Pyrroloquinoline quinone: a potential neuroprotective compound for neurodegenerative diseases targeting metabolism

Alessio Canovai[1], Pete A. Williams[2,*]

https://doi.org/10.4103/NRR.NRR-D-23-01921

Date of submission: November 23, 2023

Date of decision: January 31, 2024

Date of acceptance: February 29, 2024

Date of web publication: April 3, 2024

From the Contents

Abstract

Pyrroloquinoline quinone is a quinone described as a cofactor for many bacterial dehydrogenases and is reported to exert an effect on metabolism in mammalian cells/tissues. Pyrroloquinoline quinone is present in the diet being available in foodstuffs, conferring the potential of this compound to be supplemented by dietary administration. Pyrroloquinoline quinone's nutritional role in mammalian health is supported by the extensive deficits in reproduction, growth, and immunity resulting from the dietary absence of pyrroloquinoline quinone, and as such, pyrroloquinoline quinone has been considered as a "new vitamin." Although the classification of pyrroloquinoline quinone as a vitamin needs to be properly established, the wide range of benefits for health provided has been reported in many studies. In this respect, pyrroloquinoline quinone seems to be particularly involved in regulating cell signaling pathways that promote metabolic and mitochondrial processes in many experimental contexts, thus dictating the rationale to consider pyrroloquinoline quinone as a vital compound for mammalian life. Through the regulation of different metabolic mechanisms, pyrroloquinoline quinone may improve clinical deficits where dysfunctional metabolism and mitochondrial activity contribute to induce cell damage and death. Pyrroloquinoline quinone has been demonstrated to have neuroprotective properties in different experimental models of neurodegeneration, although the link between pyrroloquinoline quinone-promoted metabolism and improved neuronal viability in some of such contexts is still to be fully elucidated. Here, we review the general properties of pyrroloquinoline quinone and its capacity to modulate metabolic and mitochondrial mechanisms in physiological contexts. In addition, we analyze the neuroprotective properties of pyrroloquinoline quinone in different neurodegenerative conditions and consider future perspectives for pyrroloquinoline quinone's potential in health and disease.

Key Words: metabolism; mitochondria; neurodegenerative disease; neuroprotection; pyrroloquinoline quinone; retinal diseases

Introduction

Pyrroloquinoline quinone (PQQ) is a quinone first described in the 1960s as a cofactor of several bacterial dehydrogenases, including alcohol and sugar dehydrogenases (Hauge, 1964). The importance of PQQ in regulating physiological processes from fungi to mammals has been identified (Jonscher et al., 2021). Although PQQ cannot be synthesized *de novo* in mammals, trace amounts of PQQ have been measured in a concentration range from picomolar to nanomolar in many human and rodent tissues, suggesting that this compound can easily reach the body systems through external sources (Kumazawa et al., 1992). The presence of PQQ in many types of foods confers the potential for this compound to be supplemented and introduced in the organism by dietary consumption. PQQ's nutritional role in mammalian health is further supported by the wide range of defects in reproduction, growth, and immunity resulting from the dietary absence of PQQ (Akagawa et al., 2016b). For these reasons, PQQ has been considered as a "new vitamin," although this concept remains controversial and still to be properly established (Akagawa et al., 2016b). Despite this controversy to include PQQ in the long list of vitamins, the multitude of PQQ beneficial effects for human health involving a different range of physiological properties has been demonstrated in a wide range of studies. In particular, PQQ seems to be involved in cell signaling pathways regulating metabolism and mitochondrial mechanisms in many experimental models, thus providing a rationale for considering PQQ as a vital

[1]Department of Biology, University of Pisa, Pisa, Italy; [2]Department of Clinical Neuroscience, Division of Eye and Vision, St. Erik Eye Hospital, Karolinska Institutet, Stockholm, Sweden

*__Correspondence to:__ Pete A. Williams, PhD, pete.williams@ki.se.

https://orcid.org/0000-0001-6194-8397 (Pete A. Williams); https://orcid.org/0009-0007-9229-4710 (Alessio Canovai)

Funding: *PAW was supported by Karolinska Institutet in the form of a Board of Research Faculty Funded Career Position, by St. Erik Eye Hospital philanthropic donations, and Vetenskapsrådet 2022-00799.*

How to cite this article: *Canovai A, Williams PA (2025) Pyrroloquinoline quinone: a potential neuroprotective compound for neurodegenerative diseases targeting metabolism. Neural Regen Res 20(1):41-53.*

compound regulating key processes for life (Rucker et al., 2009). By regulating a wide range of mechanisms, PQQ might improve clinically relevant conditions where dysfunctional metabolism and mitochondrial activity may be the main cause or contribute together with other processes to cell stress and damage (Rucker et al., 2009; Akagawa et al., 2016b). In this context, PQQ has been demonstrated to exert neuroprotective effects in animal models of damage in the nervous system, providing evidence of the potential of this compound as a putative therapeutical tool for neurodegenerative diseases (Rucker et al., 2009; Akagawa et al., 2016b). Here, we review the general characteristics of PQQ and its modulation of metabolic and mitochondrial mechanisms. In addition, we focus our attention on analyzing the neuroprotective role of PQQ in different neurodegenerative diseases and discuss considerations for future perspectives for PQQ in health and disease.

Search Strategy

The literature search was performed based on the PubMed database to find papers related to the topic using the following keywords: "pyrroloquinoline quinone" and "neuroprotection," "ATP," "mitochondrial biogenesis," "deficiency," "metabolism," or "NAD synthesis." The search was limited to articles published between 1964 and 2023, including research papers, review articles, and clinical trials. Given the relevance of some older papers or the limited number of papers on some topics included in this review, year filtration for the most recent papers was performed when possible. The search results were further screened according to the relevance to the topic. Articles non-relevant to the topic were excluded from the analyses.

Molecular Properties of Pyrroloquinoline Quinone and Its Role in Nutrition

Molecular structure and dietary sources of PQQ

4,5-Dihydro-4,5-dioxo-1H-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylic acid (PQQ) is an aromatic o-quinone that can continuously undergo redox reactions, reducing to pyrroloquinoline quinol (PQQH2) through a semiquinone intermediate in a two-electron reduction mechanism (Cordell and Daley, 2022). This reaction occurs with the presence of organic substrates such as ascorbate, NAD(P)H, and glutathione (Cordell and Daley, 2022). $PQQH_2$ is then reoxidized by the transfer of electrons to molecular oxygen and the formation of superoxide anion, which is subsequently dismutated to hydrogen peroxide (Cordell and Daley, 2022). As this reaction of redox cycling can occur continuously, only picomoles of PQQ are required to generate micromolar amounts of products, being more efficient than many enediols (e.g., ascorbic acid or menadione), isoflavonoids, phytoalexins, and polyphenols (Paz et al., 1996; Stites et al., 2000). PQQ efficiency in redox cycling is further promoted by the fact that PQQ is not easily self-oxidized or exhausted into inactive forms (Jonscher et al., 2021). The reactions of redox cycling can be performed by both the oxidized and the reduced form of PQQ (Jonscher et al., 2021). As redox cofactor, PQQ can catalyze redox reactions involving oxidation of different substrates as thiols, riboflavin, ubiquinone, terminal cytochromes, α-tocopheroxyl radicals, and nicotinamide adenine dinucleotide cofactors (Stites et al., 2000; Ouchi et al., 2013; Várnai et al., 2018; Chan et al., 2021). For instance, PQQ also catalyzes the oxidation of primary amines to aldehydes or ketones by reacting with the ε-amino group of lysine residues in proteins such as elastin and collagen under aerobic conditions, creating covalent cross-links (Akagawa et al., 2016b). Moreover, PQQ can react with amino acids in biological tissues leading to the formation of imidazole derivatives, such as imidazolopyrroloquinoline quinone, known to have biological activities (Akagawa et al., 2016b). In addition, PQQ can act as a free radical scavenger (Ouchi et al., 2013). The protonated form of PQQ shows only partial water solubility. Due to this, a different chemical form provided as a disodium salt ($PQQNa_2$; available as BioPQQ™) was developed by Mitsubishi Gas Chemical Co., Inc. (Tokyo, Japan) to improve the solubility of this compound in water and advantage its usage in experimental conditions (Akagawa et al., 2016b).

PQQ can be derived from numerous nutritional and dietary sources, such as tea, fermented soybeans, kiwi, pepper, and parsley (Kumazawa et al., 1995; Mitchell et al., 1999). Different methods and assays for evaluating the presence of PQQ in foods have been developed, although the content of PQQ described from these is highly variable due to PQQ's tendency to produce derivatives and condensation products with other nutrients (Ameyama et al., 1985; Bergethon, 1990; Kumazawa et al., 1995; Mitchell et al., 1999; Noji et al., 2007). Analyzing the PQQ content in various dietary sources by a method based on gas chromatography/mass spectrometry, it has been estimated a PQQ content ranging from 3.7–61 ng/g wet weight (or ng/mL for liquid foods) (Kumazawa et al., 1995). Another study using a reliable liquid chromatography and electrospray-ionization tandem mass spectrometry established that PQQ was contained in food at an amount of 0.19–7.02 ng/g fresh weight or ng/mL in liquid foods, with mustard, parsley, and natto (fermented soybeans) containing the highest amount (Noji et al., 2007). In addition, a recent study combining enzymatic and mass spectrometric analyses indicated that vinegar has higher levels of PQQ than beer (Kato et al., 2018). PQQ has also been found in human milk in an estimated concentration of 20–30 or 140–180 μg/L if considered without or with its various derivatives created from the reaction with non-branched chain amino acids (Jonscher et al., 2021). The estimated amount of PQQ consumed per day is 0.1–1 mg based on the available data of food composition (Harris et al., 2013).

Nutritional role of PQQ: is PQQ a "new vitamin"?

Although reported in over hundreds of different prokaryotes, the biosynthesis of PQQ has not been demonstrated in higher organisms, suggesting that the major source of this compound in plants and animals is either from microflora or from the diet. Since the common strains of bacteria in the human gut seem to have little capacity for synthesizing PQQ, a likely route for PQQ to enter human tissues is dietary consumption (Akagawa et al., 2016b). The presence of PQQ in several different foods gives the possibility to introduce this compound through the diet and provides the potential of a putative supplementation in case of deficiency. In this respect, the nutritional

importance of PQQ in regulating mammalian health has been demonstrated under PQQ nutritional deficiency, where deficits in reproduction, growth, development, and immune performance occur (Steinberg et al., 1994., 2003). In mice fed with a PQQ-deficient diet, reproductive performance in terms of conception (the percentage of females giving birth to living pups) and fertility (indicated as the percentage of births) were impaired together with a decreased number and survival rate of pups per litter (Steinberg et al., 1994, 2003). Offspring from mice fed in the absence of PQQ seems to have a reduced growth rate, which has been demonstrated to require a dose of 300 ng/g of dietary PQQ to be optimal for survival (Steinberg et al., 1994). The reduced growth rate was further supported by the associated decrease in mRNA levels of Type I procollagen α1-chains in skin and lungs and a lower lysyl oxidase accumulation in neonatal mice, indicating a likely reduced capacity of neonatal extracellular matrix production and maturation in the absence of dietary PQQ (Steinberg et al., 2003). Mice raised in PQQ-deficient conditions displayed reduced response to mitogens by splenic cells, further supporting the likely role of PQQ as an essential nutrient for supporting animal growth (Steinberg et al., 1994). As support to a reduced immune performance in the absence of PQQ, neonates from female mice fed with diets devoid of PQQ tend to have reduced levels of interleukin 2, an autocrine and paracrine growth factor important for T-cell proliferation (Steinberg et al., 1994). Considering the nutritional importance of PQQ in regulating all these different aspects of mammalian health, this compound has previously been considered a novel vitamin. In 2003, Kasahara and Kato cloned a mouse homolog of the yeast 2-amminoadipic acid reductase, called U26, and hypothesized its action as a PQQ-dependent dehydrogenase involved in metabolic degradation of dietary lysine (Kasahara and Kato, 2003). Since the authors of this paper identified a putative PQQ-binding motif believed to be conserved in PQQ-dependent bacterial dehydrogenases, they concluded that PQQ may be qualified as a newcomer to the vitamins belonging to the B group (Kasahara and Kato, 2003). Despite these findings, a current view of PQQ as a new vitamin has been questioned, since the conclusive evidence of a mammalian PQQ-dependent enzyme is still lacking, although Akagawa and colleagues recently identified some potential candidates (Felton and Anthony, 2005; Rucker et al., 2005; Bauerly et al., 2006; Akagawa et al., 2016a). Nonetheless, the clear evidence of the regulation of several aspects of mammalian health mediated by PQQ shows how this compound may have a nutritional importance regardless of its formal inclusion in the list of vitamins.

The possibility of using PQQ as a supplement also at high doses is further suggested by its safety demonstrated by pre-clinical and clinical studies of toxicity. Different genotoxic assays *in vitro* of $PQQNa_2$, represented by Ames test, *in vitro* chromosomal aberration tests, provided negative or weak positive results at high dosages, confirming the relative safety of PQQ (Nakano et al., 2013). Some genotoxic assays were also performed *in vivo* by micronucleus assay in mice, reporting no PQQ toxicity in bone marrow erythrocytes at doses up to 2000 mg/kg (Nakano et al., 2013). The acute and subchronic toxicity of oral PQQ was studied *in vivo* in rats administered with oral doses of this compound (Nakano et al., 2014, Liang et al., 2015). Nakano and colleagues tested the acute toxicity of BioPQQ™ by treating rats through oral gavage for a 14-day preliminary and a 28-day repeated-dose study, documenting at 14 days a sex-specific increase in relative kidney weights with associated histopathology, which resulted in augmented urinary proteins and crystals after 28 days of treatment (Nakano et al., 2014). Notably, these morphological signs of disease were reversible and disappeared after a period of recovery (suggesting the PQQ can be rapidly cleared) (Nakano et al., 2014). In addition, a subchronic assessment of 13 weeks of treatment was performed in the same study, identifying no signs of evident toxicity, as histopathological changes observed in the PQQ-treated group were not dose-dependent and happened similarly to control untreated groups (Nakano et al., 2014). The authors of this study set the median lethal dose at a range of 0.5–2.0 g/kg and the no-observed-adverse-effect-level at 100 mg/kg per day (Nakano et al., 2014). Liang et al. (2015) assessed a subchronic oral toxicity of 13 weeks of treatment confirming no evident signs of toxicity in rats, determining the no-observed-adverse-effect-level at 400 mg/kg per day, the highest dose the authors tested. Data on PQQ safety have been assessed also in humans through placebo-controlled, double-blinded safety studies in healthy patients, where 20 or 60 mg/d PQQ was administered for 4 weeks (Akagawa et al., 2016b). No adverse effects were reported in standard clinical blood tests. Urinary concentration of markers of renal damage was not detected at both doses, further supporting that PQQ can be a safe compound if administered orally (Akagawa et al., 2016b).

Despite the potential of PQQ's possible supplementation and safety, the bioavailability of this compound in several body systems after oral administration seems to be low. Smidt et al. (1991) estimated the absorption of PQQ by treating Swiss-Webster mice with oral $^{[14]}C$ PQQ to evaluate its absorption, tissue distribution, and excretion. The authors of this study indicated that PQQ can be readily absorbed in the lower intestine (62%) and excreted by the kidney (81%) within the first 24 hours from the administration (Smidt et al., 1991). However, the only tissues retaining a relevant abundance of PQQ after 24 hours were the skin and kidney, with some tissues such as the adrenal gland and brain displaying almost no presence of PQQ already after 6 hours from treatment, suggesting its poor bioavailability in these organs (Smidt et al., 1991). The peak of PQQ in human serum was observed after 3 hours of administration and its clearance in the serum parallels the change in urine (Harris et al., 2013).

Pyrroloquinoline Quinone Influence on Metabolism and Mitochondrial Mechanisms

There is evidence for the capacity of PQQ to potentially modulate the basic cell metabolism under physiological contexts. PQQ may regulate cell metabolism acting on different metabolic steps, which can be modulated either singularly or concomitantly to ultimately improve metabolic processes and increase ATP production. These mechanisms seem to be regulated in a very context-dependent

manner. For instance, PQQ has been reported to modulate pathways providing metabolic substrates fueling glycolysis or tricarboxylic acid cycle and oxidative phosphorylation (OXPHOS) to increase ATP production (Owen et al., 2002). In this respect, PQQ may be responsible for regulating several pathways connected to the metabolism of amino acids and lipids. PQQ deficiency alters lysine metabolism and plasma levels of amino acids such as threonine, serine, and glycine *in vivo* (Bauerly et al., 2006). In addition, the treatment with PQQ in healthy tissues such as the liver and optic nerve impacted amino acid metabolism, further supporting the role of PQQ in modulating amino acid metabolism in several tissues (Bauerly et al., 2006; Canovai et al., 2023). PQQ might be involved in regulating lipid metabolism since the deficiency of this compound results in altered plasma lipid composition and expression of enzymes connected to lipid metabolism in the liver and heart (Bauerly et al., 2011).

Another mechanism by which PQQ may influence metabolic processes is through its capacity to act as a cofactor for metabolic enzymes including lactate dehydrogenases (LDH; Akagawa et al., 2016a). Akagawa and colleagues identified LDH-A as a mammalian PQQ-binding protein in mouse NIH/3T3 fibroblasts and further characterized the reaction catalyzed by this enzyme *in vitro* using a purified rabbit muscle LDH. In this study, the authors showed that PQQ can bind LDH as a cofactor and promote the oxidation of NADH to NAD^+, catalyzing the reverse reaction converting lactate to pyruvate (Akagawa et al., 2016a). This latter substrate can in turn enhance energy production by promoting the mitochondrial tricarboxylic acid cycle and OXPHOS, leading to increased ATP synthesis (Arnold and Finley, 2023).

Increasing intracellular content of metabolic cofactors, such as NAD^+, is another mechanism potentially improving cell metabolism and likely being regulated by PQQ. In this respect, the incubation with PQQ *in vitro* has been reported to increase intracellular NAD^+ in cell lines such as HepG2 and NIH/3T3 cells (Zhang et al., 2015; Saihara et al., 2017). An enhanced expression in the nicotinamide phosphoribosyltransferase (NAMPT) gene (a key enzyme involved in NAD synthesis) has been identified concurrently with increased NAD^+ activity after the incubation of PQQ in HepG2 cell cultures, suggesting that in some contexts PQQ may enhance NAD production through the promotion of its biosynthetic pathways (Zhang et al., 2015). As a support, the promoted increase in total NAD has been further documented *in vivo*, where Canovai et al. (2023) report an increased NAD content following PQQ administration in some districts of the visual system, such as the superior colliculus, in healthy mice.

PQQ has been reported to modulate mitochondrial mechanisms, particularly by acting on mitochondrial biogenesis. In effect, there are many studies documenting that PQQ can induce mitochondrial biogenesis through a likely influence on the activity of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and the expression of its target genes involved in the generation of new mitochondria (e.g., nuclear respiratory factor 1 and 2 and mitochondrial transcription factor A [TFAM]). These effects have been demonstrated in many different cell lines, including NIH/3T3 fibroblasts, 3T3-L1 adipocytes, SK-N-SH, HepG2 and Hepa1-6 cells, where the incubation of PQQ without the presence of stressors could promote the activation of PGC-1α and result in increased mitochondrial content and activity (Chowanadisai et al., 2010; Zhang et al., 2015; Saihara et al., 2017; Yamada et al., 2020; Ishak et al., 2021). However, the effects of PQQ on regulating the mitochondrial biogenesis in these cell lines are very context-dependent, with a wide range of effect intensity in different lines depending on the doses and incubation times used in the experiment. For instance, nanomolar doses of PQQ may promote the nuclear translocation of PGC-1α without affecting its total protein levels, which seem to be increased by the administration of micromolar doses (Chowanadisai et al., 2010; Zhang et al., 2015; Saihara et al., 2017; Yamada et al., 2020; Ishak et al., 2021). Across different cell lines, the same magnitude of effect (e.g., PGC-1α overexpression) has been documented under incubation with different concentrations of PQQ in different contexts (Yamada et al., 2020). Moreover, the same concentration of PQQ may result in different outcomes depending on the cell line, as suggested by an increase in total PGC-1α protein identified in Hepa1-6 but not in Hep2G cells following the incubation with 30 μM PQQ (Chowanadisai et al., 2010; Zhang et al., 2015). The context dependency of PQQ effects on mitochondrial mechanisms *in vitro* is further demonstrated in studies where PQQ administration was not able to induce mitochondrial biogenesis in normal human epidermal keratinocytes and dermal fibroblasts (Gruber and Holtz, 2022). The capacity of PQQ in regulating physiological mitochondrial content was further confirmed in *in vivo* systems, where the deficiency of PQQ leads to reduced mitochondrial number and function in the liver whilst having no apparent effect in the heart (Stites et al., 2006; Bauerly et al., 2011). In a recent study by Canovai et al. (2023), only a mild effect of PQQ administration on mitochondrial content in healthy retinal tissues was demonstrated after neither a short nor a long-term treatment, reporting only a small variation in NADH:Ubiquinone Oxidoreductase Subunit B8 (NDUFB8; a mitochondrial complex I marker) expression without any evident activation of mitochondrial biogenesis machinery. Taken together, these *in vivo* studies further suggest the context dependency of PQQ effectiveness in increasing mitochondrial content previously shown in *in vitro* experiments.

The regulation of metabolic substrate mobilization, the increased activity of metabolic enzymes and cofactors, and the improvement of OXPHOS through mitochondrial mechanisms can all enhance ATP production. By modulating these different mechanisms, PQQ can exert an ATP-boosting activity, which has been identified in several contexts *in vitro* and *in vivo*. ATP-boosting activity has been demonstrated by the dose-dependent induction of ATP synthesis in NIH/3T3 cells resulting from the exposure of PQQ *in vitro* (Akagawa et al., 2016a). This ATP-boosting effect has been further confirmed in other different cell lines and primary cultures, where the augmentation of cofactors and mitochondrial mechanisms seem to favor an increase in ATP pools (Saihara et al., 2017; Ebeling et al., 2020). In another study, Canovai et al. (2023) identified an increase in ATP content in *in vitro* models of dissociated cells from the brain cortex and visual

system tissues (e.g., dissociated retina, optic nerve, and superior colliculus). The authors further confirmed this ATP-boosting activity *in vivo* in healthy retinal ganglion cell-related tissues, showing a different temporal variation of ATP content among the retina, optic nerve, superior colliculus, and brain cortex (Canovai et al., 2023). In the specific context of retinal ganglion cell-related tissues, the authors attributed a likely moderate effect on mitochondrial mechanisms and the capacity of PQQ to change metabolic profiles of non-diseased retinal ganglion cell tissues, although other mechanisms could not be excluded and further investigated (Canovai et al., 2023). Considered as a whole, all these studies suggest the variability of mechanisms possibly regulated by PQQ showing the potential of this compound to influence basic cellular metabolism at different levels.

Neuroprotective Role of Pyrroloquinoline Quinone

Neuronal ATP depletion induced by metabolic and mitochondrial dysfunctions is a common feature of neurodegenerative diseases (Procaccini et al., 2016; Ferrington et al., 2020; Muddapu et al., 2020; Muench et al., 2021; Chen et al., 2022). In this context, neurons are extremely susceptible to metabolic fluctuations and require well-regulated ATP content control to sustain their high energy demand and guarantee their structural integrity and physiological activity. Slight imbalances in the mechanisms providing ATP synthesis under stress render neurons susceptible to additional disease–related stressors and trigger neurodegeneration. Given its capacity to regulate the basic cellular metabolism, PQQ may be a good candidate to improve neuronal resilience under stress by regulating all the metabolic processes promoting ATP production, thus increasing cell viability and favoring neuroprotection. In this respect, many studies have reported the neuroprotective capacity of PQQ in several neurodegenerative contexts with diverse types of acute and chronic injuries displaying different temporal and spatial dynamics. The investigation of the mechanisms by which PQQ exerts this neuroprotective action in some neurodegenerative contexts is still partially undefined, especially in determining a clear correlation between neuroprotection and metabolic regulation of PQQ under stress. There is emerging evidence of PQQ-driven improvement of metabolic processes concomitantly with neuroprotective properties. In other experiments, there is only a demonstration of neuroprotection without any data on metabolic mechanisms. Nonetheless, the neuroprotective efficacy of PQQ has been reported by many *in vitro* and *in vivo* studies.

PQQ and neuroprotection: *in vitro* evidence

Several *in vitro* studies suggest a neuroprotective potential of PQQ through the modulation of metabolism and mitochondrial mechanisms. There is mounting evidence documenting the efficacy of PQQ in counteracting *in vitro* neurodegeneration of primary cultures and cell lines under metabolic stress induced by the mitochondrial complex I inhibitor rotenone. In these studies, PQQ has been demonstrated to prevent the apoptosis of rotenone-treated SH-SY5Y cells and primary cultured midbrain neurons by restoring mitochondrial membrane potential, increasing mtDNA, and upregulating gene expression of mitochondrial complex I subunits, thus improving mitochondrial health and activity (Zhang et al., 2014, 2016; Qin et al., 2015). The administration of PQQ in rotenone-treated human SH-SY5Y cells can improve mitochondrial morphology under damage and prevent the decrease in biogenesis- and fission/fusion-related markers such as PGC-1α, TFAM, dynamin-related protein 1, and mitofusin 2 (Lu et al., 2018; Cheng et al., 2021). In these studies, ameliorated mitochondrial processes resulting from PQQ administration prevented neuronal stress-related dysfunctional features such as microtubular destabilization, tyrosine residue nitration, and dopamine redistribution (Qin et al., 2015; Zhang et al., 2016). In this context, several signaling pathways such as extracellular signal-regulated protein kinase 1/2 and AMP-activated protein kinase pathways appear to regulate the action of PQQ on mitochondrial mechanisms and antioxidant activity (Zhang et al., 2014; Cheng et al., 2021). The improved neuronal metabolism and mitochondrial function can reduce also oxidative stress, which can be a consequence of dysfunctional OXPHOS leading to increased toxic reactive oxygen species (ROS). In this respect, a reduced production of ROS concomitantly with an improved mitochondrial function and integrity has been demonstrated under rotenone injury (Zhang et al., 2014, 2016; Qin et al., 2015). The antioxidant activity of PQQ under pro-oxidative stressors seems to be also related to other mechanisms, such as the stimulation of many signaling pathways promoting the antioxidant defense and scavenging dangerous ROS, as phosphatidylinositol 3-kinase/Akt, Nrf2, and DJ-1 pathways, or by the modulation of ROS-producing receptors, as N-methyl-D-aspartate (NMDA) receptors (Aizenman et al., 1992, 1994; Scanlon et al., 1997; Zhang and Rosenberg, 2002; Nunome et al., 2008; Zhang et al., 2011, 2012b; Guan et al., 2015). These different mechanisms have been documented in different neuronal cell lines and primary cultures, such as rat primary forebrain neurons, primary hippocampal neurons, neural stem cells and progenitor cells, SHSY-5Y cells, neuroblastoma cell line (SK-N-H cells), where the administration of PQQ under pro-oxidative stress was neuroprotective. Whether these mechanisms act secondarily or in concomitance with the implementation of metabolic processes and enhance the benefits of PQQ in providing neuroprotection still needs to be clearly established. In addition, PQQ and its derivatives have been demonstrated to induce the production of nerve growth factor, a neurotrophic factor important for neuronal viability and considered to improve neuronal mitochondrial function (Yamaguchi et al., 1993, 1996; Urakami et al., 1995; Martorana et al., 2018; Ding et al., 2020). Besides the regulation of metabolic processes and antioxidant mechanisms, PQQ may exert neuroprotective effects secondarily by reducing the accumulation of toxic byproducts responsible for neuronal death. PQQ has been demonstrated to reduce *in vitro* aggregation and accumulation of aggregated amyloid-β $(Aβ)_{25–35}$, a toxic product inducing neuronal death in Alzheimer's disease, and α-synuclein, a protein involved in Parkinson's disease (PD) pathogenesis (Kobayashi et al., 2006; Zhang et al., 2009; Kim

et al., 2010; Li et al., 2021, 2022a). Taken together, these studies demonstrate the neuroprotective potential of PQQ *in vitro*, showing the complex interplay of different mechanisms by which PQQ may act to reduce neuronal cell death and provide neuroprotection. The wide range of mechanisms also depicts the context-dependent and the heterogeneity of these mechanisms, dictating the necessity to investigate PQQ mechanisms in disease- or system-specific contexts.

PQQ in neurodegenerative diseases: evidence in *in vivo* models

The neuroprotective properties of PQQ have also been assessed in several *in vivo* models of neurodegenerative disease where neuronal mitochondrial activity and energetical deficits occur (Folbergrová and Kunz, 2012; Moon and Paek, 2015; Hiebert et al., 2015; Kang et al., 2017; Park et al., 2018; Liu et al., 2018; Wang et al., 2020; Roberts, 2021; Bhatia et al., 2022; Slater et al., 2022; Li et al., 2022b; Fizíková et al., 2023). In some contexts, clear evidence of improved metabolic processes concomitantly with increased neuronal viability has been reported, whereas in some other diseases, this correlation has still to be established. The summary of *in vivo* studies testing the neuroprotection of PQQ, and the overall outcomes are detailed in **Table 1**.

Traumatic brain insults and ischemia

Brain functional impairment resulting from different types of insults, such as traumatic brain injury (TBI), intracerebral hemorrhage, and ischemic damage occur as a consequence of neuronal alterations when mitochondrial dysfunction is present (Hiebert et al., 2015; Liu et al., 2018; Li et al., 2022a). In these systems, mitochondrial impairment leads to energy depletion, ATP exhaustion, and increased ROS, triggering neuronal death. In this context, promoting neuronal metabolism by PQQ may improve neuronal energetic efficiency triggered by injury thus delaying the progression of neurodegeneration. The first study identifying PQQ neuroprotection under TBI was documented in a rat model of TBI where PQQ dose-dependently prevented behavioral deficits and morphological alterations in brain tissues (Zhang et al., 2012a). Neuroprotective properties of PQQ were further demonstrated by improved electroencephalogram and reduced apoptosis after administration of PQQ under brain damage (Ye et al., 2017; Zhang et al., 2017). Evidence of PQQ exerting neuroprotective effects has been reported in a rat model of intracerebral hemorrhage, where PQQ treatment inhibited the decline in locomotor activity, the formation of hematomas and brain edemas, reducing ROS and neuronal apoptosis following intracerebral hemorrhage (Lu et al., 2015). Treatment with PQQ has been also reported to reduce brain infarct size and neurobehavioral impairment in *in vivo* models of cerebral ischemia (Jensen et al., 1994; Zhang et al., 2006). Although the neuroprotection of PQQ has been demonstrated in all these models, the clear association of improved neuronal viability with a promoted metabolic activity still needs to be rigorously and empirically tested.

Epilepsy and schizophrenia

As metabolic and mitochondrial OXPHOS provide the vast majority of ATP for neuronal activity, the dysfunction in these mechanisms may strongly alter neuronal excitability and synaptic transmission. These are affected by many neurological and psychiatric disorders, such as epilepsy and schizophrenia (Folbergrová and Kunz, 2012; Ni et al., 2022; Fizíková et al., 2023). A growing body of evidence in the last decade reports the involvement of mitochondrial dysfunction and energetic deficit in these diseases, and the treatment with PQQ may improve clinical symptoms associated with these disorders. As support to this, PQQ has been reported to have a beneficial effect in animal models where epilepsy or schizophrenia is modeled pharmacologically. PQQ has been reported to reduce behavioral seizures *in vivo* after the induction of epileptic injury by pentylenetetrazol or bicuculline methiodide injection (Sanchez et al., 2000). In addition, the treatment with PQQ in a model of schizophrenia induced by the injection of non-competitive NMDA antagonist MK-801 was effective in reducing stereotypical behavior, ataxia, and cognitive impairment even if supplemented from pregnancy (Zhou et al., 2014, Peng et al., 2022). These beneficial effects of PQQ still need to be correlated with its capacity to modulate metabolic and mitochondrial processes, and secondary mechanisms affected by the administration of this compound cannot be excluded. Given the involvement of dysregulated activity of NMDA receptors in these disorders (Balu, 2016; Kapur, 2018) and the capacity of PQQ to modulate its activity, it is likely that the protective effect of this compound in these contexts may be favored in part by such mechanism.

Spinal cord injury

In the early stages of axonal degeneration following spinal cord injury, mitochondrial dysfunction occurs resulting in energy deficiency and ATP depletion. This promotes and exacerbates neuronal death (Liu et al., 2022; Cheng et al., 2023). PQQ administration may improve metabolism and mitochondrial function, delaying axonal degeneration and preserving spinal cord neuron activity. Functional recovery of spinal cord neurons after hemi-transection was documented following PQQ administration in a rat model of spinal cord injury, accompanied by reduced size of the lesion with increased density of axons, improved morphological features, and reduced neuronal apoptosis (Hirakawa et al., 2009; Zhou et al., 2021). Further work is needed to correlate this suggested neuroprotective property of PQQ with an ameliorated bioenergetic balance and mitochondrial function.

Alzheimer's disease

Metabolic alterations and mitochondrial dysfunctions have been reported to occur in the complex interplay of pathophysiological mechanisms influencing neuronal cell death in Alzheimer's disease (Kang et al., 2017; Bhatia et al., 2022). In this context, it has been reported that PQQ partially restores bioenergetic deficits of hippocampal synaptosomes in hemizygous transgenic McGill-R-Thy1-APP rats by improving mitochondrial function and reducing oxidative stress, thus resulting in reduced cognitive impairment (Martino Adami et al., 2017). The neuroprotective efficacy of PQQ in Alzheimer's disease is further suggested by another study in the APP/PS1

Table 1 | **Summary of *in vivo* studies testing PQQ neuroprotection in models of neurodegenerative diseases**

Disease	Species	PQQ dose	Route	Overall outcome	Reference
AD	Mouse	6, 12 mg/kg/d (given as Li3PQQ)	Gastric gavage daily for 8 wk	Improved cognitive performance and hippocampal synaptic plasticity; reduced accumulation of amyloid and phosphorylated tau	Zhao et al., 2014
AD	Rat	2 mg/kg for water administration + 20 mg/kg/d supplementation	Water from weaning to 6 mon + supplementation by oral gavage for 30 d	Prevented cognitive impairment and improved synaptosomes' bioenergetic capacity	Martino Adami et al., 2017
Epileptic seizures	Rat	20 mg/kg	i.p. injection 30 min before the induction of seizures	Reduced behavioral seizures	Sanchez et al., 2000
Hypoxia/ischemic brain	Rat	10, 20 mg/kg	i.p. injection either before or after hypoxia	Reduced infarct size	Jensen et al., 1994
ICH	Rat	5, 10 mg/kg	i.p. injection every 24 h for 2 wk before IHC and for different time points after injury (1, 2, 3, 5, 7 d)	Improved locomotor function; reduced hematoma volume and brain edema; decreased ROS and apoptosis	Lu et al., 2015
PD	Rat	6 μL of 333 μM (low dose) or 4 μL 1.5 mM (high dose)	Intracerebral injection together with rotenone (inducer of PD)	Prevented cognitive decline; decreased neural loss; increased antioxidant ability; increased expression of mitochondrial complex I markers, tyrosine hydroxylase, and vesicular monoamine transporter 2	Qin et al., 2015
PD	Rat	0.4, 2, 10 mg/kg/d	i.p. injection daily for 8 wk	Prevented cognitive decline; decreased neural loss; increased antioxidant ability; increased expression of mitochondrial complex I Ndufs1/4 and tyrosine hydroxylase	Zhang et al., 2016
PD	Rat	0.4, 2, 10 mg/kg/d	i.p. injection daily for 8 wk	Increased levels of PGC-1α, TFAM, Drp-1 and Mfn2	Lu et al., 2018
PD	Mouse	0.8, 4, 20 mg/kg/d	i.p. injection daily for 1, 2, or 3 wk	Reduced locomotor deficits and nigral dopaminergic neuron loss; diminished reduction of mitochondria number and their morphological disruption; blocked reduction in the expression of PGC-1α and TFAM	Cheng et al., 2021
PD	Fruit fly	0.3 mM	Supplemented in the cornmeal-agar medium for 25 d	Increased PPL1 dopaminergic neurons and mitochondrial area	Cheng et al., 2021
Retinal ganglion cell-related stress	Mouse	20 mg/kg/d	i.p. injection daily	Reduced retinal ganglion cell loss	Canovai et al., 2023
Reversible middle cerebral artery occlusion	Rat	1, 3, 10 mg/kg	Intravenous injection at the initiation or after ischemia	Reduced brain infarct size and improved neurobehavioral scores	Zhang et al., 2006
Schizophrenia	Mouse	0.2, 2, 20 μg/kg/d	i.p. injection for 60 d	Reduced stereotypical behaviors, ataxia, learning and memory deficits	Zhou et al., 2014
Schizophrenia	Mouse	5 μg/mL	Drinking water during pregnancy and after birth of the pups	Reduced stereotypical behaviors, ataxia, learning and memory deficits, social interaction disorders, depression	Peng et al., 2022
SCI	Rat	5 mg/kg	i.p. injection after the injury	Improved locomotor activity and neuronal morphology; reduced inflammation and apoptosis	Zhou et al., 2021
SCI	Rat	5 mg/kg	i.p. injection immediately after injury and once every 24 h for 7 d	Recovered locomotor function; reduced lesion size; increased axonal density	Hirakawa et al., 2009
TBI	Rat	2 mM	Microinjected intracerebrally after TBI	Reduced neuronal apoptosis; improved electroencephalographic responses	Zhang et al., 2017
TBI	Rat	1, 2 mM	Not specified	Reduced brain apoptosis	Ye et al., 2017
TBI	Rat	5, 7, 10 mg/kg	i.p. injection for 3 d before TBI and consecutively until the end of the experiment (9 d)	Improved behavioral performances and reduced brain injury	Zhang et al., 2012a

AD: Alzheimer's disease; Drp-1: dynamin-related protein-1; ICH: intracerebral hemorrhage; Mfn2: mitofusin 2; Ndufs: NADH:ubiquinone oxidoreductase core subunit; PD: Parkinson's disease; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator-1α; PPL1: protocerebral posterior lateral 1; ROS: reactive oxygen species; SCI: spinal cord injury; TBI: traumatic brain injury; TFAM: mitochondrial transcription factor A.

mice model, where the administration of PQQ in combination with lithium reduced the deposition of cerebral $A\beta_{1-42}$ and phosphorylated tau, resulting in decreased impairment of learning and memory and improved hippocampal synaptic plasticity (Zhao et al., 2014).

Parkinson's disease

Mitochondrial dysfunction and oxidative stress have been considered to have a central role in the establishment of PD pathogenesis and resulting in the selective death of dopaminergic neurons of the substantia nigra pars compacta (Wang et al., 2020). There is evidence suggesting the ability of PQQ to protect dopaminergic neurons from death occurring in PD by ameliorating mitochondrial processes. The administration of PQQ in a rat PD model (obtained by injecting rotenone in the medial forebrain bundle) reduced

the decline in cognitive functions and neuronal loss, improved ROS scavenging and the expression of mitochondrial complex subunits together with tyrosine hydroxylase and vesicular monoamine transporter 2 (Qin et al., 2015; Zhang et al., 2016). In this respect, the treatment with PQQ in this rat PD model could inhibit the decline in the levels of mitochondrial dynamics-related markers such as PGC-1α, TFAM, dynamin-related protein 1, and mitofusin 2 in the midbrain following rotenone injection (Lu et al., 2018). Similarly, in a mouse model of PD obtained by intraperitoneal injection of rotenone, PQQ dose-dependently reduced locomotor deficits and nigral dopaminergic neuron loss, whilst preventing mitochondrial loss and morphological impairment and increasing the levels of PGC-1α and TFAM (Cheng et al., 2021). The pharmacological stimulation of the PGC-1α ortholog spargel in Drosophila by PQQ reduced dopaminergic neural loss and increased mitochondrial area in PD flies (Ng et al., 2017). Taken together, these studies suggest the potential of PQQ as a novel compound to improve mitochondrial function and treat neuronal degeneration occurring in PD.

Retinal degenerations

Only in the last few years, the potential of PQQ as a novel therapeutic in retinal diseases has been raised. There are only a few reports describing the beneficial effects of this compound in treating retinal alterations induced by metabolic dysfunctions occurring in different retinal pathologies. A recent paper from Ebeling and colleagues is, to our knowledge, the first study showing that PQQ may have a beneficial role in treating the dry form of age-related macular degeneration, a retinal disease where photoreceptors degenerate following retinal pigment epithelium degeneration that occurs as a consequence of mitochondrial and metabolic dysfunction (Ferrington et al., 2020). In these studies, PQQ was reported to upregulate mitochondrial proteins and improve mitochondrial function and ATP production in retinal pigment epithelium cells from age-related macular degeneration donors, providing evidence of the potential of PQQ for additional studies in retinal diseases (Ebeling et al., 2020). This potential of PQQ in treating retinal neurodegenerative diseases has been further investigated in other studies focusing on disorders involving another cell type, such as retinal ganglion cells, which degenerate in several diseases including glaucoma, autosomal dominant optic atrophy, and Leber's hereditary optic neuropathy. Since in these pathological contexts, mitochondrial dysfunction and metabolic disruption concur in rendering retinal ganglion cells susceptible to damage and death, it was hypothesized that PQQ might confer bioenergetic support and protect these cells from degeneration induced by stressors. For this reason, Canovai and colleagues investigated the neuroprotective potential of PQQ in different models of retinal ganglion cell stress and studied the metabolic mechanisms by which this compound may alter the retinal bioenergetic balance. The authors of this study demonstrated that PQQ was neuroprotective in two different models of retinal ganglion cell stress, where either acute axonal damage or mitochondrial dysfunction induced an impaired bioenergetic balance with ATP depletion resulting in retinal ganglion cell death (Canovai et al., 2023). They identified an ATP-boosting activity and alteration of metabolic profiles in non-diseased retinal ganglion cell-related tissues, suggesting a likely mechanism by which PQQ exerts neuroprotective effects in retinal ganglion cell contexts, although a clear correlation between neuroprotection and improved metabolic processes still needs to be established, e.g., via specific genetic knockouts in mice (Canovai et al., 2023). Taken together, these data suggest the potential of PQQ as a novel adjuvant for the treatment of retinopathies, especially those that are characterized by metabolic dysfunction and altered bioenergetic balance.

Evidence of PQQ benefits in neuronal districts in humans

Evidence of PQQ neuronal benefits has been provided also in humans through several clinical trials describing the effect of PQQ supplementation on improving memory. A randomized, placebo-controlled, double-blinded study investigated the capacity of PQQ to improve cognitive function in elderly healthy patients by supplementing PQQ for 12 weeks and demonstrating functional improvements in attention and working memory (Itoh et al., 2016). Itoh and colleagues identified an increased prefrontal cortex blood flow and oxygen metabolism (Itoh et al., 2016; Nakano et al., 2016). The capacity of PQQ to improve cognitive function in healthy humans was further confirmed in additional clinical trials, where PQQ has been reported to improve brain function in both younger and older adults (Shiojima et al., 2022; Tamakoshi et al., 2023).

Future Perspectives

Considering the wide range and the strict context dependency of mechanisms related to metabolism and regulated by PQQ, the study of its effects in a specific system and disease is always recommended before drawing wide conclusions. Regarding neurodegenerative diseases, the necessity of fully elucidating the mechanisms behind which PQQ exerts its neuroprotective properties is fundamental. This is especially important if one considers that metabolic processes are characterized by a complex interplay of different components, which can be modulated by this compound either singularly or synergistically. In this respect, there is a need to further study what aspects of metabolism are regulated in different neurodegenerative disorders and if these mechanisms are shared among diseases or just typical of single pathological contexts for specific cell types. In addition, for several contexts, the clear correlation between neuroprotective properties of PQQ and its capacity to improve neuronal metabolism and mitochondrial function needs to be further investigated and confirmed. This correlation is required as PQQ may have many other different secondary effects, which might contribute to protecting neurons from degeneration or may be the downstream consequence of improved metabolism and neuronal viability. The molecular pathways affected by PQQ are still to be extensively characterized, although the involvement of AMP-activated protein kinase, serine–threonine liver kinase B1, phosphatidylinositol 3-kinase/Akt, and PGC-1α has been suggested in some contexts but not confirmed in others (Chowanadisai et al., 2010; Zhang et al., 2014, 2015; Saihara et al., 2017; Lu et al., 2018; Yamada et

al., 2020; Cheng et al., 2021; Ishak et al., 2021; Canovai et al., 2023). To further study what pathways may be involved in PQQ mechanisms, knockout lines, and model animal tools are essential to dissect the different actors playing in the complex regulation of such compounds. In this respect, it may be fundamental to study if PQQ binds to some specific targets and the type of interactions they establish. Moreover, it is of paramount importance to assess if the mechanisms that PQQ is able to regulate in basic non-disease conditions are still influenced by the treatment with this compound under stress conditions and *vice versa*. For instance, Canovai and colleagues reported an ATP-boosting activity of PQQ in healthy retinal ganglion cell-related tissues with a concomitant moderate effect on mitochondrial mechanisms and variations in the whole metabolome (Canovai et al., 2023). It would be interesting to assess whether the same mechanisms are regulated by PQQ in these tissues under stress conditions or if the treatment with PQQ in the presence of stressors results in different outcomes.

Since PQQ can modulate metabolic processes in different aspects, all the neurodegenerative diseases characterized by metabolic dysfunction as one of the pathophysiological events determining neuronal death may benefit from PQQ administration. Dysfunctional metabolism and OXPHOS have been reported as common mechanisms occurring in different neuronal disorders in different districts of the nervous system, such as amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis (Procaccini et al., 2016, Muddapu et al., 2020). Consequently, testing the efficacy of PQQ in providing neuroprotection in such contexts may be a good strategy for studying a novel therapeutic tool to delay the progress of the disease. In retinal diseases, there is a wide range of disorders where metabolic disruption and mitochondrial dysfunction play a critical role in determining retinal cell death. In particular, retinal ganglion cells are very susceptible retinal neurons with a fine-tuned metabolism requiring a strictly controlled ATP production for their activity. The ATP-boosting capacity and the neuroprotective capacity of PQQ might be fundamental to protect retinal ganglion cells from death, as the preliminary data of PQQ protection in models of acute retinal ganglion cell stress from Canovai and colleagues might suggest (Canovai et al., 2023). Future investigations in specific models of these diseases will be essential to further assess and confirm the neuroprotective potential of PQQ as a novel adjuvant therapy to treat such disorders.

Another issue to solve with PQQ is represented by its poor bioavailability, especially in neuronal tissues. Pharmacological studies are needed to assess the exact PQQ bioavailability and its pharmacokinetics in brain and retinal tissues, as well as the assessment of putative derivatives, which might be involved in the effects identified from the treatment of this compound. There is the necessity of finding a feasible and easy administration route with a proper bioavailability to reach the neuroprotective effect with a non-invasive administration. Dietary/oral administration, which may be the most practicable way to give PQQ since it is contained in food, has not been demonstrated to give a sufficient bioavailability in neuronal tissues from the studies held so far. Oral administration of PQQ in mice resulted in a poor brain bioavailability after 6 and 24 hours from the administration (Smidt et al., 1991). In addition, previous work by Canovai and colleagues identified a negligible effect of orally given PQQ (in the form of BioPQQ, the disodium salt) in modulating ATP and NAD content in tissues from the visual system and brain cortex, suggesting that the dietary administration at that dose could not reach an effective bioavailability in such tissues (Canovai et al., 2023). Further development is required to establish a proper dose sufficient to provide a good PQQ bioavailability to have metabolic effects and provide neuroprotection if PQQ needs to be administered by oral routes. Strategies of drug delivery systems might be useful to further improve the bioavailability of PQQ by favoring its mobility across body barriers and increasing the concentration of PQQ in body systems (e.g., absorption in the gastrointestinal tract and blood-brain barrier permeability). The possibility to synthetize chemically engineered stabilized versions or include PQQ in carries such as liposomes or nanoparticles may improve its stability and increase its bioavailability, resulting in a potentiated effect. Alternatively, the design of slow-release or packaged formulations or a combinatory treatment with other compounds, which may synergistically act with PQQ might represent different strategies to further improve the outcomes and reach a better neuroprotection.

Taken together, although promising, there is a lot of work to do before considering the translation of PQQ to clinical settings, especially in the context of neurodegenerative disease. A deep understanding of PQQ mechanisms, the assessment of its efficacy in complex models of neurodegeneration, and the study of its pharmacology in the body systems are fundamental steps that need to be done before starting the administration of PQQ in the clinical management of neurodegenerative diseases. Studies assessing the correct absorption, distribution, metabolism, and excretion in humans may add more information about PQQ pharmacology and help to design further studies evaluating its efficacy and mechanisms. Identifying the optimal route of administration and the optimal dosage of PQQ in order to have significant effects with low invasiveness and high compliance in humans would be a reasonable aim in the future to favor the use of PQQ in clinical settings.

Conclusions

The capacity of PQQ to regulate basic cellular metabolism suggests that PQQ has the potential to be a good neuroprotective compound in the pathological contexts where metabolic imbalances and ATP depletion occur (**Figure 1**). Improved metabolic and mitochondrial metabolism and homeostasis under treatment with PQQ may improve neuronal resilience and cell viability, ultimately delaying the progression of neurodegeneration. Although further studies are needed to better characterize the metabolic processes regulated by PQQ in several neurodegenerative diseases, the potential of PQQ as a novel adjuvant neuroprotectant supplementing the existing therapies is supported by several studies. The presence of PQQ in food and the possibility to administer this compound by oral supplementation presents an opportunity to use PQQ as a future tool in the clinic with a low risk of side effects if optimized for dosage and delivery system in humans.

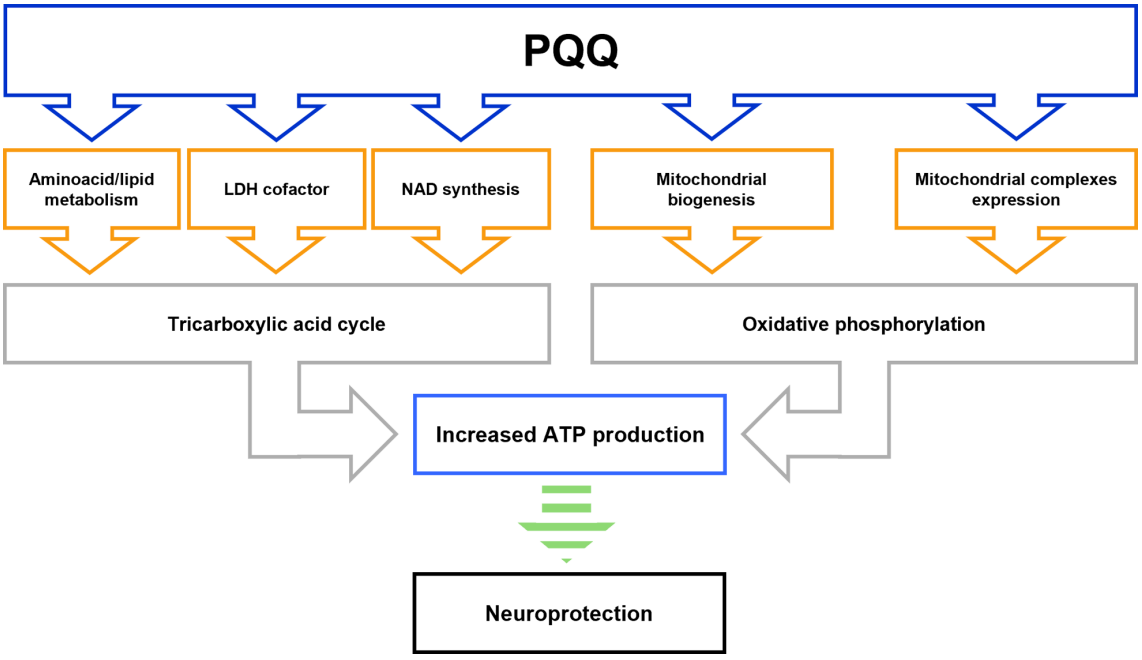

Figure 1 | Schematic diagram depicting the metabolic processes that are potentially regulated by PQQ under physiological conditions and may provide neuroprotection.
PQQ has been reported to influence many metabolic mechanisms fueling tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), thus regulating basic cell metabolism. In particular, PQQ can modulate cell metabolism by influencing amino acid and lipid metabolism, acting as lactate dehydrogenase (LDH) cofactor, promoting nicotinamide adenine dinucleotide (NAD) synthesis, inducing mitochondrial biogenesis and complexes expression. These mechanisms can be regulated by PQQ either singularly or synergistically, in a very context-dependent manner among different systems. The modulation of these metabolic processes can improve TCA cycle and potentiate the oxidative phosphorylation (OXPHOS), thus resulting in increased adenosine 5′-triphosphate (ATP) production. The neuroprotective properties of PQQ documented in many different models of neurodegeneration may be related to its capacity to promote neuronal metabolism, although in some contexts this strict association needs to be further confirmed (and hence indicated in the figure by the green dotted arrow). Created with Microsoft PowerPoint. PQQ: Pyrroloquinoline quinone.

Author contributions: *Conceptualization, manuscript writing and revision: AC, PAW; literature search and analysis: AC. All authors have read and approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Data availability statement: *The data are available from the corresponding author on reasonable request.*

Open peer reviewer: *Robert B. Rucker, University of California, Davis, USA.*
Additional file: *Open peer review report 1.*

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P-Reviewer: Rucker RB; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y