REVIEW

The effects of pyrroloquinoline quinone disodium salt on brain function and physiological processes

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Abstract : Pyrroloquinoline quinone disodium salt (PQQ) is a red trihydrate crystal that was approved as a new food ingredient by FDA in 2008. Now, it is approved as a food in Japan and the EU. PQQ has redox properties and exerts antioxidant, neuroprotective, and mitochondrial biogenesis effects. The baseline intake level of PQQ is considered to be 20 mg/day. PQQ ingestion lowers blood lipid peroxide levels in humans, suggesting antioxidant activity. In the field of cognitive function, double-blind, placebo-controlled trials have been conducted. Various improvements have been reported regarding general memory, verbal memory, working memory, and attention. Furthermore, a stratified analysis of a population with a wide range of ages revealed unique effects in young people (20–40 years old) that were not observed in older adults (41–65 years old). Specifically, cognitive flexibility and executive speed improved more rapidly in young people at 8 weeks. Co-administration of PQQ and coenzyme Q10 further enhanced these effects. In an open-label trial, PQQ was shown to improve sleep and mood. Additionally, PQQ was found to suppress skin moisture loss and increase PGC-1α expression. Overall, PQQ is a food with various functions, including brain health benefits. J. Med. Invest. 71 : 23-28, February, 2024

Keywords **:** *Pyrroloquinoline quinone, Clinical study, Brain, Cognitive*

INTRODUCTION

Pyrroloquinoline quinone disodium salt (PQQ) is a water-soluble red crystal manufactured by Mitsubishi Gas Chemical, which was approved as a new food ingredient by the Food and Drug Administration in 2008. Now, the product is also approved for consumption in Japan and the EU (1). The product name is BioPQQ in the US and Japan, and MGCPQQ in the EU. It is produced by microbial fermentation and offered in a highly purified crystal form (trihydrate) (Figure 1a) (2), which is GMP-certified by the Japan Health Food Standards Association.

PQQ (Figure 1) was discovered as a coenzyme contained in bacterial dehydrogenase (3). The primary producer of PQQ is a microorganism found in vegetables (potatoes, spinach, parsley, and green peppers), fermented foods (natto and miso), and human tissues at 1–30 ng/g, according to *in vitro*, animal, and human studies (4, 5). PQQ has gained significant attention because it exhibits growth-promoting, antioxidant, anti-inflammatory, neuroprotective, nephroprotective, mitochondrial biogenesis, and cell signaling properties (6).

1. PQQ structure and properties

Pyrroloquinoline quinone is a tricarboxylic acid with a quinone structure, pyridine, and pyrrole (Figure 1b). The quinone structure is easily reduced by biological substances (glutathione, NADH, amino acids, ascorbic acid) and changes to a hydroquinone structure (pyrroloquinoline quinol : reduced PQQ) (Figure 1c). Reduced PQQ has strong antioxidant power (7). In addition, this reduced PQQ is oxidized in the air and converted back to PQQ (8). It is known that a small amount of hydrogen peroxide is generated in the PQQ conversion process, which causes the oxidation of protein thiols (9). This results in the inhibition of protein tyrosine phosphatase 1B (PTB1B), which is a direct negative regulator of insulin receptors, insulin-like receptors, epidermal growth factor receptors (EGFR), and nerve growth factor receptors. Inhibition of PTP1B by PQQ causes a ligand-independent activation of insulin receptors and EGFRs. Therefore, PQQ may function as a growth factor (10).

Although the reduced form of PQQ has extremely high antioxidant properties, PQQ itself does not have antioxidant properties. PQQ is thought to exert its antioxidant properties through *in vivo* reduction. Oxidation and reduction play important roles in the physiological activity of PQQ, regulating the activity of lactate dehydrogenase and helping to increase ATP levels (11). In a clinical trial, antioxidant activity was measured using a method

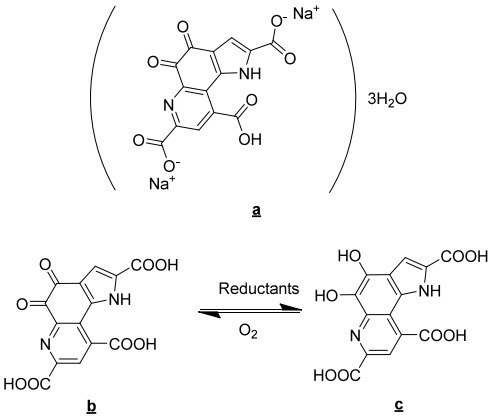

Figure 1. Structure and properties of pyrroloquinoline quinone. Top : Pyrroloquinoline quinone disodium trihydrate (PQQ, Mw 428.22 g/mol) (**a**) is a red crystal with applications in food. Bottom : Redox reaction between pyrroloquinoline quinone (**b**) and reduced pyrroloquinoline quinone (**c**).

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called TBARS. This method measures malondialdehyde, which is a byproduct of lipid peroxidation. After a single dose of PQQ (0.2 mg/kg body weight), a significant decrease in TBARS levels was observed. Furthermore, the decrease in TBARS levels was correlated with the peak plasma concentration of PQQ, demonstrating PQQ antioxidant activity in humans (12).

Moreover, growth defects and decreased immune function have been reported in mice and rats fed diets deficient in PQQ (13). In nematodes, PQQ was shown to increase the activity of the dual oxidase 2 enzyme, leading to longevity (14). Therefore, PQQ is nutritionally important and may be considered a vitamin (15). PQQ has been associated with antioxidant, mitochondrial biogenesis, and *in vitro* neuroprotective properties. In this paper, we discuss the PQQ effect on brain cognitive functions by describing the pertinent clinical trials and explaining the mechanism based on *in vitro* and *in vivo* studies.

2. Safety of PQQ ingestion

The safety of PQQ has been assessed by the European Food Safety Authority. An intake level of 20 mg/day is recommended for effective use as a functional food, which is at least 250 times higher than the estimated background intake of PQQ naturally occurring in food. No adverse effects were observed in an animal study after 90 days of oral administration at a high dose of 1,000 mg/kg/day. Additionally, no adverse effects were observed in a clinical trial in humans in which 100 mg/day of PQQ was taken for 24 weeks (16). Based on these findings, PQQ is a highly safe nutritional supplement (1).

In 1991, male Swiss-Webster mice (n = 5 at each time point) were given a single oral dose (1.5 mg/kg) of radiolabeled (^{14}C) PQQ (17). Based on the amounts retained in tissues, urine, and carbon dioxide, 3.3% of the dose was absorbed after 6 hours. Approximately 81% (range 62%–96%) of the absorbed radioactivity was excreted in the urine within this period, with the remaining 10.7% distributed in the kidneys (10.7%), liver (1.5%), skin (1.3%), blood (1.2%), and other tissue (3.7%). No radioactivity was detected in the exhaled breath.

The first study of PQQ metabolism in humans included healthy adults (5 males and 5 females) who received PQQ at doses of 0.075, 0.15, and 0.3 mg/kg/day (equivalent to 5.25, 10.5, and 21 mg PQQ/day for individuals weighing approximately 70 kg) (12). The doses were administered for 7-day periods. Approximately 0.1% of the administered PQQ was recovered in urine as nonderivatized PQQ. Serum concentrations of nonderivatized PQQ increased up to 14 nM in response to dietary intake of PQQ at a dose of 0.3 mg/kg/day.

Single doses (2 mg/kg, equivalent to 14 mg PQQ for a 70 kg body weight) were also administered to 5 male and 5 female subjects. Blood and urine samples were collected at 0, 2, 4, 8, 24, and 48 hours after dosing. Serum concentrations of PQQ reached 9 nM (approximately 3.4 ng/mL) 2 hours after dosing. The increase and elimination of PQQ concentrations in blood correlated with changes in urine concentrations.

A high-dose clinical trial based on 100 mg/day of PQQ intake was conducted in humans (16). PQQ was not detected in the blood prior to dosing. The concentration of PQQ reached 16–54 nM 3 hours after administration, but after 24 hours, only trace amounts were detected. Furthermore, after 6 days of continuous intake, PQQ was detectable even before PQQ intake, indicating that continuous administration increases basal PQQ concentrations. However, the blood concentration of PQQ varied by 62% RSD between individuals. In summary, PQQ is absorbed from the intestines and excreted in the urine. PQQ is metabolized quickly, reaching peak blood levels in 2–3 hours, and then decreasing to low levels after 24 hours. Repeated intake of PQQ is safe and potentially effective, but absorption varies greatly from person to person.

3. Clinical studies on brain function

Initially, the effect of PQQ on brain function received significant attention, and cognitive function improvement tests have mainly been conducted on human subjects. The research is summarized in Table 1. Various tests have been used to examine cognitive function. A recent report used a computer-based cognitive function test called Cognitrax to examine the effects of 20 mg/day of BioPQQ in healthy adults (20–65 years old) (18). This is the first time that PQQ was tested in young individuals (below 40 years old). In the younger group (20–40 years old), BioPQQ improved cognitive flexibility, processing, and execution speed after 8 weeks of supplementation, and in the older group, complex memory and verbal memory were enhanced after 12 weeks (Figure 2). It was unexpected that the young subjects, who are considered to have high brain function, experienced cognition improvement from PQQ. Many types of cognitive enhancement have been observed in older subjects within a limited age range (19). We believe that if the age variation in the study is reduced, significant differences among multiple types of enhancement, such as complex memory and verbal memory, can be observed

Table 1. Clinical studies on the effects of PQQ on cognition

	Cognitive function	Participant age	Condition* & finding	Ref
1	Composite memory, verbal memory (Cognitive flexibility, processing speed, executive speed)	41.5 ± 13.7 (20–40)	In the young (20–40 years), the effect appeared quickly (8 weeks)	18
2	Composite memory, verbal memory, cognitive flexibility, processing speed, executive speed reaction time, complex attention, motor speed	72.10 ± 3.77	21.5 mg/day PQQ	19
3	Attention, information identification, processing power	45–65	PQQ (20 mg/day) + CoQ10 (300 mg/day) compared with the placebo (P = 0.009)	20
4	Immediate memory	50–70	PQQ (20 mg/day) + CoQ10 (300 mg/day) group improved immediate memory when compared with the placebo at 8 weeks	21
5	Attention, working memory	58.6 ± 5.1	Lower score represents a stronger effect (attention)	23
6	language memory	50–71	PQQ (20 mg/day) compared with the placebo (P < 0.05)	24

*PQQ (20 mg/day) administered in a 12-week randomized, double-blind, placebo-controlled parallel study

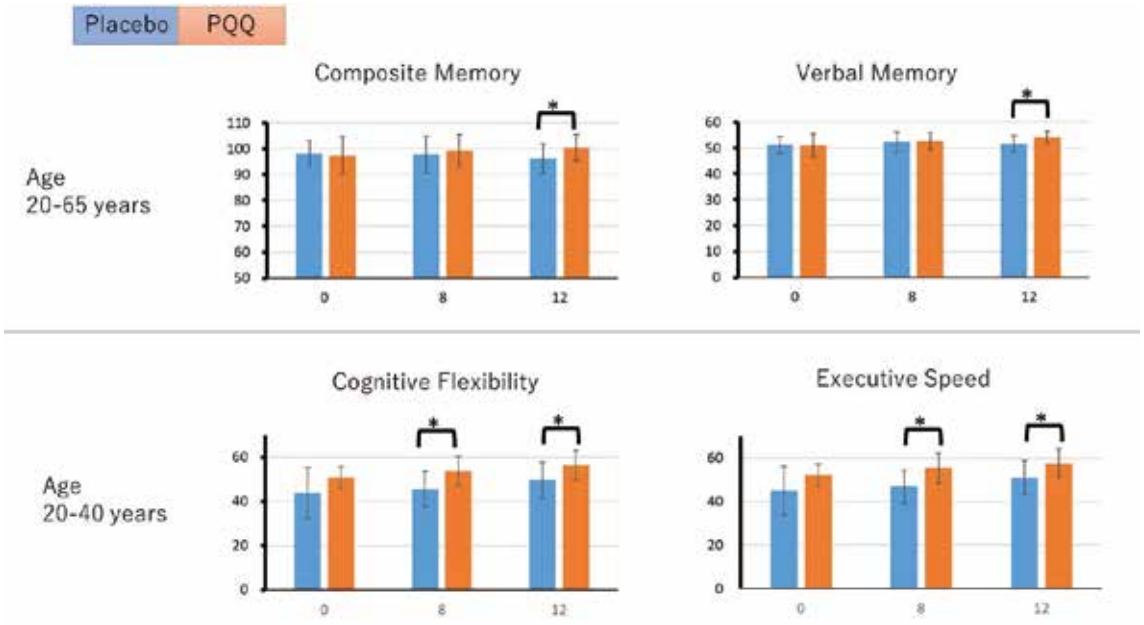

Figure 2. Cognitive tests for a wide age range of participants (20–65 years old) and younger participants (20–40 years old). Age 20–65 years group : Composite memory and verbal memory scores increased after 12 weeks. Age 20–40 years group : Cognitive flexibility and executive speed score increased after 8 weeks. (*; $p < 0.05$)

more easily in the same test. We propose the following hypothesis to explain the disparity in PQQ effectiveness between age groups. Young participants may not have demonstrated memory improvement due to their initially high baseline scores. Conversely, we predict that PQQ may significantly impact functions specific to younger individuals, such as those related to mitochondria or oxidative stress. This prediction is based on PQQ's potent abilities in mitochondrial biogenesis and antioxidant activity.

To evaluate the effects of BioPQQ (20 mg/day PQQ) alone and in combination with coenzyme Q10 (CoQ10 ; 300 mg/day) in healthy subjects, two randomized trials were conducted. A double-blind, placebo-controlled, parallel design study was conducted for 12 or 24 weeks (Table 1) (20, 21). The 12-week supplementation using BioPQQ + CoQ10 showed significant improvements in word recall compared with the placebo. BioPQQ alone tended to improve memory, but not significantly. Results of the 24-week study also showed significant improvements in short-term memory scores after 8 weeks of BioPQQ + CoQ10 supplementation, compared with the placebo. However, the effect did not persist after 24 weeks. When we stratified the data to compare those with low and high memory scores at baseline, BioPQQ + CoQ10 treatment for the low-score group showed significant improvement at weeks 8 and 16 compared with the placebo. This suggests that individuals with lower initial scores may have a greater response to BioPQQ and CoQ10 supplements than individuals with higher initial scores.

Recently, 20 mg/day of BioPQQ was tested for 12 weeks to further understand the role of PQQ on cognitive function and anxiety, resulting in improved word recall and visuospatial cognition, especially in older adults with reduced brain function (22). These improvements in cognitive function may be explained by increased prefrontal cerebral blood flow and enhanced oxygen metabolism, which was found in older adults who received the same dose of BioPQQ for 12 weeks (23). In healthy individuals with mild dementia, BioPQQ supplementation improved language scores compared with the placebo. From the Stroop test, which involves reading words with different colors and letters with different colors, an improvement in the Stroop interference rate was observed. This indicates an improvement in working memory. Moreover, the MoCA test consists of 30 points (Visuospatial : 5, Naming : 3, Attention : 6, Language : 3, Abstraction : 2, Delayed recall : 5, and Orientation : 6), and BioPQQ improved brain function in the language field in humans (24). These studies indicate that PQQ is effective in improving cognitive function in healthy people.

4. Molecular mechanism of PQQ effects

PQQ has gained attention for its potential cognitive-enhancing properties. Based on *in vitro* and *in vivo* studies, PQQ improves cognitive function by exerting neuroprotective and cell function enhancement effects. Figure 3 shows the putative mechanism of PQQ effects on brain cognitive functions. First, PQQ has neuroprotective activities (25-28), which means it can help protect neurons from damage and degeneration. As a potent antioxidant, PQQ protects brain cells from oxidative stress and damage caused by free radicals of reactive oxygen species, mainly by modulating NMDA receptors and activating the Akt/GSK3β signal pathway (29, 30). Furthermore, PQQ has anti-inflammatory properties that reduce inflammation in the brain, thereby preserving cognitive function. In a study of microglia cells, a type of cell located throughout the brain and spinal cord, pretreatment using PQQ significantly decreased NO and PGE2 production and suppressed the expression of pro-inflammatory mediators, such as iNOS, COX-2, TNF-α, IL-1β and IL-6, in lipopolysaccharide-induced inflammation cells. PQQ also reduced neuroinflammation via downregulated NF-κB and p38/JNK activation in microglia cells (31, 32). Considering that oxidative stress and chronic inflammation have been implicated in cognitive decline and neurodegenerative diseases (33), PQQ has the potential to be a viable therapeutic agent for slowing the progression of neurodegenerative disorders. PQQ

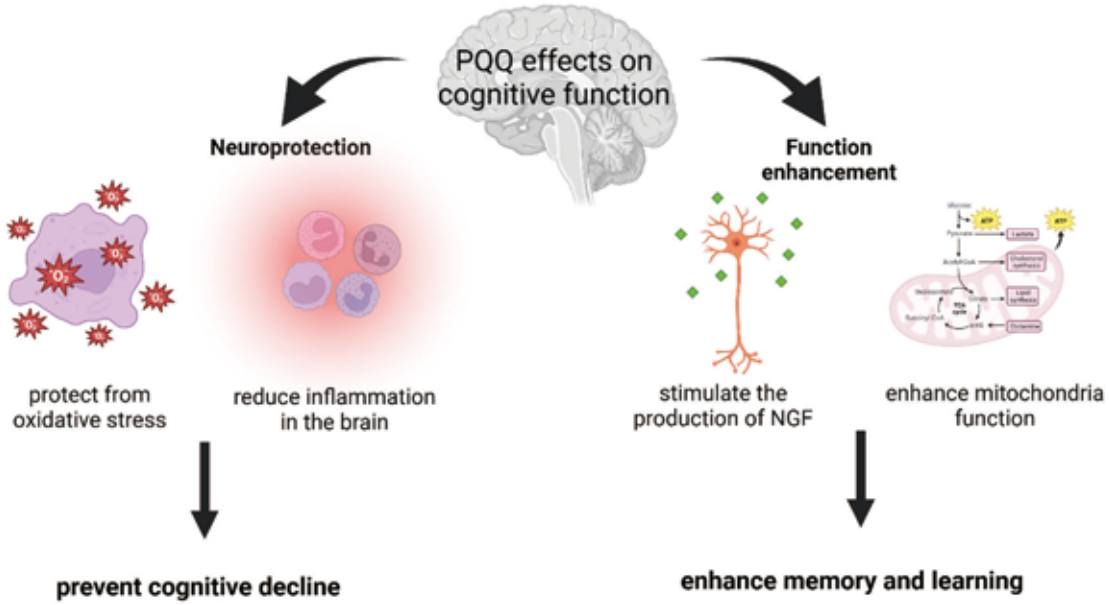

Figure 3. The mechanism of PQQ effects on brain cognitive functions.

neuroprotection may also slow down age-related cognitive decline. Notably, PQQ also showed a neuroprotective effect on traumatic brain injury in a rodent study (34).

Second, studies suggest that PQQ supplementation enhances memory and cognitive performance, particularly in tasks related to memory and learning. These effects may be related to the promotion of nerve growth factor (NGF) production (35, 36) and mitochondrial function (37). PQQ stimulates the production of NGF, an essential protein for the growth, maintenance, and repair of nerve cells (neurons), and PQQ supports mitochondria, including those in brain cells, by increasing PGC-1α gene expression, which is a transcriptional coactivator and central inducer of mitochondrial biogenesis. By enhancing mitochondrial function, PQQ may improve overall cellular energy production, which can benefit cognitive function (32, 37).

5. Other clinical studies of PQQ benefits

5.1. Stress, fatigue, and sleep

Seventeen adult men and women participated in an open-label clinical trial designed to evaluate the efficacy of PQQ treatment (20 mg/day for 8 weeks) on stress, fatigue, quality of life, and sleep (38). Changes in stress, fatigue, quality of life measures, and sleep were assessed using various questionnaires. The short-form results for mood state profiles showed that all six measures of vitality, fatigue, tension-anxiety, depression, anger-hostility, and confusion were significantly improved after PQQ administration compared with those before PQQ administration, demonstrating that PQQ improves mood and reduces stress. Quality of life, appetite, obsessions, and pain measures were also significantly improved. Moreover, the Oguri/Shirakawa/Azumi Sleep Inventory (middle-aged and elderly version) revealed significant improvements in drowsiness upon awakening, sleep onset, sleep maintenance, and sleep time, suggesting that PQQ improves sleep quality.

5.2. Skin water retention

A study was conducted using 22 women (29–47 years old) with healthy dry skin (no atopic dermatitis or psoriasis), 11 of whom took PQQ and 11 of whom took a placebo (capsules without PQQ) (39), although three people withdrew from the placebo group. Oral administration of PQQ (20 mg/day for 8 weeks) significantly inhibited the increase in transepidermal water evaporation in the forearm. In addition, the participants reported positive impressions regarding the improvements in their skin conditions. In a dry skin mouse model study, oral intake of PQQ (0.0089% in the diet, *w*/*w*, for 6 weeks) significantly decreased the number of mast cells in the dermis and the number of CD3+ T cells in the epidermis. These results suggest that oral intake of PQQ improves the skin conditions in female humans with dry skin and mice with compromised skin barrier function.

5.3. Sports training (muscles and metabolism)

Concerning the effects of PQQ on mitochondrial biogenesis, it was reported that PQQ increased the gene expression of PGC-1α (40). Twenty-three men were randomized to receive PQQ or placebo treatments (20 mg/day). Both groups followed a supervised 6-week endurance exercise training program. There were no significant differences in aerobic performance after endurance training between the two groups ($p > 0.05$). However, regardless of group, there was a significant improvement in the peak oxygen consumption and gross motor test period after endurance training ($p < 0.05$). The PQQ group had significantly increased PGC-1α protein levels from baseline after endurance training compared with the placebo group ($p < 0.05$). PQQ supplementation does not appear to induce ergogenic effects on aerobic performance or body composition, but it may affect mitochondrial biogenesis by significantly increasing PGC-1α. Thus, we expect that long-term intake of PQQ leads to the expression of muscle-related functions.

CONCLUSION AND FUTURE EXPECTATION

PQQ is a functional food that is produced with high purity. Herein, we discussed the function of PQQ in improving brain function, especially cognitive function, in healthy humans. PQQ

may be useful for slowing the progression of neurodegenerative disorders such as Alzheimer's disease (41), Parkinson's disease (42), and intracerebral hemorrhage (43). However, more research is required to completely clarify its mode of action and possible therapeutic implications in this field.

In addition to promoting brain functions, PQQ has an inhibitory effect on fat accumulation during high-fat diet consumption in animal studies (44, 45), and PQQ was shown to improve hearing loss (46) and extend lifespan (47). Therefore, it may be effective in improving fat metabolism and fighting age-related disorders. Moreover, PQQ may be effective in combination with nutrients that increase muscle mass, and it may improve gut health by supporting intestinal bacteria. We believe that functions related to body homeostasis will be subject to clinical trials in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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