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# An Innovative Quinone (Pyrroloquinoline Quinone) and its Antiproliferative Effects

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## ABSTRACT

The pyrroloquinoline quinine is a cofactor discovered in bacteria. It is associated with various bacterial soluble and membrane enzymes that directly oxidize sugars, alcohols, aldehydes. In higher organisms, it has been reported that pyrroloquinoline quinine acts as a potent free radical scavenger and it seems to intervene in different processes causing remarkable benefits. One of the most important effects is that pyrroloquinoline quinine induced apoptosis in different cancer cell lines. It is interesting to observe the role of pyrroloquinoline quinine as pro-apoptotic agent. This review shows the most relevant aspects of this cofactor and its antiproliferative effects.

**Key Words:** Pyrroloquinoline quinone, PQQ, Cofactor, Effect, Antiproliferative

## INTRODUCTION

PQQ is a substance of quinoid nature discovered as a cofactor in different bacterial genera (Amador-Bravo, 2016; Ameyama *et al*., 1991; Choi *et al*., 2008; Misra *et al.*, 2012). As a cofactor, it catalyzes the oxidation of organic compounds such as monosaccharides, alcohols and short chain aldehydes. It has been reported that PQQ is linked covalently and non-covalently to enzymes (Attwood *et al*., 1991; Flores-Encarnación *et al*., 2004; Goodwin and Anthony, 1998; Matsushita *et al*., 2002; Naveed *et al.*, 2016). Due to its quinoid nature, PQQ has very active carbonyl groups, being a powerful antioxidant agent. It has been observed that the presence of PQQ in certain bacterial genera facilitates the activation of alternative metabolic pathways for the utilization of sugars; it also favors the production of high quantities of acidic substances in the external environment of bacteria by direct oxidation of sugars or alcohols (Choi *et al.*, 2008). PQQ is a novel quinone of bacterial origin that has changed the vision regarding diseases such as cancer because PQQ has been proposed as a possible alternative for the treatment of this disease, according to results obtained in different cell lines.

In recent years, the benefits of PQQ have been demonstrated when this substance is administered in plants or diet of different experimental animals(Amador-Bravo *et al*., 2016; Bauerly *et al*., 2011; Choi *et al*., 2008; Flores-Encarnación *et al*., 2014; Harris *et al*., 2013; Misra *et al*., 2012; Oteino *et al*., 2015). For example, it has a been attributed to PQQ the promotion of growth factors in tomato plantations, increasing amount of macronutrients and number of fruits. In rats, the use of a diet supplemented with PQQ showed a significant change in the learning (Amador-Bravo *et al*., 2016; Fukui *et al.,* 2001; Harris *et al.,* 2013; Ohwada *et al*., 2008). It has been reported that PQQ acts as a potent free radical scavenger; it suppresses the production of superoxide radicals(Hamagishi *et al*., 1988; Matsumoto *et al*., 1988; Zhang *et al*., 2013). PQQ has been described as a new vitamin and it seems to intervene in different processes in higher organisms causing remarkable benefits(McIntire, 1998). In recent years, the effect of PQQ on different cancer cell lines has been studied and it has been observed that PQQ induces apoptosis (Min *et al*., 2014). This review shows the most relevant aspects of PQQ and its antiproliferative effects.

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## PQQ

PQQ is a soluble anionic compound of low molecular weight, which has been classified as a new vitamin and as an essential nutrient, since it has been proven that it plays important roles: in cell proliferation, it is an antioxidant of lipid peroxidation and its beneficial effects have also been observed in cellular lesions (Shui *et al.*, 2015; Azizi *et al.*, 2014). PQQ is a nutrient that is well distributed in nature and serves as a non-covalent cofactor of redox reactions in certain bacterial dehydrogenase (named quinoproteins) (Flores-Encarnación *et al.*, 2004; Matsushita *et al.*, 2002; Tao *et al.*, 2007). PQQ is not synthesized in mammals, however it has been found in several levels of concentration in plants, in certain foods, such as kiwi, egg, wine, even in human breast milk (Noji *et al.*, 2007). It has been found that PQQ develops many important functions in humans and animals, including roles in nutrition, protection of the heart by ischemia, preventing damage to the liver by alcohol, sequestering free radicals from the body, increasing the level of nerve growth factor (in astrocytes) and inhibiting melanin production in melanoma cells (Fukui *et al.*, 2001; Wang *et al.*, 2014).

## PQQ as a vitamin

PQQ has been proposed as a new vitamin because it had beneficial effects on healthy cells at low concentrations (nanomolar to micromolar order) (Chowanadisai *et al.*, 2010; Steinberg *et al.*, 2003). It is known that glutamate is the free amino acid more abundant in the central nervous system but excess glutamate can affect progenitor cells and induces apoptosis in neural trunkand other cells(Pavlovic *et al.*, 2006). However, *in vitro* studies have shown that when the cells were cultured at different PQQ concentrations (3 nM to 30 mM), it was observed that PQQ favored cell proliferation and significantly attenuated cell damage induced by glutamate (Shui *et al.*, 2015). On the other hand, it is known that vitamins perform their function in team and in certain specific places of the body. Some authors have studied the effect of PQQ and vitamin E in peripheral nerves such as sciatica. They discovered that PQQ together with vitamin E favored the fastest recovery from nerve damage (increasing the regeneration of axons). Therefore, those two agents were been proposed for an effective regeneration in peripheral nerve lesions (Azizi *et al.,* 2014; Naveed*et al.*, 2016).Tao *et al.*, (2007) proposed to PQQ as a cardioprotective agent after observing a remarkable reduction of peroxides treating adult rat myocardium cells with $H_2O_2$ and PQQ.

## PQQ as growth promoter

This novel quinone was proposed as a potent growth factor in mice and as a promoter of DNA synthesis in human fibroblasts(Amador-Bravo *et al.*, 2016;Chowanadisai *et al.*, 2010;Harris *et al.*, 2013; Misra *et al.*, 2012). Kumazawa *et al.*, (2007) observed in NIH3T3mouse fibroblasts that PQQ increased cell proliferation through of signals related to Rats and it was observed that effect of PQQ derived from regulation of nitric oxide (NO) levels. Those studies contributed to expand understanding of cellular mechanisms, cell signaling and gene expression relevant to PQQ in mammals (Kumazawa *et al.*, 2007).

On the other hand, it has been reported that coenzymes such as PQQ showed a stimulating effect on the synthesis of nerve growth factor in mouse fibroblasts and BALBc/3T3 cell line, concluding that PQQ plays a important role in neuronal survival (Azizi *et al.*, 2014; Misra *et al.*, 2012; Murase *et al.*, 1993). The effect of PQQ has also been studied in fibroblasts, myocytes and mouse brainmicrovascular endothelial cells, where it was observed that PQQ in nanomolar concentrations protected these cells from high glucose-induced damage, thus reducing apoptosis and increasing the number of mitochondria in the cells. Apparently the protective effect was due to intracellular expression of hypoxia-inducible factor 1 alpha subunit (HIF-1α) (Wang *et al.,* 2014). It is known that liver fibrosis develops when there is chronic inflammation and destruction of liver cells, however it has been observed that PQQ has a suppressive, anti-oxidant and anti-fibrogenic effect. It has been reported that PQQ exerted a potent anti-fibrotic activity and reactive oxygen species (ROS) scavenging activity in Balb/C mouse models of liver fibrosis (Jia *et al.*, 2015). In the majority of the studies that have been carried out, the effect of PQQ in nanomolar concentration has been tested, however in the last years other studies have been developed in different cell lines of malignant cells, showing that in micromolar quantities PQQ has apoptotic effects (Min *et al.*, 2014).

## The antiproliferative effects of PQQ

It has been reported that the murine melanoma cell line B16F1is characterized because melanocytes produce a large amount of tyrosinase enzyme. Tyrosinase is a key enzyme in melanin synthesis and that in high amounts produces hyperpigmentation of the skin and even cancer (melanoma) (Sato *et al.*, 2008).Sato and Toriyama (2009) reported that PQQ between 12.5 to 25 μM inhibited the synthesis of mRNA that codes for tyrosinase involved in the production of melanin. These authors observed a decrease in cell proliferation and melanin production. Although the mechanism of action is still unknown, it has been proposed PQQ as a possible treatment against melanogenesis and hyperpigmentation disorders. In cell lines A-549 (adenocarcinoma of human lung), Neuro-2A (mouse neuroblastoma) and HCC-LM3 (human hepatocellular carcinoma), it has been observed that PQQ at concentrations 30 to 75 μM suppressed cell proliferation by inducing apoptosis. In addition, it was observed that PQQ increased the activity of caspase-3, produced cell cycle arrest in G0/G1 phase and produced the intracellular accumulation of reactive oxygen species (ROS) and the decline of

ATP levels (Min *et al.,* 2014). In the cell line A431 (human squamous cell carcinoma), it has been observed that PQQ at concentrations in the nanomolar order, promoted cell proliferation increasing growth up to 180%, however at concentrations in the micromolar order PQQ induced apoptosis (Kimura *et al.*, 2012). In the cell line U937 (human promonocitic leukemia), it was reported that PQQ at concentrations of 50-100 µM induced a depletion of glutathione and, consequently, an increase in reactive oxygen species (ROS). The decrease in glutathione led to the cells suffering necrosis, indicating that PQQ increased cytotoxicity due to the change in the cellular redox state. Thus, glutathione depletion can change the mode of cell death to necrosis in the presence of PQQ. The modulation of intracellular glutathione could be a strategy to enhance the cytotoxicity of PQQ (Nunone *et al.*, 2008; Shankar *et al*., 2013). As a scavenger of reactive oxygen species, PQQ appears to be a potent neuroprotector (Scanlon *et al.*, 1997). Zhang *et al*. (2009 ) reported that the addition of 1 to 20 µM of PQQ in the human neuroblastoma cell line SH-SY5Y, together with the beta-amyloid protein (Aβ), prevents the damage caused by the latter, thus avoiding apotosis. Beta-amyloid proteins have been proposed as one of the causes of Alzheimer's disease that produces neurotoxicity (increasing the production of reactive oxygen species) and induces apoptosis of neurons (Zhang *et al*. (2013). The alpha-synuclein (α-syn) is a small soluble protein expressed primarily at presynaptic terminals in the central nervous system and it is related to several neurodegenerative diseases, including Parkinson's disease (Amador-Bravo *et al*., 2016). The recent data suggest that α-syn has a role in regulating membrane stability and neuronal plasticity (Overk *et al.*, 2014). When the α-syn is mutated the function is lostcausing the formation of bodies of Lewis, cytotoxicity, apoptosis in neurons of the substantia nigra and therefore Parkinson's disease (Kim *et al*., 2010; Kobayashi *et al.*, 2010;Overk *et al.*, 2014; Recchia *et al.*, 2004). On the other hand, the rotenone is a substance that has been used as a natural pesticide. Its use has increased in recent years. However, rotenone can cross the brain barrier by penetrating the cell membrane and acting as a potent inhibitor of mitochondrial complex I leading to cell death. It has been tested in several cellular models that PQQ added to different concentrations in the presence of rotenone, protects the cells from damage and delays their harmful effects (Qin *et al*., 2015).

## CONCLUSION

PQQ is a novel cofactor that can act as a vitamin in nanomolar concentrations; at higher concentrations PQQ could be used for the treatment of certain diseases. PQQ can induce apoptosis in cancer cells, it is also protective of neurons, of myocardium and stimulates the cognitive system, among other things. However, PQQ can also have pro-oxidant characteristics and by binding to certain compounds can exacerbate cell toxicity.

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## CONFLICT OF INTEREST

Authors have no conflict of interest.

## REFERENCES

1. Amador-Bravo D, Flores-Encarnación M, Aguilar-Gutiérrez GR, Sánchez-Cuevas M. Pyrroloquinoline quinone: a brief overview of its biological potential. Basic Res J Med Clin Sci. 2016; 5: 1-5.
2. Ameyama M, Matsushita K, Shinawaga E, Adachi O. Biochemical and physiological functions of pyrroloquinoline quinone. Vit and Horm. 1991; 46: 229-278.
3. Attwood MM, Johannes P, Van Dijken P, Pronk JT. Glucose metabolism and gluconic acid production by *Acetobacter diazotrophicus*. J Ferment Bioengin. 1991; 72: 101-105.
4. Azizi A, Azizi S, Heshmatian B, Amini K. Improvement of functional recovery of transected peripheral nerve by means of chitosan grafts filles with vitamin E, pyrroloquinoline quinone and their combination. Intern J Surg. 2014; 12: 76-82.
5. Bauerly K, Harris C, Chowanadisai W, Graham J, Havel PJ, Tchaparian E, Satre M, Karliner JS, Rucker RB. Altering pyrroloquinoline quinone nutritional status modulates mitochondrial, lipid, and energy metabolism in rats. Plos ONE. 2011; 6: E21779.
6. Choi O, Kim J, Kim JG, Jeong Y, Moon JS, Park CS. Pyrroloquinoline quinone is a plant growth promotion factor produced by *Pseudomonas fluorescens* B16. Plant Physiol. 2008; 146: 657-668.
7. Chowanadisai W, Bauerly KA, Tchaparian E, Wong A, Cortopassi GA, Rucker RB. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1α expression. The J Biol Chem. 2010; 285: 142-152.
8. Flores-Encarnación M, González-Gutiérrez JY, Amador-Bravo D, Bravo-Juárez L, Cabrera-Maldonado C. A bacterial novel quinone participating in multiple functions in higher organisms. Glob Adv Res J Med Med Sci. 2014; 3: 132-138.
9. Flores-Encarnación M, Sánchez-Cuevas M, Ortiz-Gutiérrez F. Las PQQ deshidrogenasas. Un novedoso ejemplo de quinoproteínas bacterianas. Rev Latinoam Microbiol. 2004; 46: 47-59.
10. Fukui K, Hayasaka T, Shinkai T, Suzuki S, Abe K, Urano S. Impairment of learning and memory in rats caused by oxidative stress and aging, and changes in antioxidative defense systems. Annal NY Acad Sci. 2001; 928: 168-175.
11. Goodwin PM, Anthony C. The biochemistry, physiology and genetics of PQQ and PQQ-containing enzymes. Adv Microb Physiol. 1998; 40:1-80.
12. Hamagishi Y, Murata S, Kamei K, Oki T, Ameyama M. Novel pharmacological activity of a novel cofactor PQQ. Radical scavenger-like activity. Abstr Annu Meet JpnPharmacol Soc. 1988. 109 th., pp. 42.
13. Harris CB, Chowanadisai W, Mishchuk DO, Satre MA, Slupsky CM, Rucker RB. Dietary pyrroloquinoline quinone (PQQ) alters

indicators of inflammation and mitochondrial-related metabolism in human subjects. J Nutr Biochem. 2013; 24:2076-2084.
14. Jia D, Duan F, Peng P, Sun L, Ruan Y, Gu J. Pyrroloquinoline quinone supresses liver fibrogenesis in mice. PLoS ONE. 2015;10: e0121939.
15. Kim J, Harada R, Kobayashi M, Kobayashi N, Sode K. The inhibitory effect of pyrroloquinoline quinone on the amyloid formation and cytotoxicity of truncated alpha-synuclein. Mol Neurodegen. 2010; 5:20-31.
16. Kimura K, Takada M, Ishii T, Tsuji-Naito K, Akagawa M. Pyrroloquinoline quinone stimulates epithelial cell proliferation by activating epidermal growth factor receptor through redox cycling. Free Radical Biol. Med. 2012; 53:1239-1251.
17. Kong L, Yang C, Yu L, Smith W, Zhu S, Zhu J, Zhu Q. Pyrroloquinoline quinone inhibits RANKL-mediated expression of NFATc1 in part via suppression of *c*-Fos in mouse bone marrow cells and inhibits wear particle-induced ostelysis in mice. PLoS ONE. 2013; 8:e61013.
18. Kobayashi M, Kim J, Fukuda M, Ogasawara D, Kobayashi N, Han S, Nakamura C, InadaM, Miyaura C, Ikebukuro K, Sode K. Pyrroloquinoline quinone inhibits the fibrillation of amyloid proteins. Prion. 2010; 4:26-31.
19. Kumazawa T, Hiwasa T, Takiguchi M, Suzuki O, Sato K. Activation of Ras signaling pathways by pyrroloquinoline quinone in NIH3T3 mouse fibroblasts. Intern J Mol Med. 2007; 19: 765-770.
20. Matsushita K, Toyama H, Adachi O. Quinoproteins: structure, function, and biotechnological applications. Appl Microbiol Biotechnol. 2002; 58:13-22.
21. Matsumoto T, Susuki O, Hayakawa H, Omiso S, Hayakawa N, Nimura Y. Effects of exogenous PQQ on mortality rate and some biochemical parameters during endotoxin shock in rats. In PQQ and quinoproteins. JA Jongejan and JA Duine (eds). 1988. Kluwer. The Hague. pp. 162-164.
22. McIntire WS. Newly discovered redox cofactors: possible nutritional medical and pharmacological relevance to higher animals. Ann Rev Nutr. 1988; 18:145-177.
23. Min Z, Wang L, Jin J, Wang X, Zhu B, Chen H, Cheng Y. Pyrroloquinoline quinone induces cancer cell apoptosis via mitochondrial-dependent pathway and down-regulating cellular Bcl-2 protein expression. J Cancer. 2014; 5:609-624.
24. Misra HS, Rajpurohit YS, Khairnar NP. Pyrroloquinoline quinone and its versatile roles in biological processes. J Biosci. 2012; 37:313-325.
25. Murase K, Hattori A, Kohno M, Hayashi K. Stimulation of nerve growth factor synthesis/secretion in mouse astroglial cells by coenzymes. Biochem Mol Biol Intern. 1993; 30:615-621.
26. Naveed M, Tariq K, Ahmad H, Mumtaz AS. The life history of pyrroloquinoline quinone (PQQ): a versatile molecule with novel impacts on living systems. Intern J Mol Biol. 2016; 1:1-20.
27. Noji N, Nakamura T, Kitahata N, Taguchi K, Kudo T, Yoshida S, Tsujimoto M, Sugiyama T, Asami T. Simple and sensitive method for pyrroloquinoline quinone (PQQ) analysis in various foods using liquid chromatography/electrospray-ionization tandem mass spectrometry. J Agric Food Chem. 2007; 55:7258-7263.
28. Nunome K, Miyazaki S, Nakano M, Iguchi-Ariga S, Ariga H. Pyrroloquinoline quinone prevents oxidative stress-induced neuronal death probably through changes in oxidative status of DJ-1. Biol Pharm Bulletin. 2008; 31:1321-1326.
29. Ohwada K, Takeda H, Yamazaki M, Isogai H, Nakano M, Shimomura M. Pyrroloquinoline quinone (PQQ) prevents cognitive deficit caused by oxidative stress in rats. J Clin Biochem Nutr. 2008; 42:29-34.
30. Oteino N, Lally RD, Kiwanuka S, Lloyd A, Ryan D, Germainde KJ, Dowling DN. Plant growth promotion induced by phosphate solubilizing endophytic *Pseudomonas* isolates. Front Microbiol. 2015; 6:1-9.
31. Overk CR, Cartier A, Shaked G, Rockenstein E, Ubhi K, Spencer B, Masliah E. Hippocampal neuronal cells that accumulate αsynuclein fragments are move vulnerable to Aβ oligomer toxicity via mGluR5-implications for dementia with Lewy bodies. Mol Neurodegener. 2014; 9:1-18.
32. Pavlovic V, Cekic S, Sokolovic D, Djindjic B. Modulatory effect of monosodium glutamate on rat thymocyte proliferation and apoptosis. Bratisl Lek Listy. 2006; 107:185-191.
33. Qin J, Wu Q, Yu S, Gao X, Zhang J, Dong X, Ji J, Zhang Y, Zhou L, Zhang Q, Ding F. Pyrroloquinoline quinone conferred neuroprotection in rotenone models of Parkinson´s disease. Toxicol Letters. 2015; 238:70-82.
34. Kumazawa T, Hiwasa T, Takiguchi M, Susuki O, Sato K. Activation of Ras signaling pathways by pyrroloquinoline quinone in NIH3T3 mouse fibroblasts. Intern J Mol Med. 2007; 19:765-770.
35. Recchia A, Debetto P, Negro A, Guidolin D, Skaper SD, Giusti P. Alfa-synuclein and Parkinson's disease. FASEB J. 2004; 18:617-626.
36. Sato K, Takahashi H, Iraha R, Toriyama M. Down-regulation of tyrosinase expression by acetylsalicylic acid in murine B16 melanoma. Biol Pharm Bull. 2008; 31:33-37.
37. Sato K, Toriyama M. Effect of pyrroloquinoline quinone (PQQ) on melanogenic protein expression in murine B16 melanoma. J Dermatol Sci. 2009; 53:140-145.
38. Scanlon J, Aizenman E, Reynolds I. Effects of pyrroloquinoline quinone on glutamate-induced production of reactive oxygen species in neurons. Eur J Pharmacol. 1997; 326:67-74.
39. Shankar BS, Pandey R, Amin P, Misra HS, Sainis KB. Role of glutathione in augmenting the anticancer activity of pyrroloquinoline quinone (PQQ). Redox Report. 2013; 15:146-154.
40. Shui G, Jianqiang X, Yifu G, Dan G, Tianqing L, Xuehu M, Zhanfeng C. Pyrroloquinoline quinone against glutamate-induced neurotoxicity in cultured neural stem and progenitor cells. Intern J Develop Neurosci. 2015; 42:37-45.
41. Steinberg F, Stites TE, Anderson P, Storms D, Chan I, Eghbali S, Rucker R. (2003). Pyrroloquinoline quinone improves growth and reproductive performance in mice fed chemically defined diets. Exp Biol Med (Maywood). 2003; 228:160-166.
42. Tao R, Karliner J, Simonis U, Zheng J, Zhang J, Honbo N, Alano C. (2007). Pyrroloquinoline quinone preserves mitochondrial function and prevents oxidative injury in adult rat cardiac myocytes. Biochem Biophys Res Comm. 2007; 363:257-262.
43. Wang Z, Chen G, Yu G, Liu C. Pyrroloquinoline quinone protects mouse brain endothelial cells from high glucose-induced damage *in vitro*. Acta Pharmacol Sinica. 2014; 35:1402-1410.
44. Zhang Q, Ding M, Cao Z, Zhang J, Ding F, Ke K. Pyrroloquinoline quinone protects rat brain cortex against. Neurochem Res. 2013; 38:1661-1671.
45. Zhang J, Zhang R, Meng X. Protective effect of pyrroloquinoline quinone against Aβ-induced neurotoxicity in human neuroblastoma SH-SY5Y cells. Neuroscie Lett. 2009; 464:165-169.