

An Antioxidant Drug For The Treatment Of Pd Using Nanoemulsion

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Abstract

Dopaminergic (DAergic) neurons of the Substantia Nigra are selectively killed in Parkinson's disease (PD), a degenerative neurological illness. Yet without a cure, PD is an illness whose pathophysiology is poorly understood. The primary focus of today's pharmaceutical therapies is the alleviation of symptoms to enhance quality of life. As a result, the search for new PD treatments that can not only improve symptoms is urgent, but also arrest or reverse the neuronal damage that has been shown to impede the disease's development. An approach based on spontaneous emulsification was used to create the nanoemulsion, which was then homogenized under high pressure. Nigral degeneration is accelerated by oxidative stress in both sporadic and familial PD. We begin by taking a look at how much is now understood about how oxidative stress, mitochondrial dysfunction, and PD are all linked. The results of administering drugs that reduce oxidative stress or alleviate mitochondrial dysfunction to animal models or PD patients are then examined.

Keywords: Antioxidants, mitochondria, oxidative stress, mitochondria-targeted antioxidant;

INTRODUCTION

We begin by taking a look at how much is now understood about how oxidative stress, mitochondrial dysfunction, and PD are all linked. The results of administering drugs that reduce oxidative stress or alleviate mitochondrial dysfunction to animal models or PD patients are then examined. The SN is responsible for coordinating and planning movements, while the striatum is responsible for ensuring that they are executed smoothly and without imbalance. Resting tremor, muscle stiffness, bradykinesia, and postural instability are the primary clinical features of PD and are consistent with dopamine depletion.

Yet, despite the fact that the cellular mechanisms leading to this illness have been further elucidated thanks to the identification of monogenic, heritable types of the disease (5-10% of all cases), PD is still mostly an idiopathic neurological disease. It is yet unclear what causes sporadic PD, however age is thought to be a major risk factor. Data is piling up suggesting that oxidative stress and mitochondrial dysfunction are major contributors to the disease's onset. The usual droplet size of a nanoemulsion is 20-200 nm. By using a surfactant or a surfactant and co-surfactant combination, two or more immiscible liquids may be combined to form a single phase in a kinetically stable isotropic system known as a Smix system. They promote mucosal drug penetration and the solubility of lipophilic medicines. To create nanoemulsion with an adequately small particle size, one must use a highemulsification technique.

When compared to the gastrointestinal system and liver, the nasal route is one of the most permeable and highly vascularized because of its huge surface area (150 cm²), high total blood flow per cm³, and low enzyme levels. Intranasal medication delivery is being researched intensively as a viable, non-invasive option for direct brain administration that avoids substantial hepatic and intestinal processing and successfully bypasses the blood-brain barrier (BBB) (Mittal et al 2014, Haque et al 2012). The nervous system, the circulatory system, the spinal fluid,

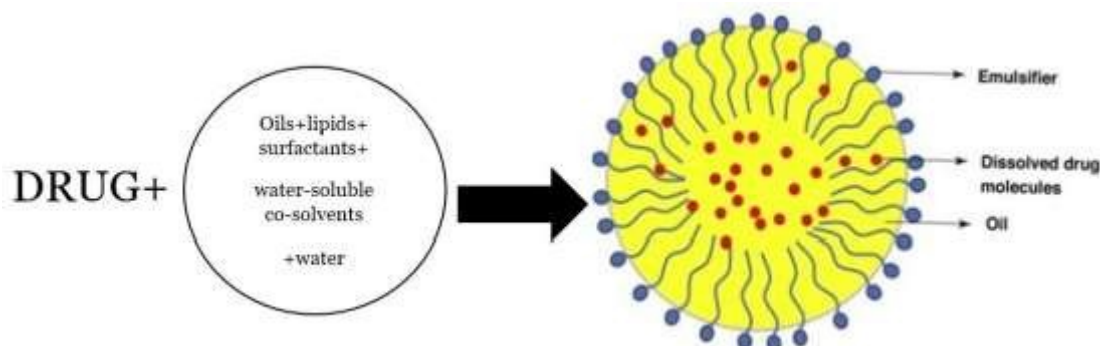
and the lymphatic system are all examples of such pathways. Levodopa is the drug of choice for treating PD since it may pass the blood-brain barrier (BBB) and relieve motor dysfunction symptoms. However, regular use of the medication has been linked to impairments in motor skills including walking, posture, speech, and balance. Since oxidative stress has been linked to the progression of PD, it is likely that PD symptoms might be alleviated with nasal delivery of the antioxidant at a therapeutic dose.

The substantial conversion to sulfates and glucuronides in the gut and liver reduces the drug's bioavailability when taken orally. Although resveratrol has been found to be clinically effective in the treatment of PD, it is a potent antioxidant with poor absorption. When a drug is taken orally, just a fraction of its potency makes it to the brain. It also has trouble penetrating the BBB's defenses. The main emphasis of this research is on the use of resveratrol nanoemulsion loaded with vitamin E for intranasal administration as a therapy for Parkinson's disease. The goal of this study is to increase CNS availability while decreasing systemic availability, hence solving the problem created by extensive presystemic metabolism.

Nanoemulsion Ingredients: The refractive index, phase behavior, density, viscosity, and interfacial tension of the oil phase all have a role in the stability and development of NEs, as well as their functional properties. Tri-, di-, or monoacylglycerols, free fatty acids, mineral oils, vegetable oils, etc. are all examples of lipids, oils, and NE triglycerides that may be found in NE formulations because of their solubility in water. The overall medication solubility is taken into consideration while choosing the oil. Very medicinal oil phases are often employed in the synthesis of NE.

By lowering the interfacial tension, emulsifiers promote the creation of stable, microscopic droplets. Emulsifiers such as sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, sodium deoxycholate (bile salt), and lecithin (phosphatidylcholine) are widely used. Stabilizers and the surface-active chemicals that shield tiny droplets during NE production are called emulsifiers. Droplets are less likely to agglomerate and collide because to the emulsifiers, which also increases the kinetic stability of the Solution. Emulsifiers are utilized as a surfactant in the NEs synthesis, although lipids and proteins were also used. Casein and polyethylene-glycol (PEG)-containing block copolymers are two examples of surfactants that have been suggested for use in NE.

In order to maintain NE stability. Polyethylene glycol, ethylene glycol, propylene glycol, glycerine, and ethanol are all examples of co-surfactants that may be used. Co-solvent and polar solvent both make up the aqueous phase of a NE. The breakdown of NE caused by gravity, coalescence, flocculation, and Ostwald ripening may be prevented by adding a stabilizer agent.



LITERATURE REVIEW

Niyaz Ahmad, et al. (2017), The likelihood of cerebral ischemia-reperfusion (IR) injury is decreased when antioxidants, which have been demonstrated to have neuroprotective effect, come into contact with free radical

produced neuronal damage. Because of its poor solubility and absorption properties, the antioxidant medication safranal has a limited serum and tissue bioavailability, despite its potential function in the amelioration of cerebral ischemia. The goals of this research are twofold: first, to assess the efficacy of non-invasive nasal route administration of drugs to the brain in an animal model of middle cerebral artery occlusion (MCAO); and second, to develop a nanoemulsion based on the principle of increasing bioavailability to mitigate oxidative stress-induced brain injury. Viscosity, mean globule size, zeta potential, and drug content. These are the SMNE's optimum physicochemical properties. Biochemical indicators of therapeutic effectiveness, such as glutathione reductase (GR), glutathione peroxidase, lipid peroxidation, catalase, and superoxide dismutase, were investigated in the brains of rats treated to 2 hours of MCAO followed by 22 hours of reperfusion. Studies on neurobehavioral and antioxidant properties, in addition to histological analyses, of MCAO-induced brain ischemia rats treated with SMNE given i.n. (intranasally) improved significantly. The final toxicity tests showed that the SMNE we created was completely safe.

Chen, Chiung-Mei, and Kuo-Hsuan Chang. Neurodegeneration of dopaminergic (DAergic) neurons and aberrant -synuclein buildup in the substantia nigra are the root causes of Parkinson's disease (PD) in 2019. (SN). Therefore, it is logical to think that chemicals associated with oxidative stress might serve as biomarkers for Parkinson's disease. Treatment of PD may benefit from the use of antioxidants, which may reduce oxidative stress. While several antioxidants have undergone clinical studies for Parkinson's disease, none have shown clear evidence of slowing or reversing neurodegeneration. Desferrioxamine, melatonin, pioglitazone, melatonin, and desferrioxamine are among them. Consistent but gradual loss of neuronal function; lack of indicators for the disease's premotor stage, and the inability to effectively transport drugs over the blood-brain barrier all contribute to the complexity of clinical trials. Future investigations in PD patients using innovative antioxidative therapies will need solutions to these obstacles.

Maria de Jesus Loera-Arias, et al. (2018), As oxidative stress has been linked to the development of Parkinson's disease (PD), researchers have been looking at antioxidant molecules as a possible therapeutic therapy for PD. Antioxidants have shown promise in preserving neuronal survival and function in preclinical models of PD, but their effects as disease modifiers in human therapeutic trials have fallen short of expectations. The challenge confronting translational medicine today is how to adapt clinical trials to standardized criteria for assessing molecules, with the end goal of reducing response variability. In this review, we examine the possible benefits and drawbacks of using therapeutic compounds derived from non-enzymatic antioxidants in the treatment of patients with PD.

Benjamin G. Trist, Dominic J. Hare, Kay L. Double (2019), The accompanying rise in societal and economic costs is exponential, underscoring the pressing need for efficient disease-modifying therapies. Dopaminergic neuron loss in the substantia nigra pars compacta and subsequent dopaminergic pathway depletion cause motor dysfunction. An exact molecular mechanism for the neurodegenerative cascade is yet unknown, however oxidative stress is a known contributor. This article will explain the molecular processes behind the high steady-state of oxidative stress in the substantia nigra of healthy older individuals, as well as the chemical environment that predisposes neurons to oxidative damage in Parkinson's disease. Targeting cellular redox activity has shown little success in the treatment of Parkinson's disease. This article will examine the function of oxidative stress in both aging and the development of illness. New evidence for a central biochemical role of redox imbalance in the etiology of Parkinson's disease is presented, along with the argument that better in vivo measurement of oxidative stress, dopaminergic neurotransmission, and cell death pathways is essential for the identification of novel disease biomarkers and the development of effective new treatments.

Ashhar M, (2017). The neurodegeneration seen in Parkinson's disease (PD) has been linked to oxidative stress,

according to research by Usama To better treat PD and decrease oxidative stress, we tested an intranasal nanoemulsion of Bromocriptine Mesylate (BRM) and glutathione (GSH). Confocal laser scanning microscopy (CLSM) was used to measure how deeply the nanoemulsion penetrated, and it was found that the nanoemulsion penetrated more deeply than the suspension. Nasal cilio toxicity testing verified the nanoemulsion's biocompatibility. The DPPH assay was used to determine the nanoemulsion's antioxidant properties. Researchers conducted biochemical estimation tests on Wistar rats to determine the effects of nanoemulsion on oxidative stress. In a haloperidol-induced model of PD, intranasal injection of nanoemulsion significantly increased levels of glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT), while drastically reducing levels of thiobarbituric acid reactive substances (TBARS). As a result of nanoemulsion treatment, levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-) were also observed to be dramatically reduced. Nanoemulsion's capacity to reduce oxidative stress demonstrates BRM and GSH's synergistic antioxidant effects.

PARKINSON'S DISEASE: OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

Complex I and III of the mitochondrial electron transport chain are major sites where superoxide radicals are generated. $\bullet\text{O}_2$, once produced, may trigger the formation of further ROS like H_2O_2 and $\bullet\text{OH}$. The latter may be made by the Harber-Weiss reaction or the Fenton reaction when intracellular iron is present. Peroxynitrite (ONOO), a highly reactive nitrogen species, is formed when $\bullet\text{O}_2$ combines spontaneously with NO produced inside the cell. Due to their high oxygen consumption and high energy demands, as well as their poor regeneration ability as a result of being post-mitotic, neurons are thought to be particularly vulnerable to ROS-induced injury. The susceptibility of neural tissues to chronic and degenerative disorders like PD may be explained by these characteristics. Highly reactive oxygen species (ROS) may damage cells by reacting with a wide variety of biological components, including nucleic acids, proteins, and lipids.

In the DAergic cells of PD brains, both of these markers have been detected. 8-hydroxyguanosine, a typical product formed from nucleic acids oxidation, is also elevated at the level of nigral neurons in these individuals. Proteins are another substrate for ROS-mediated oxidation. Again, Protein carbonylation, a hallmark of oxidative protein breakdown produced by reactive oxygen species, has been found in many studies to be abnormally high in the brains of PD patients. While the aforementioned findings are intriguing, they do not establish whether oxidative stress drives PD or is only a byproduct of neuronal cell death.

Postmortem studies showing a decline in complex I activity in the SN of PD patients who had passed away were the first to suggest a direct link between mitochondrial malfunction and PD. There was a link between mitochondrial dysfunctions and elevated oxidative stress, supporting the theory that complex I is a major mitochondrial source of superoxide radical generation. The discovery of genetic origins of familial PD has provided more evidence in recent years. The proteins Parkin, PINK1, and Fbxo7 have all been linked to crucial roles in the mitophagic process, which involves the selective removal of damaged mitochondria. Errors in these proteins have direct consequences for mitochondrial structure and function. Although the precise biological role of DJ-1 has not been determined, it is believed to include cellular responses to oxidative stress. DJ-1 may help maintain stable mitochondrial activity in the face of oxidative stress by cooperating with the PINK1/parkin pathway. Exposure to environmental chemicals, which disrupt mitochondrial processes, has been identified as a major risk factor for idiopathic Parkinson's disease (PD). When tested in animal models, these same poisons exhibit parkinsonian characteristics. In conclusion, if not in the genesis of the illness itself, then at least in the progression of cellular damage associated with it. Neuronal death seems to be linked to oxidative stress and related processes, such as protein aggregation, mitochondrial dysfunction, protein clearance, etc. Oxidative stress is typically evident in cyclical interactions between various activities, even though a causal link cannot always be established.

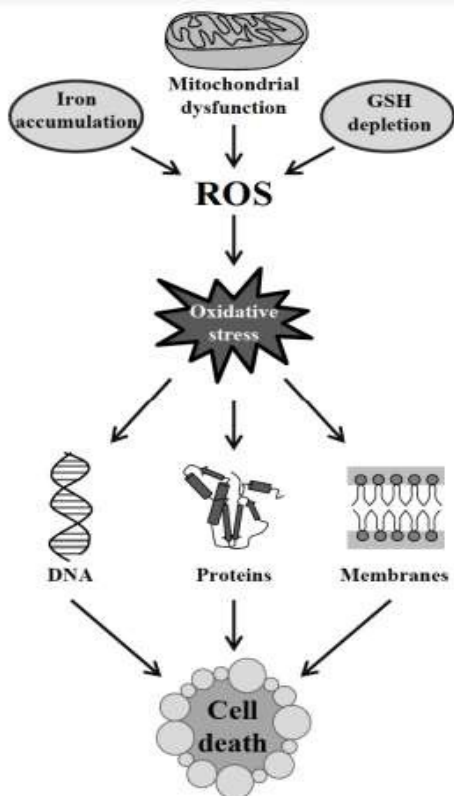


Fig. (1). Mitochondrial dysfunction and oxidative stress as a contributing factor in Parkinson's disease.

Inside a cell, mitochondria are the primary sites of ROS production. Patients' SNs had complex I insufficiency, iron buildup, and GSH deficiencies, according to postmortem examinations. Highly reactive oxygen species (ROS) may react with a variety of biological components, including lipids, proteins, and nucleic acids. Patients with PD have oxidative damage to their DAergic neurons, as shown by the presence of lipid peroxidation, protein carbonylation, and 8-hydroxyguanosine.

Antioxidant molecules have been considered useful therapeutic agents for the treatment of PD because of the roles that oxidative stress and mitochondrial dysfunction play in the development of the disease. Several animal models including neurotoxins have been crucial in unraveling PD etiology, and these models are widely used to evaluate the effectiveness of potential therapies for PD. The significant sensory and motor impairments reported in PD patients are mimicked in these animal models due to the loss of dopaminergic neurons. MPTP, a neurotoxic, is likely responsible for the most often used model. The monoamine oxidase enzyme system in the brain converts MPTP into 1-methyl-4-phenylpyridinium ion (MPP⁺) once it has been taken. The DA transporter is responsible for the selective uptake of MPP⁺ by dopaminergic neurons. MPP⁺ is harmful because it activates complex I in the mitochondria, leading to oxidative stress. Rats and mice were given 6-OHDA through intrastriatal injection, whereas rotenone and paraquat were given orally or intracerebrally, are other useful models [40]. The chemical structure of many antioxidants is shown in Fig. 2, and in the following sections we will explain some findings gained using these compounds.

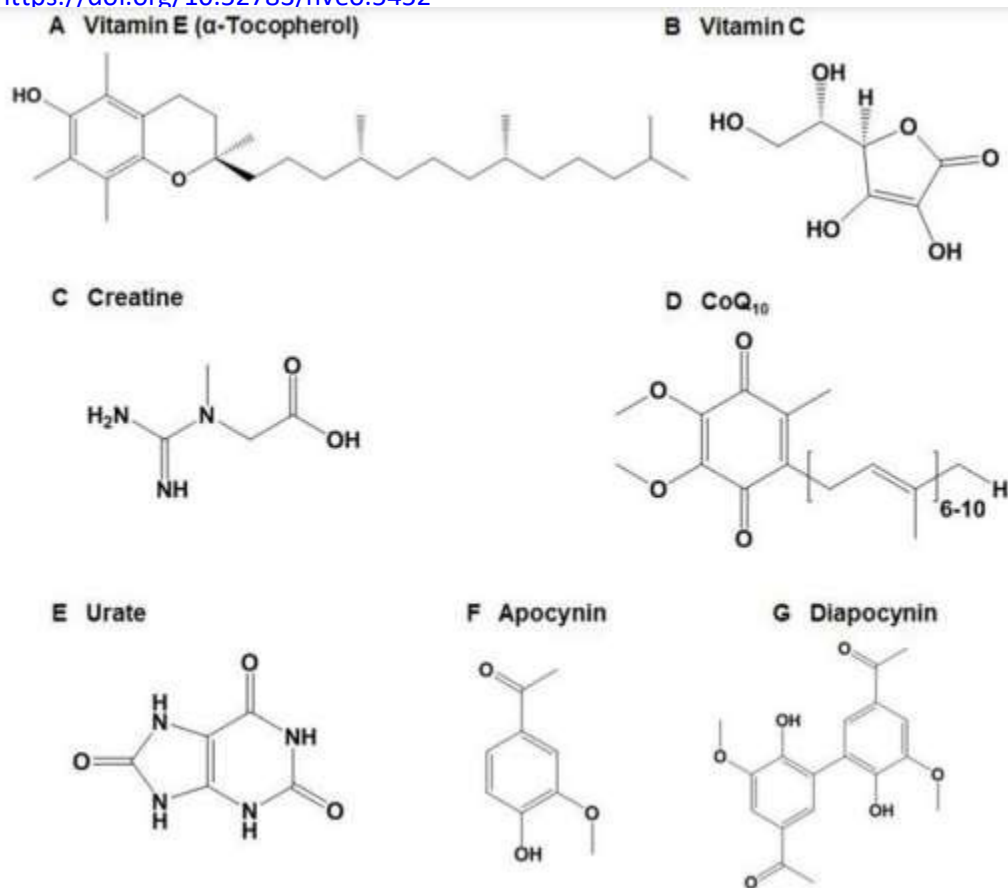


Figure 2. PD model structures for a range of small-molecule antioxidants

Antioxidant therapy

When it comes to treating PD, antioxidants that target oxidative stress and mitochondrial dysfunction have emerged as promising therapeutic agents because these variables play essential roles in nigrostriatal dopaminergic neurodegeneration in this complex, multifaceted illness. The present evidence on neuroprotective antioxidant medicines' ability to prevent or delay the onset of PD will be summarized here.

Vitamin antioxidants

Many vitamin antioxidants, including those in Fig. 2A and 2B, have been studied for their possible neuroprotective effects. MPTP induced dopaminergic neurotoxicity was worse in vitamin E deficient mice [93]. It has been observed that vitamin E protects the brains of mice from iron-induced oxidative stress, suggesting it may have neuroprotective properties against PD. Rats given 6-OHDA still had their nerve cells protected by vitamin E. Observational studies in humans show that high doses of vitamins E and C may help reduce the progression of PD. The results of double-blind, randomized controlled trials on vitamin E and PD were disappointing.

Creatine

Creatine (Fig. 2C) is a naturally occurring nitrogenous guanidine molecule that provides energy to muscle and nerve cells by forming high energy phosphate linkages. In addition to being a potent antioxidant, creatine has been shown to inhibit iron accumulation and the opening of mitochondrial permeability transition pores. In animal studies, before it was used on humans, its neuroprotective effects were established [104]. Recent studies have revealed that creatine may protect dopaminergic neurons and their fibers against the neurotoxins m-

phenylpyrrolidone (MPP+) and 6-hydroxydopamine (6-OHDA). In an MPTP-induced rat model of Parkinson's disease, creatine prevented the death of dopaminergic neurons. Two grams of creatine per day was proven to improve behavioral difficulties in a clinical study including 200 persons diagnosed with PD during the first five years. A further 18-month follow-up research showed that creatine's neuroprotective effects persisted following creatine delivery [107]. Creatine did not affect PD ratings or dopamine transporter imaging in a 2-year placebo-controlled trial of 60 people, however patients' mood behavior (a non-motor sign of PD) did improve. The National Institutes of Health (NIH) has just begun recruiting volunteers for a phase III clinical research that will test the effects of 10 grams of creatine per day on 1720 people with PD over the course of several years. The research project involving 52 hospitals should wrap up in five to seven years.

CoQ10

The neuroprotective effects of CoQ10 in PD are promising, as well (Fig. 2D). Taking CoQ10 supplements may be helpful for people with PD since postmortem studies have revealed that PD patients have considerably reduced CoQ10 levels. Patients with PD had higher amounts of oxidized CoQ10 and lower levels of CoQ10 overall in their plasma and platelets compared to age-matched controls. Since then, other *in vivo* and *in vitro* models of PD have shown CoQ10's neuroprotective properties. CoQ10 specifically reduced mitochondrial dysfunction and neurodegeneration caused by paraquat and rotenone in rat mesencephalic primary neurons. Iron-induced apoptosis in dopaminergic neurons was also studied, and results showed that CoQ10 had a neuroprotective function. Pretreatment of neurons with coenzyme Q10 (CoQ10) has been proven to protect mitochondrial membrane potential and reduce ROS production inside mitochondria. Coenzyme Q10 protected dopaminergic neurons in aged mice exposed to the MPTP paradigm against depletion and death. In a model that simulates the progressive nature of PD, known as the chronic MPTP model, CoQ10 also protected against toxicity.

Urate

Iron chelation and reactive oxygen species (ROS) scavenging are two of urate's many functions. Models of Parkinson's disease in cells and animals, urate reduces oxidative stress and protects dopaminergic cells. Many prospective cohort studies in humans found that those with greater blood urate levels had a much lower probability of getting PD. Patients with PD who consumed more urate had a slower decline toward a disability endpoint that necessitated dopamine medication, according to another prospective trial.

Apocynin and its derivative

An efficient NADPH oxidase inhibitor, apocynin is an antioxidant found in plants. It prevents the cytosolic components of NADPH oxidase from assembling with their membrane counterparts. During dementia, NADPH is a significant contributor to cellular ROS production. Apocynin prevents the oxidative stress and cell death of dopaminergic neurons caused by MPP+ *in vitro*. Apocynin, on the other hand, has not been found to have any pro-oxidant properties or positive effects. Diapocynin, a more potent inhibitor of NADPH oxidase than apocynin itself, may be synthesized from apocynin *in vivo* (Fig. 2G). The lipophilicity of diapocynin is greater than that of apocynin. While further research is required, these results imply that diapocynin may have neuroprotective effects against PD in both animals and humans.

Mitochondria-targeted antioxidant therapy

Murphy et al. found a group of mitochondria-targeted antioxidants (MTAs) that may be taken orally and include MitoQ, MitoVitE, and MitoTEMPOL, all of which support this hypothesis. These molecules are significantly superior than their non-targeted parent antioxidants in guarding against mitochondrial oxidative damage because

they are able to cross all biological membranes and concentrate inside mitochondria.

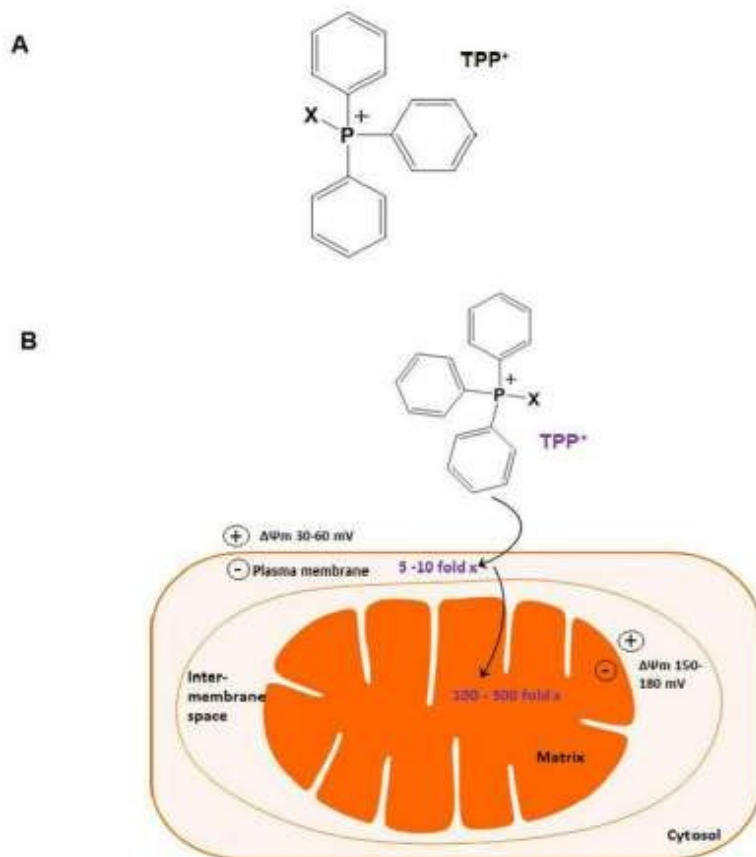


Figure 3. Accumulation of certain lipophilic cationic antioxidants in mitochondria.

CONCLUSION

Although promising results in animal models of PD, numerous antioxidants, including vitamin E, creatine, coenzyme Q10, and mitoquinone, failed to demonstrate substantial impacts on the progression of the illness in people, as reviewed in the current study. There are a few different factors that need to be taken into account while attempting to explain these very discouraging outcomes. To begin, although there are many animal models available, none of them accurately represent the whole spectrum of PD-related clinical and behavioral characteristics. Most pre-clinical research has relied on an MPTP-based model since it seems to generate an irreversible and severe parkinsonian state with many of the hallmark symptoms of PD. But it's not a flawless prototype by any means. Lewy bodies, a hallmark of the illness, have not been consistently identified, for instance, in MPTP-induced models. The use of innovative mitochondrially targeted nanomaterials for the delivery of antioxidants has shown promise as a potential approach to the creation of disease modifying medications for the treatment of neurodegenerative disorders like Parkinson's disease.

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