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Review Article

Role of Coenzyme Q10 in Aging, Oxidative Stress, Cancer & Critically Ill Patients

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Abstract

Aging is a slow process of physiological changes that lead to a decline in the biological activities of organisms. Stopping or reversing this process has been the subject of extensive research for centuries. In aging, mitochondria, which are ubiquitously present in the cells and tissues of the body, play a seminal role. There has been a close association between the optimum function of mitochondria and aging. Coenzyme Q10 (CoQ10), a well-known, integral cofactor of the electron transport chain in the mitochondria of human cells, is a powerful antioxidant and a free radical scavenger. With advancing age, a significant reduction occurs in natural levels of CoQ10. A low level of CoQ10 is found to compromise mitochondrial activity, increase oxidative stress, and lead to clinically heterogeneous diseases, including cancers. Supplementation with CoQ10 is believed to augment mitochondrial activity, confer antioxidant protection to cells and tissues, and retard the onset of various disorders. These observations lead the researchers to explore the anti-aging potential of CoQ10 and its utility in dietary therapies to counteract the negative impact of aging and boost longevity. In this review, we compiled, reviewed, and discussed various age-related pathologies in the context of CoQ10 deficiency and the effect of CoQ10 supplementation on improving these conditions.

Keywords: Coenzyme Q10, cancer, aging, oxidative stress, mitochondria

1. Introduction

Coenzyme Q or ubiquinone occurs naturally in the hydrophobic region of the phospholipid bilayer of all biological membranes (Varela-López et al. 2016). It can also be produced synthetically, making it accessible for cases where deficiency is suspected. Endogenous CoQ 10 enzyme is an integral component of the mitochondrial electron transport chain, a vital player in intracellular metabolism, and an essential antioxidant (Hidalgo-Gutiérrez et al. 2021). At least 14 proteins are required to synthesize CoQ10 in mammalian cells. The initial step of this pathway involves the formation of a 4-hydroxybenzoic acid (4-HB) head and the hydrophobic polyisoprenoid tail. The amino acid phenylalanine or tyrosine serves as the precursor of 4-HB formation. Subsequently, the addition of isopentenyl diphosphate molecules (obtained through the mevalonate pathway) catalyzed by the enzyme polyprenil diphosphate synthase forms geranylgeranyl diphosphate or farnesyl diphosphate, which subsequently yields the polyisoprenoid tail (Shukla and Dubey 2018). PDSS1 and PDSS2 work together as a heterodimer to accelerate the reaction that combines isoprene units, which are the building blocks of polyisoprenoid tail. Enzymes encoded by *COQ2*, *COQ3*, *COQ5*, *COQ6*, and *COQ7* are also implicated in multiple biochemical reactions during CoQ10 synthesis. For instance,

the conjugation of benzoquinone to the side chain is catalyzed by the enzyme transcribed from *COQ2*, which is located in the inner membrane of the mitochondria (Doimo et al. 2014).

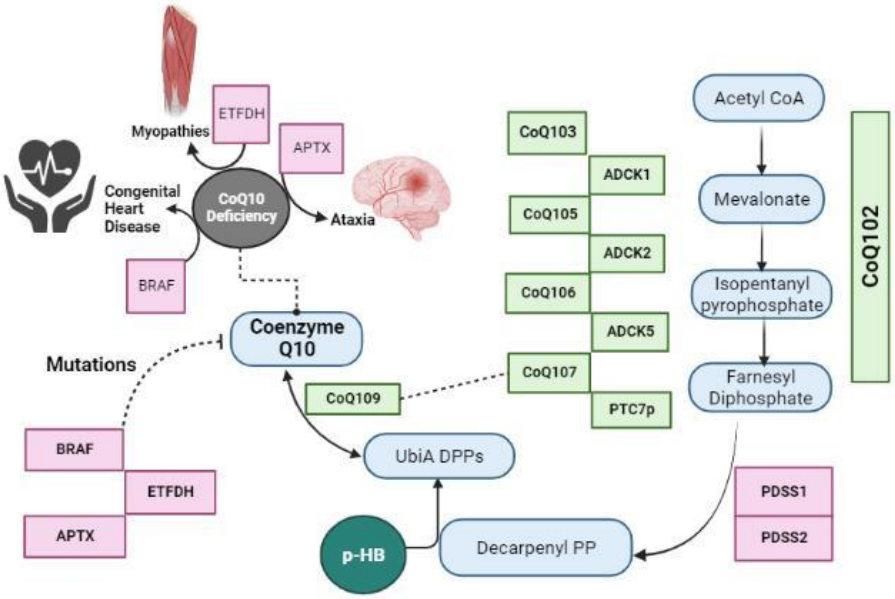
Additionally, the enzymes encoded by the remaining genes mentioned above modify the benzoquinone ring of CoQ10 via methylation, decarboxylation, and hydroxylation (Kawamukai 2016). COQ9 has been reported to attach itself to various biosynthetic intermediates of CoQ10, such as demethoxyubiquinone (DMQ), a COQ7 substrate, through physical interaction with COQ7 itself (García-Corzo et al. 2012, Lohman et al. 2014). Researchers have also found that ADCK1, ADCK2, ADCK5, and PTC7p proteins have displayed the ability to influence the rate at which CoQ10 is formed (Kawamukai 2016). While the complete process of CoQ10 biosynthesis is still ambiguous, incomplete information regarding extra mitochondrial biosynthesis is also reported. UBIAD1 is a non-mitochondrial prenyltransferase that contains a UbiA prenyltransferase domain, a homolog of the mitochondrial enzyme CoQ2. UBIAD1 is found in the Golgi apparatus (Mugoni et al. 2013). And has been reported to support the biosynthesis of CoQ10 in this organelle (Mugoni et al. 2013).

Plasma levels of CoQ_{10} range between 0.40 and 1.91µmol/L (0.34–1.65µg/mL) in normal individuals(Barcelos and Haas 2019). Different articles state different concentrations of CoQ10 in different organs. For instance, in the lungs, the level is 8 µg/g, and 114 µg/g in the heart. General recommendations for CoQ10 supplementation in healthy elderly individuals typically range from 30 to 200 mg daily. Some studies suggest higher doses of up to 1,200 mg/day may be beneficial for specific health concerns (Hathcock and Shao 2006).

2. Genetic Mutations in CoQ10 Pathway & Diseases

CoQ10 deficiency is categorized into two types: primary and secondary. The primary category arises from genetic mutations in the CoQ10 synthesis pathway, whereas secondary deficiencies are caused by certain diseases or their medications. Mutations in genes involved in the biosynthesis of CoQ10 form the basis of mitochondrial diseases and may be associated with clinically heterogeneous pathologies. The five significant phenotypes of primary CoQ10 deficiency identified so far are (1) infantile multisystem form, (2) isolated myopathy, characterized by muscle weakness, myoglobinuria, exercise intolerance, and elevated creatine kinase (CK) (Kaeberlein et al. 2005) (3) encephalomyopathy (recurrent myoglobinuria, encephalopathy, and mitochondrial myopathy), (4) cerebellar ataxia (cerebellar atrophy associated with other neurologic manifestations and, occasionally, endocrine dysfunctions, and (5) nephropathy. (Figure 1). Some patients have also exhibited retinopathy, optic atrophy, sensorineural hearing loss, and hypertrophic cardiomyopathy (Alcázar-Fabra, Trevisson, and Brea-Calvo 2018). Moreover, individuals harboring mutations in the serine/threonine-protein kinase B-raf gene or *BRAF* are found to exhibit cardiofaciocutaneous (CFC) syndrome, while mutations in the electron-transferring flavoprotein dehydrogenase gene (*ETFDH*) are held responsible for isolated myopathy. Similarly, mutations in the aprataxin- *APTX*-gene, which present as oculomotor apraxia and ataxia, are also attributed to CoQ10 deficiency (Desbats et al. 2015). Single nucleotide substitutions, deletions, and duplications in mitochondrial DNA (mtDNA) display associations with CoQ10 deficiency (Desbats et al. 2015). Relations between secondary CoQ10 deficiency in mouse models and mitochondrial

Figure 1 Genetic mutations in the CoQ10 pathway result in diseases.



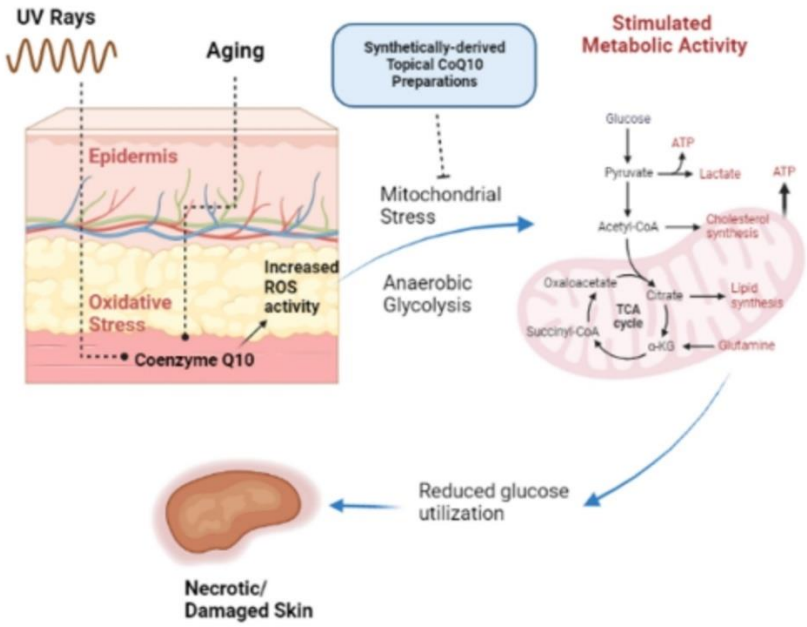
diseases have also been observed (Kühl et al. 2017) particularly in models associated with resistance to insulin and adipose and muscle tissue (Fazakerley et al. 2018). The wide range of clinical presentations related to CoQ10 deficiencies is attributed to its unique structural features, characteristics, and different metabolic functions.

3. CoQ10 and the Ageing Skin

Continuous exposure to environmental stress has a significant impact on the physiological behavior of the cutaneous cells of our skin and the skin as an entire organ. As the skin cells age, various factors such as ultraviolet (UV) radiation and, more importantly, intrinsic as well as extrinsic reactive oxygen species (ROS) contribute to an increased accumulation of ROS inside the cells. This excessive buildup of ROS ultimately leads to impaired mitochondrial functioning and cellular damage (Ames, Shigenaga, and Hagen 1993). Consequently, the cell adapts to this damage by shifting to anaerobic glycolysis as a compensatory mechanism (McKenzie et al. 2007, von Kleist-Retzow et al. 2007).

CoQ10 is classically known to be an essential component of the electron transport chain in the mitochondria. Therefore, it is reasonable to infer that the provision of CoQ10 can improve energy metabolism in cells. As the age increases, the antioxidant capacity of cells weakens, and exposure to UV radiation further depletes CoQ10 reserves in skin cells and augments the intracellular concentration of ROS (Hoppe et al. 1999). As mentioned earlier, loss of mitochondrial function due to old age may promote non-mitochondrial compensatory pathways, e.g., glycolysis. This inference is corroborated by reports indicating increased glucose uptake and elevated lactate production in aged fibroblasts *in vitro* (Poot et al. 1987, Zwerschke et al. 2003). Compared to the other dermal layers, CoQ10 concentration is ten times greater in the epidermis (Shindo et al. 1994). The epidermis, the outermost skin layer, is exposed to the most significant environmental stressors and UV radiation, which diminishes CoQ10 in

Figure 2. Schematic representation of reversible effects of synthetically derived CoQ10 in aging skin.

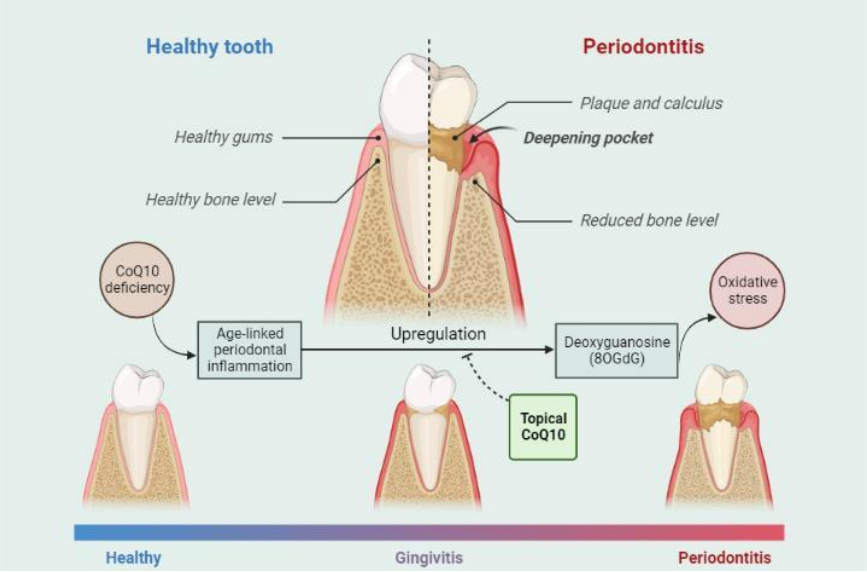


the skin, among the other antioxidants (Podda et al. 1998).

A randomized, controlled study was conducted on 73 healthy, non-smoking female volunteers aged 20-66 years. Participants applied two CoQ10 formulations (348 µM and 870 µM ubiquinone) twice daily for two weeks. The results showed that topically applied CoQ10 effectively penetrates the skin, undergoes metabolic transformation, and exhibits antioxidant properties, supporting cellular energy levels. This is particularly important for older individuals and for replenishing declining CoQ10 levels in the skin (Knott et al. 2015).

CoQ10 formulation, once applied, can provide great benefits to the keratinocytes found in the epidermal skin layer. Furthermore, after applying CoQ10 topical preparation for a short period, protective effects on mitochondrial function and improved mitochondrial activity have been observed *in vivo* even after exposure to UV radiation (Figure 2). Despite extensive scientific research, the exact pathways that connect poor mitochondrial functioning and increased glycolytic flux with advanced age are yet to be established; however, it is believed that AMP-activated protein kinase (AMPK), which serves as a super metabolic regulator, is also a regulator of energy metabolism overall (Hardie, Salt, and Davies 2000). Studies show that suboptimal glucose utilization in epidermis keratinocytes is due to a shift to anaerobic glycolysis due to age-dependent mitochondrial dysfunction and subsequent loss of aerobic metabolic capacity (Sreedhar, Aguilera-Aguirre, and Singh 2020). Evidence highlights the positive anti-aging potential of CoQ10 as shown by the rapid pro-mitochondrial benefits seen post-application of a CoQ10 topical preparation; therefore, it hints at the potential use of CoQ10 formulations in anti-aging cosmeceuticals (Hseu et al. 2019).

Figure 3. Periodontal inflammation and the role of CoQ10.



4. CoQ10 and Oxidative Stress

It has been shown that oxidative stress plays a significant role in Cadmium (Cd)-mediated cytotoxicity(Ann et al. 2010, Ercal, Gurer-Orhan, and Aykin-Burns 2001). Due to the ability of CoQ10 to be reformed via reduction mechanisms inside cells, it confers protection to vital biomolecules such as DNA, proteins, and lipids from being subjected to oxidation (Crane 2001). CoQ10 has been observed to preserve the mitochondrial membrane by free radical ROS scavenging in oxidative stress models (Somayajulu et al. 2005, Song et al. 2017). Moreover, protection against Cd-stimulated oxidative damage has been observed in CoQ10 pretreated rats (Ognjanović et al. 2008). In patients suffering from a wide range of pathologies, such as cardiac diseases (hypertension and heart failure), as well as neurodegenerative disorders such as Parkinson's disease, CoQ10 provided a shield against oxidative stress (Fotino, Thompson-Paul, and Bazzano 2013, Rosenfeldt and Linden 2007, Seet et al. 2014, Spindler, Beal, and Henchcliffe 2009). Owing to its safety and fewer side effects, CoQ10 has become more frequent, along with other antioxidants, in treating oxidative stress linked with Cd. Hepatoprotective effects of CoQ10 against statin-induced hepatotoxicity are also thought to be mediated through its antioxidant actions (Jahan et al. 2022). Vitamin C and vitamin E recycling and regeneration are just some of the many pathways by which CoQ10 augments the antioxidant defense mechanism of cells (Beyer 1994, Lass and Sohal 2000, Ognjanović et al. 2010).

In recent years the scientists have also explored the connection between CoQ10 and ferroptosis. Ferroptosis is a type of iron-dependent cell death marked by a large amount of iron accumulation and lipid peroxidation. Ferroptosis-inducing factors can directly or indirectly affect glutathione peroxidase through different pathways, resulting in a decrease in antioxidant capacity and accumulation of lipid reactive oxygen species (ROS) in cells, ultimately leading to oxidative cell death. (Qi et al. 2022). Doll et al. and Bersuker et al performed a study to identify Ferroptosis suppressors that can function independently of the key regulator glutathione peroxidase (Fikry et al. 2024). By

using a CRISPR Cas9 knockout screen, they identified gene apoptosis-inducing factor mitochondrial 2 (AIFM-2), which was later named ferroptosis suppressor protein 1 (FSP1). FSP-1 was found to effectively combat lethal lipid peroxidation in the absence of glutathione peroxidase. Moreover, it was found that myristoylated FSP anchored to the plasma membrane served as a crucial enzyme that reduced ubiquinone to ubiquinol, restoring the reduced pool of CoQ10. The reduced form of CoQ10 acts as a powerful antioxidant that suppresses lipid peroxidation through free radical scavenging (Doll et al. 2019).

~~5.~~ Role of CoQ10 in Modulating Severity of Illness

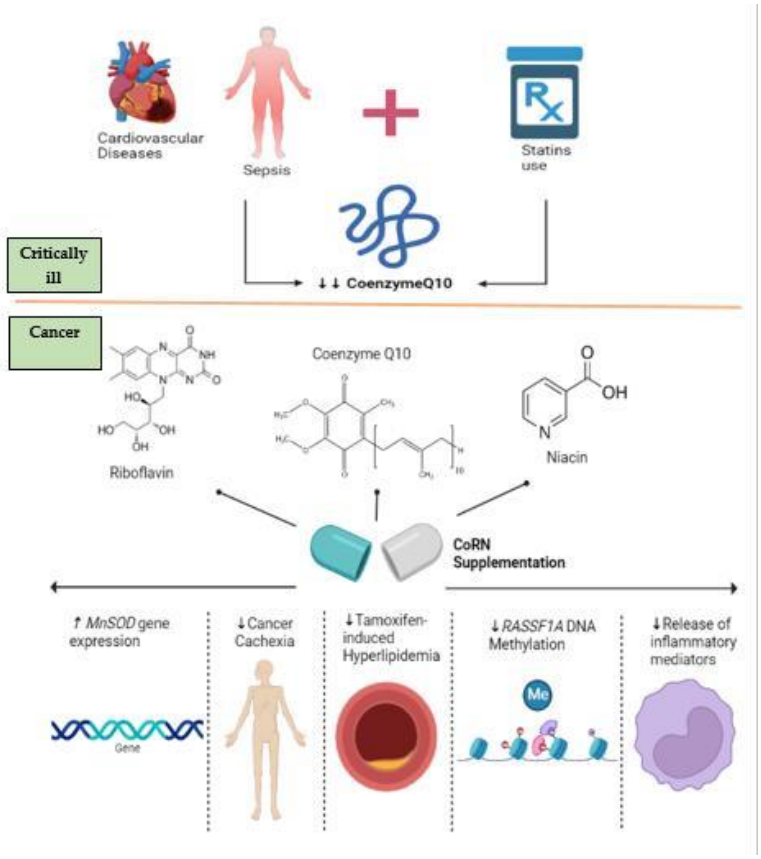
Little research and seldom clinical studies have been conducted to investigate the effect of CoQ10 supplementation in severe illnesses. According to one study, patients critically ill with cardiovascular diseases and depleted CoQ10 exhibit a high risk of mortality (Shimizu et al. 2017). A randomized controlled study was performed on 38 critically ill sepsis patients. These individuals were divided into two groups. One group was given a placebo, whereas the other was administered ubiquinol (reduced form CoQ10) 400 mg daily for 7 days. Despite a significant elevation in CoQ10 levels, no significant benefit was seen in the test group compared to the placebo group regarding clinical patient or secondary outcomes such as mitochondrial damage, inflammation, and endothelial function (Donnino et al. 2011). However, it is important to consider that in sepsis patients who are critically ill, the clinical use of statins is quite frequent (Dobesh and Olsen 2014), and it is a well-established fact that statins can block CoQ10 synthesis, leading to the depletion of CoQ10 reserves inside cells (Okuyama et al. 2015).

6. CoQ10 and Selenium

Ubiquinone and Ubiquinol are the oxidized and reduced forms of CoQ10, respectively. For normal mitochondrial activity, which involves cellular respirations and antioxidant functions, the interconversion of CoQ10 into its oxidized and reduced forms should remain unhindered. CoQ10 is reduced to ubiquinol, through a two-step process involving electron and proton gain catalyzed by various oxidoreductases. This reduction enables CoQ10 to transfer two electrons, facilitating essential cellular functions like energy production and antioxidant activity. (Mantle, Dewsbury, and Hargreaves 2024). Thioredoxin reductase 1(TrxR1), the most efficient enzyme responsible for the catalysis of ubiquinone reduction to Ubiquinol contains selenium in the form of selenocysteine, which is located in the active site of its structure(Zhong and Holmgren 2000). Therefore, it is reasonable to conclude that depletions in CoQ10 and selenium can negatively impact mitochondrial functioning by inhibiting the inter-conversion step. Selenocysteine, selenoprotein, and subsequent thioredoxin reductase synthesis can also be affected by changes in CoQ10 levels(Moosmann and Behl 2004). Consequently, selenium deficiencies can lead to reduced selenoproteins through inhibited CoQ10 production.

KISEL-10 (Pharma Nord ApS, based in Vejle, Denmark) is a supplement that contains CoQ10 and selenium in combination. A prospective, randomized, double-blind, placebo-controlled trial was conducted in Sweden (Linköping University and Karolinska University Hospital) to investigate the effects of selenium and coenzyme Q10 (CoQ10) supplementation (200 µg and 200mg per day) on cardiovascular health and mortality in elderly citizens. typically, doses range from 100-300 mg. C-reactive protein, copeptin, and adrenomedullin levels and other biomarkers of inflammation and oxidative

Figure 4 CoQ10 is also helpful for critically ill and cancer patients.



were found to have been significantly decreased in the supplemented group when compared to that of the placebo group (Alehagen et al. 2015, Alehagen, Aaseth, and Johansson 2015). Also, when compared to the placebo group, cardiovascular mortality dropped by 50% in the supplemented group (Alehagen et al. 2013). This study highlighted the potential of selenium and coenzyme Q10 supplementation in enhancing cardiovascular health and reducing mortality risks in elderly populations with low baseline levels of these nutrients.CoQ10 is typically administered orally, although a few clinical studies reported intravenous administration, whereas selenium can be given orally or intravenously (Okamura et al. 1984, Tsubaki et al. 1984).

7. CoQ10 and Periodontal Tissues

The anti-aging and antioxidant potential of CoQ10 has been demonstrated in various studies (Blatt and Littarru 2011, Temova Rakuša and Roškar 2021, Ayunin et al. 2022, Marcheggiani et al. 2021), which have shown its propensity to protect against oxidative stress and promote overall cellular health (Shetty, Forster, and Sumien 2013, Temova Rakuša and Roškar 2021). Based on this evidence, it is reasonable to conclude that CoQ10 can also mitigate age-linked inflammation in the periodontal tissues. Notably, numerous clinical studies have reported significant relief in chronic periodontitis after CoQ10 supplementation (Hanioka et al. 1994) (Ryo et al. 2011).

The application of CoQ10 on rat periodontal tissues has also revealed anti-aging effects. Deoxyguanosine (8-OGdG) levels increase in the serum with age, indicating oxidative stress (Yoneda et al. 2013). In 6-month-old rats, after treatment with topical CoQ10 preparation, a significant decline in 8-OHdG levels was observed. Furthermore, in the control group, the rats of the same age subjected to CoQ10 expressed lower 8-OHdG, also considered a biomarker for DNA damage via oxidation (Tomofuji et al. 2006). Thus, age-related oxidation and damage within the periodontal tissues can be reduced via CoQ10 as per the aforementioned results.

Additionally, concomitant administration of topical CoQ10 with conventional non-surgical treatment at the periodontal level exhibited marked improvement in chronic periodontitis as per a clinical investigation (Hanioka et al. 1994). Working as an endogenous antioxidant, CoQ10 levels increase in the gingivitis during inflammatory conditions to effectively combat progressive periodontitis (Prakash, Sunitha, and Hans 2010). Moreover, the anti-aging effect on normal periodontal tissues of CoQ10 has also been reported (Figure 3) (Yoneda et al. 2013).

8. CoQ10 and DNA Repair in Cancer Patients

A combination of CoQ10 (100mg Kaneka Corporation, Osaka, Japan), riboflavin (10mg Madras Pharmaceuticals, Chennai, India), and Niacin (50mg Madras Pharmaceuticals, Chennai, India) (CoRN) has been the subject of multiple scientific studies (Premkumar et al. 2008, Yuvaraj et al. 2009, Tippairote et al. 2022). In one such study, increased expression of the tumor suppressor gene *MnSOD* was observed after concomitant use of CoRN with the cytotoxic drug tamoxifen(Perumal, Shanthi, and Sachdanandam 2005c). Moreover, CoRN has been shown to restore both non-enzymatic and enzymatic antioxidant systems, including lipid peroxide, to normal levels (Figure 4) (Perumal, Shanthi, and Sachdanandam 2005a). Enhancing the gluconeogenesis pathway to mitigate energy loss and subsequently protect against cancer cachexia is also an effect of this combination (Perumal, Shanthi, and Sachdanandam 2005b). Similarly, treatment with Tamoxifen reduced hyperlipidemia in breast cancer patients who used CoRN supplementation as their lipid levels returned to normal (Yuvaraj et al. 2007). Tumor marker levels of carcinoembryonic antigen have also been reduced (Premkumar et al. 2007a), along with a marked decrease in interleukins (IL-1b, IL-6, IL-8) and other cytokines such as vascular endothelial growth factor and TNF-α (Premkumar et al. 2007b). Ten Patients administered CoRN demonstrated a complete absence of Ras-association domain family 1, isoform A (RASSF1A) DNA methylation (Premkumar et al. 2008). RASSF1A DNA methylation is a convenient indicator of whether patients undergoing adjuvant tamoxifen treatment are responding well, as it aids in the timely detection of relapse (Fiegl et al. 2005). The lack of RASSF1A DNA methylation in the serum of these patients proved that CoRN could help prevent relapses in these patients.

9. Future Directions

Healthcare and treatment have steadily improved life expectancy over the past century. However, advanced age is accompanied by a persistent decline in physiological functions, which can lead to several debilitating diseases. Ageing is an inevitable complex physiological process governed by various factors. Several theories have been proposed to explain the process of aging. Damage resulting from oxidative stress is one of the most accepted theories implicating dysfunctional mitochondria as a significant contributor to aging. Many studies link CoQ10 deficiency to various clinical

mitochondrial diseases, a critical component of the mitochondrial electron transport pathway. The convincing data from these studies suggest that supplementation with CoQ10 may be a promising approach to preventing or mitigating mitochondrial damage.

Due to the free radical scavenging and the antioxidant propensity of CoQ10, it is widely used as a dietary supplement. A high concentration of CoQ10 is typically found in tissues with high energy demands, such as skeletal muscles and cardiac tissues (114 μg/g) (Gutierrez-Mariscal et al. 2021), and neurons. However, CoQ10 tissue concentration decreases with increased age and oxidative stress. As a result, numerous conditions have been linked to low levels of CoQ10, including cancer, fibromyalgia, muscular disorders, heart failures, neurodegenerative disease, and other age-related disorders. These observations accentuate its bioenergetic role and form the basis for CoQ10 clinical application and recommendation.

Despite promising results from various studies on CoQ10, extensive recommendations by medical practitioners, and wide availability over the counter, CoQ10 has not gained FDA approval to treat any medical condition. The clinical trials conducted to investigate CoQ10 efficacy yielded inconsistent outcomes. Multiple factors, such as lack of effectiveness, inadequate safety, problems related to patient recruitment, retention, and enrollment, insufficient funding to complete trials, and flawed study plans, might have contributed to the failure of clinical trials. Therefore, further studies and clinical trials with a good design based on a robust hypothesis involving a more significant number of participants undergoing treatment for long periods are needed to evaluate the safety, efficacy, and risk-benefit ratio of CoQ10.

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Conflicts of Interest

The authors of the study have no conflict of interest with this study.

Ethics Approval

NA

Consent to Participate

NA

Availability of Data

The data used in this manuscript is available from the corresponding author.

Author Contributions

Both authors contributed equally to this manuscript.

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