ORIGINAL RESEARCH

Nutrafoods (2018) 17:125-129
DOI 10.17470/NF-018-1013-3

Received: July 15, 2018
Accepted: July 25, 2018

Pyrroloquinoline quinone (PQQ): the next essential nutrient and supplement superstar

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ABSTRACT

Pyrroloquinoline quinone (PQQ) is a novel vitamin-like compound that acts as an essential active factor in the functioning of mitochondria. However, as higher organisms do not seem to biosynthesize PQQ, the major source in humans is the diet. In addition to its role in mitochondria, PQQ stimulates growth and serves as a cofactor for a special class of enzymes involved in cellular functions including cellular growth, development, differentiation and survival. It also has possible pharmacological effects via activation of AMP-kinase (AMPk). Given the nutritional importance and numerous physiological effects of PQQ, there are many possible clinical applications. The most obvious are those chronic degenerative conditions that revolve around low mitochondrial function and aging, including degenerative neurological disease (e.g., Alzheimer's and Parkinson's disease), chronic inflammation, metabolic syndrome and obesity. It also holds promise as a clinical aid for simply improving energy levels and cognition. This review will highlight the pharmacology, clinical applications and dosage recommendations for this promising natural product.

Keywords

Pyrroloquinoline quinone
Mitochondrial function
Mitochondrial biogenesis
Oxidoreductases
Cognitive function enhancement
Activation of AMP-kinase

Introduction

Pyrroloquinoline quinone (PQQ) is a novel vitamin-like compound that acts as a necessary active factor in the functioning of mitochondria [1–3]. PQQ plays an essential role in human nutrition and will likely be recognized as an essential vitamin in the future [4].

In 1979, PQQ was the third coenzyme for oxidoreductases to be discovered after nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). The omission of PQQ from chemically defined diets in mammals results in growth impairment, compromised immune status, and abnormal reproductive function [5]. The nutritional requirements for PQQ are probably in line with folic acid and biotin in terms of micrograms per day versus milligrams per day compared with other B vitamins. As with essential nutrients, the immune system seems particularly sensitive to low PQQ levels: PQQ deprivation is accompanied by multiple defects in immune function and loss of the ability of white blood cells to respond properly [1]. Preclinical studies and initial clinical evaluation indicate that PQQ has a wide range of clinical applications [1–4].

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PQQ in nature

Higher organisms do not seem to biosynthesize PQQ. Hence, the major source of PQQ in both plants and animals is believed to be derived from microorganisms. However, common strains of bacteria in the intestinal tract appear to synthesize little PQQ, so the major source is the diet. PQQ has been found in all plant foods analyzed to date [1]. PPQ-rich foods include parsley, green peppers, kiwi fruit, papaya and tofu [6]. These foods contain about 2–3 μg per 100 g. Green tea provides about the same amount per 4 oz serving. It is estimated that humans consume 0.1–1.0 mg PQQ and its derivatives per day.

Pharmacology

PQQ stimulates growth and serves as a cofactor for a special class of enzymes involved in cellular functions including cellular growth, development, differentiation and survival [1]. An important role of PQQ involves direct action on key enzymes in mitochondria. As a result, PQQ

improves energy production [1, 2, 7]. PQQ is also as an extremely powerful antioxidant capable of catalyzing continuous cycling (the ability to perform repeated oxidation and reduction reactions) to a much greater degree than other antioxidants. For example, PQQ is able to carry out 20,000 catalytic conversions compared with only 4 for vitamin C [1, 2].

In addition to PQQ's powerful antioxidant effect, it protects against mitochondrial damage. PQQ both protects mitochondria from oxidative stress and also promotes the spontaneous generation of new mitochondria within aging cells, a process known as mitochondrial biogenesis or mitochondriogenesis [1, 2, 8, 9], greatly improving mitochondrial function.

Given the nutritional importance and numerous physiological effects of PQQ, it can provide considerable benefits in conditions that revolve around low mitochondrial function including in aging, many brain and neurological diseases (e.g., Alzheimer's and Parkinson's disease), and other chronic degenerative disorders. Current research has primarily focused on its ability to protect memory and cognition in aging animals and humans. Some of the effects noted in animal studies include:

- Reversal of cognitive impairment caused by chronic oxidative stress and improved performance on memory tests in animal models [1, 2, 10]
- Stimulation of the production and release of nerve growth factor [1, 2, 11]
- Protection against the self-oxidation of the DJ-1 gene, an early step in the onset of Parkinson's disease [1, 12]
- Protection of brain cells against oxidative damage in stroke models [1, 2, 13]
- Blocking the formation of inducible nitric oxide synthase (iNOS), a major source of the reactive nitrogen species (RNS) that are so damaging to brain cells [1, 2, 14]
- Protection against the likelihood of severe stroke in an experimental animal model of stroke [1, 2, 15]
- Protection of the brain against neurotoxicity induced by powerful toxins, including mercury, glutamate and oxidopamine (a potent neurotoxin used by scientists to induce Parkinsonism in laboratory animals) [1, 2, 16, 17]
- Prevention of the development of alpha-synuclein, a protein associated with Parkinson's disease [1, 2, 18]
- Protection of nerve cells from the damaging effects of the beta-amyloid protein linked with Alzheimer's disease [1, 2, 19]
- Reduction of LDL cholesterol, presumably by activating AMP-kinase (AMPk) [2, 19].

Clinical applications

Theoretically, PQQ may increase mitochondrial function and energy production in individual cells throughout the body. Another key pharmacological action of PQQ is activation of AMPk, an enzyme found inside living cells that serves as a 'master regulating switch' in energy metabolism. Low levels of AMPk activity are associated with:

- Accelerated aging
- Chronic inflammation
- High blood cholesterol and triglycerides
- Increased visceral 'belly' fat
- Insulin resistance
- Mitochondrial insufficiency and dysfunction
- Neurodegeneration
- Obesity
- Poor blood sugar control.

Since PQQ increases mitochondrial function and also activates AMPk, researchers believe that it is only a matter of time before clinical data are produced showing PQQ is helpful for a long list of health challenges [1, 2].

The ability of PQQ to enhance mitochondrial energy production is supported by numerous animal studies [1, 2, 7, 20] and one human study where PQQ was administered as a single agent to 10 subjects (5 females, 5 males) between the ages of 21 and 34 years. The subjects were given PQQ (BioPQQ™, which is a form of PQQ produced through a natural fermentation process) in a single dose (0.2 mg PQQ/kg) after which multiple measurements were taken of plasma and urine PQQ levels and changes in antioxidant potential over a 48-hour period [21]. Results indicated a significant increase in antioxidant potential even after only one dose. The same subjects were also given a daily dose of 0.3 mg PQQ/kg and had their blood measured for markers of inflammation (plasma C-reactive protein and interleukin (IL)-6) and urinary metabolites related to energy metabolism before PQQ administration and 72 hours later. PQQ supplementation resulted in significant decreases in the levels of plasma C-reactive protein and IL-6. Furthermore, the changes in urinary metabolites were consistent with enhanced mitochondria-related functions. The data are among the first to link the systemic effects of PQQ in animals to corresponding effects in humans [21].

There are also some clinical data suggesting PQQ exerts a health benefit via activation of AMPk. In a study with BioPQQ™, in test subjects with initial levels of LDL cholesterol above 140 mg/dl, 6 weeks of PQQ supplementation

produced a statistically significant decrease in total cholesterol (falling from an average of 247 to 216 mg/dl) and LDL-cholesterol (falling from an average of 156 to 132 mg/dl). Results persisted at 12 weeks. These results are thought to be due to PQQ activating AMPk [22].

Insulin resistance

Given the action on mitochondrial function and AMPk, PQQ holds great promise in many metabolic disorders, but especially in the treatment of insulin resistance and type 2 diabetes, and as an anti-obesity agent. There are a number of additional mechanisms of action that support these clinical applications. First, it is now well established that type 2 diabetes can be characterized as a mitochondrial disorder [23]. It is also well established that the mitochondrial dysfunction of diabetic subjects is closely related to both the degree of hyperglycaemia, and also diet, physical activity, sleep, stress and other lifestyle factors [24]. As described above, PQQ supplementation has been shown to enhance mitochondrial function and biogenesis. In animal studies, PQQ deficiency increased the plasma glucose level, reduced hepatic mitochondrial content by 20–30%, and elevated plasma lipid levels, while PQQ supplementation reversed the mitochondrial alterations and metabolic impairment and significantly improved the lipid profile in diabetic rats [20]. The mechanisms responsible for the increased mitochondrial biogenesis and improved function by PQQ are stimulated by the transcriptional coactivator, peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), through activation of the nuclear respiratory factor (NRF-1 and NRF-2). The transcription factor cAMP-responsive element-binding protein (CREB) increases transcription of PGC-1α via a conserved CREB-binding site in the proximal promoter and is activated by exercise or fasting. PQQ elevates PGC-1α promoter activity by the same mechanism. PQQ exposure also increases the levels of NRF-1 and NRF-2, resulting in upregulation of the mitochondrial transcription factor A and mitochondrial gene expression [25]. PQQ exerts additional mechanisms on insulin signalling and enhances glucose uptake through the translocation of glucose transporters. Hence, all of the existing data clearly suggest that PQQ can be useful in insulin resistance and type 2 diabetes [2].

Enhancing cognitive function

Another body tissue that clearly benefits from improved mitochondrial function is the human brain. The positive effects of PQQ on learning and memory have been demonstrated in animal models [1, 2]. The effects were consistent in both young and old animals. While PQQ was effective on its own in some of these studies, when it was combined coenzyme Q10 (CoQ10), even better results were observed. This synergistic effect was further demonstrated in a human double-blind, placebo-controlled clinical trial conducted in Japan in 2007 [26]. In this study of 71 middle-aged and elderly people aged 40–70, supplementation with 20 mg per day of PQQ (as BioPQQ™) resulted in improvements on tests of higher cognitive function using the Stroop test compared with the placebo group. However, in the group receiving 20 mg of PQQ along with 300 mg of CoQ10, the results were even more dramatic. PQQ and CoQ10 are both involved in mitochondrial energy production, so these results are not that surprising.

Another double-blind study used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in 65 subjects between 50 and 70 years of age who presented with self-identified forgetfulness or forgetfulness identified by a family member, colleague or acquaintance. The neuropsychological battery questions allow repeated and quick evaluation of higher brain function disorders associated with a variety of brain diseases. RBANS measures five domains: immediate memory, visuospatial/constructional ability, language, attention and delayed memory. The three arms of the study were: PQQ (20 mg/day), PQQ (20 mg/day)+CoQ10 (300 mg/day), and placebo. All three groups showed a significantly better total score over time, but the improvement in immediate memory scores at week 8 were significantly better in the PQQ+CoQ10 group than in the placebo group. For analysis of immediate memory, subjects were stratified into two subgroups according to baseline total scores. Although no significant difference was present between groups in the high-scoring subgroup, the PQQ+CoQ10 group in the low-scoring subgroup showed a significantly better score at week 8 and week 16 than the placebo group. This finding shows that individuals with lower RBANS scores may improve more in response to PQQ+CoQ10 supplementation than individuals with higher scores [27].

However, many patients, especially those under 50 years of age, may not need simultaneous use of PQQ and CoQ10 unless they are taking a drug that interferes with CoQ10 synthesis, such as cholesterol-lowering statins. That said, there are a couple of double-blind studies in elderly subjects taking PQQ alone which show less impressive results than the study with CoQ10. In one of these studies, 41 elderly healthy

subjects were administered 20 mg of PQQ per day or a placebo for 12 weeks. No significant improvements were noted in the Stroop test or reverse Stroop test, but improvements in visual-spatial cognitive function were noted in the Touch M test in subjects taking PQQ [28].

In another trial relating to cognitive function, 17 healthy middle-age and elderly subjects ingested 20 mg of PQQ daily for 8 weeks. The results of the Profile of Mood States–Short Form showed that all six measures of vigour, fatigue, tension-anxiety, depression, anger-hostility and confusion significantly improved following PQQ supplementation compared with baseline scores. Improvements were also noted for drowsiness at awaking, sleep onset and maintenance, and sleep duration. These improvements correlated with changes in the cortisol awakening response [29].

PQQ enhances cerebral blood flow and oxygen utilization in the prefrontal cortex. In a study of 20 healthy subjects between 50 and 70 years of age, 20 mg of PQQ (as BioPQQ™) or placebo was administered orally once daily for 12 weeks. Transcranial near-infrared stimulation (tNIRS) showed that PQQ increased haemoglobin concentration and reduced absolute tissue oxygen saturation in the right prefrontal cortex, resulting in enhanced cognitive function [30].

Dosage

While the nutritional requirement for PQQ is likely below 500 µg daily, higher amounts are required in order to get a measurable response in mitochondrial function in adult animals. The current dosage recommendation of 10–20 mg of PQQ daily in humans is based upon the equivalent dose in animals which has consistently improved various mitochondrial functions. There are also some clinical and observational studies that justify the dosage.

Toxicity

There are no known side effects or toxicity with PQQ at recommended levels. In a double-blind safety study, human volunteers were given PQQ at dosage of either 20 or 60 mg/day, or placebo for 4 weeks. No adverse effects were observed in any group. The urinary concentration of N-acetyl-β-D-glucosaminidase (NAG), a sensitive biomarker for renal tubular damage, was also determined in the study. Levels did not change in any group [2].

Toxicology studies in animals show an excellent PQQ safety profile with the LD50 being 1,000–2,000 mg PQQ/kg body weight in male and 500–1,000 mg PQQ/kg body weight in female rats. The no-observed-adverse effect level (NOAEL) in rats is 400 mg PQQ/kg body weight [31]. PQQ is not genotoxic [32].

Drug interactions

There are no known drug interactions with PQQ at recommended levels.

REFERENCES

1. Rucker R, Chowanadisai W, Nakano M (2009) Potential physiological importance of pyrroloquinoline quinone. Altern Med Rev 14(3):268–277
2. Akagawa M, Nakano M, Ikemoto K (2016) Recent progress in studies on the health benefits of pyrroloquinoline quinone. Biosci Biotechnol Biochem 80(1):13–22
3. Paz MA, Martin P, Fluckiger R *et al* (1996) The catalysis of redox cycling by pyrroloquinoline quinone (PQQ), PQQ derivatives, and isomers and the specificity of inhibitors. Anal Biochem 238:145–149
4. Kasahara T, Kato T (2003) Nutritional biochemistry: a new redox-cofactor vitamin for mammals. Nature 422:832
5. Steinberg F, Stites TE, Anderson P *et al* (2003) Pyrroloquinoline quinone improves growth and reproductive performance in mice fed chemically defined diets. Exp Biol Med (Maywood) 228:160–166
6. Kumazawa T, Sato K, Seno H *et al* (1995) Levels of pyrroloquinoline quinone in various foods. Biochem J 307:331–333
7. Chowanadisai W, Bauerly KA, Tchaparian E *et al* (2010) Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression. J Biol Chem 285(1):142–152
8. Stites T, Storms D, Bauerly K *et al* (2006) Pyrroloquinoline quinone modulates mitochondrial quantity and function in mice. J Nutr 136:390–396
9. Chowanadisai W, Bauerly K, Tchaparian E, Rucker RB (2007) Pyrroloquinoline quinone (PQQ) stimulates mitochondrial biogenesis. FASEB J 21:854
10. Ohwada K, Takeda H, Yamazaki M *et al* (2008) Pyrroloquinoline quinone (PQQ) prevents cognitive deficit caused by oxidative stress in rats. J Clin Biochem Nutr 42:29–34
11. Yamaguchi K, Sasano A, Urakami T, Tsuji T, Kondo K (1993) Stimulation of nerve growth factor production by pyrroloquinoline quinone and its derivatives in vitro and in vivo. Biosci Biotechnol Biochem 57(7):1231–1233
12. Nunome K, Miyazaki S, Nakano M, Iguchi-Ariga S, Ariga H (2008) Pyrroloquinoline quinone prevents oxidative stress-induced neuronal death probably through changes in oxidative status of DJ-1. Biol Pharm Bull 31(7):1321–1326

13. Zhang Y, Feustel PJ, Kimelberg HK (2006) Neuroprotection by pyrroloquinoline quinone (PQQ) in reversible middle cerebral artery occlusion in the adult rat. Brain Res 1094:200–206
14. Hirakawa A, Shimizu K, Fukumitsu H, Furukawa S (2009) Pyrroloquinoline quinone attenuates iNOS gene expression in the injured spinal cord. Biochem Biophys Res Commun 378:308–312
15. Jensen FE, Gardner GJ, Williams AP *et al* (1994) The putative essential nutrient pyrroloquinoline quinone is neuroprotective in a rodent model of hypoxic/ischemic brain injury. Neuroscience 62:399–406
16. Zhang P, Xu Y, Sun J *et al* (2009) Protection of pyrroloquinoline quinone against methylmercury-induced neurotoxicity via reducing oxidative stress. Free Radic Res 43:224–233
17. Zhang Q, Shen M, Ding M, Shen D, Ding F (2011) The neuroprotective action of pyrroloquinoline quinone against glutamate-induced apoptosis in hippocampal neurons is mediated through the activation of PI3K/Akt pathway. Toxicol Appl Pharmacol 252(1):62–72
18. Kim J, Harada R, Kobayashi M, Kobayashi N, Sode K (2010) The inhibitory effect of pyrroloquinoline quinone on the amyloid formation and cytotoxicity of truncated alpha-synuclein. Mol Neurodegener 5:20
19. Kim J, Kobayashi M, Fukuda M *et al* (2010) Pyrroloquinoline quinone inhibits the fibrillation of amyloid proteins. Prion 4(1):26–31
20. Bauerly K, Harris C, Chowanadisai W *et al* (2011) Altering pyrroloquinoline quinone nutritional status modulates mitochondrial, lipid, and energy metabolism in rats. PLoS One 6:e21779
21. Harris CB, Chowanadisai W, Mishchuk DO *et al* (2013) Dietary pyrroloquinoline quinone (PQQ) alters indicators of inflammation and mitochondrial-related metabolism in human subjects. J Nutr Biochem 24(12):2076–2084
22. Nakano M, Kawasaki Y, Suzuki N, Takara T (2015) Effects of pyrroloquinoline quinone disodium salt intake on the serum cholesterol levels of healthy Japanese adults. J Nutr Sci Vitaminol 61(3):233–240
23. Gonzalez-Franquesa A, Patti ME (2017) Insulin resistance and mitochondrial dysfunction. Adv Exp Med Biol 982:465–520
24. Bhatti JS, Bhatti GK, Reddy PH (2017) Mitochondrial dysfunction and oxidative stress in metabolic disorders - a step towards mitochondria based therapeutic strategies. Biochim Biophys Acta 1863(5):1066–1077
25. Chowanadisai W, Bauerly KA, Tchaparian E, Wong A, Cortopassi GA, Rucker RB (2010) Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1α expression. J Biol Chem 285:142–152
26. Nakano M, Ubukata K, Yamamoto T, Yamaguchi H (2009) Effect of pyrroloquinoline quinone (PQQ) on mental status of middle-aged and elderly persons. FOOD Style 21 13(7):50–53
27. Koikeda T, Nakano M, Masuda K (2011) Pyrroloquinoline quinone disodium salt improves higher brain function. Med Consult New Remedies 48:519–527
28. Itoh Y, Hine K, Miura H *et al* (2016) Effect of the antioxidant supplement pyrroloquinoline quinone disodium salt (BioPQQ™) on cognitive functions. Adv Exp Med Biol 876:319–325
29. Nakano M, Yamamoto T, Okumura H, Tsuda A, Kowatari Y (2012) Effects of oral supplementation with pyrroloquinoline quinone on stress, fatigue, and sleep. Funct Foods Health Dis 2:307–324
30. Nakano M, Murayama Y, Hu L *et al* (2016) Effects of antioxidant supplements (BioPQQ™) on cerebral blood flow and oxygen metabolism in the prefrontal cortex. Adv Exp Med Biol 923:215–222
31. Liang C, Zhang X, Wang W, Song Y, Jia X (2015) A subchronic oral toxicity study on pyrroloquinoline quinone (PQQ) disodium salt in rats. Food Chem Toxicol 75:146–150
32. Nakano M, Suzuki H, Imamura T, Lau A, Lynch B (2013) Genotoxicity of pyrroloquinoline quinone (PQQ) disodium salt (BioPQQ™). Regul Toxicol Pharmacol 67:189–197