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MITOCHONDRIA - TARGETED ANTIOXIDANT: AGING

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ABSTRACT: The mitochondrion, the "power house of cell", plays a central role in energy-generating processes so called as ''master of life and death''. A decline in mitochondrial function plays a key role in the aging process and increases the incidence of age-related disorders. With advanced age, mitochondrial DNA volume, integrity and functionality decrease due to accumulation of mutations and oxidative damage induced by reactive oxygen species (ROS). In aged subjects, mitochondria are characterized by impaired function such as lowered oxidative capacity, reduced oxidative phosphorylation, decreased ATP production, significant increase in ROS generation, and diminished antioxidant defense. Antioxidant defense system, which is responsible for eliminating a wide range of oxidants, especially reactive oxygen species (ROS). As mitochondria are the major site for production of large amount of ROS, mitochondria-targeted antioxidant therapies have shown great effectiveness against the damage caused by enhanced ROS generation, is discussed in this review article.

INTRODUCTION: Mitochondria are double-membrane organelles that are found in most eukaryotic cells and that execute many metabolic functions including ATP synthesis through oxidative phosphorylation (OXPHOS) [1]. The electron transport chain (ETC) consists of about 80 different polypeptides, which are organized into five transmembrane protein complexes (I-V). The proton gradient generated by complexes I, III and IV is released through ATP synthase or complex V, which results in phosphorylation of adenosine di phosphate (ADP) to ATP [2]. In addition to the OXPHOS machinery, mitochondria are also known as metabolic signalling center of the cells, Performing many important biological functions such as regulation of apoptosis maintenance of cytosolic calcium homeostasis, lipid biosynthesis and iron sulphur cluster biogenesis [1, 3, 4]. Mitochondria undergo constant morphological changes by the process of continuous cycles of fusion and fission that determines their morphology and most mitochondrial functions.

Mitochondria are structurally complex and highly dynamic motile organelles [5]. Its unique structure is consisted of four distinct sub-structures with different specific functions: the mitochondrial matrix, the inner mitochondrial membrane (IMM), the outer mitochondrial membrane (OMM) and the inter membrane space (IMS).

The structure of the inner mitochondrial membrane (IMM) is extensively folded and compartmentalized. The numerous invaginations of the membrane are called cristae, which house the 4 complexes of the mitochondrial respiratory chain

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and ATP synthase, controlling the vital levels of cellular bioenergetics **Fig. 1**. This primary function of the mitochondrion is responsible for supplying cellular energy, the reason why we call it power plant of the cell. However, it is not the only important function of mitochondria in the cell [6].

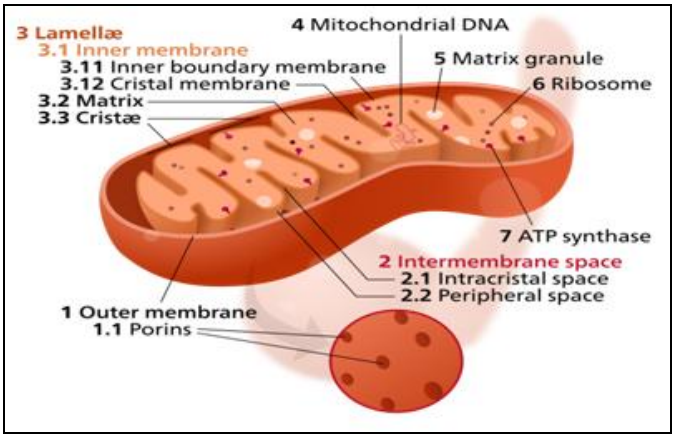


FIG. 1: MITOCHONDRIA

Mitochondria are double membrane encoded organelles with their own genome that consume oxygen and substrates to generate the vast majority of ATP while producing reactive oxygen species in the process. They also participate in a wide range of other cellular processes, including signal transduction, cell cycle regulation, oxidative stress, thermogenesis, and apoptosis. In doing so, they are highly dynamic organelles that are continuously remodeling through biogenesis, fission, fusion, and autophagy, thus responding to and modulating cellular dynamics. They undergo biogenesis to meet increased energy demands in response to exercise, and they ensure cellular quality by initiating an apoptotic program to remove defective cells.

Energetics of Mitochondria: Mitochondria transduce energy from substrates through the tricarboxylic acid (TCA) cycle and the electron transport system (ETS) **Fig. 2** to generate ATP. The ETS consists of multi polypeptide complexes (I–V) embedded in the inner mitochondrial membrane (IMM) that receive electrons from reducing equivalents NADH and FADH2, generated by dehydrogenase activity in the TCA cycle. The electrons are transferred along the complexes with O_2 serving as the final acceptor at complex IV [7]. The reduction potential (propensity to accept an electron) increases along the chain of complexes, and the energy generate is sufficient to drive the translocation of hydrogen ions across the IMM. This creates a proton gradient and membrane potential (collectively termed the proton motive force) that drives the synthesis of ATP as protons flow back to the matrix *via* complex V (ATP synthase). This process is also called oxidative phosphorylation (OXPHOS). However, the ETS is not a perfectly efficient system and significant (and highly variable) proton "leak" occurs by the movement of hydrogen ions back into the matrix space that is not mediated through complex V. In this manner, proton transfer can be uncoupled from ATP phosphorylation, and this inefficiency contributes to the demand for reducing equivalents. Mitochondria are therefore thought to have a much greater capacity to generate ATP than what is usually required [8].

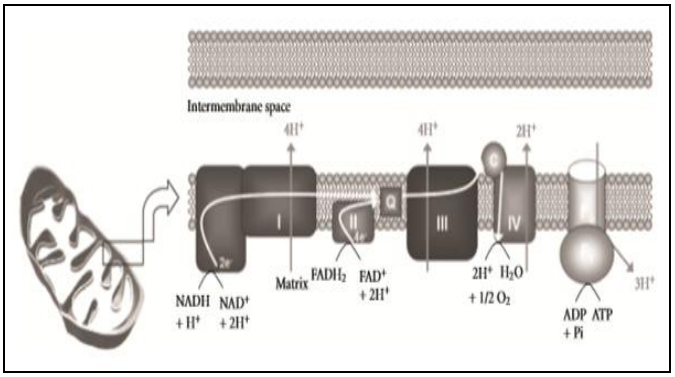


FIG. 2: ELECTRON TRANSPORT SYSTEM

Because of this metabolic latitude, many assume that mild impairment in mitochondrial function per se does not cause cellular disturbances associated with aging and with chronic diseases [8]. Indeed, whether mitochondrial dysfunction is a cause or a consequence of cellular impairment and the aging process is a subject of intense debate. Moreover, the definition of mitochondrial dysfunction itself has been the subject of controversy. For example, alterations in mitochondrial mRNA transcripts may not result in changes in protein levels, so it is not wholly clear whether this state - whether compensatory or not - can be counted as a disruption in normal function [9]. Given their central role in cellular homeostasis, mitochondrial dysfunction has been linked to many age-related disorders including mitochondrial diseases, cancers, metabolic diseases and diabetes, inflammatory conditions, neuropathy, and neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's disease [10, 11].

Mitochondrial dysfunction, including decreased oxidative capacity and increased oxidative damage, is thought to substantially contribute to biological aging [12, 13].

Mitochondria in Aging: Aging is thought to be a time dependent degenerative process caused by accumulated damage that leads to cellular dysfunction, tissue failure, and death. The aging process results in a gradual and progressive structural and functional deterioration of biomolecules that is associated with many pathological conditions, including cancer, neurodegenerative diseases, sarcopenia (loss of muscle mass) and liver dysfunction [14]. The exact causes of ageing are unknown; current theories are assigned to the damage concept, whereby the accumulation of damage (such as DNA breaks, oxidized DNA and / or mitochondrial malfunctions) may cause biological systems to fail, or to the programmed ageing concept, whereby internal processes (such as DNA telomere shortening) may cause ageing [15].

Although several theories have been proposed to explain the fundamental mechanisms mediating these age-related diseases and conditions, the free-radical theory of aging is by far the most popular. This theory proposes that cumulative damage to biological macromolecules by oxygen radicals (reactive oxygen species; ROS) leads to irreversible cell damage and an overall functional decline [16]. The free-radical theory has also been extended to include mitochondria, as the accumulation of aging-associated mutations and deletions in mitochondrial DNA (mtDNA) can impair the function of the respiratory chain and enhance ROS production [13, 17]. The increased ROS production can subsequently lead to a vicious cycle of exponentially increasing levels of mtDNA damage and oxidative stress in the cell **Fig. 3** [18 - 20]. Although various genetic problems in mitochondria cause phenotypes that resemble premature aging, additional support for this theory was provided by studies showing a direct link between mtDNA mutations and mammalian aging [21].

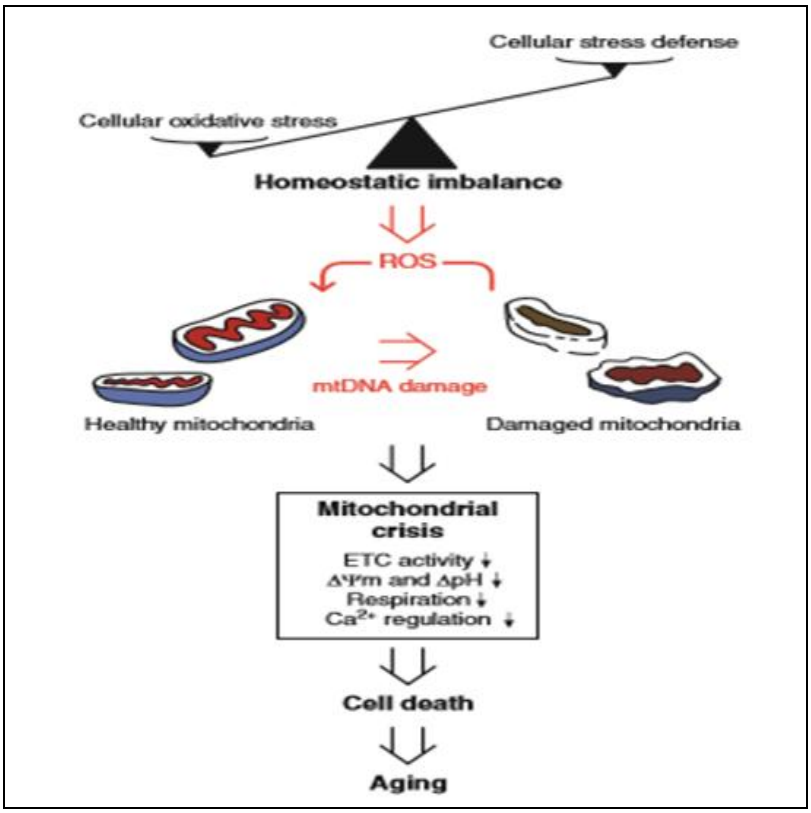


FIG. 3: MITOCHONDRIAL DYSFUNCTION IN AGING

In particular, mice with a proofreading-deficient version of PolgA, the catalytic subunit of mitochondrial DNA polymerase (POLG), accumulate mtDNA mutations that are associated with impaired respiratory-chain function and increased levels of apoptosis. These mtDNA-

mutator mice, with accelerated levels of mutations, had a shorter life span and displayed age-related phenotypes [such as hair loss, kyphosis (curvature of the spine), osteoporosis and sarcopenia] at an early age [4, 22]. Interestingly, these changes were not accompanied by increased levels of oxidative stress, a finding that has also been confirmed in humans [23]. This has resulted in much controversy regarding the idea that mtDNA mutations contribute to aging through increased ROS production and enhanced levels of oxidative stress in mitochondria. However, it is possible that the accumulation of mtDNA mutations that occur with age leads to alterations in cell-signaling pathways that can induce cell dysfunction and initiate apoptosis, irrespective of increased ROS production and oxidative stress in mitochondria. Whether mtDNA mutations play a causal role in the aging process is still an ongoing debate; however, the fact that a functional decline in mitochondria occurs with age and that properly functioning mitochondria are crucial for longevity and minimizing age-related diseases cannot be refuted [24].

Reactive Oxygen Species: Reactive oxygen species (ROS) are highly reactive molecules that consist of a number of diverse chemical species including superoxide anion (O_2^-), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2). Because of their potential to cause oxidative deterioration of DNA, protein, and lipid, ROS have been implicated as one of the causative factors of aging. As ROS are generated mainly as by products of mitochondrial respiration, mitochondria are thought to be the primary target of oxidative damage and play an important role in aging [16, 25].

There are several sources of ROS within a cell. ROS are generated as by-products of aerobic respiration and various other catabolic and anabolic processes [26]. Once they are produced, ROS react with lipids, proteins, and nucleic acids causing oxidative damage to the macromolecules [27 - 30]. ROS readily attack DNA and generate a variety of DNA lesions, such as oxidized DNA bases, a basic sites, and DNA strand breaks, which ultimately lead to genomic instability [31]. 7, 8-dihydro-8-oxodeoxyguanosine (8-oxo-dG) is one of the most abundant and well-characterized DNA lesions caused by ROS. Consistently, many studies have shown that 8-oxo-dG, one of the common oxidative lesions, is detected at higher level in mtDNA than nuclear DNA, suggesting that mtDNA is more susceptible to oxidative damage [32]. It is a highly mutagenic lesion that results in G:C to T:A transversion [33]. Mitochondrial complexes I and III are the main sites of superoxide generation and contribute the most to ROS production [34]. The reactive oxygen species, including $O_2^{\bullet-}$ and H_2O_2, can cause oxidative damage to surrounding structures and the particularly vulnerable mtDNA, which is in close proximity to the primary site of ROS production. Oxidation by ROS results in the synthesis of faulty proteins, oxidized lipids, and mtDNA mutations, which may lead to cellular and mitochondrial dysfunction. These processes are implicated in the mitochondrial theory of aging, which holds that the accumulation of ROS damage over time leads to age-associated mitochondrial impairment [16, 35, 36]. This increase in ROS production is associated with oxidation of ETS complex V, leading to decreased ATP production, increased levels of 8 oxo deoxy guanosine (8-oxoG) from DNA oxidation, increased levels of protein carbonyls, and increased nitration [36 - 40].

In particular, proteomic studies have found increased nitration of complex II and altered carbonylation of complex I, complex V, and isocitrate dehydrogenase [41]. To limit the cellular damage caused by ROS, mammalian cells have evolved a number of sophisticated defense mechanisms. ROS-generated DNA lesions are repaired mainly by base excision repair as well as other DNA repair pathways including nucleotide excision repair, double-strand break repair, and mismatch repair [42, 43].

In addition, the damaging effects of ROS can be neutralized *via* elevated antioxidant defense, which includes superoxide dismutase, catalase, and glutathione peroxidase to scavenge ROS to nontoxic forms [44]. Cumulative oxidative damage may in part be attributed to a reduction in ETS activity that would extend the length of time that electrons remain at complexes I and III, increasing the potential for donation of electrons to oxygen [45]. In theory, it could also be attributed to reduced activity of antioxidant defenses, including manganese superoxide dismutase (MnSOD), catalase (CAT), and glutathione peroxidase (GPx).

These enzymes work together to convert $O_2^{\bullet-}$ to H_2O_2, which is then further reduce to H_2O [46 - 48].

Mitochondria are the major producer of ROS in mammalian cells, the close proximity to ROS places mitochondrial DNA (mtDNA) prone to oxidative damage [7]. The bulk of mitochondrial ROS is generated at the electron transport chain [49, 50]. Electrons leak from the electron transport chain directly to oxygen, producing short-lived free radicals such as superoxide anion(O_2^-) [51, 52] O_2^- can be converted to non radical derivatives such as hydrogen peroxide (H_2O_2) either spontaneously or catalyzed by superoxide dismutase (SOD) [53 - 55]. H_2O_2 is relatively stable and membrane permeable. It can be diffused within the cell and be removed by cytosolic antioxidant systems such as catalase, glutathione peroxidase, and thioredoxin peroxidise [56, 57].

In addition to being generated during cellular metabolism in mitochondria, ROS can be produced in response to different environmental stimuli such as growth factors, inflammatory cytokines, ionizing radiation, UV, chemical oxidants, chemo-therapeutics, hyperoxia, toxins, and transition metals [58 - 61]. Other than mitochondrial respiration, a number of cytosolic enzymes are able to generate ROS [62]. The nicotinamide adenine dinucleotide phosphate (NADPH) oxidases are a group of plasma membrane-associated enzymes found in a variety of cell types [63]. The function of NADPH oxidases is to produce superoxide from oxygen using electrons from NADPH [64]. Although it remains unclear whether increased ROS levels area consequence of mitochondrial dysfunction or the cause of disruption to this organelle, it is clear that increased ROS levels are critical in many pathologic disorders.

The mitochondrial theory of aging, extended from the free radical theory, proposes that oxidative damage generated during oxidative phosphory-lation of mitochondrial macromolecules such as mtDNA, proteins, or lipids is responsible for aging [65]. As mtDNA encodes essential components of oxidative phosphorylation and protein synthesis machinery, oxidative damage induced mtDNA mutations that impair either the assembly or the function of the respiratory chain will in turn trigger further accumulation of ROS, which results in a vicious cycle leading to energy depletion in the cell and ultimately cell death [13, 20, 65 - 67]. Therefore, over the past decade, this organelle has become an attractive target for the delivery of therapeutic treatment, including antioxidants.

Targeting Antioxidants to Mitochondria: An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property [68]. These low molecular weight antioxidants can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Antioxidants act as radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal - chelating agents [69]. Antioxidants are molecules that inhibit oxidants from reacting with other molecules by the transfer of electrons, thereby removing the potential for damage and maintaining cellular redox homeostasis [70, 71].

There are several different types of antioxidants, and they can be broadly grouped into 2 major categories: endogenous (adaptive) and exogenous [72 - 74]. Both these enzymatic and non enzymatic antioxidants exist in the intracellular and extracellular environment to detoxify ROS. The adaptive or endogenous antioxidant defense system consists of both enzymatic antioxidants, such as the SODs, GPx, catalase, TPx and the non enzymatic antioxidants, which are represented by a-tocopherol (Vitamin E), glutathione, and bilirubin [71, 73 - 75].

These antioxidants are synthesized in the body, and a large proportion of these cytoprotective proteins are encoded by the Nrf2 (nuclear factor erythroid 2-related factor 2)-Keap1 (kelch-like ECH-associated protein1) pathway [76, 77]. Exogenous antioxidants (either naturally obtained from the diet or derived synthetically) include tiron (4, 5-dihydroxy-1,3-benzenedisulfonic), carotenoids (clycopene and lutein), flavonoids (anthocyanidins), and Vitamins (A and C) [78, 79]. Both endogenous and exogenous antioxidants are widely distributed in the body; however, they are differentially distributed within the cells, with the most localized within the cytosol and a small number localized within the mitochondria [80 - 82].

Mechanism of Action of Antioxidants: Two principle mechanisms of action have been proposed for antioxidants [83]. The first is a chain- breaking mechanism by which the primary antioxidant donates an electron to the free radical present in the systems. The second mechanism involves removal of ROS / reactive nitrogen species initiators (secondary antioxidants) by quenching chain-initiating catalyst. Antioxidants may exert their effect on biological systems by different mechanisms including electron donation, metal ion chelation, co- antioxidants, or by gene expression regulation [84].

Levels of Antioxidant Action: The antioxidants acting in the defense systems act at different levels such as preventive, radical scavenging, repair and de novo, and the fourth line of defense, *i.e.*, the adaptation. The first line of defense is the preventive antioxidants, which suppress the formation of free radicals. Although the precise mechanism and site of radical formation *in vivo* are not well elucidated yet, the metal- induced decompositions of hydroperoxides and hydrogen peroxide must be one of the important sources. To suppress such reactions, some antioxidants reduce hydroperoxides and hydrogen peroxide before hand to alcohols and water, respectively, without generation of free radicals and some proteins sequester metal ions. Glutathione peroxidase, glutathione-s-transferase, phospholipid hydro-peroxide glutathione peroxidise (PHGPX), and peroxidase are known to decompose lipid hydroperoxides to corresponding alcohols.

PHGPX is unique in that it can reduce hydroperoxides of phospholipids integrated into biomembranes. Glutathione peroxidase and catalase reduce hydrogen peroxide to water. The second line of defense is the antioxidants that scavenge the active radicals to suppress chain initiation and / or break the chain propagation reactions. Various endogenous radical-scavenging antioxidants are known: some are hydrophilic and others are lipophilic. Vitamin C, uric acid, bilirubin, albumin, and thiols are hydrophilic, radical-scavenging antioxidants, while Vitamin E and ubiquinol are lipophilic radical-scavenging antioxidants. Vitamin E is accepted as the most potent radical- scavenging lipophilic antioxidant. The third line of defense is the repair and de novo antioxidants. The proteolytic enzymes, proteinases, proteases, and peptidases, present in the cytosol and in the mitochondria of mammalian cells, recognize, degrade, and remove oxidatively modified proteins and prevent the accumulation of oxidized proteins. The DNA repair systems also play an important role in the total defense system against oxidative damage. Various kinds of enzymes such as glycosylases and nucleases, which repair the damaged DNA, are known. There is another important function called adaptation where the signal for the production and reactions of free radicals induces formation and transport of the appropriate antioxidant to the right site [85].

Life span is determined by the rate of free radical damage at the cellular and tissue levels. Cells protect themselves from oxidative damage by expressing a variety of non-enzymatic and enzymatic antioxidant defenses that convert ROS into less harmful byproducts. Thus, equilibrium between oxidants and antioxidants is essential to prevent cellular functional impairment. From this perspective, lowering ROS levels by increasing cellular antioxidant defenses should slow the progression of age-related alterations and eventually result in the life span prolongation. In contrast to expectations, genetic manipulations of antioxidant defense genes in animal models show no clear correlation between oxidative damage and life span regulation [86 - 88]. For instance, over expression of mitochondrial antioxidant enzymes did not extend life spans in different species and even resulted in the shortening of life spans in some cases [89].

While there are reports that dietary supplementation with antioxidants may improve cellular functions, decrease oxidative stress, and reverse age-related decline in antioxidant defenses in rodents, numerous human intervention studies suggest that dietary antioxidant supplementation with Vitamin E, beta carotene, or Vitamin A has no beneficial effect in prevention of age-related diseases and may even lead to an overall increase of mortality [90 - 92]. Thus, in contrast to the popular notion that increased intake of antioxidants like Vitamin C and Vitamin E will have beneficial effects on health and life span, these studies suggest that antioxidants should be used with care as therapeutic tools. The efficacy of a given

antioxidant might also depend on the presence of the other antioxidants or on certain physiological conditions.

Although it is unclear whether mitochondria play a causative role in the pathology of neuro-degenerative diseases, aging, and carcinogenesis, mitochondria-targeted antioxidants have been shown to be potent at sequestering reactive oxygen intermediates [80, 81, 93]. The use of mitochondrial-targeted antioxidants is a step toward understanding whether antioxidants can be efficient preventive or therapeutic tools against age-related diseases. Similar to what has been reported concerning antioxidant defense status, the rate of ROS production also does not clearly correlate with species-specific life span. The ability of mitochondria-targeted antioxidants to confer greater protection against oxidative damage in the mitochondria than untargeted cellular antioxidants provide has been attributed to their ability to cross the mitochondrial phospholipids bilayer and eliminate ROS at the heart of the source [80, 82, 94].

During the past decade, considerable progress in developing mitochondria targeted antioxidants had been made. A well established approach is conjugation to lipophilic cation, such as triphenyl phosphonium (TPP) [94]. phosphonium derivatives have been used traditionally to determine the mitochondrial inner membrane potential. Triphenyl phosphonium cations consist of a positively charged phosphorus atom surrounded by a large hydrophobic surface, thereby giving it the ability to directly and rapidly permeate the lipid bilayers while retaining the positive charge. This positive charge is used to facilitate TPP cation accumulation within the mitochondrial matrix driven by the large mitochondrial memebrne potential (ΔΨm) of 150 - 180 mV (negative inside), which was generated by the proton gradient during the transfer of an electron to oxygen.

The plasma membrane potential (30 - 60 mV negative inside) enables upto a 10-fold accumulation of TPP in the cytoplasm **Fig. 4**. The large negative potential gradient across the mitochondrial inner membrane potentiates the redistribution of TPP from the intracellular space in the mitochondria, leading to a 100-500 fold higher concentration of TPP inside mitochondria [95].

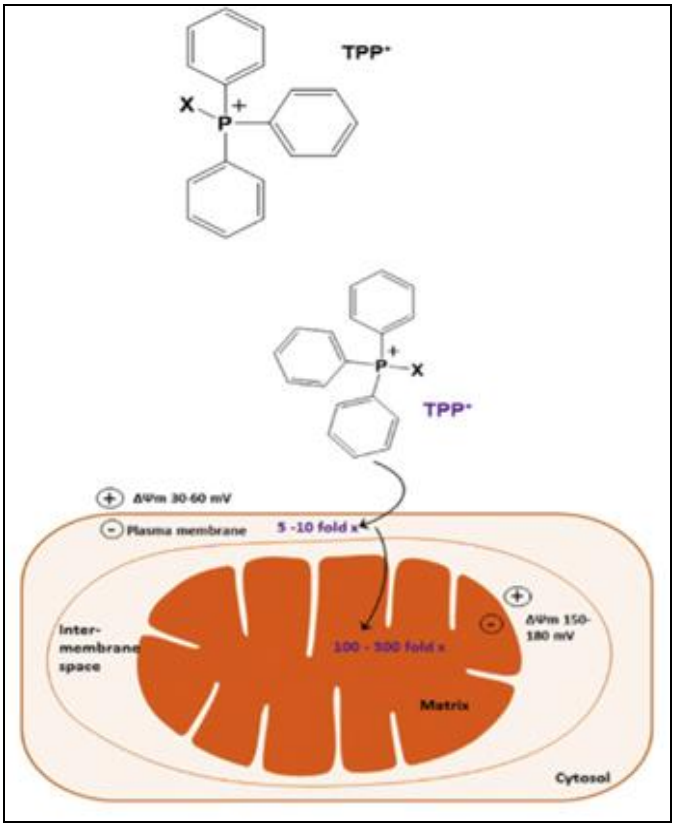


FIG. 4: MITOCHONDRIAL ACCUMULATION OF TARGETED CATIONIC ANTIOXIDANTS (TPP)

A series of orally bioavailable mitochondria targeted antioxidants (MTAs) were discovered, including MitoQ, MitoVit E, MitoTEMPOL. These compounds are known to pass through all the biological membranes and accumulate within mitochondria more easily than their non-targeted antioxidants, rendering them far more effective in protecting against mitochondrial oxidative damage. Work by several investigators has provided strong evidence for the argument that mitochondria targeted antioxidants, such as MitoQ could be effective antioxidant therapies against the damage caused by enhanced ROS generation [94, 95].

Triphenyl Phosphonium Based Mitochondria Targeted Antioxidant:

MitoQ: {10- (6'-ubiqunolyl)- decyl triphenyl phosphonium bromide and 10-(6,-uniquinonyl)-decyl triphenyl phosphonium bromide}.

MitoQ (mitoquinone) is the most studied and widely used antioxidant targeted to mitochondria. It consist of TPP covalently attached to the ubiquinone moiety of the endogenous antioxidant CoQ_{10} through a ten carbon aliphatic carbon chain **Fig. 5A**. MitoQ predominantly accumulates in

mitochondria, where it is primarily absorbed to the matrix facing surface of the inner mitochondrial membrane with the ubiquinone component penetrating deeply into the hydrophobic interior of the membrane [95]. Like the parent antioxidant CoQ_{10}, MitoQ continuously scavenges peroxyl, peroxynitrite and superoxide, thus can protect mitochondria against lipid peroxidation. After detoxifying oxidants, MitoQ is recycled back to the active ubiquinol antioxidant form by the respiratory chain complex II. Under certain conditions, it may become pro-oxidant and proapoptotic due to the redox cycling of the quione and generation of superoxide [96].

MitoVitE: {[2- (3, 4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)ethyl]triphenyl phosphonium bromide}.

MitoVitE (mitotocopherol) was the first mitochondria targeted antioxidant to be discovered, and consist of TPP conjugated to the α-tocopherol moiety of vitamin E through a two carbon chain **Fig. 5B**. Internalized MitoVitE is immobilized by insertion in the bilipid layer of the mitochondrial inner membrane. Like MitoQ, MitoVit E appers to protect mitochondria and cwlls from oxidative damage by inhibiting lipid peroxidation [97].

MitoTEMPOL: {(4- hydroxy- 2, 2, 6, 6, -tetra methyl piperidine-1-oxyl) triphenyl phosphonium bromide}.

MitoTEMPOL is another TPP^+ derivative, but one with the stable piperidine nitroxide radical TEMPOL (4- hydroxy- 2, 2, 6, 6,-tetra methyl piperidine-1-oxyl) **Fig. 5C**, which accepts an electron from the potent radical scavenger hydroxylamine. MitoTEMPOL may act as a cytosolic SOD mimetic, which converts superoxide molecules into water, and is able to detoxify ferrous ion by oxidizing it to ferric ion. The conjugated compound accumulated inside energized, isolated mitochondria [98].

MitoPBN: {[4- [4- [[(1, 1- dimethylethyl) oxido-imino]methyl]phenoxy]butyl]triphenylphosphoniu m bromide}.

Nitrones and phenyl tert-butyl nitrone (PBN) in particular have been investigated as neuro-protective agents and antioxidants **Fig. 5E**. Although reacts readily with carbon-centered radicals, it apparently does not function as a chain breaking antioxidants and does not react with superoxide. Because of the selectivity of PBN in reacting with carbon centered radicals, a mitochondrial targeted analogue, MitoPBN was prepared to dissect the roles of ROS in the activation of uncoupling proteins (UCPs); studies shows that MitoVitE and MitoQ block super oxide induced activation of UCPs [99].

MitoPeroxidase: {2-[4-(4-triphenylphosphoniobu-toxy)- phenyl]- 1, 2- benzisoselenazol- 3(2H)-one iodide}.

MitoPeroxidase is a mitochondria targeted analogue of ebselen, which is a organ selenium compound that shows antioxidant effects through its glutathione peroxidase like action **Fig. 5F**. MitoPeroxidase and ebselen inhibit mitochondrial respiration and decrease the mitochondrial memebrane potential. The binding of MitoPeroxidase to isolated mitochondria was studied with a TPP^+ sensitive electrode. Binding of MitoPeroxidase to mitochondria is rapid, and the addition of deenergized mitochondria decreases the concentration of free MitoPeroxidase. Mito Peroxidase and ebselen degrade phospholipid hydroperoxides and prevent Fe^{2+} / H_2O_2 induced lipid peroxidation in intact mitochondria, but these antioxidant effects requires glutathione or thioredoxin to generate the selenol form of MitoPeroxidase and ebselen [100].

"Sk" Compounds: An alternative series of mitochondria targeted antioxidants, termed as "SkQs", developed by using plastoquinone to replace the ubiquinone antioxidant moiety of MitoQ. The compound SkQ1 **Fig. 5D**, which is a TPP+ derivative conjugated with plastoquinone itself, is the most studied Sk compound.SkQ1 performed as a potent antioxidant in isolated mitochondria. Cell culture studies have confirmed that very low concentrations of SkQ1 and its analogues inhibited cell death induced by hydrogen peroxide. Extensive animal studies have demonstrated beneficial roles of SkQ1 and related compounds in a number of diseases associated with elevated oxidative stress [101].

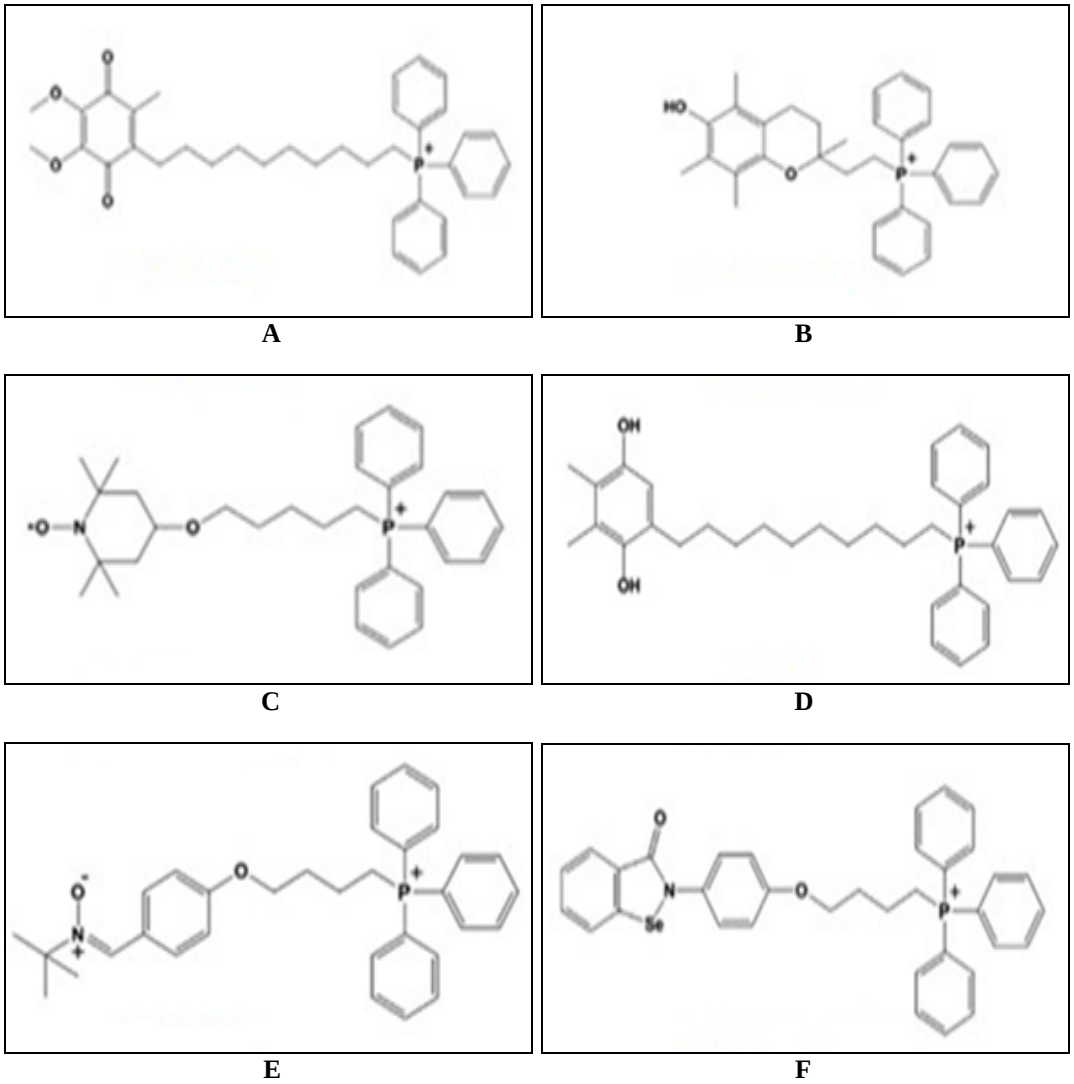


FIG. 5: A) MitoQ; B) MitoVitE; C) MitoTEMPOL; D) SkQ1; E) MitoPBN; F) MitoPeroxidase

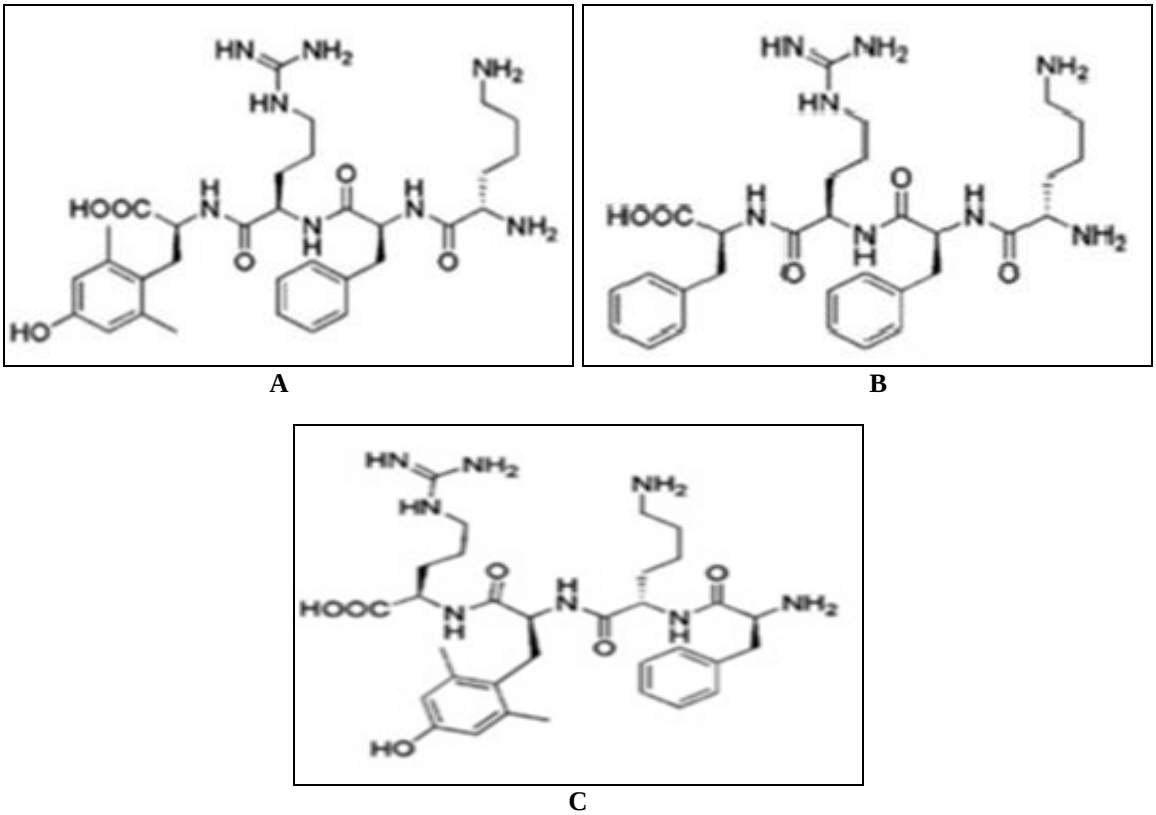
Amino Acid and Peptide - Based, Mitochondria Targeted Antioxidants:

SS tetrapeptides: SS tetrapeptids are aromatic-cationic peptides that bear the structural modification of alternating aromatic and basic amino acid residues along with a 2', 6'-dimethyltyrosine (Dmt) residue. The SS tetra-peptides were originally prepared in an attempt to develop centrally acting opioid analgesics [102].

The compounds studied include Dmt-D-Arg-Phe-Lys-NH_2(SS-02), Phe- D-Arg-Phe-Lys-NH_2(SS-20) (a tetrapeptide that lacks the antioxidant Dmt), D- Arg- Dmt- Lys- Phe- NH_2 (SS-31), Dmt-D-Arg-Phe-atnDap-NH_2(SS-19), a fluorescent analog in which β- anthraniloyl- L- α- β- diaminiopropionic acid replaces Lys was prepared to study mitochondrial and cellular uptake **Fig. 6A, 6B, 6C**. SS-02 scavenges H_2O_2 and inhibits the oxidation of linoleic acid and low density lipoproteins (LDL), thereby demonstrating the antioxidant properties of these tetrapeptides. SS-31, which contains the same amino acid residues as SS-02 but in a different sequence, shows antioxidant properties similar to SS-02, but analogs SS-20, which lack the Dmt residue, did not demonstrate antioxidant activity. These may have the advantage in excerting effective antioxidant action in depolarized mitochondria [102, 103].

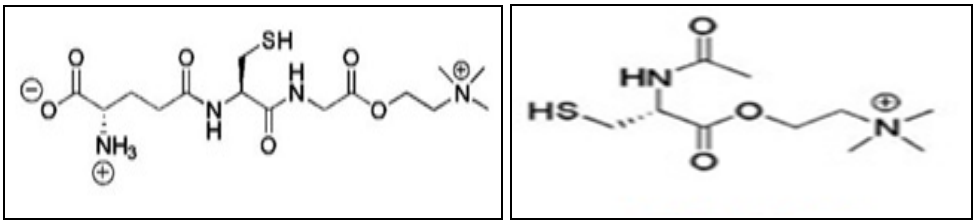
Choline Esters of Glutathione and N-acetyl-L-cysteine: Glutathione (L-γ-glutamyl-L-cysteinyl-glycine) is the most abundant nonprotein thiol in cells. Glutathione plays an critical role in antioxidant defence mechanisms and in the detoxification of endobiotic and xenobiotic electrophiles. Mitochondria are not component to synthesize glutathione, and glutathione is transported from the cytoplasm to the mitochondria.

Dicarboxylate and 2-oxoglutarate carriers serve to transport glutathione into mitochondria. The mitochondrial glutathione pool is approximately 15 % of total cellular glutathione, but the mitochondrial glutathione pool plays a critical role in cytoprotection. To increase the mitochondrial content of glutathione and other thiol-based antioxidants may serve to protect mitochondria, along with cells and organs, against oxidative damage. Glutathione choline esters and N-acetyl-L-cysteine choline ester **Fig. 7A, 7B**, which are hydrophilic antioxidants designed to exploit the high negative internal potential of mitochondria, which should lead to their concentration in mitochondria [104].



A **B** **C**

FIG. 6: A) SS-02; B) SS-20; C) SS-31



A **B**

FIG. 7: A) MitoGSH; B) MitoNAC

CONCLUSION: Mitochondria are attractive targets for drug delivery because of their roles in cellular energy metabolism, programmed cell death, Ca^{++} homeostasis, cell signalling. A decline in mitochondrial function plays a key role in the aging process and increases the incidence of age-related disorders. Direct mechanisms of mitochondrial damage include the inhibition of electron transport chain complexes, transcriptions of these complexes and enzymes required for glycolysis and b-oxidation. Indirect mechanisms include damage *via* ROS overproduction or decrease in endogenous antioxidants. The field of antioxidants turned out to be much more challenging; much effort has been directed to the study of the efficacy of different antioxidants in human diseases. Redox homeostasis is maintained by the antioxidant defense system, which is

responsible for eliminating a wide range of oxidants, including reactive oxygen species (ROS), lipid peroxides, and metals. Mitochondria-targeted antioxidants are widely studied because the mitochondria, the major producers of intracellular ROS, have been linked to the cause of aging and other chronic diseases.

Mitochondria-targeted antioxidants have shown great potential because they cross the mitochondrial phospholipid bilayer and eliminate ROS at the heart of the source. Mitochondria targeted antioxidants have shown great promise, with compounds such as MitoQ currently in clinical trials; however, further investigative work is needed, to improve the potency of current antioxidants and therapeutic treatments. There is also a need to develop novel experimental strategies to interfere with ROS production in a selective way, to reduce oxidative damage without affecting cell signalling.

An increased basic understanding of the role for ROS in different cellular processes should make it possible to substantially improve the design of human intervention studies aimed at reducing the oxidative damage associated with disease and aging. The search for effective therapies should include treatments that target mitochondria or pathways affected by mitochondrial function. In the future, well-designed and well-executed clinical trials will provide more definitive information on the therapeutic efficacy of agents aimed at improving mitochondrial health.

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