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COENZYME Q_{10}: A POTENTIAL BREAKTHROUGH IN PHYSIOLOGICAL DYSFUNCTIONS

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ABSTRACT: Coenzyme Q_{10} (ubiquinone) is a lipophilic benzoquinone substance. It is a pivotal component to the oxidative phosphorylation in the inner mitochondrial membrane of all aerobic cells as well as diminishes reactive oxygen species (ROS). Exogenous sources for CoQ_{10} are grapes seed oil, walnuts, pistachios, spinach, and sesame seed. At present, it is being utilized as an antioxidant agent. Recent studies have revealed its neuroprotective action. In the present review, the comprehensive pharmacological benefits of coenzyme Q_{10} on the central nervous system (CNS) has been revealed. Many studies were taken into considerations and compiled in accordance with their activities. Amongst those, the study using in-vitro models referring to neuronal toxicity and animal models of neurodegenerative diseases have been covered. Multiple outcomes have now evolved assisting the role of reactive oxygen species and neuroinflammation in the pathogenesis of the neurodegenerative disorder. The drug coenzyme Q_{10} has been administered in a human subject with reference to their age and body weight. In case of increased oxidative stress and few selective cases of gene mutation, the energy production in mitochondria is highly impaired and the deficiency also happens in brain cells which is a leading cause in pathogenesis of premature aging and neurodegenerative diseases. Potential neuroprotective effects of coenzyme Q_{10} have also been emphasized in several neurodegenerative disorders such as Parkinson's disease (PD), Huntington's disease and Alzheimer's disease (AD). This article contributes a pervasive review on the utility of coenzyme Q_{10} in the management as well as in the prevention of many illnesses as for example, hyperlipidemia, coronary artery disease, myocardial infarction and kidney disease.

INTRODUCTION: In the present scenario, the oxidative stresses are growing day by day and the bumpy lifestyles have become a matter of agitation. Many free radicals are found in nature due to environmental pollution which affects human life in many ways [1, 2].

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These highly reactive entities created by the pollutants can damage the vital parts of our body when they come in contact. Free radicals are repetitively being produced by both exogenous and endogenous sources.

The exogenous source is radiation, pathogens, chemical, smoking and pollutants, while the endogenous source is mitochondrial oxidative phosphorylation (during the electron transport chain mitochondria consumes almost 98% of molecular oxygen), lipid peroxidation chain reaction and other several metabolic processes. If reactive oxygen species (ROS) and nitrogen

reactive species (NRS) yield in controlled form, execute imperative functions and positively involved in defense mechanism of cells and tissues against pervaded pathogens, in addition to synchronized various process including cellular growth, and proliferation glucose metabolism, activation of transcription factor, phosphorylation of specific protein [3]. Apart from the serviceable effect, increased levels of ROS swiftly react with proteins, nucleic acid, and membrane lipids which disturbs ion homeostasis. It may also cause gene mutation which leads to alteration in biological and structural functions of various other molecules [4, 5]. In response to prevent the destructive effects of free radicals inside the normal physiological function, the body produces an endogenous substance, free-radical scavenger (CoQ_{10}) that quickly fuses with free radicals [6] and neutralized it. The Free radicals are unstable and deleterious molecules, freely strolling inside the cells to regain stability. The propensity and reaction rate of free radicals with different organelles inside living cells and tissues leading to cellular damage. This damage may increase chronic diseases such as cancer, tumor formation, osteoporosis and other health illness [7, 8].

Coenzyme Q_{10} & Biological System: Coenzyme Q_{10} (CoQ_{10}) is a fat-soluble, vitamin-like naturally occurring substance. Synthesized endogenously in all respiring eukaryotic cells. CoQ_{10} is pivotal to the oxidative phosphorylation process as an electron carrier in the inner mitochondrial membrane (energy production) as well as actively involved in diminishing of free radicals **Fig. 1**.

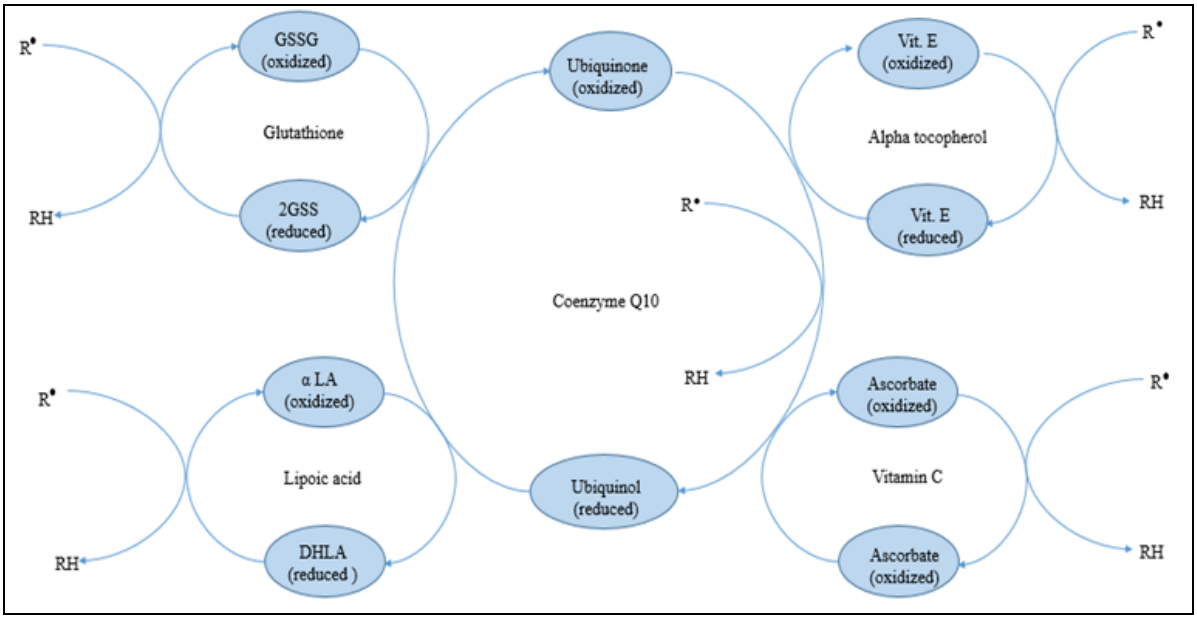

FIG. 1: FREE RADICAL SCAVENGING PROPERTY OF COENZYME Q_{10}

Source of Coenzyme Q_{10}: Predominantly it is found in the mitochondria of the heart, liver, kidney, and pancreas because these organs have the highest ATP requirement for vital physiological function. Coenzyme Q_{10} also presents in a small amount in a wide range of foods such as grape seed oil, walnuts, pistachios, spinach, sesame seed and olive oil and with higher concentration found in organs such as liver, heart and kidney. Tissue concentration of CoQ_{10} is maximum at about 20 years of age and progressively decreases with age [9].

Archives: The American biochemist Dr. Frederic L carne discovered Coenzyme Q_{10} from bovine heart mitochondria, at the University of Wisconsin, USA. After the discovery of coenzyme Q_{10} another scientist, Morton introduced a new compound that had the same function as coenzyme Q_{10} from rat liver and named it as ubiquinone.

Wolf DE and Karl Folkers determined the explicit chemical structure of Coenzyme Q_{10}: 2,3 dimethoxy-5 methyl -6 decarprenyl benzoquinone at Merck laboratories. In 1986, Folkers got prestigious Priestly Medal for his research in CoQ_{10} by the American Chemical Society. In a similar context, a British biochemist Peter Dennis Mitchell had been awarded the Nobel Prize in chemistry for his discovery of the chemiosmotic mechanism of ATP synthesis at Glynn Research Centre.

Coenzyme Q_{10} in Adjuvant Therapy: The level of CoQ_{10} in the body decreases with age, stress and mutation in genes that cause CoQ_{10} deficiency, which results in heterogeneous disorders such as encephalomyopathy, nephropathy and cerebral ataxia [10]. Tissue concentration of ubiquinone may be below in patients with a heart problem, cancer, neuronal disorder, and diabetes, while the adequate concentration of coenzyme Q_{10} is vital for energy production in the body. Isopentenyl pyrophosphate is an intermediary precursor of CoQ_{10} and cholesterol synthesis both follow the same biosynthetic pathway.

Statins (Lovastatin, simvastatin, pravastatin) are the most frequently prescribed blood cholesterol-lowering drugs (HMG-CoA reductase inhibitor), inhibit the mevalonate pathway which leads to obstruction of CoQ_{10} biosynthesis, can result in reducing muscle or serum levels of CoQ_{10} [11]. So, many other drugs such as Nitrogen-Bisphosphonates (risedronate and zoledronate) widely used in the bone fragility disorders [12], antihypertensive and β1 blockers (propranolol, metoprolol) drugs has been shown to diminish an intermediary precursor of CoQ_{10} biosynthesis, therefore the patient is not capable of producing adequate CoQ_{10}. [13, 14]

Coenzyme Q_{10} is being used as adjuvant therapy in the treatment of various illnesses such as heart health, blood sugar level, bronchi health, gum health, oxidative stress, vision, cancer anti-inflammatory and mental health.

Review of Literatures: Serebruany VL *et al*., demonstrated that dietary supplementation of Coenzyme Q_{10} (ubiquinone) has shown a cardioprotective role in several clinical studies. He examined the effect of CoQ_{10} on surface antigens and platelet size in human volunteers and measured receptor expression with the help of flow cytometry. Observed the inhibition of platelet vitronectin receptor expression, along with a reduction in platelet size and discussed a link between CoQ_{10} and platelet vitronectin receptor expression, therefore concluded, dilatory supplementation with CoQ_{10} perceived clinical benefits in the treatment of cardiovascular disease [15]. Khan NA *et al.* even found that the cardioprotective effect of CoQ_{10} by regulation of Bcl-2 gene expression and revealed a protective effect on apoptotic rat heart [16]. Yang X *et al.*, discussed about the interconnection between presenilin1 (PS1) protein (encoded by PSEN1 gene) and Alzheimer disease (AD). Inferred that mutation in the PSEN1 gene increases Aβ42 relative to Aβ40 in cultured cells and brains of transgenic mice bearing L286V PS1. These mutations manifest notably higher intracellular amyloid-beta (Aβ) and lead to neurodegeneration without the formation of extracellular plaques, again *in-vitro* studies displayed that oxidative stress corresponds with amyloid-beta overproduction. Transgenic mice were fed with CoQ_{10}, and demonstrated the reduction in the level of Aβ42 by 23% in the cortex of transgenic mice in the treatment group. Drawing the conclusion from the above data suggested that CoQ_{10} would be a useful perspective drug for the therapy of Alzheimer's disease [17].

Brea-Calvo G *et al.*, scrutinized clinically heterogeneous autosomal recessive disorder that is caused by mutations in several genes involved in CoQ_{10} biosynthesis. At least ten enzymes participate in CoQ_{10} biosynthesis, which is located in mitochondria and reported CoQ_4 play a structural role in establishing a multi-heteromeric complex that contains most of the CoQ_{10} biosynthetic enzymes. They included many volunteers in his study, these are two unrelated individuals present with severe hypotonia, bradycardia, respiratory insufficiency and heart failure, two sisters showed antenatal cerebellar hypoplasia, neonatal respiratory distress syndrome, and fifth subjects was an early onset but slowly progressive. All affected subjects showed that a reduced amount of Q_{10} and often displayed a decrease in Q_{10} dependent ETC complex activity. They concluded, a mutation in CoQ_4 may lead to heterogeneous disorder [18].

Akram Nezhadi *et al.*, found that the behavioral recovery and histological outcome after combination treatment of the bone marrow stromal cell (BMSC) graft and Coenzyme Q_{10} in a rat model of Parkinson's disease. $BMSC_s$ are the most promising candidate in the transplantation of a degenerative nervous system without any immunological problems, it also known for trophic factor expression leads to promising result in

axonal regeneration, (an increase neuronal property and functional recovery) combined treatment of CoQ_{10} and BMSC showed that better recovery in lesion group as compared to individual treatment of CoQ_{10} and found increased level of tyrosine hydroxylase gene expression. The study reported that combined treatment can be effective in Parkinson's disease [19].

Yeung CK *et al.,* discussed that varying doses of CoQ_{10} in hemodialysis patients also detailed the safety, tolerability, efficacy and effect of CoQ_{10} on free radicals. He discussed at high doses (1800 mg/day) CoQ_{10} supplimation is a safe, well-tolerated and essential cofactor for energy production in the mitochondrial respiratory chain as well as decrease reactive oxygen species in patient during hemodialysis treatment [20]. Yakugaku Xasshi *et al.,* also reported that about an alternative medical assessment for neuroprotective therapy. He established coenzyme Q_{10} is an imperative lipophilic compound of mitochondria to cure Parkinson's disease. In the present scenario, the available pharmacotherapy and surgical approaches can ameliorate the only symptom of PD. Consequently, he explored the neuroprotective activity of CoQ_{10} in PD. finally he concluded oral CoQ_{10} administration that prevented the degeneration of dopaminergic neurons in the striatum of brain[21].

Shazia Ashraf *et al.,* concluded that how to coenzyme Q_{10} biosynthesis are interfered in steroid-resistant nephrotic syndrome (SRNS) also focused ADCK4 gene involved in coenzyme Q_{10} biosynthesis pathway and mutation in ADCK4 gene which actively participates in the pathogenesis of SRNS as well as disrupt CoQ_{10} biosynthesis [22].

Mohammad Ali Eghbal *et al.,* and other researchers discussed major side effects of statin drugs in isolated rat hepatocytes and found the deficiency of coenzyme Q_{10} against statin toxicity. He observed different parameters in his *in-vitro* study such as reactive oxygen species (ROS), formation, cell death, and mitochondrial membrane potential. *In-vitro* experimental data expressed cell death as well GSSG is decreased by coenzyme Q_{10}. Therefore, CoQ_{10} may use as an adjuvant therapy along with statins drug which remarkably decreases liver toxicity [23].

Carrasco J *et al.,* reported that extracorporeal shockwave lithotripsy (ESWL) causes major renal injury as well as mentioned the protective effect of coenzyme Q_{10} in ESWL on the basis of available data. He noticed an increased glomerular filtration rate in his study along with a reduction in the concentrations of albumin, creatinine, macro-globulin (β2M) in the coenzyme Q_{10} treated group. Further, he concluded CoQ_{10} actively involved in maintaining renal function, vasoactive hormonal activities and inflammatory parameters after extracorporeal shockwave lithotripsy [24].

Greenlee *et al*. reviewed the etiology, evaluation and treatment of doxorubicin-induced cardiotoxicity that is used in breast cancer treatment. Cardiomyopathy changes and congestive heart failure observed in 3 to 20 / of the breast cancer patients because of DRX toxicity. DRX increases the generation of free radicals primarily within mitochondria of heart cells. This study analyzed DRX efficacy had not altered by CoQ_{10}. But it has been considered as cardioprotective in cancer treatment [25]. Romero-Moya *et al*. discussed that mutation in coenzyme Q (CoQ) genes that are (liable for coenzyme Q_{10} biosynthesis) diminishes CoQ10 biosynthesis. This mutation can outcome in mitochondrial dysfunction mainly in cells of the brain and skeletal muscles because these organs entails high energy for their biological function. He investigated that mutation in CoQ_4 genes may lead to mitochondrial heterogonous disorder [26].

Coenzyme Q_{10} - Primary and Secondary Deficiency: Ogasahara *et al.,* in 1989, discussed CoQ_{10} deficiency in patients [27]. CoQ_{10} deficiency in tissue or plasma level may be due to its bioavailability impairment or due to its altered biosynthesis which can lead to a variety of disease states, extremely cardiovascular disease, coronary artery disease, myocardial infarction, reperfusion injury, encephalomyopathy, neurodegenerative disease and cerebral ataxia. Moreover, the deficiency of vitamin B_6 and ascorbic acid can also impair the biosynthesis of coenzyme $Q_{10,}$ because it is essential nutrition for the biochemical pathway in CoQ_{10} synthesis.

There are many genetic disorders that may diminish the biosynthesis of coenzyme $Q_{10,}$ *via* mutation in genes such as PDSS1, PPSS2, CoQ4,

CoQ6, ADCK3, and ADCK4. It has also been reported in several diseases that primarily affect the mitochondrial function of the brain, skeletal muscle and myocardial cells. The deficiency of CoQ_{10} levels can be either primary or secondary. In many studies has been indicated primary deficiency can result from a gene mutation that is involved in CoQ_{10} synthesis. Many other neurological abnormalities such as poor muscle tone (hypotonia), seizures, progressive muscle stiffness (spasticity), neurological abnormalities, nephrotic syndrome, cardiomyopathy and cerebral ataxia all come under the primary CoQ_{10} deficiency [28].

Secondary deficiency has been related to several disorders such as lactic acidosis, stroke-like episode, cardiovascular disease, neurological, mitochondrial disorders and it may be associated with hydroxymethylglutary- coenzyme A reductase inhibitors such as statins (anti-hyper cholesteric drugs) [29].

Biosynthesis of Coenzyme Q_{10}: Human cells synthesize CoQ_{10} in the mitochondrial inner membrane from amino acids tyrosine or phenylalanine [30]. 4- Hydroxybenzoate and polyprenyl chain are not only principal compounds of CoQ_{10} biosynthesis but also dependents on sufficient levels of vitamins such as folic acid, pyridoxine, riboflavin and niacin [31]. Human CoQ consists of ten isoprene units in the side chain of isoprenoid. Dimethylallyl pyrophosphate (DMAPP) and its isomer isopentenyl pyrophosphate (IPP) is the precursor of the isoprene unit.

Elongation of the isoprene tail is formed by a heterotetrameric protein which is encoded by PDSS1, and PDSS2 genes, after this benzoquinone ring modified in the inner mitochondrial membrane at least 12 protein (CoQ) are involved, which are necessary for the formation of synthome (multiprotein complex). Mevalonate pathway is liable for the biosynthesis of CoQ_{10}, cholesterol, dolichol, heam A and isoprenylated proteins [32]. Finally, eight steps are required in the biosynthesis of Coenzyme Q_{10}.

CONCLUSION: Coenzyme Q_{10} (ubiquinone) is a vitamin-like substance that is being used as an antioxidant, in addition to its role in the mitochondrial electron transport chain (ETC) as electron carrier from complex I and II to complex III. It is also known as ubiquinone and biosynthesized by a precursor called 1, 4-benzoquinone, where Q refers to the quinine moiety and ten (10) refers to the quantity of isoprenyl subunits. It offers a substantial advantage in dietary supplementation. Coenzyme Q_{10} is retained in the body better and increases tissue concentrations in the organ-system because of its fat-soluble nature. Besides these properties, it exhibits a range of activity and clinical corollaries which has not been shown by other dietary supplements.

It is evident from the existing literature that coenzyme Q_{10} has many potential benefits when it was consumed by human recipients. It is also being utilized as an adjuvant drug in order to alleviate certain diseases (ref). Hence, it can be concluded that the drug has a higher significance in pharmacology and therapeutics. It is obvious that coenzyme Q_{10} exerted effective treatments of many disorders and it is widely recognized as a potential medicine. It manifests a significant role in the health management and treatment of illnesses.

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