to coenzyme Q10 supplementation (Ross et al., 2000; Traver et al., 1997; Fischer et al., 2011).

Methods. A narrative review was undertaken to integrate scientific literature on *NQO1* biology, the functional implications of allelic variation at the *NQO1* rs1800566 locus, coenzyme Q10 metabolism, oxidative pathways involved in skin aging, and antioxidant interventions relevant to *NQO1*-dependent redox regulation. Particular emphasis was placed on mechanistic studies and human investigations that informed genotype–phenotype relationships in skin biology and antioxidant defense, with a focus on biologically plausible links between genetic variation, redox homeostasis, and cutaneous physiology. Additional consideration was given to studies elucidating the molecular and metabolic pathways through which *NQO1* may influence quinone reduction, antioxidant capacity, and tissue responses to oxidative stress. The evidence was synthesized qualitatively, with priority assigned to reports that provided mechanistic coherence between experimental observations and their potential physiological relevance for the skin. This approach enabled an integrated interpretation of genetic, biochemical, and translational findings within the broader context of redox biology and cutaneous aging research (Sepetiene et al., 2023; Freriksen et al., 2014).

Results. The literature defines a coherent mechanistic continuum linking *NQO1*-mediated quinone reduction to cellular redox homeostasis, coenzyme Q10 biology, and cutaneous aging processes. *NQO1* plays a central role in quinone detoxification and in the maintenance of intracellular redox balance, including the handling of ubiquinone-related substrates. Allelic

variation at the *NQO1* rs1800566 locus includes a missense substitution that has been associated with reduced NQO1 protein stability and diminished enzymatic activity and has further been linked to interindividual differences in coenzyme Q10 status in humans. In view of the established contribution of oxidative stress to both intrinsic and extrinsic skin aging, reduced NQO1-dependent redox buffering may contribute to cytokine induction, matrix metalloproteinase activation, collagen disorganization, and progressive photoaging-associated tissue decline. Collectively, these findings support coenzyme Q10 as the most pathway-congruent compound and provide a rationale for combined supplementation with coenzyme Q10, vitamins C and E, alpha-lipoic acid, zinc, and manganese under conditions of reduced quinone-reducing capacity (Ross et al., 2000; Fischer et al., 2011; Papaccio et al., 2022).

Discussion. Current evidence supports a biologically coherent interpretation in which reduced *NQO1* activity compromises the conversion of oxidized quinone species into their more antioxidant-active reduced forms and, consequently, diminishes the capacity of the skin to counteract oxidative injury. The available mechanistic, biochemical, and translational data consistently indicate that variation in *NQO1*-dependent redox regulation is relevant to cutaneous oxidative resilience. Accordingly, a coherent interpretation is that a reduced-function *NQO1* background increases antioxidant requirements and supports combined topical and systemic antioxidant supplementation in conjunction with photoprotective measures. This interpretation is further supported by the central role of oxidative stress in photoaging biology and by the close integration of quinone metabolism with broader cellular antioxidant networks. In this context, *NQO1* is an established component of the molecular framework that contributes to interindividual differences in cutaneous responses to environmental oxidative stress and the efficacy of antioxidant-based interventions (Sepetiene et al., 2023; Papaccio et al., 2022).

Subjects: Genetics, Beauty. **Keywords:** Genetics, Polymorphism, Beauty, Q10.

INTRODUCTION

Skin aging is a multifactorial biological process in which oxidative stress occupies a central mechanistic role. Chronological aging and environmentally influenced cutaneous aging are both characterized by a persistent imbalance between oxidant generation and antioxidant defense, with downstream consequences for lipids, proteins, mitochondrial integrity, extracellular matrix turnover, and inflammatory signaling. These alterations progressively impair tissue homeostasis and contribute to functional and structural decline of the skin over time. Because such processes do not occur uniformly across individuals, inherited variation in antioxidant and detoxification pathways is a plausible contributor to interindividual differences in cutaneous aging trajectories. In this context, genetic variability influences not only susceptibility to oxidative damage, but also the magnitude of response to antioxidant-based preventive or supportive interventions. Furthermore, the view that skin aging reflects the interaction between cumulative environmental stressors and the capacity of

endogenous protective systems to preserve redox balance and tissue integrity is clearly supported (Rinnerthaler et al., 2015; Papaccio et al., 2022; Sepetiene et al., 2023).

Within this framework, variation in *NQO1* is of particular interest because of its relevance to quinone reduction, coenzyme Q10 redox metabolism, and epidermal antioxidant defense. Available evidence indicates that *NQO1*-related enzymatic function varies across a continuum, with direct effects on the efficiency of quinone handling and the maintenance of intracellular redox balance. These functional differences determine the capacity of cutaneous tissues to buffer oxidative stress and contribute to interindividual variation in skin-aging-associated processes. In addition, this biological gradient provides a mechanistic basis for considering how *NQO1*-dependent redox metabolism may shape antioxidant requirements at the tissue level. Accordingly, *NQO1* represents a biologically plausible molecular factor linking common genetic variation to oxidative resilience in the skin and to the expected responsiveness to quinone-based antioxidant strategies (Siegel et al., 1999; Traver et al., 1997).

MECHANISTIC CONTRIBUTION OF *NQO1* TO UBIQUINONE METABOLISM, CELLULAR REDOX BUFFERING, AND OXIDATIVE STRESS RESPONSES IN THE SKIN

NQO1 encodes an FAD-dependent cytosolic oxidoreductase that uses NADH or NADPH to catalyze the obligatory two-electron reduction of quinones to hydroquinones. This is biologically important because one-electron quinone reduction can generate semiquinones that re-enter redox cycling and amplify oxidative stress. By favoring two-electron reduction, *NQO1* functions as a detoxification and redox-buffering enzyme. The same enzymatic logic is relevant to endogenous antioxidant systems, since quinone-containing molecules are often more protective in their reduced states. In this way, *NQO1* contributes to maintenance of cellular antioxidant tone rather than acting as a single-pathway enzyme with isolated effects (Ross et al., 2000; Traver et al., 1997).

With respect to coenzyme Q10, the biologically relevant distinction is between the oxidized form, ubiquinone, and the reduced form, ubiquinol. Ubiquinol is the more potent chain-breaking antioxidant form in membranes, whereas ubiquinone is the oxidized state that must be reduced to regain full antioxidant activity. Available biochemical and human genetic data support a role for *NQO1* in ubiquinone-related redox metabolism, and human pilot data indicate that the reduced-function *NQO1* variant is associated with altered coenzyme Q10 status (Ross et al., 2000; Fischer et al., 2011). Reduced *NQO1* activity therefore impairs efficient redox activation and recycling of coenzyme Q10 toward its antioxidant-active state.

This is especially relevant in skin, where oxidative stress is continuously driven by ultraviolet radiation, pollution, and inflammatory signaling. The epidermal Nrf2 axis induces a battery of protective genes, among them *NQO1*, and studies in keratinocytes show that *NQO1* participates in the response to photo-oxidative stress. In human epidermal cells, activation of Nrf2-associated programs attenuates reactive oxygen species and inflammatory cytokine production after ultraviolet challenge, while *NQO1* expression serves as part of this defensive architecture (Marrot et al., 2008; Kim et al., 2014; Takei et al., 2015).

MOLECULAR AND CUTANEOUS CONSEQUENCES OF RS1800566-MEDIATED IMPAIRMENT OF *NQO1*-DEPENDENT QUINONE REDUCTION

Allelic variation at the NQO1 rs1800566 locus includes a functionally important missense change in the NQO1 protein, which has been associated with reduced protein stability and diminished enzymatic activity. Experimental evidence indicates that this amino acid exchange is not biologically neutral; rather, it impairs protein stability, disrupts the native conformation, and promotes rapid ubiquitination followed by proteasomal degradation. The resulting reduction in the cellular pool of stable, catalytically competent *NQO1* leads to attenuation of *NQO1*-dependent quinone-reducing capacity (Siegel et al., 2001; Lienhart et al., 2014). Earlier genotype–phenotype studies further established the physiological relevance of this variant by showing markedly reduced *NQO1* activity in carriers of the reduced-function allele, with intermediate activity in heterozygotes and near-complete deficiency in homozygous reduced-function genotypes (Traver et al., 1997; Siegel et al., 1999). The broader clinical literature likewise supports the view that allelic variation at the NQO1 rs1800566 locus is functionally meaningful rather than merely a statistical marker, as associations with disease susceptibility in tissues exposed to oxidative or xenobiotic stress indicate measurable biological consequences in vivo and strengthens the interpretation that reduced-function allelic variation at this locus can alter host defense against quinone-related oxidative stress (Freriksen et al., 2014).

The most immediate functional consequence of impaired *NQO1* activity is a diminished capacity to reduce quinone substrates into less radical-generating and more antioxidant-active forms, thereby weakening maintenance of redox balance. In the context of coenzyme Q10 biology, impaired *NQO1* activity reduces the conversion of ubiquinone to the antioxidant-active ubiquinol pool, a finding confirmed by human data linking the reduced-function variant to altered coenzyme Q10 status (Fischer et al., 2011). From a cutaneous perspective, this functional deficit is particularly relevant because oxidative stress is a central driver of matrix degradation and tissue senescence. Reactive oxygen species enhance inflammatory signaling and activate transcriptional programs that increase matrix metalloproteinase expression, while collagen fragmentation further perpetuates oxidative imbalance in dermal fibroblasts, thereby establishing a self-reinforcing cycle of collagen disorganization and declining tissue resilience (Rinnerthaler et al., 2015; Fisher et al., 2009; Papaccio et al., 2022). Accordingly, impaired *NQO1* function reduces the efficiency with which the skin responds to ultraviolet- and pollution-induced oxidative injury, with downstream consequences including enhanced inflammatory signaling, increased matrix-degrading enzyme activity, and greater vulnerability of collagen and basement-membrane structures (Marrot et al., 2008; Takei et al., 2015; Fisher et al., 2009).

MECHANISM-BASED ANTIOXIDANT AND MICRONUTRIENT STRATEGIES FOR REDUCED *NQO1*-DEPENDENT REDOX CAPACITY

From a translation perspective, reduced *NQO1*-dependent quinone reduction is most appropriately addressed by interventions that support both the proximal coenzyme Q10 pathway and complementary antioxidant systems involved in cutaneous redox homeostasis. This framework favors a network-oriented strategy in which pathway-congruent and adjunctive active compounds

are combined to limit oxidative injury, preserve extracellular matrix integrity, and strengthen cellular antioxidant resilience. Such an approach is particularly relevant when endogenous quinone activation is expected to be less efficient (Ross et al., 2000; Fischer et al., 2011; Pullar et al., 2017; Treiber et al., 2012).

Coenzyme Q10

Coenzyme Q10 is the pathway-congruent compound most directly connected to the affected biochemical step. Topical investigations demonstrate that coenzyme Q10 reaches viable epidermal layers, increases cutaneous Q10 levels, and exerts antioxidant effects, and experimental and clinical studies confirm beneficial effects on oxidative and wrinkle-associated pathways. Human intervention data additionally show improvement in visible skin parameters, including wrinkle depth and skin smoothness, establishing coenzyme Q10 as a biologically relevant cutaneous antioxidant in skin-aging applications (Inui et al., 2008; Knott et al., 2015; Žmitek et al., 2017).

At the same time, reduced *NQO1* function increases the rationale for combined antioxidant supplementation. Because endogenous quinone-reducing capacity is reduced, coenzyme Q10 supplementation is appropriate in combination with compounds acting through partly independent biochemical pathways. Coenzyme Q10 remains the central component of intervention, and its antioxidant benefit is enhanced through co-administration of adjunctive compounds that support redox homeostasis beyond the *NQO1*-dependent bottleneck (Ross et al., 2000; Fischer et al., 2011).

Vitamin C

Vitamin C is a particularly relevant adjunct because it acts in the aqueous phase, supports collagen synthesis, and contributes to regeneration of the antioxidant network. Clinical and translational studies have demonstrated improvement of photodamaged skin with topical vitamin C, while broader evidence supports its role in collagen biosynthesis, barrier function, and oxidative defense in the skin. As a water-soluble antioxidant, vitamin C reinforces aqueous redox defense and contributes to collagen synthesis and skin structural integrity. In this context, it represents a relevant adjunctive compound for reinforcing cutaneous antioxidant capacity and matrix homeostasis (Fitzpatrick and Rostan, 2002; Humbert et al., 2003; Pullar et al., 2017).

Vitamin E

Vitamin E is likewise highly relevant because it is a major naturally occurring lipid-soluble antioxidant in skin and contributes to protection against oxidative stress-associated damage, including photoaging. Its importance is further underscored by evidence that cutaneous vitamin E levels are affected by ultraviolet exposure, supporting a role for this antioxidant in the maintenance of skin defense under environmentally induced oxidative stress. Vitamins C and E act cooperatively, and addition of ferulic acid to a topical formulation containing these antioxidants improved formulation stability and doubled photoprotection of skin. Taken together, these findings support the inclusion of vitamin E in combination antioxidant approaches designed to reinforce cutaneous defense and to enhance the efficacy of topical photoprotective strategies (Nachbar and Korting, 1995; Lin et al., 2005).

Alpha-Lipoic Acid

Alpha-lipoic acid is another mechanistically plausible adjunct within this framework. Clinical data support the use of topical alpha-lipoic acid in photoaged facial skin, and experimental findings

indicate that it can enhance collagen biosynthesis through TGF-β/Smad-associated signaling in dermal fibroblasts. Its relevance therefore extends beyond free-radical quenching alone and includes potential support of extracellular matrix homeostasis under conditions of persistent oxidative stress. These findings demonstrate that alpha-lipoic acid contributes both to the attenuation of visible cutaneous aging features and to preservation of dermal structural integrity. In this context, its biological value lies in the convergence of antioxidant activity with regulatory effects on fibroblast-mediated matrix maintenance, supporting its inclusion in mechanism-based intervention strategies for oxidative skin aging (Beitner, 2003; Tsuji-Naito et al., 2010).

Zinc and Manganese

Zinc and manganese occupy a more supportive, network-oriented role and contribute to endogenous antioxidant defense. Zinc has long been recognized as a relevant cutaneous antioxidant factor, whereas manganese is particularly important in relation to mitochondrial superoxide dismutase biology. Experimental and review data establish that these micronutrients support enzymatic antioxidant systems and contribute to protection against oxidative injury in skin fibroblasts. Such effects are especially relevant under conditions of sustained oxidative stress, in which preservation of mitochondrial redox control and fibroblast resistance to oxidant injury influence the progression of cumulative dermal damage. In this context, their principal value lies in strengthening the endogenous antioxidant infrastructure of the skin. Accordingly, zinc and manganese are best regarded as complementary components of a broader antioxidant strategy (Rostan et al., 2002; Treiber et al., 2012; Parat et al., 1995).

TABLE 1: SELECTED STUDIES RELEVANT TO *NQO1* VARIATION, COENZYME Q10 REDOX BIOLOGY, AND OXIDATIVE-STRESS SUSCEPTIBILITY

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Traver et al., 1997	**Design:** Functional polymorphism study. **Population:** Human genotype–phenotype material with enzymatic characterization. **SNP:** rs1800566.	Characterized a functionally important *NQO1* polymorphism associated with markedly reduced enzyme activity.
Siegel et al., 1999	**Design:** Genotype–phenotype study. **Population:** Human carriers with different *NQO1* genotypes. **SNP:** rs1800566.	Demonstrated an activity gradient across genotypes, with intermediate activity in heterozygotes and marked deficiency in homozygous variant carriers.

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Siegel et al., 2001	**Design:** Molecular protein study. **Population:** Experimental cellular models expressing wild-type and variant *NQO1* protein. **SNP:** rs1800566.	Showed rapid polyubiquitination and proteasomal degradation of the variant protein, explaining reduced functional enzyme availability.
Lienhart et al., 2014	**Design:** Structural/biochemical study. **Population:** Recombinant protein and structural biochemical models. **SNP:** rs1800566.	Demonstrated that the amino acid exchange destabilizes native *NQO1* structure and impairs protein integrity.
Fischer et al., 2011	**Design:** Human genetic association study. **Population:** Human participants assessed coenzyme Q10-pathway variation and coenzyme Q10 status. **SNP:** rs1800566.	Linked *NQO1*-related genetic variation to interindividual differences in coenzyme Q10 status.
Freriksen et al., 2014	**Design:** Human case–control genetic association study. **Population:** Human clinical cohort in a tissue exposed to oxidative/xenobiotic stress. **SNP:** rs1800566.	Supported the in vivo relevance of reduced-function allelic variation at this locus by showing association with disease susceptibility, consistent with altered host defense against quinone-related oxidative stress.

CONCLUSION

NQO1 is identified as a biologically relevant determinant of cutaneous redox homeostasis and of the efficiency with which quinone-based antioxidants contribute to tissue protection. Through its role in two-electron quinone reduction, *NQO1* limits the formation of radical-generating intermediates, supports quinone detoxification, and contributes to maintenance of coenzyme Q10 in its antioxidant-active reduced state. Reduced-function allelic variation at the NQO1 rs1800566 locus is therefore of clear functional significance, as it reduces *NQO1* protein stability and enzymatic capacity and thereby provides a mechanistic basis for interindividual differences in oxidative resilience and susceptibility to skin-aging-associated tissue alterations (Ross et al., 2000; Siegel et al., 2001; Fischer et al., 2011).

From a cutaneous perspective, diminished *NQO1*-dependent redox buffering reduces the efficiency of oxidative stress neutralization, increases activation of inflammatory and matrix-degrading

pathways, and impairs preservation of extracellular matrix integrity. Within this framework, coenzyme Q10 is the central pathway-congruent active compound, and the available evidence establishes its use as the core component of a combined antioxidant strategy. Vitamins C and E, alpha-lipoic acid, zinc, and manganese represent mechanistically complementary compounds because they reinforce antioxidant defense through additional aqueous, lipid, mitochondrial, and matrix-supportive pathways that are not solely dependent on *NQO1*-mediated quinone reduction. Accordingly, an unfavorable *NQO1* background supports combined topical and systemic antioxidant supplementation to maintain cutaneous resilience under conditions of sustained oxidative stress (Papaccio et al., 2022; Pullar et al., 2017).

Overall, *NQO1* variation is a functionally meaningful modifier of antioxidant requirements and influences responsiveness to targeted redox-based interventions. This interpretation places *NQO1* within a broader precision-oriented framework of skin biology, in which inherited differences in antioxidant capacity help explain variation in tissue vulnerability and may inform more mechanism-based preventive and supportive strategies.

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