Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

MitoQ

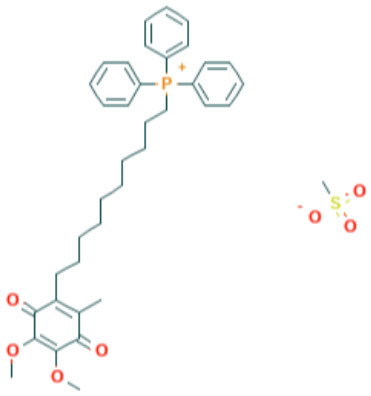
Evidence Summary

Consistent evidence suggests that MitoQ can reduce oxidative stress in mitochondria; though whether this will impact clinical outcomes in humans is unknown.

Neuroprotective Benefit: MitoQ may reduce the burden of oxidative stress in Alzheimer's disease, though there is not strong evidence it would change clinical outcomes in patients.

Aging and related health concerns: MitoQ shows consistent antioxidant properties, though whether it would have beneficial effects on clinical outcomes in humans is not known.

Safety: Some evidence from clinical studies suggest there are gastrointestinal side effects at higher doses, though no large, extended clinical trials have been conducted.

Availability: Available as a supplement from MitoQ.	**Dose**: 10mg/day recommended by manufacturer; 40mg to 80mg/day used in clinical trials.	**Chemical formula:** $C_{38}H_{47}O_7PS$ **MW:** 678.8g/mol  **Source:** Pubchem
Half life: Not known	**BBB**: Penetrant (in animals)	
Clinical trials: 4 completed, none in Alzheimer's disease; largest trial included 128 Parkinson's patients.	**Observational studies**: 0	

What is it?

MitoQ is a mitochondria-targeted antioxidant. It is composed of ubiquinone bound by a ten-carbon chain to triphenylphosphonium (TPP^+). Ubiquinone is a component of the electron transport chain and can be reduced by mitochondrial complex 2 to ubiquinol. Ubiquinol acts as an antioxidant when it is oxidized back to ubiquinone by reactive oxygen species (ROS) in the mitochondria. Complex 2 then regenerates ubiquinol from ubiquinone allowing MitoQ to continually reduced ROS. TPP^+ is a lipophilic cation that brings the ubiquinone moiety to the inner mitochondrial membrane while remaining on the matrix side of the membrane. These mitochondrial-targeted antioxidants accumulate several hundred-fold within the mitochondria, *in vitro*. Uptake into mitochondria is driven by the mitochondria plasma membrane potential (Smith and Murphy, 2010).

MitoQ was developed in Michael Murphy's lab at the Medical Research Council in the UK. They reported that administration of 500µM of MitoQ in drinking water to mice over 10 days accumulated in multiple tissues, including the brain (Smith et al, 2003). It's bioavailability was estimated at ~10% due to first-pass metabolism in the liver and intestinal walls (Zinovkin and Zamyatnin, 2019).

Neuroprotective Benefit for: MitoQ may reduce the burden of oxidative stress in Alzheimer's disease, though there is not strong evidence it would change clinical outcomes in patients.

Types of evidence:

- 1 RCT in Parkinson's disease
- 4 preclinical studies in Alzheimer's models
- 7 preclinical studies in other neurological conditions

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None

Human research to suggest benefits to patients with dementia
None

Human research to suggest benefits to patients with Parkinson's disease
In 128 patients with newly diagnosed Parkinson's disease, MitoQ (40mg or 80mg/day) had no effect on clinical outcome measures (the UPDRS) over 12 months. More patients discontinued in the MitoQ group (13 in 80mg, 2 in 40mg, and 1 in placebo), mostly due to gastrointestinal side effects (Snow et al, 2010). Reasons suggested for the failed trial include treating patients too late in the disease progression and insufficient brain penetration of MitoQ.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
In vitro, MitoQ prevented Aβ-induced neuronal death, ROS production, and change in mitochondrial membrane depolarization. In Alzheimer's mice treated with MitoQ from a young age for five months, treatment improved cognition, reduced oxidative stress, increased synaptic markers, reduced gliosis, and reduced levels of amyloid (McManus et al, 2011). In older Alzheimer's mice (beginning treatment at 12 months of age), MitoQ treatment for five months improved cognitive performance, increased markers of synapses, reduced oxidative stress, reduced astro- and micro-gliosis, and reduced tau and ptau levels. MitoQ also increased lifespan of Alzheimer's mice to a similar extent as control mice – although the study was not long enough to test the full extent of an increase in lifespan (Young and Franklin, 2019). *In vitro* studies suggest that MitoQ can increase neurite outgrowth in neurons from an Alzheimer's mouse model and protect against Aβ toxicity in cells (Manczak et al, 2010).

In a *C. elegans* model of Alzheimer's disease, MitoQ extended lifespan by 15% and delayed paralysis (a marker of healthspan in these worms). MitoQ had no effect on oxidative stress, mtDNA damage, or oxygen consumption rate and ATP levels (measures of mitochondrial metabolism). However, MitoQ increased mitochondrial complex I and IV activity and increased the level of certain cardiolipin species (Ng et al, 2014).

Other neurological outcomes
ALS: In a mouse model of ALS, treatment with MitoQ early in the disease improved mitochondrial function in the muscle and spinal cord, reduced levels of 3-nitrotyrosine and gliosis in the spinal cord, improved motor unit integrity at the neuromuscular junction, and increased lifespan (Miquel et al, 2014).

Parkinson's: In a mouse model of Parkinson's disease, 14-day treatment with MitoQ increased the number of dopaminergic neurons and increased the expression of PGC-1α (a gene involved in mitochondrial fusion) (Xi et al, 2018).

Multiple sclerosis: In a mouse model of multiple sclerosis (EAE injection), pretreatment with MitoQ delayed the onset of neurological symptoms and treatment with MitoQ after EAE injection reduced the severity of neurological symptoms. In the spinal cord, MitoQ reduced microgliosis, IL-6 expression, and neurodegeneration (Mao et al, 2013).

Aged animals: In aged rats, 5-week treatment with MitoQ (500μM in drinking water) reduced markers of oxidative damage (malondialdehyde, protein carbonylation, and nitrosative stress), improved mitochondrial complex I and IV activity, increased the mitochondrial membrane potential, and increased mitochondrial ATP levels (Maiti et al, 2018).

Traumatic brain injury: When administered 30 minutes after a traumatic brain injury in mice, MitoQ (4mg/kg and 8mg/kg, but not 2mg/kg) improved neurological outcomes and reduced brain edema. It increased the activity of antioxidant enzymes (superoxide dismutase – SOD, and glutathione peroxidate – GPx) and reduced a marker of oxidative stress (malondialdehyde – MDA). In addition, it reduced neuronal apoptosis and increased nuclear Nrf2 levels and the expression of proteins downstream of Nrf2 (Zhou et al, 2018).

Subarachnoid hemorrhage: In a rat model of subarachnoid hemorrhage, administration of MitoQ 1 hour after hemorrhage improved neurological outcomes and reduced brain edema (in the 3mg/kg but not

1mg/kg or 9mg/kg groups). This was accompanied by an increase in Nrf2 expression, improved mitochondrial morphology, and improved blood brain barrier integrity (measured by increased claudin-5 expression and reduced brain albumin levels) (Zhang et al, 2019).

Angelman Syndrome: In a mouse model of Angelman Syndrome, MitoQ increased synaptic plasticicy and improved memory (Satini et al, 2015).

APOE4 interactions:
None Reported

Aging and related health concerns: MitoQ shows consistent antioxidant properties, though whether it would have beneficial effects on clinical outcomes in humans is not known.

Types of evidence:

- One systematic review of preclinical studies for aging-related biomarkers
- 1 RCT in healthy older adults with endothelial dysfunction
- 8 preclinical studies in age-related models (vascular, diabetes)

Aging Biomarkers
In a meta-analysis of aging-related biomarkers from preclinical studies, Braakhuis et al (2018) reported that three biomarkers were included in enough studies to conduct a meta-analysis (3-nitrotyrosine, 8 studies; mitochondrial membrane potential, 4 studies; and protein carbonyls, 8 studies). MitoQ significantly reduced 3-nitrotyrosine levels, increased mitochondria membrane potential, and non-significantly reduced protein carbonyl levels.

Human research to suggest benefits for age-related diseases
In 20 healthy older adults (avg. age 68) with impaired endothelial function (brachial artery flow-mediated dilation <60%), 6-week cross-over treatment with MitoQ (20mg/day) improved endothelial-dependent flow-mediated dilation (FMD) by 42% (but had no effect on endothelial-independent FMD) and reduced aortic stiffness (carotid-femoral pulse wave velocity) in patients with elevated aortic stiffness. MitoQ reduced oxidized-LDL but had no effect on circulating inflammatory markers (CRP or IL-6) (Rossman et al, 2018).

Vascular models:
In a model of pressure overload-induced heart failure, MitoQ (100μM in drinking water) failed to improve cardiac functioning. It had a few minor benefits in some measures of mitochondrial function, but not all (Ribeiro Junior et al, 2018). In aged mice, 4-week treatment with MitoQ (250μM) reduced aortic stiffness (aortic pulse-wave velocity) and increased elastin expression, but had no effect on collagen expression or the expression of pro-inflammatory cytokines (e.g. IL-6, IL-10, IFN-γ, IL-1β) in the aorta (Gioscia-Ryan et al, 2018). Another study from the same group showed that 4-week treatment with MitoQ increased endothelium-dependent (but not independent) dilation, reduced mitochondria-specific superoxide production, and reduced 3-nitrotyrosine levels. It also increased the aortic expression of PGC-1α, superoxide dismutase (MnSOD), and reduced expression of COX-IV (Gioscia-Ryan et al, 2014).

In a mouse model of ischemia-reperfusion of the kidney, administration of MitoQ 15 minutes prior to ischemia reduced kidney damage (as measured by creatine levels) and reduced oxidative damage (as measured by protein carbonyl content and mtDNA damage) (Dare et al, 2015). In a model of hemorrhagic shock with reperfusion, administration of MitoQ had mixed effects with a reduction in morbidity, no effect on liver necrosis, a trend toward increased lipid peroxidation, elevated GPx activity, reduced catalase activity, and a reduction in inflammation (hepatic IL-6 and TNFα) (Powell et al, 2015).

Diabetes models:
In an *ex vivo* study of leukocytes from patients with type 2 diabetes, MitoQ reduced mitochondrial ROS levels, leukocyte adhesion properties, and reduced the expression of inflammatory markers (NFkB and TNFα) (Escribano-Lopez et al, 2016).

In a mouse model of diabetic kidney disease, MitoQ (0.6mg/kg/day) over 12 weeks had no effects on plasma glucose or insulin levels. Beneficial effects on renal function were similar to an ACE inhibitor (ramipril), but there were no additive effects when given together (Ward et al, 2017). In a mouse model of metabolic disease, 14-week treatment with MitoQ prevented an increase in fat, improved energy expenditure, reduced liver lipid content, reduced serum liver enzymes, and reduced serum lipid markers (cholesterol, triglycerides, and LDL). Although it had no effect on atherosclerotic plaque size, it did reduce the proliferation of plaque-associated macrophages. It reduced mtDNA damage in the liver but had no effect on protein carbonyl content (Mercer et al, 2012).

Safety: Some evidence from clinical studies suggest there are gastrointestinal side effects at higher doses, though no large, extended clinical trials have been conducted.

Types of evidence:

- 4 RCTs

MitoQ has been tested in 128 Parkinson's patients over 12 months (40mg or 80mg/day) (Snow et al, 2010), 20 healthy patients over 3 weeks (10mg/day) (Shill et al, 2016), in 20 healthy older adults with endothelial dysfunction over 6 weeks (20mg/day) (Rossman et al, 2018), and in 30 patients with chronic hepatitis C over 28 days (40mg or 80mg/day) (Gane et al, 2010). The only adverse effects so far reported are gastrointestinal side effects (at 40mg and 80mg doses).

Drug interactions:
Not currently known. Although, theoretically, it may interact with other mitochondria-targeted antioxidants (e.g Skq1 and SS-31).

Sources and dosing:
MitoQ is being developed by Antipodean Pharmaceuticals. It is also sold as a supplement by MitoQ. Recommended doses are 10mg/day with therapeutic doses in the Parkinson's trial at 40mg or 80mg/day.

Research underway:
One pilot study of MitoQ in Alzheimer's patients is underway. It is a 2-day cross-over trial in 12 patients looking at carotid artery blood flow, oxidative stress, cerebrovascular oxygenation, EEG, and endothelial function (NCT03514875). Other clinical trials are ongoing including fatigue in multiple sclerosis, cardiovascular function, peripheral artery disease, and chronic kidney disease (link).

Search terms:
MitoQ

Websites:

- Clinicaltrials.gov
- Pubmed
- Pubchem
- Drugbank.ca

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.