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(54) Title: ADJUNCTIVE THERAPY FOR THE TREATMENT OF MITOCHONDRIAL DISORDERS WITH QUINONES AND NAPHTHOQUINONES

(57) Abstract: The present invention relates to an adjunctive therapy for the treatment of mitochondrial disorders comprising the administration of an effective amount of one or more quinones and one or more naphthoquinones to a patient in need thereof. The present invention also relates to an adjunctive therapy for the treatment of mitochondrial disorders comprising the administration of an effective amount of one or more quinones or their reduced form hydroquinones and one or more naphthoquinones or their reduced form naphthohydroquinones to a patient in need thereof.



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ADJUNCTIVE THERAPY FOR THE TREATMENT OF MITOCHONDRIAL DISORDERS WITH QUINONES AND NAPHTHOQUINONES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 61/520,387, filed June 8, 2011. The entire contents of that application are hereby incorporated by reference herein.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to an adjunctive therapy for the treatment of mitochondrial disorders comprising the administration of an effective amount of one or more quinones and one or more naphthoquinones to a patient in need thereof. The present invention also relates to an adjunctive therapy for the treatment of mitochondrial disorders comprising the administration of an effective amount of one or more quinones or their reduced form hydroquinones and one or more naphthoquinones or their reduced form naphthohydroquinones to a patient in need thereof.

BACKGROUND OF THE INVENTION

[0003] Mitochondria are organelles in eukaryotic cells, popularly referred to as the “powerhouse” of the cell. The molecule adenosine triphosphate (ATP) functions as an energy “currency” or energy carrier in the cell, and eukaryotic cells derive the majority of their ATP from biochemical processes carried out by mitochondria. These biochemical processes include the citric acid cycle (the tricarboxylic acid cycle, or Krebs’s cycle), which generates reduced nicotinamide adenine dinucleotide (NADH + H⁺) from oxidized nicotinamide adenine dinucleotide (NAD⁺), and oxidative phosphorylation (OXPHOS), during which NADH + H⁺ is oxidized back to NAD⁺. (The citric acid cycle also reduces flavin adenine dinucleotide, or FAD, to FADH₂; FADH₂ also participates in oxidative phosphorylation.) Mitochondria also play an active role in survival and death signaling and cellular calcium homeostasis. Defects in mitochondrial function are associated with mitochondrial dysfunction and

numerous neurodegenerative diseases affecting oxidative metabolism and impairing energy production.

[0004] Mitochondrial disorders are caused by mutations in mitochondrial genes, in nuclear genes encoding for subunits of the respiratory chain complexes or in genes coding for proteins involved in the nuclear-mitochondrial communication.

[0005] The respiratory chain is located in the inner mitochondrial membrane and consists of five multimeric protein complexes: Complex I (approximately 46 subunits), Complex II (approximately 4 subunits), Complex III (approximately 11 subunits), Complex IV (approximately 13 subunits) and Complex V (approximately 16 units). The respiratory chain also requires two small electron carriers, ubiquinone (coenzyme Q10) and cytochrome *c*. ATP synthesis involves two coordinated processes. First electrons (actually hydrogen ions derived from NADH and FADH₂ in intermediary metabolism) are transported horizontally from complexes I and II to coenzyme Q to Complex III to cytochrome *c* to Complex IV, and ultimately to the final electron acceptor, molecular oxygen, thereby producing water. At the same time, protons are pumped "vertically" across the mitochondrial inner membrane (i.e. from the matrix to the inter membrane space) by complexes I, II, III and IV. ATP is generated by the influx of these protons back into the mitochondrial matrix through complex V (ATP synthetase) (Di Mauro, S., *Mitochondrial Medicine*, (2006) 7-9.) The energy released as these electrons traverse the complexes is used to generate a proton gradient across the inner membrane of the mitochondrion, which creates an electrochemical potential across the inner membrane.

[0006] *Complex I* (NADH dehydrogenase, also called NADH:ubiquinone oxidoreductase) removes two electrons from NADH and transfers them to a lipid-soluble carrier, ubiquinone (Q). The reduced product, ubiquinol (QH₂) is free to diffuse within the membrane. At the same time, Complex I moves four protons (H⁺) across the membrane, producing a proton gradient. Complex I is one of the main sites at which premature electron leakage to oxygen occurs, thus being one of the main sites of production of a harmful free radical called superoxide.

[0007] *Complex II* (succinate dehydrogenase) is not a proton pump. It serves to funnel additional electrons into the quinone pool (Q) by removing electrons from succinate and transferring them (via FAD) to Q. Complex II consists of four protein subunits: SDHA, SDHB, SDHC, and SDHD. Other electron donors (e.g., fatty acids

and glycerol 3-phosphate) also funnel electrons into Q (via FAD), again without producing a proton gradient.

[0008] *Complex III* (cytochrome *bc₁* complex) removes two electrons from QH₂ and transfers them to two molecules of cytochrome *c*, a water-soluble electron carrier located within the inter-membrane space. At the same time, it moves two protons across the membrane, producing a proton gradient (in total 4 protons: 2 protons are translocated and 2 protons are released from ubiquinol). When electron transfer is hindered (by a high membrane potential, point mutations or respiratory inhibitors such as antimycin A), Complex III may leak electrons to oxygen resulting in the formation of superoxide, a highly-toxic species, which is thought to contribute to the pathology of a number of diseases, including aging.

[0009] *Complex IV* (cytochrome *c* oxidase) removes four electrons from four molecules of cytochrome *c* and transfers them to molecular oxygen (O₂), producing two molecules of water (H₂O). At the same time, it moves four protons across the membrane, producing a proton gradient.

[0010] *Complex V* (mitochondrial ATP synthetase) which is not directly associated with Complexes I, II, III and IV uses the energy stored by the electrochemical gradient to convert ADP into ATP.

[0011] Genetic defects which affect cellular energy states can lead to severe disease states. One such disease linked to dysfunction in a respiratory chain is Leber's Hereditary Optic Neuropathy (LHON). The disease is characterized by blindness which occurs on average between 27 and 34 years of age (World-Wide-Web address ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=535000); blindness can develop in both eyes simultaneously, or sequentially (one eye will develop blindness, followed by the other eye shortly thereafter). Other symptoms may also occur, such as cardiac abnormalities and neurological complications.

[0012] Dominant Optic Atrophy (DOA) also known as autosomal dominant optic atrophy, Kjer type; Kjer optic atrophy; or Kjer's autosomal dominant optic atrophy, is characterized by a slow progressive bilateral loss of central vision starting in childhood and progressing in adult life. Vision loss in DOA is due to optic nerve fiber loss from mitochondrial dysfunction. Dominant optic atrophy is associated with mutation of the OPA1 gene. Six other chromosomal genes are described as causing optic atrophy: OPA2 (obscure), OPA3 (dominant), OPA4 (dominant), OPA5 (dominant), OPA6 (recessive) and OPA7 (dominant).

[0013] DOA results in significant visual impairment with about half of all affected individuals failing the driving standards, and 13-46% being registered as legally blind. The predominant color defect in DOA is dyschromatopsia involving both the blue-yellow and the red-green axes. Patients with DOA experience diffuse atrophy of the retinal ganglion cell layer, loss of myelin and fibrillary gliosis along the anterior visual pathways extending to the lateral geniculate body.

[0014] Another syndrome resulting from a respiratory chain disorder is mitochondrial myopathy, encephalopathy, lacticidosis, and stroke (MELAS). The disease can manifest itself in infants, children, or young adults. Strokes, accompanied by vomiting and seizures, are one of the most serious symptoms; it is postulated that the metabolic impairment of mitochondria in certain areas of the brain is responsible for cell death and neurological lesions, rather than the impairment of blood flow as occurs in ischemic stroke. Other severe complications, including neurological symptoms, are often present, and elevated levels of lactic acid in the blood occur.

[0015] Another syndrome resulting from a respiratory chain disorder is Myoclonus Epilepsy Associated with Ragged-Red Fibers (MERRF) syndrome, one of a group of rare muscular disorders that are called mitochondrial encephalomyopathies. Mitochondrial encephalomyopathies are disorders in which a defect in the genetic material arises from a part of the cell structure that releases energy -mitochondria. This can cause a dysfunction of the brain and muscles (encephalomyopathies). The mitochondrial defect as well as "ragged-red fibers" (an abnormality of tissue when viewed under a microscope) are always present. The most characteristic symptom of MERRF syndrome is myoclonic seizures that are usually sudden, brief, jerking, spasms that can affect the limbs or the entire body. Impairment of the ability to coordinate movements (ataxia), as well as an abnormal accumulation of lactic acid in the blood (lactic acidosis) may also be present in affected individuals. Difficulty speaking (dysarthria), optic atrophy, short stature, hearing loss, dementia, and involuntary jerking of the eyes (nystagmus) may also occur.

[0016] Another syndrome resulting from a respiratory chain disorder is Pearson syndrome, characterized by symptoms associated with bone marrow and pancreas dysfunction. It is caused by single mitochondrial DNA deletions. Those who survive infancy usually develop Kearns-Sayre syndrome.

[0017] Another syndrome resulting from a respiratory chain disorder is Co-Enzyme Q10 Deficiency, the symptoms of which include encephalomyopathy, mental

retardation, exercise intolerance, ragged-red fibers, and recurrent myoglobin in the urine.

[0018] Another syndrome resulting from a respiratory chain disorder is Complex I Deficiency or NADH dehydrogenase NADH-CoQ reductase deficiency, the symptoms of which are classified by three major forms: (1) fatal infantile multisystem disorder, characterized by developmental delay, muscle weakness, heart disease, congenital lactic acidosis, and respiratory failure; (2) myopathy beginning in childhood or in adult life, manifesting as exercise intolerance or weakness; and (3) mitochondrial encephalomyopathy (including MELAS), which may begin in childhood or adult life and consists of variable combinations of symptoms and signs, including ophthalmoplegia, seizures, dementia, ataxia, hearing loss, pigmentary retinopathy, sensory neuropathy, and uncontrollable movements.

[0019] Another syndrome resulting from a respiratory chain disorder is Complex II Deficiency or succinate dehydrogenase deficiency, the symptoms of which include encephalomyopathy and various manifestations, including failure to thrive, developmental delay, hypotonia, lethargy, respiratory failure, ataxia, myoclonus and lactic acidosis.

[0020] Another syndrome resulting from a respiratory chain disorder is Complex III Deficiency or Ubiquinone-cytochrome *c* oxidoreductase deficiency, symptoms of which are categorized in four major forms: (1) fatal infantile encephalomyopathy, congenital lactic acidosis, hypotonia, dystrophic posturing, seizures, and coma; (2) encephalomyopathies of later onset (childhood to adult life): various combinations of weakness, short stature, ataxia, dementia, hearing loss, sensory neuropathy, pigmentary retinopathy, and pyramidal signs; (3) myopathy, with exercise intolerance evolving into fixed weakness; and (4) infantile histiocytoid cardiomyopathy.

[0021] Another syndrome resulting from a respiratory chain disorder is Complex IV Deficiency or Cytochrome *c* oxidase deficiency, caused by a defect in Complex IV of the respiratory chain, the symptoms of which can be categorized in two major forms: (1) encephalomyopathy, which is typically normal for the first 6 to 12 months of life and then show developmental regression, ataxia, lactic acidosis, optic atrophy, ophthalmoplegia, nystagmus, dystonia, pyramidal signs, respiratory problems and frequent seizures; and (2) myopathy: Two main variants: (a) fatal infantile myopathy: may begin soon after birth and accompanied by hypotonia, weakness, lactic acidosis, ragged-red fibers, respiratory failure, and kidney problems; and (b) benign infantile

myopathy: may begin soon after birth and accompanied by hypotonia, weakness, lactic acidosis, ragged-red fibers, respiratory problems, but (if the child survives) followed by spontaneous improvement.

[0022] Another syndrome resulting from a respiratory chain disorder is Complex V Deficiency or ATP synthase deficiency which includes symptoms such as slow, progressive myopathy.

[0023] Another syndrome resulting from a respiratory chain disorder is CPEO or Chronic Progressive External Ophthalmoplegia syndrome which includes symptoms such as visual myopathy, retinitis pigmentosa, or dysfunction of the central nervous system.

[0024] Another syndrome involving respiratory chain proteins is Kearns-Sayre syndrome (KSS). KSS is characterized by a triad of features including: (1) typical onset in persons younger than age 20 years; (2) chronic, progressive, external ophthalmoplegia; and (3) pigmentary degeneration of the retina. In addition, KSS may include cardiac conduction defects, cerebellar ataxia, and raised cerebrospinal fluid (CSF) protein levels (e.g., >100 mg/dL). Additional features associated with KSS may include myopathy, dystonia, endocrine abnormalities (e.g., diabetes, growth retardation or short stature, and hypoparathyroidism), bilateral sensorineural deafness, dementia, cataracts, and proximal renal tubular acidosis. Thus, KSS may affect many organ systems.

[0025] Friedreich's ataxia (FRDA or FA) is an autosomal recessive neurodegenerative and cardiodegenerative disorder caused by a mutation in gene FXN (formerly known as X25), that codes for frataxin, located on chromosome 9. Frataxin is believed to be important for the assembly of iron-sulfur clusters in mitochondrial respiratory-chain complexes; it may play a role in iron transport; it may play a role in iron storage; it may stimulate oxidative phosphorylation; and it may have anti-oxidant function (see Sturm, B. *et al.*, *J. Biol. Chem.* (2005) 280:6701). Frataxin itself, however, does not appear to be incorporated into any of mitochondrial complexes I-V. Estimates of the prevalence of FRDA in the United States range from 1 in every 22,000-29,000 people (see World-Wide-Web address nlm.nih.gov/medlineplus/ency/article/001411.htm) to 1 in 50,000 people (World-Wide-Web address umc-cares.org/health_info/ADAM/Articles/001411.asp). The disease causes the progressive loss of voluntary motor coordination (ataxia) and cardiac complications. Symptoms typically begin in childhood, and the disease

progressively worsens as the patient grows older; patients eventually become wheelchair-bound due to motor disabilities. Erythropoietin has been proposed for the treatment of FRDA; see International Patent Application No. WO 2006/050819 and Sturm, B. *et al.*, *Eur. J. Clin. Invest.* 2005, 35:711. MitoQ has also been proposed for treating FRDA (see U.S. Patent Application Publication No. 2005/0043553). The compound idebenone has also been proposed for treatment of FRDA. Preliminary testing has been done in humans, to see if idebenone could be a safe and effective treatment for Friedreich's ataxia (Tonon, C. *et al.*, *Expert Opin. Pharmacother.* 2008, 9 (13): 2327–37). In a different experiment, a one-year test on eight patients, idebenone reduced the rate of deterioration of cardiac function in patients with Friedreich's ataxia, but did not halt the progression of ataxia (Buyse, G. *et al.*, *Neurology* 2003, 60 (10): 1679–81.)

[0026] Yet other syndromes, named overlap syndromes, combine the clinical features of different typical mitochondrial syndromes. One such syndrome characterized by clinical features of both myoclonus epilepsy ragged-red fibers (MERRF) and Kearns–Sayre syndrome (KSS), and due to a mitochondrial DNA (mtDNA) mutation at nucleotide 3255 (G3255A) of the tRNA^{Leu(UUR)} gene has been described by Nishigaki, Y *et al.*, *Neuromuscular Disorders* (2003) 13:334-340. This particular overlap syndrome manifests sensorineural deafness, atypical pigmentary retinopathy, myoclonus epilepsy, ptosis, ophthalmoparesis, migraine headaches, hypothyroidism, and testosterone insufficiency.

[0027] There is insufficient clinical evidence to say whether idebenone is a treatment for Friedreich's Ataxia, and therefore no government agency has approved the marketing of idebenone for this purpose but on July 23, 2008, Health Canada issued a Notice of Compliance under the Notice of Compliance with Conditions (NOC/c) Policy to Santhera Pharmaceuticals (Switzerland) Ltd. for the drug product Catena®. The product was authorized under the NOC/c Policy on the basis of the promising nature of the clinical evidence, and the need for a confirmatory study to verify its clinical benefit. However, Santhera Pharmaceuticals announced recently that a Phase III study evaluating Catena®/Sovrima® for the treatment of Friedreich's Ataxia missed its primary endpoint.

<http://www.santhera.com/index.php?docid=212&vid=&lang=en&newsdate=201005&newsid=1417424&newslang=en>.

[0028] Leigh syndrome is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system. Leigh syndrome can be maternally inherited due to mutation in mitochondria DNA (mtDNA) genes (Clafaloni, E. *et al.*, *Journal of Pediatrics* 1993, 12(3) 419-422), sex-linked due to pyruvate dehydrogenase deficiency, or autosomal recessive due to mutations in nuclear encoded respiratory chain complex subunits or complex assembly genes (Zhu, Z. *et al.*, *Nature Genetics* 1998, 337-343.) Leigh syndrome can be caused by mutations in mitochondrial DNA or by deficiencies of pyruvate dehydrogenase. Symptoms of Leigh syndrome usually begin between the ages of 3 months to 2 years and progress rapidly. In most children, the first signs may be poor sucking ability and loss of head control and motor skills. These symptoms may be accompanied by loss of appetite, vomiting, irritability, continuous crying, and seizures. As the disorder progresses, symptoms may also include generalized weakness, lack of muscle tone, and episodes of lactic acidosis, which can lead to impairment of respiratory and kidney function. Heart problems may also occur. In rare cases, Leigh's disease can begin during late adolescence or early adulthood and progress more slowly. One of the most common defects found in Leigh patients is the severe and generalized cytochrome c oxidase (COX, complex IV) deficiency. COX is a 13-subunit complex embedded in the inner membrane of the mitochondria that carries out the terminal step in the electron-transport chain. Mitochondrial DNA encodes the three subunits containing the catalytic core and the electron-transfer functions, while nuclear DNA encodes the other 10 subunits involved in the regulation and assembly of the enzyme. A disease termed "Leigh-like syndrome" is also recognized, which is characterized by neurologic abnormalities atypical for but suggestive of Leigh syndrome (Finsterer, J., "Leigh and Leigh-like syndrome in children and adults," *Pediatr. Neurol.* 2008; 39:223-235). The incidence of Leigh syndrome is estimated at 1 in 40,000 live births (Finsterer, J. *ibid.*) and is the most common mitochondrial disease of infancy.

[0029] Mutation in the complex IV assembly genes, particularly SURF1, is an important cause of isolated COX deficiency that results in Leigh syndrome. The SURF1 gene is located on chromosome 9q34 in a highly conserved cluster of housekeeping genes and is ubiquitously expressed. The SURF1 protein is required to correct assembly of complex IV but it is not a constituent of this enzyme. Specifically SURF1 is a chaperone responsible for the incorporation of heme A into nascent complex IV subunits during early steps of complex IV formation (Stiburek, L. *et al.*, *Biochemical Journal* 2003, 392, 625-632 and Barrientos, A. *et al.*, *Journal of*

Biological Chemistry 2009, 284(38), 25735-25741.) It was discovered that patients with SURF1 mutations showed accumulation of early COX assembly intermediates and decreased amounts of completed complex IV. In most cases significant reduction of COX activity to 10-25% of the lowest control values was observed in all tissues associated with SURF1 syndrome (Pecina, P. *et al.*, *Biochimica et Biophysica Acta* 2003, 1639 (1) 53-63.)

[0030] Very few treatments are available for patients suffering from these diseases. Administration of coenzyme Q10 (CoQ₁₀) (van Maldergem, L. *et al.*, *Annals of Neurology* 2002, 52(6) 750-754), idebenone (Haginoya, K. *et al.*, *Journal of Neurological Sciences* 2009, 278 (1-2) 112-114), dichoroacetate and vitamin supplements (Finsterer, J., *European Journal of Paediatric Neurology* 2010, 14(1) 29-44), has shown only transient beneficial effects in individual cases. Management of the disease has also been attempted using thiamine Di Rocco, C. *et al.*, *European Journal of Paediatric Neurology* 2000, 4(3). 115-117, L-carnitine (Toth, G *et al.*, *Journal of Inherited Metabolic Disease* 2001, 24(3) 421-422 and ketogenic diet (Pinkus, J. *et al.* *Archives of Neurology* 1971, 24, 511-517.) Patients with Leigh syndrome typically die before the age of five years, often from respiratory failure. Tocotrienol quinones have been proposed for the treatment of Leigh and Leigh-like syndrome in co-assigned US Patent Application USAN 61/291,784.

[0031] Tocotrienol quinones have also been proposed for the treatment of mitochondrial diseases in co-assigned US Patent Application USAN 11/445,582.

[0032] Naphthoquinones have also been proposed for the treatment of mitochondrial diseases in co-assigned US Patent Application USAN 61/342,869.

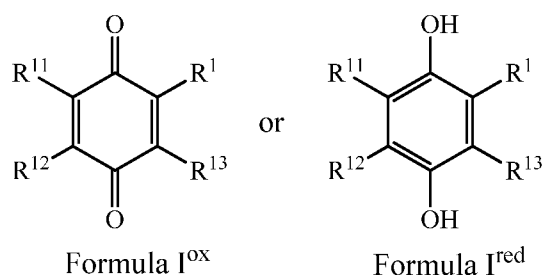
[0033] Accordingly, there is a serious and unmet need for effective treatments of symptoms involving dysfunctions resulting from mitochondrial defects.

SUMMARY OF THE INVENTION

[0034] The present invention is based on the discovery disclosed herein that adjunctive administration of one or more quinones of Formula I^{ox} or their reduced form of Formula I^{red} and one or more naphthoquinones of Formula II^{ox} or their reduced form of Formula II^{red} can be used for the treatment of disorders due to mitochondrial defects or malfunctions in a person in need thereof. The adjunctive administration of one or more compounds of Formula I^{ox} or I^{red} and one or more

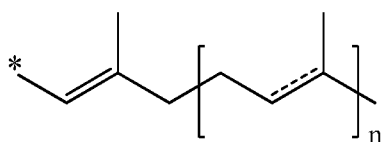
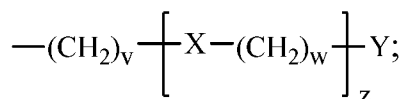
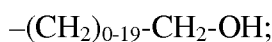
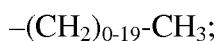
compounds of Formula I^{ox} or I^{red} can also be used for the treatment of impaired oxidative metabolism and energy production resulting from a mitochondrial defect or deficiency in a person in need thereof. The present invention also provides a method for treatment of mitochondrial dysfunctions comprising administration of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red} wherein the amount of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red} are selected to produce a synergistic effect. The present invention also provides a method for treatment of mitochondrial disorder comprising administration of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red} wherein the amount of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red} are selected to produce an additive effect.

[0035] In some embodiments, the invention embraces adjunctive administration of one or more quinones of Formula I^{ox} or their reduced form of Formula I^{red} and one or more naphthoquinones of Formula II^{ox} or their reduced form of Formula II^{red}, wherein Formulas I^{ox} and I^{red} are:

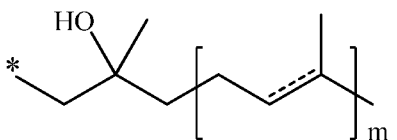


where,

R¹ is selected from the group consisting of :



and



the * indicates the point of attachment to R¹;

the bond indicated by a dashed line can be double or single;

R¹¹, R¹² and R¹³ are independently of each other hydrogen; $-(C_1-C_6)\text{alkyl}$; or

$-O(C_1-C_6)\text{alkyl}$;

X is $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

Y is hydrogen; $-\text{OR}^{14}$, $-\text{CN}$ or $-\text{COOR}^{15}$;

R¹⁴ and R¹⁵ are independently of each other selected from hydrogen, $-(C_1-C_6)\text{alkyl}$,
and $-(C_1-C_6)\text{haloalkyl}$;

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the
same or different;

m is 1-12, with the proviso that when m is an integer from 2 to 12, each unit can be
the same or different;

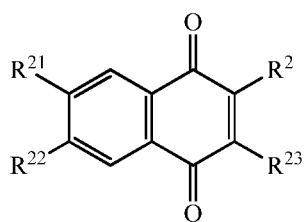
v is 1-10;

w is 1-5; and

z is 1-3, with the proviso that when z is an integer of 2 to 3, w is optionally variable
from 1-5 in each occurrence of the group;

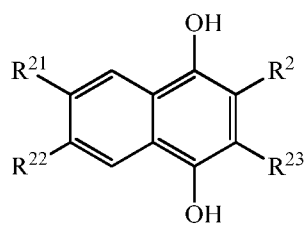
and

wherein Formulas II^{ox} and II^{red} are:



Formula II^{ox}

or



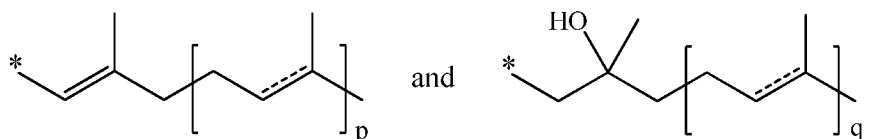
Formula II^{red}

where,

R² is selected from the group consisting of:

$-(\text{CH}_2)_{0-19}-\text{CH}_3$;

$-((\text{CH}_2)_2-\text{CH}(\text{CH}_3))_{1-20}-\text{CH}_3$;



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)$ alkyl; or $-O(C_1-C_6)$ alkyl;

R^{23} is independently of each other hydrogen; $-(C_1-C_6)$ alkyl; $-OH$; or $-O(C_1-C_6)$ alkyl;

p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different; and

q is 1-12, with the proviso that when q is an integer from 2 to 12, each unit can be the same or different;

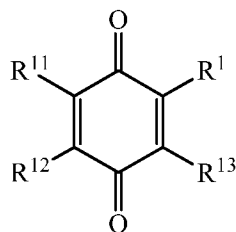
or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate of formulas I^{ox} , I^{red} , II^{ox} or II^{red} .

[0036] In some embodiments, the one or more quinones of Formula I^{ox} is selected from alpha tocopherol quinone, beta tocopherol quinone, gamma-tocopherol quinone, delta tocopherol quinone, alpha tocotrienol quinone, beta tocotrienol quinone, gamma-tocotrienol quinone, delta-tocotrienol quinone, ubiquinone and idebenone.

[0037] In some embodiments, the one or more quinones of Formula I^{red} is selected from alpha tocopherol hydroquinone, beta-tocopherol hydroquinone, gamma-tocopherol hydroquinone, delta-tocopherol hydroquinone, alpha-tocotrienol hydroquinone, beta-tocotrienol hydroquinone, gamma-tocotrienol hydroquinone, delta-tocotrienol hydroquinone and ubiquinol.

[0038] In some embodiments, the invention embraces adjunctive administration of one or more quinones of Formula I and one or more naphthoquinones of Formula II,

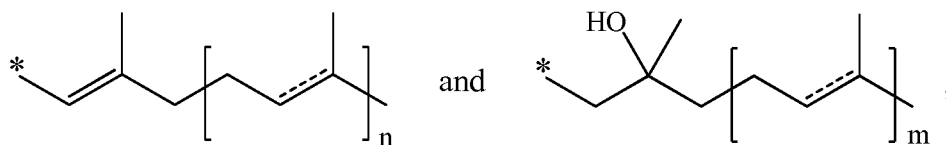
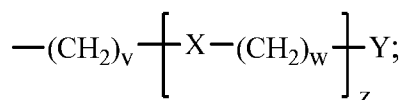
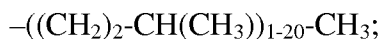
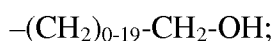
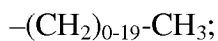
wherein Formula I is:



Formula I

where,

R^1 is selected from the group consisting of:



the * indicates the point of attachment to R^1 ;

the bond indicated by a dashed line can be double or single;

R^{11} , R^{12} and R^{13} are independently of each other hydrogen; $-(C_1-C_6)$ alkyl; or

$-O(C_1-C_6)$ alkyl;

X is $-CH=CH-$ or $-C\equiv C-$;

Y is hydrogen; $-OR^{14}$, $-CN$ or $-COOR^{15}$;

R^{14} and R^{15} are independently of each other selected from hydrogen, $-(C_1-C_6)$ alkyl, and $-(C_1-C_6)$ haloalkyl;

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the same or different;

m is 1-12, with the proviso that when m is an integer from 2 to 12, each unit can be the same or different;

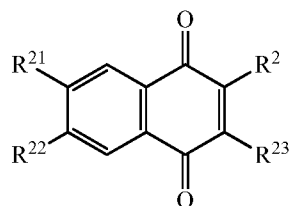
v is 1-10;

w is 1-5; and

z is 1-3, with the proviso that when z is an integer of 2 to 3, w is optionally variable from 1-5 in each occurrence of the group;

and

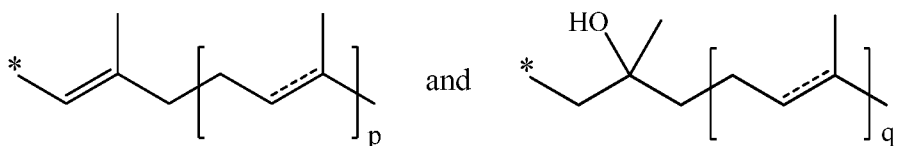
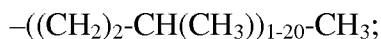
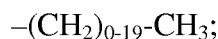
wherein Formula II is:



Formula II

where,

R^2 is selected from the group consisting of:



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or $-O(C_1-C_6)alkyl$;

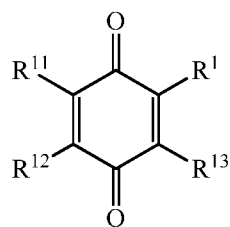
R^{23} is independently of each other hydrogen; $-(C_1-C_6)alkyl$; $-OH$; or $-O(C_1-C_6)alkyl$;

p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different; and

q is 1-12, with the proviso that when q is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate of Formulas I or II.

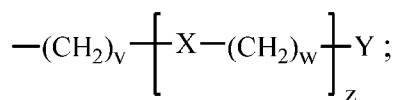
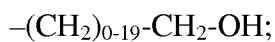
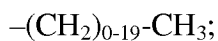
[0039] In some embodiments, the one or more quinones of Formula I are selected from one or more quinones of Formula Ia:



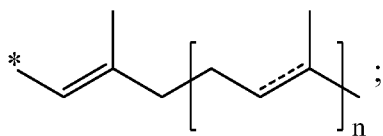
Formula Ia

where,

R¹ is selected from the group consisting of :



and



the * indicates the point of attachment to R¹;

the bond indicated by a dashed line can be double or single;

R¹¹, R¹² and R¹³ are independently of each other hydrogen; -(C₁-C₆)alkyl; or

-O(C₁-C₆)alkyl; and

X is -CH=CH- or -C≡C-;

Y is hydrogen; -OR¹⁴, -CN or -COOR¹⁵;

R¹⁴ and R¹⁵ are independently of each other selected from hydrogen, -(C₁-C₆)alkyl, and -(C₁-C₆)haloalkyl;

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the same or different;

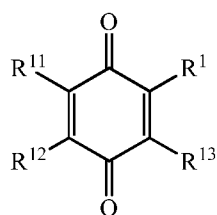
v is 1-10;

w is 1-5; and

z is 1-3, with the proviso that when z is an integer of 2 to 3, w is optionally variable from 1-5 in each occurrence of the group;

or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate thereof.

[0040] In some embodiments, the one or more quinones of Formula I are selected from one or more quinones of Formula Ia:



Formula Ia

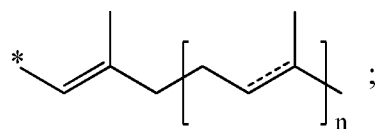
where,

R^1 is selected from the group consisting of:

$-(CH_2)_{0-19}-CH_3$;

$-(CH_2)_{0-19}-CH_2-OH$;

$-((CH_2)_2-CH(CH_3))_{1-20}-CH_3$; and



the * indicates the point of attachment to R^1 ;

the bond indicated by a dashed line can be double or single;

R^{11} , R^{12} and R^{13} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or

$-O(C_1-C_6)alkyl$; and

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the same or different;

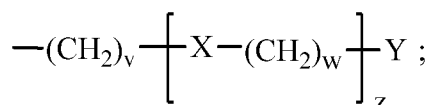
or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate thereof.

[0041] In some embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is $-(CH_2)_{0-19}-CH_3$.

[0042] In some embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is $-(CH_2)_{0-19}-CH_2-OH$.

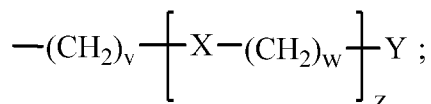
[0043] In some embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is $-((CH_2)_2-CH(CH_3))_{1-20}-CH_3$.

[0044] In some embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is :



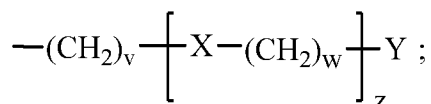
where X is $-CH=CH-$.

[0045] In some embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is :



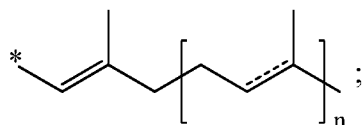
where X is $-C\equiv C-$.

[0046] In some exemplary embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is :



v is 4, w is 3, z is 1, X is $-C\equiv C-$, Y is OH, and the compound is 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone.

[0047] In some embodiments, the one or more quinones of Formula Ia are selected from quinones wherein R^1 is:



and n is 0-12, wherein when n is 2-12, each unit can be the same or different.

[0048] In some embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} and R^{12} are independently selected from hydrogen, $-(C_1-C_6)alkyl$, and $-O(C_1-C_6)alkyl$; and R^{13} is $-(C_1-C_6)alkyl$. In other embodiments, the

quinone of Formula Ia is selected from quinones wherein R^{11} and R^{12} are independently selected from hydrogen, methyl, and methoxy; and R^{13} is methyl.

[0049] In some embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} and R^{12} are independently of each other $-O(C_1-C_6)alkyl$; and R^{13} is hydrogen or $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} and R^{12} are methoxy; and R^{13} is hydrogen or methyl.

[0050] In some embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} , R^{12} and R^{13} are independently selected from hydrogen and $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} , R^{12} and R^{13} are independently selected from hydrogen or methyl.

[0051] In some embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} , R^{12} and R^{13} are independently of each other $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} , R^{12} and R^{13} are methyl.

[0052] In some embodiments, the quinone of Formula Ia is selected from quinones wherein R^{11} , R^{12} and R^{13} are hydrogen.

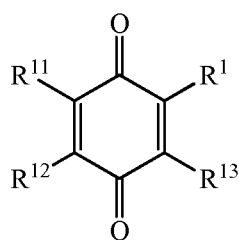
[0053] In some embodiments, the quinone of Formula Ia is selected from quinones wherein the bond indicated by a dashed line is a double bond. In some embodiments, the quinone of Formula Ia is selected from quinones wherein the bond indicated by a dashed line is a single bond.

[0054] In some embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer 0. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer one. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer two. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer three. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer four. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer five. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer six. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer seven. In other embodiments, the quinone of Formula Ia is selected from

quinones wherein n is the integer eight. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer nine. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer ten. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer eleven. In other embodiments, the quinone of Formula Ia is selected from quinones wherein n is the integer twelve.

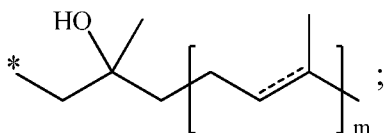
[0055] In some embodiments, the quinone of Formula Ia is Idebenone. In other embodiments, the quinone of Formula Ia is ubiquinone or CoQ10. In other embodiments, the quinone of Formula Ia is CoQ2. In other embodiments, the quinone of Formula Ia is CoQ4. In some embodiments the quinone of Formula Ia is 2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione.

[0056] In some embodiments, the one or more quinones of Formula I are selected from quinones of Formula Ib:



Formula Ib

where, R^1 is:



the * indicates the point of attachment to R^1 ;

the bond indicated by a dashed line can be double or single;

R^{11} , R^{12} and R^{13} are independently of each other hydrogen; $-(C_1-C_6)$ alkyl; or

$-O(C_1-C_6)$ alkyl; and

m is 1-12, with the proviso that when m is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate thereof.

[0057] In some embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} and R^{12} are independently selected from hydrogen, $-(C_1-C_6)alkyl$, and $-O(C_1-C_6)alkyl$; and R^{13} $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} and R^{12} are independently selected from hydrogen; methyl, and methoxy; and R^{13} is methyl.

[0058] In some embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} and R^{12} are independently of each other $-O(C_1-C_6)alkyl$; and R^{13} is hydrogen or $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} and R^{12} are methoxy; and R^{13} is hydrogen or methyl.

[0059] In some embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} , R^{12} and R^{13} are independently selected from hydrogen and $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} , R^{12} and R^{13} are independently selected from hydrogen and methyl.

[0060] In some embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} , R^{12} and R^{13} are independently of each other $-(C_1-C_6)alkyl$. In other embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} , R^{12} and R^{13} are methyl.

[0061] In some embodiments, the quinone of Formula Ib is selected from quinones wherein R^{11} , R^{12} and R^{13} are hydrogen.

[0062] In some embodiments, the quinone of Formula Ib is selected from quinones wherein the bond indicated by a dashed line is a double bond. In some embodiments, the quinone of Formula Ib is selected from quinones wherein the bond indicated by a dashed line is a single bond.

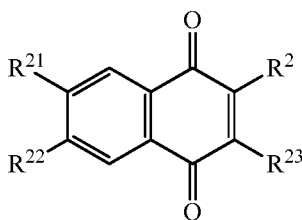
[0063] In some embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer 0. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer one. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer two. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer three. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer four. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer five. In other

embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer six. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer seven. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer eight. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer nine. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer ten. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer eleven. In other embodiments, the quinone of Formula Ib is selected from quinones wherein m is the integer twelve.

[0064] In some embodiments, the quinone of Formula Ib is selected from one or more tocopherol quinones. In other embodiments, the quinone of Formula Ib is alpha-tocopherol quinone. In other embodiments, the quinone of Formula Ib is beta-tocopherol quinone. In other embodiments, the quinone of Formula Ib is gamma-tocopherol quinone. In other embodiments, the quinone of Formula Ib is delta-tocopherol quinone.

[0065] In some embodiments, the quinone of Formula Ib is selected from one or more tocotrienol quinones. In other embodiments, the quinone of Formula Ib is alpha-tocotrienol quinone. In other embodiments, the quinone of Formula Ib is beta-tocotrienol quinone. In other embodiments, the quinone of Formula Ib is gamma-tocotrienol quinone. In other embodiments, the quinone of Formula Ib is delta-tocotrienol quinone.

[0066] In some embodiments, the one or more naphthoquinone of Formula II are selected from naphthoquinones of Formula IIa:



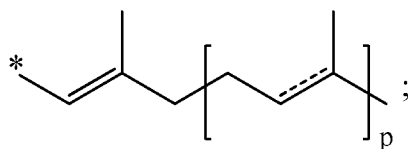
Formula IIa

where,

R^2 is independently selected from the group consisting of :

$-(CH_2)_{0-19}-CH_3$;

$-((CH_2)_2-CH(CH_3))_{1-20}-CH_3$; and



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or $-O(C_1-C_6)alkyl$;

R^{23} is independently of each other hydrogen; $-(C_1-C_6)alkyl$; $-OH$; or $-O(C_1-C_6)alkyl$; and

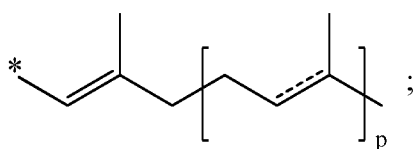
p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate thereof.

[0067] In some embodiments, the one or more naphthoquinones of Formula IIa are selected from naphthoquinones wherein R^2 is $-(CH_2)_{0-19}-CH_3$.

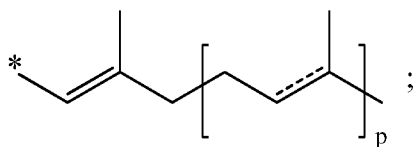
[0068] In some embodiments, the one or more naphthoquinones of Formula IIa are selected from naphthoquinones wherein R^2 is $-((CH_2)_2-CH(CH_3))_{1-20}-CH_3$.

[0069] In some embodiments, the one or more naphthoquinones of Formula IIa are selected from naphthoquinones wherein R^2 is



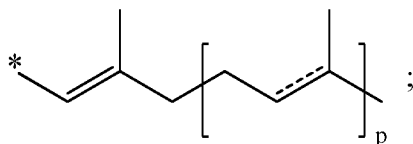
and p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different.

[0070] In some embodiments, the one or more naphthoquinones of Formula IIa are selected from naphthoquinones wherein R^2 is



p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different and the bond represented by a dashed line is a single bond in every unit.

[0071] In some embodiments, the one or more naphthoquinones of Formula IIa is selected from naphthoquinones wherein R^2 is



p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different and the bond represented by a dashed line is a double bond in every unit.

[0072] In some embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, $-(C_1-C_6)alkyl$ and $-O(C_1-C_6)alkyl$; and R^{23} is $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, methyl and methoxy; and R^{23} is methyl.

[0073] In some embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, $-(C_1-C_6)alkyl$ and $-O(C_1-C_6)alkyl$; and R^{23} is $-OH$. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, methyl and methoxy; and R^{23} is hydroxy.

[0074] In some embodiments, the naphthoquinone of Formula IIa is selected from quinones wherein R^{21} and R^{22} are independently of each other $-O(C_1-C_6)alkyl$; and R^{23} is hydrogen or $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIa is selected from quinones wherein R^{21} and R^{22} are methoxy; and R^{23} is hydrogen or methyl.

[0075] In some embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} , R^{22} and R^{23} are independently selected from hydrogen and $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} , R^{22} and R^{23} are independently selected from hydrogen or methyl.

[0076] In some embodiments, the naphthoquinone of Formula IIa is selected from quinones wherein R^{21} , R^{22} and R^{23} are independently of each other $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIa is selected from quinones wherein R^{21} , R^{22} and R^{23} are methyl.

[0077] In some embodiments, the naphthoquinone of Formula IIa is selected from quinones wherein R^{21} , R^{22} and R^{23} are hydrogen.

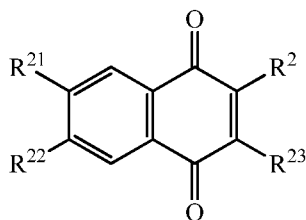
[0078] In some embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer 0. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer one. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer two. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer three. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer four. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer five. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer six. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer seven. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer eight. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer nine. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer ten. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer eleven. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein p is the integer twelve.

[0079] In another embodiment, the naphthoquinone is selected from one or more naphthoquinones of Formula IIa wherein said naphthoquinones are selected from the group of Vitamin K1, Vitamin K2 and mixtures thereof.

[0080] In another embodiment, the naphthoquinone is selected from a naphthoquinone of Formula IIa where R^{21} and R^{22} are hydrogen, R^{23} is methyl, p is 3 and the bond indicated with a dashed line is a single bond in every unit, said naphthoquinone being Vitamin K1 also known as phylloquinone, phytonadione, or phytomenadione.

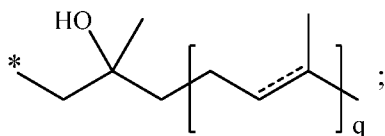
[0081] In another embodiment, the naphthoquinone of Formula IIa is a Vitamin K2 compound, where R²¹ and R²² are hydrogen, R²³ is methyl, and the bond indicated with a dashed line is a double bond in every unit. In another embodiment, the naphthoquinone of Formula IIa is selected from vitamin MK-2: (2-(3,7-dimethylocta-2,6-dien-1-yl)-3-methylnaphthalene-1,4-dione); vitamin MK-3: (2-methyl-3-(3,7,11-trimethyldodeca-2,6,10-trien-1-yl)naphthalene-1,4-dione); vitamin MK-4: (2-methyl-3-[3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl]naphthoquinone); vitamin MK-5: (2-methyl-3-(3,7,11,15,19-pentamethylcosa-2,6,10,14,18-pentaen-1-yl)naphthalene-1,4-dione); vitamin MK-6: 2-(3,7,11,15,19,23-hexamethyltetracos-2,6,10,14,18,22-hexaen-1-yl)-3-methylnaphthalene-1,4-dione); vitamin MK-7: (2-methyl-3-3,7,11,15,19, 23,27-heptamethyloctacos-2,6,10,14,18, 22,26-heptaen-1-yl]naphthoquinone); vitamin MK-8: (2-methyl-3-(3,7,11,15,19,23,27,31-octamethyldotriaconta-2,6,10,14,18,22,26,30-octaen-1-yl)naphthalene-1,4-dione); vitamin MK-9: 2-methyl-3-(3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl)naphthalene-1,4-dione); vitamin MK-10: (2-(3,7,11,15,19,23,27,31,35,39-decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaen-1-yl)-3-methylnaphthalene-1,4-dione); vitamin MK-11: (2-methyl-3-((2,6,10,14,18,22,26,30,34,38)-3,7,11,15,19,23,27,31,35,39,43-undecamethyltetratetraconta-2,6,10,14,18,22,26,30,34,38,42-undecaen-1-yl)naphthalene-1,4-dione); vitamin MK-12 (2-((2,6,10,14,18,22,26,30,34,38,42)-3,7,11,15,19,23,27,31,35,39,43,47-dodecamethyloctatetraconta-2,6,10,14,18,22,26,30,34,38,42,46-dodecaen-1-yl)-3-methylnaphthalene-1,4-dione); and vitamin MK-13 (2-methyl-3-((2,6,10,14,18,22,26,30,34,38,42,46)-3,7,11,15,19,23,27,31,35,39,43,47,51-tridecamethyldopentaconta-2,6,10,14,18,22,26,30,34,38,42,46,50-tridecaen-1-yl)naphthalene-1,4-dione). In other embodiments the naphthoquinone of Formula IIa is selected from vitamin MK-2, vitamin MK-3, vitamin MK-4, vitamin MK-5, vitamin MK-6, and vitamin MK-7. In another embodiment, the naphthoquinone of Formula IIa is vitamin MK2. In another embodiment, the naphthoquinone of Formula IIa is vitamin MK-4. In another embodiment, the naphthoquinone of Formula IIa is vitamin MK7. In another embodiment the naphthoquinone of Formula IIa is administered as a fermented soy bean food known as natto.

[0082] In some embodiments, the one or more naphthoquinones of Formula II are selected from naphthoquinones of Formula Iib:



Formula IIb

where, R^2 is independently selected from:



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or $-O(C_1-C_6)alkyl$;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; $-OH$; or $-O(C_1-C_6)alkyl$; and

q is 1-12, with the proviso that when q is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, prodrug, metabolite, salt, crystalline form, non-crystalline form, hydrate or solvate thereof.

[0083] In some embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, $-(C_1-C_6)alkyl$ and $-O(C_1-C_6)alkyl$; and R^{23} is $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, methyl and methoxy and R^{23} is methyl.

[0084] In some embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, $-(C_1-C_6)alkyl$ and $-O(C_1-C_6)alkyl$; and R^{23} is $-OH$. In other embodiments, the naphthoquinone of Formula IIa is selected from naphthoquinones wherein R^{21} and R^{22} are independently selected from hydrogen, methyl and methoxy; and R^{23} is hydroxy.

[0085] In some embodiments, the naphthoquinone of Formula IIb is selected from quinones wherein R^{21} and R^{22} are independently of each other $-O(C_1-C_6)alkyl$; and

R^{23} is hydrogen or $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIb is selected from quinones wherein R^{21} and R^{22} are methoxy; and R^{23} is hydrogen or methyl.

[0086] In some embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein R^{21} , R^{22} and R^{23} are independently selected from hydrogen and $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein R^{21} , R^{22} and R^{23} are independently selected from hydrogen or methyl.

[0087] In some embodiments, the naphthoquinone of Formula IIb is selected from quinones wherein R^{21} , R^{22} and R^{23} are independently of each other $-(C_1-C_6)alkyl$. In other embodiments, the naphthoquinone of Formula IIb is selected from quinones wherein R^{21} , R^{22} and R^{23} are methyl.

[0088] In some embodiments, the naphthoquinone of Formula IIb is selected from quinones wherein R^{21} , R^{22} and R^{23} are hydrogen.

[0089] In some embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein the bond indicated by a dashed line is a double bond. In some embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein the bond indicated by a dashed line is a single bond.

[0090] In some embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer 0. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer one. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer two. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer three. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer four. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer five. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer six. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer seven. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer eight. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer nine. In other embodiments, the naphthoquinone of Formula IIb is selected

from naphthoquinones wherein q is the integer ten. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer eleven. In other embodiments, the naphthoquinone of Formula IIb is selected from naphthoquinones wherein q is the integer twelve.

[0091] In some embodiments, the naphthoquinone of Formula IIb is selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione.

[0092] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and Vitamin K. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and Vitamin K. In some embodiments the adjunctive therapy comprises beta-tocopherol quinone and Vitamin K. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and Vitamin K. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and Vitamin K.

[0093] In some embodiments, the adjunctive therapy comprises one or more tocopherol hydroquinones and Vitamin K. In some embodiments the adjunctive therapy comprises alpha-tocopherol hydroquinone and Vitamin K. In some embodiments the adjunctive therapy comprises beta-tocopherol hydroquinone and Vitamin K. In some embodiments the adjunctive therapy comprises gamma-tocopherol hydroquinone and Vitamin K. In some embodiments the adjunctive therapy comprises delta-tocopherol hydroquinone and Vitamin K.

[0094] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and Vitamin K. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and Vitamin K. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and Vitamin K. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and Vitamin K. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and Vitamin K.

[0095] In some embodiments, the adjunctive therapy comprises one or more tocotrienol hydroquinones and Vitamin K. In some embodiments the adjunctive therapy comprises alpha-tocotrienol hydroquinone and Vitamin K. In some embodiments the adjunctive therapy comprises beta-tocotrienol hydroquinone and

Vitamin K. In some embodiments the adjunctive therapy comprises gamma-tocotrienol hydroquinone and Vitamin K. In some embodiments the adjunctive therapy comprises delta-tocotrienol hydroquinone and Vitamin K.

[0096] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and Vitamin K1. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and Vitamin K1. In some embodiments the adjunctive therapy comprises beta-tocopherol quinone and Vitamin K1. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and Vitamin K1. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and Vitamin K1.

[0097] In some embodiments, the adjunctive therapy comprises one or more tocopherol hydroquinones and Vitamin K1. In some embodiments the adjunctive therapy comprises alpha-tocopherol hydroquinone and Vitamin K1. In some embodiments the adjunctive therapy comprises beta-tocopherol hydroquinone and Vitamin K1. In some embodiments the adjunctive therapy comprises gamma-tocopherol hydroquinone and Vitamin K1. In some embodiments the adjunctive therapy comprises delta-tocopherol hydroquinone and Vitamin K1.

[0098] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and Vitamin K1. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and Vitamin K1. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and Vitamin K1. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and Vitamin K1. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and Vitamin K1.

[0099] In some embodiments, the adjunctive therapy comprises one or more tocotrienol hydroquinones and Vitamin K1. In some embodiments the adjunctive therapy comprises alpha-tocotrienol hydroquinone and Vitamin K1. In some embodiments the adjunctive therapy comprises beta-tocotrienol hydroquinone and Vitamin K1. In some embodiments the adjunctive therapy comprises gamma-tocotrienol hydroquinone and Vitamin K1. In some embodiments the adjunctive therapy comprises delta-tocotrienol hydroquinone and Vitamin K1.

[0100] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and Vitamin K2. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and Vitamin K2. In some embodiments the

adjunctive therapy comprises beta-tocopherol quinone and Vitamin K2. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and Vitamin K2. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and Vitamin K2.

[0101] In some embodiments, the adjunctive therapy comprises one or more tocopherol hydroquinones and Vitamin K2. In some embodiments the adjunctive therapy comprises alpha-tocopherol hydroquinone and Vitamin K2. In some embodiments the adjunctive therapy comprises beta-tocopherol hydroquinone and Vitamin K2. In some embodiments the adjunctive therapy comprises gamma-tocopherol hydroquinone and Vitamin K2. In some embodiments the adjunctive therapy comprises delta-tocopherol hydroquinone and Vitamin K2.

[0102] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and Vitamin K2. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and Vitamin K2. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and Vitamin K2. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and Vitamin K2. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and Vitamin K2.

[0103] In some embodiments, the adjunctive therapy comprises one or more tocotrienol hydroquinones and Vitamin K2. In some embodiments the adjunctive therapy comprises alpha-tocotrienol hydroquinone and Vitamin K2. In some embodiments the adjunctive therapy comprises beta-tocotrienol hydroquinone and Vitamin K2. In some embodiments the adjunctive therapy comprises gamma-tocotrienol hydroquinone and Vitamin K2. In some embodiments the adjunctive therapy comprises delta-tocotrienol hydroquinone and Vitamin K2.

[0104] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and Vitamin MK4. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises beta-tocopherol quinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and Vitamin MK4.

[0105] In some embodiments, the adjunctive therapy comprises one or more tocopherol hydroquinones and Vitamin MK4. In some embodiments the adjunctive

therapy comprises alpha-tocopherol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises beta-tocopherol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises gamma-tocopherol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises delta-tocopherol hydroquinone and Vitamin MK4.

[0106] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and Vitamin MK4. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and Vitamin MK4.

[0107] In some embodiments, the adjunctive therapy comprises one or more tocotrienol hydroquinones and Vitamin MK4. In some embodiments the adjunctive therapy comprises alpha-tocotrienol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises beta-tocotrienol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises gamma-tocotrienol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises delta-tocotrienol hydroquinone and Vitamin MK4.

[0108] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and a Vitamin MK7. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises beta-tocopherol quinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and Vitamin MK7.

[0109] In some embodiments, the adjunctive therapy comprises one or more tocopherol hydroquinones and Vitamin MK7. In some embodiments the adjunctive therapy comprises alpha-tocopherol hydroquinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises beta-tocopherol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises gamma-tocopherol hydroquinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises delta-tocopherol hydroquinone and Vitamin MK7.

[0110] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises beta-tocopherol quinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and Vitamin K2 administered as natto.

[0111] In some embodiments, the adjunctive therapy comprises one or more tocopherol hydroquinones and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises alpha-tocopherol hydroquinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises beta-tocopherol hydroquinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises gamma-tocopherol hydroquinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises delta-tocopherol hydroquinone and Vitamin K2 administered as natto.

[0112] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and Vitamin MK7. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and Vitamin MK7.

[0113] In some embodiments, the adjunctive therapy comprises one or more tocotrienol hydroquinones and Vitamin MK7. In some embodiments the adjunctive therapy comprises alpha-tocotrienol hydroquinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises beta-tocotrienol hydroquinone and Vitamin MK4. In some embodiments the adjunctive therapy comprises gamma-tocotrienol hydroquinone and Vitamin MK7. In some embodiments the adjunctive therapy comprises delta-tocotrienol hydroquinone and Vitamin MK7.

[0114] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and Vitamin K2

administered as natto. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and Vitamin K2 administered as natto.

[0115] In some embodiments, the adjunctive therapy comprises one or more tocotrienol hydroquinones and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises alpha-tocotrienol hydroquinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises beta-tocotrienol hydroquinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises gamma-tocotrienol hydroquinone and Vitamin K2 administered as natto. In some embodiments the adjunctive therapy comprises delta-tocotrienol hydroquinone and Vitamin K2 administered as natto.

[0116] In some embodiments, the adjunctive therapy comprises one or more tocopherol quinones and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises alpha-tocopherol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises beta-tocopherol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises gamma-tocopherol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-

6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises delta-tocopherol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione.

[0117] In some embodiments, the adjunctive therapy comprises one or more tocotrienol quinones and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises alpha-tocotrienol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises beta-tocotrienol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises gamma-tocotrienol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments the adjunctive therapy comprises delta-tocotrienol quinone and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione.

[0118] In some embodiments, the adjunctive therapy comprises idebenone and Vitamin K. In other embodiments, the adjunctive therapy comprises idebenone and Vitamin K1. In other embodiments, the adjunctive therapy comprises idebenone and Vitamin K2. In other embodiments, the adjunctive therapy comprises idebenone and Vitamin MK4. In other embodiments, the adjunctive therapy comprises idebenone and Vitamin MK7.

[0119] In some embodiments, the adjunctive therapy comprises Coenzyme Q10 or dihydro-CoQ10, and Vitamin K. In other embodiments, the adjunctive therapy comprises Coenzyme Q10 or dihydro-CoQ10, and Vitamin K1. In other embodiments, the adjunctive therapy comprises Coenzyme Q10 or dihydro-CoQ10, and Vitamin K2. In other embodiments, the adjunctive therapy comprises Coenzyme Q10 or dihydro-CoQ10, and Vitamin MK4. In other embodiments, the adjunctive therapy comprises Coenzyme Q10 or dihydro-CoQ10, and Vitamin MK7.

[0120] In some embodiments, the adjunctive therapy comprises Coenzyme Q2 or dihydro-CoQ2, and Vitamin K. In other embodiments, the adjunctive therapy comprises Coenzyme Q2 or dihydro-CoQ2, and Vitamin K1. In other embodiments, the adjunctive therapy comprises Coenzyme Q2 or dihydro-CoQ2, and Vitamin K2. In other embodiments, the adjunctive therapy comprises Coenzyme Q2 or dihydro-CoQ2, and Vitamin MK4. In other embodiments, the adjunctive therapy comprises Coenzyme Q2 or dihydro-CoQ2, and Vitamin MK7.

[0121] In some embodiments, the adjunctive therapy comprises Coenzyme Q4 or dihydro-CoQ4, and Vitamin K. In other embodiments, the adjunctive therapy comprises Coenzyme Q4 or dihydro-CoQ4, and Vitamin K1. In other embodiments, the adjunctive therapy comprises Coenzyme Q4 or dihydro-CoQ4 and Vitamin K2. In other embodiments, the adjunctive therapy comprises Coenzyme Q4 or dihydro-CoQ4, and Vitamin MK4. In other embodiments, the adjunctive therapy comprises Coenzyme Q4 or dihydro-CoQ4, and Vitamin MK7.

[0122] In some embodiments, the adjunctive therapy comprises 2,3,5-trimethyl-6-(12- hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and Vitamin K. In other embodiments, the adjunctive therapy comprises 2,3,5-trimethyl-6-(12- hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and Vitamin K1. In other embodiments, the adjunctive therapy comprises 2,3,5-trimethyl-6-(12- hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and Vitamin K2. In other embodiments, the adjunctive therapy comprises 2,3,5-trimethyl-6-(12- hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and

Vitamin MK4. In other embodiments, the adjunctive therapy comprises 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and Vitamin MK7.

[0123] In some embodiments, including any of the foregoing embodiments the adjunctive therapy comprises administration of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red} by any suitable means, simultaneously, sequentially, separately or in a single pharmaceutical composition.

[0124] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red}. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, a compound of Formula I^{ox} and a compound of Formula II^{ox}. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, a tocopherol quinone or tocotrienol quinone and a Vitamin K. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, a compound of Formula I^{red} and a compound of Formula II^{red}. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, a tocopherol quinone or a tocotrienol hydroquinone and a naphthohydroquinone of Vitamin K.

[0125] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, idebenone and Vitamin K1. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, CoQ10 or dihydro-CoQ10, and Vitamin K1. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, CoQ2 or dihydro-CoQ2, and Vitamin K1. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, CoQ4 or dihydro-CoQ4, and Vitamin K1. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone. and Vitamin K1.

[0126] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, alpha-tocopherol quinone or alpha-tocotrienol quinone, and Vitamin K1. In some embodiments, the

co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, beta-tocopherol quinone or beta-tocotrienol quinone, and Vitamin K1. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, gamma-tocopherol quinone or gamma-tocotrienol quinone, and Vitamin K1. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, delta-tocopherol quinone or delta-tocotrienol quinone, and Vitamin K1.

[0127] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, alpha-tocopherol hydroquinone or alpha-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K1. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, beta-tocopherol hydroquinone or beta-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K1. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, gamma-tocopherol hydroquinone or gamma-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K1. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, delta-tocopherol hydroquinone or delta-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K1.

[0128] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, idebenone and Vitamin K2. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, CoQ10 or dihydro-CoQ10, and Vitamin K2. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, CoQ2 or dihydro-CoQ2, and Vitamin K2. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, CoQ4 or dihydro-CoQ4, and Vitamin K2. In other embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and Vitamin K2.

[0129] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, alpha-tocopherol

quinone or alpha-tocotrienol quinone, and Vitamin K2. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, beta-tocopherol quinone or beta-tocotrienol quinone, and Vitamin K2. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, gamma-tocopherol quinone or gamma-tocotrienol quinone, and Vitamin K2. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, delta-tocopherol quinone or delta-tocotrienol quinone, and Vitamin K2.

[0130] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, alpha-tocopherol hydroquinone or alpha-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K2. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, beta-tocopherol hydroquinone or beta-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K2. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, gamma-tocopherol hydroquinone or gamma-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K2. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier, delta-tocopherol hydroquinone or delta-tocotrienol hydroquinone, and a naphthohydroquinone of Vitamin K2.

[0131] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more compounds of Formula Ia, and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more compounds of Formula IIa. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a tocopherol quinone or a tocotrienol quinone; and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound selected from a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments, the co-therapy comprises a pharmaceutical composition

comprising a pharmaceutically acceptable carrier and alpha-tocotrienol quinone or alpha-tocotrienol quinone; and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and beta-tocopherol quinone or beta-tocotrienol quinone; and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and gamma-tocopherol quinone or gamma-tocotrienol quinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and delta-tocopherol quinone or delta-tocotrienol quinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione.

[0132] In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a tocopherol hydroquinone or a tocotrienol hydroquinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-

methylnaphthalene-1,4-diol; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-diol; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-diol. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and alpha-tocopherol hydroquinone or alpha-tocotrienol hydroquinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-diol; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-diol; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-diol. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and beta-tocopherol hydroquinone or beta-tocotrienol hydroquinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-diol; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-diol; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-diol. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and gamma-tocopherol hydroquinone or gamma-tocotrienol hydroquinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-diol; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-diol; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-diol. In some embodiments, the co-therapy comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and delta-tocopherol hydroquinone or delta-tocotrienol hydroquinone and another pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-diol; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-diol; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-diol.

[0133] In another aspect, the invention provides a composition comprising one or more compounds of Formula I^{ox} or I^{red}, and one or more compounds of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a composition comprising a tocopherol quinone or a tocotrienol quinone, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a composition comprising a tocopherol hydroquinone or a tocotrienol hydroquinone, naphthohydroquinone of vitamin K and a pharmaceutically acceptable carrier.

[0134] In another aspect, the invention provides a pharmaceutical composition comprising one or more compounds of Formula I^{ox} or I^{red}, and one or more compounds of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising idebenone, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ10 or dihydro-CoQ10, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ2 or dihydro-CoQ2, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ4 or dihydro-CoQ4, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising idebenone, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising a tocopherol quinone or a tocotrienol quinone, vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising a tocopherol hydroquinone or a tocotrienol hydroquinone, naphthohydroquinone of vitamin K and a pharmaceutically acceptable carrier.

[0135] In some of the foregoing embodiments, the composition is for the treatment of mitochondrial diseases. In other embodiments the compositions comprise a quinone of Formula I^{ox} or I^{red}, a naphthoquinones of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier in amounts wherein the quinone and the naphthoquinone exhibit a synergistic effect.

[0136] In another aspect, the invention provides a pharmaceutical composition comprising one or more compounds of Formula I^{ox} or I^{red}, and one or more compounds of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising idebenone, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ10 or dihydro-CoQ10, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ2 or dihydro-CoQ2, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ4 or dihydro-CoQ4, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising idebenone, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising a tocopherol quinone or a tocotrienol quinone, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising a tocopherol hydroquinone or a tocotrienol hydroquinone, naphthohydroquinone of vitamin K1 and a pharmaceutically acceptable carrier.

[0137] In some of the foregoing embodiments, the composition is for the treatment of mitochondrial diseases. In other embodiments the compositions comprise a quinone of Formula I^{ox} or I^{red}, a naphthoquinone of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier in amounts wherein the quinone and the naphthoquinone exhibit a synergistic effect.

[0138] In another aspect, the invention provides a pharmaceutical composition comprising one or more compounds of Formula I^{ox} or I^{red}, and one or more compounds of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising idebenone, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ10 or dihydro-CoQ10, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising

CoQ2 or dihydro-CoQ2, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising CoQ4 or dihydro-CoQ4, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising idebenone, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising a tocopherol quinone or a tocotrienol quinone, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a pharmaceutical composition comprising a tocopherol hydroquinone or a tocotrienol hydroquinone, naphthohydroquinone of vitamin K2 and a pharmaceutically acceptable carrier.

[0139] In some of the foregoing embodiments, the composition is for the treatment of mitochondrial diseases. In other embodiments the compositions comprise a quinone of Formula I^{ox} or I^{red}, a naphthoquinone of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier in amounts wherein the quinone and the naphthoquinone exhibit a synergistic effect.

[0140] In another aspect the invention provides a process for making a pharmaceutical composition comprising mixing one or more compounds of Formula I^{ox} or I^{red}, one or more one or more compounds of Formula II^{ox} or II^{red} and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing idebenone, a vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing CoQ10 or dihydro-CoQ10, a vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing CoQ2 or dihydro-CoQ2, a vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing CoQ4 or dihydro-CoQ4, a vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone, a vitamin K and a pharmaceutically acceptable carrier. In some

embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing a tocopherol quinone selected from alpha-tocopherol quinone, beta-tocopherol quinone, delta-tocopherol quinone, and gamma-tocopherol quinone or mixtures thereof, a vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing a tocotrienol quinone selected from alpha-tocotrienol quinone, beta-tocotrienol quinone, delta-tocotrienol quinone, and gamma-tocotrienol quinone or mixtures thereof, a vitamin K and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing alpha-tocopherol quinone or alpha-tocotrienol quinone, vitamin K1 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing alpha-tocopherol quinone or alpha-tocotrienol quinone, vitamin K2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing alpha-tocopherol quinone or alpha-tocotrienol quinone, vitamin MK2 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing alpha-tocopherol quinone or alpha-tocotrienol quinone, vitamin MK4 and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing alpha-tocopherol quinone or alpha-tocotrienol quinone, vitamin MK7 and a pharmaceutically acceptable carrier.

[0141] In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing a compound of Formula Ib, a compound of Formula IIb and a pharmaceutically acceptable carrier. In some embodiments, the invention provides a process for making a pharmaceutical composition comprising mixing a quinone selected from alpha-tocopherol quinone, beta-tocopherol quinone, delta-tocopherol quinone, gamma-tocopherol quinone, alpha-tocotrienol quinone, beta-tocotrienol quinone, delta-tocotrienol quinone, and gamma-tocotrienol quinone or mixtures thereof, a compound of Formula IIb selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-

6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione and a pharmaceutically acceptable carrier.

[0142] In another aspect, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of one or more compounds of Formula I^{ox} or I^{red}, and one or more compounds of Formula II^{ox} or II^{red}, wherein the amount of compound of Formula I^{ox} or I^{red} and the amount of compound of Formula II^{ox} or II^{red} are selected to produce an additive or synergistic effect.

[0143] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of idebenone, and one or more compounds of Vitamin K, wherein the amount of idebenone and the amount of Vitamin K are selected to produce an additive or synergistic effect.

[0144] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of CoQ10 or dihydro-CoQ10, and one or more compounds of Vitamin K, wherein the amount of CoQ10 or dihydro-CoQ10 and the amount of Vitamin K are selected to produce an additive or synergistic effect.

[0145] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadienyl)-1,4-benzoquinone, and one or more compounds of Vitamin K, wherein the amount of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadienyl)-1,4-benzoquinone and the amount of Vitamin K are selected to produce an additive or synergistic effect.

[0146] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of one or more tocopherol quinones or tocotrienol quinones, and one or more compounds of Vitamin K, wherein the amount of tocopherol quinone(s) or tocotrienol quinone(s) and the amount of Vitamin K are selected to produce an additive or synergistic effect.

[0147] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of idebenone, and Vitamin K1, wherein the amount of idebenone and the amount of Vitamin K1 are selected to produce an additive or synergistic effect.

[0148] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of CoQ10 or dihydro-

CoQ10, and Vitamin K1, wherein the amount of CoQ10 or dihydro-CoQ10 and the amount of Vitamin K1 are selected to produce an additive or synergistic effect.

[0149] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone, and Vitamin K1, wherein the amount of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone and the amount of Vitamin K1 are selected to produce an additive or synergistic effect.

[0150] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocopherol quinone and of Vitamin K1, wherein the amount of alpha-tocopherol quinone and the amount of Vitamin K1 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocopherol quinone and of Vitamin K2, wherein the amount of alpha-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocopherol quinone and of Vitamin MK4, wherein the amount of alpha-tocopherol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocopherol quinone and of Vitamin MK7, wherein the amount of alpha-tocopherol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocopherol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of alpha-tocopherol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0151] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of idebenone, and one or more compounds of Vitamin K2, wherein the amount of idebenone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect.

[0152] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of CoQ10 or dihydro-CoQ10, and one or more compounds of Vitamin K2, wherein the amount of CoQ10 or dihydro-CoQ10 and the amount of Vitamin K2 are selected to produce an additive or synergistic effect.

[0153] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadienyl)-1,4-benzoquinone, and one or more compounds of Vitamin K2, wherein the amount of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadienyl)-1,4-benzoquinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect.

[0154] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocotrienol quinone and the amount of one or more compounds of Vitamin K2, wherein the amount of alpha-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocotrienol quinone and of Vitamin K2, wherein the amount of alpha-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocotrienol quinone and of Vitamin MK4, wherein the amount of alpha-tocotrienol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocotrienol quinone and of Vitamin MK7, wherein the amount of alpha-tocotrienol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of alpha-tocotrienol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-

trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of alpha-tocotrienol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0155] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocopherol quinone and of Vitamin K2, wherein the amount of beta-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocopherol quinone and of Vitamin K2, wherein the amount of beta-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocopherol quinone and of Vitamin MK4, wherein the amount of beta-tocopherol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocopherol quinone and of Vitamin MK7, wherein the amount of beta-tocopherol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocopherol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of beta-tocopherol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione, and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-

6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0156] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocotrienol quinone and of Vitamin K2, wherein the amount of beta-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocotrienol quinone and of Vitamin K2, wherein the amount of beta-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocotrienol quinone and of Vitamin MK4, wherein the amount of beta-tocotrienol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocotrienol quinone and of Vitamin MK7, wherein the amount of beta-tocotrienol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of beta-tocotrienol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of beta-tocotrienol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0157] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocopherol quinone and of Vitamin K1, wherein the amount of gamma-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial

disorders with a therapeutically effective amount of gamma-tocopherol quinone and of Vitamin K2, wherein the amount of gamma-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocopherol quinone and of Vitamin K2, wherein the amount of gamma-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocopherol quinone and of Vitamin MK4, wherein the amount of gamma-tocopherol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocopherol quinone and of Vitamin MK7, wherein the amount of gamma-tocopherol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocopherol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of gamma-tocotrienol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0158] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocotrienol quinone and of Vitamin K2, wherein the amount of gamma-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocotrienol quinone and of Vitamin K2, wherein the amount of gamma-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders

with a therapeutically effective amount of gamma-tocotrienol quinone and of Vitamin K2, wherein the amount of gamma-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocotrienol quinone and of Vitamin MK4, wherein the amount of gamma-tocotrienol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocotrienol quinone and of Vitamin MK7, wherein the amount of gamma-tocotrienol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of gamma-tocotrienol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of gamma-tocotrienol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0159] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocopherol quinone and of Vitamin K2, wherein the amount of delta-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocopherol quinone and of Vitamin K2, wherein the amount of delta-tocopherol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocopherol quinone and of Vitamin MK4, wherein the amount of delta-tocopherol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a

therapeutically effective amount of delta-tocopherol quinone and of Vitamin MK7, wherein the amount of delta-tocopherol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocopherol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione, wherein the amount of delta-tocotrienol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0160] In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocotrienol quinone and of Vitamin K2, wherein the amount of delta-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocotrienol quinone and of Vitamin K2, wherein the amount of delta-tocotrienol quinone and the amount of Vitamin K2 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocotrienol quinone and of Vitamin MK4, wherein the amount of delta-tocotrienol quinone and the amount of Vitamin MK4 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocotrienol quinone and of Vitamin MK7, wherein the amount of delta-tocotrienol quinone and the amount of Vitamin MK7 are selected to produce an additive or synergistic effect. In some embodiments, the invention provides methods of treating mitochondrial disorders with a therapeutically effective amount of delta-tocotrienol quinone and of a compound selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-

trimethylnaphthalene-1,4-dione, wherein the amount of delta-tocotrienol quinone and the amount of 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione; and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione are selected to produce an additive or synergistic effect.

[0161] In some embodiments, including any of the foregoing embodiments, the mitochondrial disorder is caused by mutations in mitochondrial genes. In other embodiments, the mitochondrial disorder is caused by mutations in nuclear genes encoding for subunits of the respiratory chain complexes. In other embodiments, the mitochondrial disorder is caused by mutations in genes coding for proteins involved in the nuclear-mitochondrial communication. In other embodiments, the mitochondrial disorder is caused by defects in cytochrome c oxidase (COX) or complex IV. In other embodiments, the mitochondrial disorder is caused by the inability of heme A to be incorporated into nascent complex IV subunits.

[0162] In some embodiments, including any of the foregoing embodiments, the invention provides methods of treating mitochondrial disorders selected from the group consisting of inherited mitochondrial diseases; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, and Stroke (MELAS); Leber's Hereditary Optic Neuropathy (LHON); Optic Dominant Atrophy (DOA); Leigh syndrome or Leigh-like syndrome; SURF1; Kearns-Sayre syndrome (KSS); Friedreich's Ataxia (FRDA); overlap syndromes such as KSS/MERRF, other myopathies; cardiomyopathy; encephalomyopathy; renal tubular acidosis; neurodegenerative diseases; Parkinson's Disease; Alzheimer's Disease; Amyotrophic Lateral Sclerosis (ALS); motor neuron diseases; other neurological diseases; epilepsy; genetic diseases; Huntington's disease (HD); mood disorders; schizophrenia; bipolar disorder; age-associated diseases; cerebral vascular accidents, macular degeneration; diabetes; and cancer, in a person in need thereof.

[0163] In another embodiment, including any of the foregoing embodiments, the mitochondrial disorder is a mitochondrial respiratory chain disorder. In some embodiments, the mitochondrial respiratory chain disorder is a respiratory protein chain disorder. In another particular embodiment, the disorder is CoQ₁₀ deficiency.

[0164] In another embodiment, including any of the foregoing embodiments, the mitochondrial disorder is selected from the group consisting of inherited

mitochondrial diseases; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, and Stroke (MELAS); Leber's Hereditary Optic Neuropathy (LHON); Optic Dominant Atrophy (DOA); Leigh syndrome or Leigh-like syndrome; SURF1; Kearns-Sayre syndrome (KSS); Friedreich's Ataxia (FRDA).

[0165] In another embodiment of the invention, including any of the foregoing embodiments, the mitochondrial disorder is Friedreich's Ataxia (FRDA). In another embodiment of the invention, the mitochondrial disorder is Leber's Hereditary Optic Neuropathy (LHON). In another embodiment of the invention, the mitochondrial disorder is Optic Dominant Atrophy (DOA). In another embodiment of the invention, including any of the foregoing embodiments, the mitochondrial disorder is mitochondrial myopathy, encephalopathy, lactacidosis, and stroke (MELAS). In another embodiment of the invention, including any of the foregoing embodiments, the mitochondrial disorder is Kearns-Sayre syndrome (KSS). In another embodiment of the invention, the mitochondrial disorder is Myoclonic Epilepsy with Ragged Red Fibers (MERRF). In another embodiment of the invention, including any of the foregoing embodiments, the disorder is an overlap syndrome. In another embodiment of the invention, including any of the foregoing embodiments, the disorder is an overlap syndrome such as KSS/MERFF. In another embodiment of the invention, including any of the foregoing embodiments, the disorder is Parkinson's disease. In another embodiment of the invention, including any of the foregoing embodiments, the disorder is Huntington's disease (HD). In another embodiment of the invention including any of the foregoing embodiments, the disorder is amyotrophic lateral sclerosis (ALS). In yet another embodiment of the invention including any of the foregoing embodiments, the disorders are cerebral vascular accidents, such as stroke. In yet another embodiment of the invention, including any of the foregoing embodiments, the mitochondrial disorder is Leigh syndrome. In yet another embodiment of the invention, including any of the foregoing embodiments, the mitochondrial disorder is Leigh-like syndrome. In another embodiment of the invention, including any of the foregoing embodiments, the mitochondrial disorder is SURF1.

[0166] In another aspect, the invention relates to the treatment of a patient suffering from a mitochondrial disorder has one or more symptoms selected from the group consisting of: one or more lesions in the central nervous system; one or more

lesions in the brain; one or more lesions in the basal ganglia; one or more lesions in the thalamus; one or more lesions in the brain stem; one or more lesions in the dentate nuclei; one or more lesions in the optic nerves; one or more lesions in the spinal cord; degeneration of the central nervous system; degeneration of the brain; degeneration of the basal ganglia; degeneration of the thalamus; degeneration of the brain stem; degeneration of the dentate nuclei; degeneration of the optic nerves; degeneration of the spinal cord; progressive neurological deterioration; psychomotor retardation; mental retardation; tremors; spasms; myoclonic spasms; seizures; hypotonia; weakness; fatigue; ataxia; difficulty in walking; gastrointestinal abnormalities; eye abnormalities; vision loss; nystagmus; optic atrophy; hearing loss, poor reflexes; abnormal reflexes; absent reflexes; abnormal Babinski test; difficulty in breathing; difficulty in speaking; difficulty in swallowing; failure to thrive; low body weight; growth retardation; impaired kidney function; terminal stupor; lactic acidosis; poor sucking ability, loss of head control; loss of motor skills; loss of appetite; vomiting; irritability; and continuous crying.

[0167] In one embodiment, the individual suffering from a mitochondrial disorder, has one or more symptoms selected from the group consisting of ataxia, difficulty in walking, poor balance, inability to climb steps, inability to sit without assistance; inability to independently stand with support; inability to turn while sitting; inability to scoot or slide while sitting; inability to move extremities purposefully; inability to perform fine motor tasks; difficulty in sleeping; disrupted sleep patterns; gastrointestinal problems; impaired hand-eye coordination, impaired hearing and difficulty in breathing.

[0168] In one embodiment, the individual suffering from a mitochondrial disorder has one or more symptoms selected from the group consisting of speech problems; difficulty in speaking in complete sentences; difficulty in enunciating; difficulty in counting aloud; poor voice and word association; cognitive difficulties, and difficulty in responding to verbal communication appropriately.

[0169] In another aspect, the invention relates to the treatment of a patient suffering from Leigh syndrome or Leigh-like syndrome, such as an individual suffering from SURF1, has one or more symptoms selected from the group consisting of: one or more lesions in the central nervous system; one or more lesions in the brain; one or more lesions in the basal ganglia; one or more lesions in the thalamus; one or more lesions in the brain stem; one or more lesions in the dentate nuclei; one or

more lesions in the optic nerves; one or more lesions in the spinal cord; degeneration of the central nervous system; degeneration of the brain; degeneration of the basal ganglia; degeneration of the thalamus; degeneration of the brain stem; degeneration of the dentate nuclei; degeneration of the optic nerves; hearing loss, degeneration of the spinal cord; progressive neurological deterioration; psychomotor retardation; mental retardation; tremors; spasms; myoclonic spasms; seizures; hypotonia; weakness; fatigue; ataxia; difficulty in walking; gastrointestinal abnormalities; eye abnormalities; vision loss; nystagmus; optic atrophy; poor reflexes; abnormal reflexes; absent reflexes; abnormal Babinski test; difficulty in breathing; difficulty in speaking; difficulty in swallowing; failure to thrive; low body weight; growth retardation; impaired kidney function; terminal stupor; lactic acidosis; poor sucking ability, loss of head control; loss of motor skills; loss of appetite; vomiting; irritability; and continuous crying.

[0170] In one embodiment, the individual suffering from Leigh syndrome or Leigh-like syndrome, such as an individual suffering from SURF1, has one or more symptoms selected from the group consisting of ataxia, difficulty in walking, poor balance, inability to climb steps, inability to sit without assistance; inability to independently stand with support; inability to turn while sitting; inability to scoot or slide while sitting; inability to move extremities purposefully; inability to perform fine motor tasks; difficulty in sleeping; disrupted sleep patterns; gastrointestinal problems; impaired hand-eye coordination, impaired hearing and difficulty in breathing.

[0171] In one embodiment, the individual suffering from Leigh syndrome or Leigh-like syndrome, such as an individual suffering from SURF1, has one or more symptoms selected from the group consisting of speech problems; difficulty in speaking in complete sentences; difficulty in enunciating; difficulty in counting aloud; poor voice and word association; cognitive difficulties, and difficulty in responding to verbal communication appropriately.

[0172] In another aspect, the individual suffering from a mitochondrial disorder has been diagnosed with FRDA and has one or more symptoms selected from the group consisting of ataxia, difficulty in walking, poor balance, inability to climb steps, inability to sit without assistance; inability to independently stand with support; inability to turn while sitting; inability to scoot or slide while sitting; inability to move extremities purposefully; inability to perform fine motor tasks; difficulty in sleeping;

disrupted sleep patterns; impaired hand-eye coordination, impaired vision, and impaired hearing.

[0173] In one embodiment, the individual suffering from a mitochondrial disorder has been diagnosed with FRDA and has one or more symptoms selected from the group consisting of speech problems; difficulty in speaking in complete sentences; and difficulty in enunciating.

[0174] In another aspect, the individual suffering from a mitochondrial disorder has been diagnosed with LHON and has one or more symptoms selected from the group loss of visual acuity; loss of central vision; impairment of central vision; impairment of color vision; centrocecal scotomas; temporal pallor of the optic disc; circumpapillary telangiectatic microrangiopathy; sparing of pupillary light responses; swelling of the retinal nerve fiber layer around the disc (pseudoedema) or optic atrophy.

[0175] In one embodiment, the individual suffering from a mitochondrial disorder has been diagnosed with LHON and has one or more symptoms selected from the group loss of visual acuity; loss of central vision; impairment of central vision; impairment of color vision; or optic atrophy.

[0176] Also included in the present invention is the use of one or more tocopherol quinones or tocotrienol quinones, particularly tocotrienol quinone, and one or more naphthoquinone quinones, particularly a vitamin K in the preparation of a medicament for treating a mitochondrial disorder in a person in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0177] The present invention relates to an adjunctive therapy for the treatment of mitochondrial disorders comprising the administration of an effective amount of one or more quinone compounds of Formula I^{ox} or their reduced hydroquinone form of Formula I^{red} and one or more naphthoquinone compounds of Formula II^{ox} or their reduced naphthohydroquinone form of Formula II^{red} to a patient in need thereof.

[0178] In one aspect, tocopherol quinones contemplated for use in the adjunctive therapy for the treatment, include alpha-tocopherol quinone, beta-tocopherol quinone, gamma-tocopherol quinone, and delta-tocopherol quinone. The tocopherol quinones with the naturally occurring tocopherol configuration are used in one embodiment of

the invention, but other stereoisomers and/or mixtures of stereoisomers in any ratio, such as racemic mixtures, can also be used in the invention.

[0179] In one aspect, tocotrienol quinones contemplated for use in the adjunctive therapy for the treatment, include alpha-tocotrienol quinone, beta-tocotrienol quinone, gamma-tocotrienol quinone, and delta-tocotrienol quinone. The tocotrienol quinones with the naturally occurring tocotrienol configuration are used in one embodiment of the invention, but other stereoisomers and/or mixtures of stereoisomers in any ratio, such as racemic mixtures, can also be used in the invention.

[0180] Tocopherol quinones and tocotrienol quinones can be used in their oxidized form, or can be used in their reduced hydroquinone form. The quinone (cyclohexadienedione) form and hydroquinone (benzenediol) form are readily interconverted with appropriate reagents. The quinone can be treated in a biphasic mixture of an ethereal solvent with a basic aqueous solution of $\text{Na}_2\text{S}_2\text{O}_4$ (Vogel, A.I. et al. Vogel's Textbook of Practical Organic Chemistry, 5th Edition, Prentice Hall: New York, 1996; Section 9.6.14 Quinones, "Reduction to the Hydroquinone"). Standard workup in the absence of oxygen yields the desired hydroquinone. The hydroquinone form can be oxidized to the quinone form with oxidizing agents such as ceric ammonium nitrate (CAN) or ferric chloride. The quinone and hydroquinone forms are also readily interconverted electrochemically, as is well known in the art. See, e.g., Section 33.4 of Streitweiser & Heathcock, Introduction to Organic Chemistry, New York: Macmillan, 1976.

[0181] The description of compounds herein also includes all stereoisomers of the compounds, including diastereomers and enantiomers, and mixtures of stereoisomers in any ratio, including, but not limited to, racemic mixtures. Unless stereochemistry is explicitly indicated in a structure, the structure is intended to embrace all possible stereoisomers of the compound depicted. If stereochemistry is explicitly indicated for one portion or portions of a molecule, but not for another portion or portions of a molecule, the structure is intended to embrace all possible stereoisomers for the portion or portions where stereochemistry is not explicitly indicated.

[0182] The compounds can be administered in prodrug form. Prodrugs are derivatives of the compounds, which are themselves relatively inactive but which convert into the active compound when introduced into the subject in which they are used by a chemical or biological process in vivo, such as an enzymatic conversion. Suitable prodrug formulations include, but are not limited to, peptide conjugates of

the compounds disclosed herein and esters of compounds disclosed herein. Further discussion of suitable prodrugs is provided in H. Bundgaard, *Design of Prodrugs*, New York: Elsevier, 1985; in R. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Boston: Elsevier, 2004; in R.L. Juliano (ed.), *Biological Approaches to the Controlled Delivery of Drugs* (Annals of the New York Academy of Sciences, v. 507), New York: New York Academy of Sciences, 1987; and in E.B. Roche (ed.), *Design of Biopharmaceutical Properties Through Prodrugs and Analogs* (Symposium sponsored by Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, November 1976 national meeting, Orlando, Florida), Washington : The Academy, 1977.

[0183] In another aspect, the naphthoquinones contemplated for adjunctive therapy in the treatment of mitochondrial disorders are selected from one or more compounds having Vitamin K activity. In another aspect, the naphthoquinones contemplated for adjunctive therapy in the treatment of mitochondrial disorders are selected from one or more compounds having Vitamin K1 activity. In another aspect, the naphthoquinones contemplated for adjunctive therapy in the treatment of mitochondrial disorders are selected from one or more compounds having Vitamin K2 activity. In another aspect, the naphthoquinones contemplated for adjunctive therapy in the treatment of mitochondrial disorders are selected from 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3-methylnaphthalene-1,4-dione; 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)naphthalene-1,4-dione and 2-(3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl)-3,6,7-trimethylnaphthalene-1,4-dione.

[0184] By "synergy" or "synergistic effect" when used in connection with a description of the efficacy of a combination of agents, is meant any measured effect of the combination which is greater than the value predicted from a sum of the effects of the individual agents. (Greco, W.R. *et al.*, *Pharmacol. Rev.* 1995, 47:331-385).

[0185] By "individual," "subject," or "patient," is meant an animal, preferably a mammal, for example a human, who is object of treatment, observation or experiment.

[0186] "Treating" a disease with the compounds and methods discussed herein is defined as administering one or more of the compounds discussed herein, with or without additional therapeutic agents, in order to reduce or eliminate either the disease or one or more symptoms of the disease, or to retard the progression of the disease or

of one or more symptoms of the disease, or to reduce the severity of the disease or of one or more symptoms of the disease. "Suppression" of a disease with the compounds and methods discussed herein is defined as administering one or more of the compounds discussed herein, with or without additional therapeutic agents, in order to suppress the clinical manifestation of the disease, or to suppress the manifestation of adverse symptoms of the disease. The distinction between treatment and suppression is that treatment occurs after adverse symptoms of the disease are manifest in a subject, while suppression occurs before adverse symptoms of the disease are manifest in a subject. Suppression may be partial, substantially total, or total.

[0187] Because mitochondria diseases are due to genetic mutations, genetic screening can be used to identify patients at risk of the disease. For example, disorders such as Leigh syndrome and SURF1, deficiencies in cytochrome c oxidase can arise from mutations in Complex IV of the mitochondrial respiratory chain. The compounds disclosed herein can be administered to, and the methods of the invention disclosed herein can be used to treat, asymptomatic patients with mutations in the mitochondrial respiratory chain, such as in Complex IV, who are at risk of developing the clinical symptoms of the disease, in order to suppress the appearance of any adverse symptoms or lessen the severity of symptoms that may occur. The compounds disclosed herein can be administered to, and the methods of the invention disclosed herein can be used to treat, asymptomatic patients with defects in cytochrome c oxidase, who are at risk of developing the clinical symptoms of the disease, in order to suppress the appearance of any adverse symptoms or lessen the severity of symptoms that may occur. The compounds disclosed herein can be administered to, and the methods of the invention disclosed herein can be used to treat, symptomatic patients with mutations in Complex IV in order to treat the disease.

[0188] "Therapeutic use" of the compounds discussed herein is defined as using one or more of the compounds discussed herein to treat or suppress a disease, as defined above. The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. A "therapeutically effective amount" of a compound when administered to a subject, is sufficient to reduce or

eliminate either a disease or one or more symptoms of a disease, or to retard the progression of a disease or of one or more symptoms of a disease, or to reduce the severity of a disease or of one or more symptoms of a disease, or to suppress the clinical manifestation of a disease, or to suppress the manifestation of adverse symptoms of a disease. A therapeutically effective amount can be given in one or more administrations.

[0189] The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. "Straight-chain alkyl" or "linear alkyl" group refers to alkyl groups that are neither cyclic nor branched, commonly designated as "n-alkyl" groups. One subset of alkyl groups is (C₁-C₆)alkyl which include groups such as methyl, ethyl, n-propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, n-pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and any other alkyl group containing between one and five carbon atoms, where the (C₁-C₆)alkyl groups can be attached via any valence on the (C₁-C₆) alkyl groups.

[0190] The term "alkoxy" refers to the group -O-alkyl, wherein alkyl is as defined herein. One subset of alkoxy groups is (C₁-C₆)alkoxy which include groups such as methoxy, ethoxy, n-propoxy, iso-propoxy, cyclo-propoxy, n-butoxy, tert-butoxy, sec-butoxy, cyclo-butoxy, n-pentoxy, cyclo-pentoxy, n-hexoxy, cyclo-hexoxy, 1,2-dimethylbutoxy, and the like.

[0191] The term "(C₁-C₆)haloalkyl" refers to any (C₁-C₆)alkyl having at least one halogen substituent, the halogen can be attached via any valence on the (C₁-C₆)alkyl group. One subset of (C₁-C₆)haloalkyl is -CF₃, -CCl₃, -CBr₃ and -CI₃. Another subset is the subset with exactly one halogen substituent. Another subset is the subset with exactly two halogen substituents.

[0192] Wherein the present invention is directed to co-therapy comprising administration of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red}, "therapeutically effective amount" shall mean that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response; and in particular embodiments the combined effect elicits a synergistic response. For example, the therapeutically effective amount of co-therapy comprising administration of a quinone and a naphthoquinone would be the amount of quinone and the amount of naphthoquinone

that when taken together or sequentially have a combined effect that is therapeutically effective. Further, it will be recognized by one skilled in the art that in the case of co-therapy or adjunctive therapy with a therapeutically effective amount, as in the example above, the amount of the quinone and the amount of naphthoquinone individually may or may not be therapeutically effective.

[0193] As used herein, the term "co-therapy" or "adjunctive therapy" shall mean treatment of a subject in need thereof, with administration of one or more compounds of Formula I^{ox} or I^{red} and one or more compounds of Formula II^{ox} or II^{red}, wherein the compounds are administered by any suitable means, simultaneously, sequentially, separately or in a single pharmaceutical formulation. Where the compounds are administered in separate dosage forms, the number of dosages administered for each compound may be the same or different. The compounds may be administered via the same or different routes of administration. The compounds may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

[0194] As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

Synthesis and Sources of Compounds

[0195] The compounds of the present invention can be readily prepared by a variety of methods known in the art. Certain quinones of Formula I^{ox} or their reduced hydroquinone form of Formula I^{red} and their preparation have been described in the literature, for example in co-assigned US applications Nos. 11/445,582, 11/521,887 and 11/710,042.

[0196] Certain naphthoquinones of Formula II^{ox} or their reduced naphthoquinone forms of Formula II^{red} and their preparation have been described for example, in Isler, O.; *et al.*, *Helvetica Chimica Acta* (1958), 41, 786-807 or Isler, O. *et al.* *Chimia* (1958), 12, 69. Preparation processes of naphthoquinone derivatives of the invention have also been covered in the patent literature, for example in US Applications No. 4,374,775; 4,906,411; 5,329,026; 5,412,124; 5,476,955; 5,637,741, 5,677,471; 5,770,774; 6,579,994; and in PCT No. WO/2008/031283. Vitamins K1, K2 and K3 are commercially available for example from Sigma-Aldrich (St. Louis, MO).

Additional syntheses of Vitamin K analogues have been described in Weichet J. *et al.*, *Collection of Czechoslovak Chemical Communications* (1964) 29, 197-205.

[0197] Natural or synthetic sources of vitamin K which can be used according to the present invention include the following: phylloquinone from natural sources such as vegetable extracts, fats and oils, synthetic phylloquinone, synthetic vitamin K₃ (menadione), different forms of vitamin K₂ such as synthetic MK-2, MK-3, MK-4, MK-5, MK-6, MK-7, MK-8, MK-9, MK-10, MK-11, MK-12 and MK-13, natto (food prepared from fermented soy-bean, rich in Vitamin K₂), and other fermented foods or dairy products rich in Vitamin K₁ and/or Vitamin K₂.

Monitoring Treatment Efficacy Using Biomarkers

[0198] Several metabolic biomarkers can be used to monitor the efficacy of compounds in treatment of mitochondrial disorders. These biomarkers include, but are not limited to, lactic acid (lactate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; pyruvic acid (pyruvate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; lactate/pyruvate ratios, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; phosphocreatine levels, NADH (NADH + H⁺) or NADPH (NADPH + H⁺) levels; NAD or NADP levels; ATP levels; anaerobic threshold; reduced coenzyme Q (CoQ^{red}) levels; oxidized coenzyme Q (CoQ^{ox}) levels; total coenzyme Q (CoQ^{tot}) levels; oxidized cytochrome *c* levels; reduced cytochrome *c* levels; oxidized cytochrome *c*/reduced cytochrome *c* ratio; acetoacetate levels, β-hydroxy butyrate levels, acetoacetate/β-hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels; levels of reactive oxygen species; and levels of oxygen consumption (VO₂), levels of carbon dioxide output (VCO₂), and respiratory quotient (VCO₂/VO₂). Exercise intolerance can also be used as an indicator of the efficacy of compounds in treatment of mitochondrial disorders. Several of these clinical markers are measured routinely in exercise physiology laboratories, and provide convenient assessments of the metabolic state of a subject.

[0199] Pyruvate, a product of the metabolism of glucose, is removed by reduction to lactic acid in an anaerobic setting; the degree to which this process occurs is dependent on the function of the mitochondrial respiratory chain. Dysfunction of the respiratory chain can lead to an abnormally high conversion of pyruvate to lactate, supported by the elevated lactate/pyruvate ratios observed in mitochondrial cytopathies (Scriver, CR. The metabolic and molecular bases of inherited disease. 7th

ed. New York: McGraw-Hill, Health Professions Division; 1995; Munnich, A. *et al.*, *J. Inherit. Metab. Dis.* 1992, 15(4):448-455). Blood lactate/pyruvate ratio is, therefore, widely used as a noninvasive test for detection of mitochondrial cytopathies and toxic mitochondrial myopathies. (See Chariot, P. *et al.*, *Arch. Pathol. Lab. Med.* 1994, 118(7):695-697; Chariot, P. *et al.*, *Arthritis Rheum.* 1994, 37(4):583-586.) Total concentration levels of lactate and total concentration levels of pyruvate that are elevated above the normal range are also observed in Leigh syndrome, and those elevated total concentrations can serve as additional biomarkers in addition to the elevated lactate/pyruvate ratio. Another biomarker which can be monitored is CoQ₁₀ concentration.

[0200] Biomarkers and techniques for measurement of biomarkers that can be used to monitor the efficacy of treatment include, but are not limited to:

[0201] *Magnetic resonance spectroscopy:* Brain lactate measurement and quantification directly reflect cellular electron balance and indirectly reflect energy production. Magnetic resonance spectroscopy can be used to assess metabolic parameters of the brain with a focus on lactate, i.e., central nervous system (CNS) concentration of lactate and lactate/pyruvate ratio. MRS has been used to measure lactate using proton MRS (1H-MRS) (Kaufmann, DC *et al.*, *Neurology* 2004, 62(8):1297-302). Phosphorous MRS (31P-MRS) has been used to demonstrate low levels of cortical phosphocreatine (PCr) (Matthews, PM *et al.*, *Ann. Neurol.* 1991, 29(4):435-8), and a delay in PCr recovery kinetics following exercise in skeletal muscle (Matthews, PM *et al.*, *Ann. Neurol.* 1991, 29(4):435-8; Barbiroli, B. *et al.*, *J. Neurol.* 1995, 242(7):472-7; Fabrizi, GM *et al.*, *J. Neurol. Sci.* 1996, 137(1):20-7).

[0202] Proton Magnetic Resonance Spectroscopy (MRS) is used to measure the levels of different metabolic compounds in the brain of mitochondrial patients, that emit a unique resonance frequency expressed as chemical shifts in parts per million (ppm). Patients with mitochondrial disease are evaluated for lactate, N-acetyl aspartate (NAA), succinate, total creatine, choline (Cho) and myo-inositol. Lactate is not detected in normal patients; however, if metabolism shifts to anaerobic glycolysis in mitochondrial respiratory chain deficiencies, lactate levels increase (see Barkovich, AJ *et al.*, *AJNR Am. J. Neuroradiol.* 1993, 14, (5) 1119-1137.) One of the best biomarkers for neuronal integrity is NAA which is localized to neurons and dendrites (see Clark, JB, *Dev. Neurosci.* 1998, 20 (4-5)271-276). Reductions of NAA levels when normalized to creatine are seen in mitochondrial disease patients. The signal for

choline (Cho) includes free choline, phosphoryl choline and phosphatidylcholine which constitute myelin. Cho elevations reflect membrane turnover and demyelination. Deficient respiratory chain activity produces increases in succinate concentration detectable by this method (see Brockmann, K. *et al.*, *Ann. Neurol.* 2002, 52 (1) 38-45). Proton MRS obtained over conventional MRI, provides additional information through visualization of metabolic changes.

[0203] Another procedure that may be used is brain imaging with single photon emission computed tomography (SPECT, or less commonly, SPET), a nuclear medicine tomographic imaging technique using gamma rays. This procedure allows brain blood flow to be assessed with a nuclear gamma camera by revealing the relative blood flow in different parts of the brain. One such technique uses ^{99m}Tc -HMPAO (hexamethylpropylene amine oxime) as the gamma-emitting tracer used in this imaging.

[0204] *Lactic acid (lactate) levels:* Brain lactate measurement and quantification directly reflect cellular electron balance and indirectly reflect energy production. Lactate levels can be measured by taking samples of appropriate bodily fluids such as whole blood, plasma, or cerebrospinal fluid. Using magnetic resonance, lactate levels can be measured in virtually any volume of the body desired, such as the brain. Whole blood, plasma, and cerebrospinal fluid lactate levels can be measured by commercially available equipment such as the YSI 2300 STAT Plus Glucose & Lactate Analyzer (YSI Life Sciences, Ohio).

[0205] *NAD, NADP, NADH and NADPH levels:* Measurement of NAD, NADP, NADH ($\text{NADH} + \text{H}^+$) or NADPH ($\text{NADPH} + \text{H}^+$) can be measured by a variety of fluorescent, enzymatic, or electrochemical techniques, e.g., the electrochemical assay described in US Patent Publication No. US 2005/0067303.

[0206] *Oxygen consumption (vO_2 or VO_2), carbon dioxide output (vCO_2 or VCO_2), and respiratory quotient ($\text{RQ} = \text{VCO}_2/\text{VO}_2$):* vO_2 is usually measured either while resting (resting vO_2) or at maximal exercise intensity (vO_2 max). Optimally, both values will be measured. However, for severely disabled patients, measurement of vO_2 max may be impractical. Measurement of both forms of vO_2 is readily accomplished using standard equipment from a variety of vendors, e.g., Korr Medical Technologies, Inc. (Salt Lake City, Utah). VCO_2 can also be readily measured, and the ratio of VCO_2 to VO_2 under the same conditions (VCO_2/VO_2 , either resting or at maximal exercise intensity) provides the respiratory quotient (RQ).

[0207] *Other oxygen metabolism deficiencies:* Other problems with oxygen metabolism which can be measured include deficit in peripheral oxygen extraction (A-VO₂ difference) and an enhanced oxygen delivery (hyperkinetic circulation) (Taivassalo, T. *et al.*, *Brain* 2003, 126(Pt 2):413-23). This can be demonstrated by a lack of exercise induced deoxygenation of venous blood with direct AV balance measurements (Taivassalo, T. *et al.*, *Ann. Neurol.* 2002, 51(1):38-44) and non-invasively by near infrared spectroscopy (Lynch, D.R. *et al.*, *Muscle & Nerve* 2002, 25(5):664-73; van Beekvelt, MC *et al.*, *Ann. Neurol.* 1999, 46(4):667-70). Decreased affinity for oxygen of cytochrome-c oxidase has been observed in cultured fibroblasts from Leigh syndrome patients with SURF1 mutations (Pecina, P. *et al.*, *Am. J. Physiol. Cell Physiol.* 2004, 287(5):C1384-8).

[0208] *Oxidized Cytochrome c, reduced Cytochrome c, and ratio of oxidized Cytochrome c to reduced Cytochrome c:* Cytochrome c parameters, such as oxidized cytochrome c levels (Cyt C_{ox}), reduced cytochrome c levels (Cyt C_{red}), and the ratio of oxidized cytochrome c/reduced cytochrome c ratio (Cyt C_{ox})/(Cyt C_{red}), can be measured by *in vivo* near infrared spectroscopy. See, e.g., Rolfe, P., “*In vivo* near-infrared spectroscopy,” *Ann. Rev. Biomed. Eng.* 2000, 2:715-54 and Strangman, G. *et al.*, “Non-invasive neuroimaging using near-infrared light” *Biol. Psychiatry* 2002, 52:679-93. See also Pecina, P. *et al.*, *Am. J. Physiol. Cell Physiol.* 2004, 287(5):C1384-8, showing decreased affinity for oxygen of cytochrome-c oxidase in cultured fibroblasts from Leigh syndrome patients with SURF1 mutations.

[0209] *Exercise tolerance/Exercise intolerance:* Exercise intolerance is defined as “the reduced ability to perform activities that involve dynamic movement of large skeletal muscles because of symptoms of dyspnea or fatigue” (Piña, I *et al.*, *Circulation* 2003, 107:1210.) Exercise intolerance is often accompanied by myoglobinuria, due to breakdown of muscle tissue and subsequent excretion of muscle myoglobin in the urine. Various measures of exercise intolerance can be used, such as time spent walking or running on a treadmill before exhaustion, time spent on an exercise bicycle (stationary bicycle) before exhaustion, and similar tests.

[0210] *Acetoacetate/3-hydroxybutyrate (acetoacetate/ β -hydroxybutyrate) ratio:* Changes in the redox state of liver mitochondria can be investigated by measuring the arterial ketone body ratio (acetoacetate/3-hydroxybutyrate: AKBR) (Ueda, Y. *et al.*, *J. Cardiol.* 1997, 29(2):95-102).

[0211] *8-hydroxy-2'-deoxyguanosine (8-OHdG):* Urinary excretion of 8-hydroxy-2'-deoxyguanosine (8-OHdG) often has been used as a biomarker to assess the extent of repair of ROS-induced DNA damage in both clinical and occupational settings (Erhola, M. *et al.*, *FEBS Lett.* 1997, 409(2):287-91; Honda, K. *et al.*, *Leuk. Res.* 200024(6):461-8; Pilger, A., *Free Radic. Res.* 2001, 35(3):273-80; Kim, JY *et al.*, *Environ Health Perspect.* 2004, 112(6):666-71.)

[0212] *Routine plasma analytes:* Blood ketone body ratios including lactate: pyruvate, and beta-hydroxy butyrate:acetoacetate reflect electron balance. Alterations in these ratios can be used to assess systemic metabolic function. Increased blood lactate, increased blood pyruvate, increased blood alanine, and blood pH (to check for metabolic acidosis) can also be monitored.

[0213] *Other blood, metabolic, or enzymatic biomarkers:* patients can be monitored for an increase in the number of white blood cells, and for cytochrome c oxidase deficiency.

[0214] *Routine measures of cardiac function:* Mitochondrial diseases are frequently characterized by altered heart function. 12-lead ECG can be employed to measure QT/QTc. Transthoracic echocardiography can be used to assess dynamic cardiac function.

[0215] *Measurements of brainstem function:* brainstem auditory evoked response (BAER), somatosensory-evoked potentials (SEP or SSEP), blink reflex, and polysomnography (PSG) can be monitored in patients to assess brainstem function.

[0216] *Other reflexes:* Babinski test (Babinski reflex, Babinski sign), which can indicate motor neuron damage.

[0217] *Metabolomic analysis of plasma and urine:* Urine analysis can be performed on the patient, and can include measurement of the following organic acids: lactic acid, pyruvic acid, succinic acid, fumaric acid, 2-ketoglutaric acid, methyl malonic acid, 3-oh butyric acid, acetoacetic acid, 2-keto-3-methylvaleric acid, 2-keto-isocaproic acid, 2-keto-isovaleric acid, ethylmalonic acid, adipic acid, suberic acid, sebacic acid, 4-OH-phenylacetic acid, 4-OH-phenyllactic acid, 4-OH-phenylpyruvic acid, succinylacetone, and creatinine. Urine analysis performed on the patient can also include measurement of the following amino acids: proline, glutamine, threonine, serine, glutamic acid, arginine, glycine, alanine, histidine, lysine, valine, asparagine, methionine, phenylalanine, isoleucine, leucine, tyrosine,

hydroxyproline, creatinine, aspartic acid, cysteine, ornithine, citrulline, homocysteine, and taurine. In a panel of metabolic analytes, the following can be measured: sodium, potassium, chloride, bicarbonate, anion gap, glucose (serum), urea nitrogen (blood), creatinine, calcium, bilirubin, aspartate amino transferase, alanine amino transferase, alkaline phosphatase, total protein (serum), albumin (serum), and hemolysis index. Recently, the Critical Path Initiative has put forth a battery of biomarkers to predict drug toxicity that can also reflect renal mitochondrial function. Alterations in KIM-1, Albumin, Total Protein, β 2-microglobulin, Cystatin C, Clusterin, Trefoil Factor-3, and Neutrophil Gelatinase–Associated Lipocalin can be used to both detect (if present) a subclinical nephropathy and assemble a more accurate depiction of the natural history of SURF1 renal function. Finally, Haas, RH *et al.*, *Mol Genet Metab.* 2008, 94(1):16-37 describes various tests, such as MRS-based biochemical analysis, that can be used in the present invention.

Formulations and Routes of Administration

[0218] Wherein the present invention is directed to the administration of co-therapy, the compounds may be co-administered simultaneously, sequentially, separately or in a single pharmaceutical composition. Where the compounds are administered separately, the number of dosages of each compound given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently. Further, where the compounds are administered separately, the dosage forms of administration of each compound, may not necessarily be the same, e.g. where one compound may be administered in a solid, oral form and another may be administered intravenously or subcutaneously.

[0219] Optimal dosages and dosage regimens to be administered may be readily determined by those skilled in the art, and will vary with the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, physical activity, time of administration and concomitant diseases, will result in the need to adjust dosages and/or regimens.

[0220] For pharmaceutical administration, quinones and naphthoquinones may be administered by any suitable means, as would be apparent to one skilled in the art. Examples of daily dosages which can be used are an effective amount within the dosage range of about 0.1 mg/kg to about 300 mg/kg body weight, or within about 0.1

mg/kg to about 100 mg/kg body weight, or within about 0.1 mg/kg to about 80 mg/kg body weight, or within about 0.1 mg/kg to about 50 mg/kg body weight, or within about 0.1 mg/kg to about 30 mg/kg body weight, or within about 0.1 mg/kg to about 10 mg/kg body weight, or within about 1.0 mg/kg to about 80 mg/kg body weight, or within about 1.0 mg/kg to about 50 mg/kg body weight, or within about 1.0 mg/kg to about 30 mg/kg body weight, or within about 1.0 mg/kg to about 10 mg/kg body weight, or within about 10 mg/kg to about 80 mg/kg body weight, or within about 50 mg/kg to about 150 mg/kg body weight, or within about 100 mg/kg to about 200 mg/kg body weight, or within about 150 mg/kg to about 250 mg/kg body weight, or within about 200 mg/kg to about 300 mg/kg body weight, or within about 250 mg/kg to about 300 mg/kg body weight, or about 0.1, about 5, about 10, about 15, about 20, about 25, about 30, about 40, about 50, about 60, about 70, about 75, about 80, about 90, about 100, about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 mg total. The compound(s) may be administered in a single daily dose, or the total daily dosage may be administered in divided dosage of two, three or four times daily.

[0221] Quinones and naphthoquinones may be administered in any suitable form that will provide sufficient plasma and/or central nervous system levels of the compounds. The compounds can be administered enterally, orally, parenterally, sublingually, by inhalation (e.g. as mists or sprays), rectally, or topically in unit dosage formulations containing conventional nontoxic pharmaceutically acceptable carriers, excipients, adjuvants, and vehicles as desired. For example, suitable modes of administration include oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intraarterial, intramuscular, intraperitoneal, intranasal (e.g. via nasal mucosa), subdural, rectal, gastrointestinal, and the like, and directly to a specific or affected organ or tissue. For delivery to the central nervous system, spinal and epidural administration, or administration to cerebral ventricles, can be used. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous injection, intraarterial injection, intramuscular injection, intrasternal injection, or infusion techniques. The compounds are mixed with pharmaceutically acceptable carriers, excipients, adjuvants, and vehicles appropriate for the desired route of administration.

[0222] In some embodiments, particularly those for the treatment of mitochondrial disorders affecting the eyes, such as but not limited to LHON or DOA, the compounds may also be administered by an ocular route, and the excipient will be an "ophthalmically acceptable" vehicle. An "ophthalmically acceptable" component, as used herein, refers to a component which will not cause any significant ocular damage or ocular discomfort at the intended concentration and over the time of intended use. Solubilizers and stabilizers are deemed to be non-reactive. An "ophthalmically acceptable vehicle" refers to any substance or combination of substances which are non-reactive with the compounds and suitable for administration to a patient. Suitable vehicles may be non-aqueous liquid media including the physiologically acceptable oils such as silicone oil, USP mineral oil, white oil, poly(ethylene-glycol), a polyethoxylated castor oil and vegetable oils, for example corn oil, peanut oil, or the like. Other suitable vehicles may be aqueous or oil-in-water solutions suitable for topical application to the patient's eyes. These vehicles may be preferred based on ease of formulation, as well as a patient's ability to easily administer such formulations by means of instilling one to two drops of the solutions in the affected eyes. The formulations may also be suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid formulations. and fat bases, such as natural wax e.g. white bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax e.g. solid paraffin, microcrystalline wax; hydrocarbons e.g. liquid paraffin, white petrolatum, yellow petrolatum; or combinations thereof. The formulations may be applied by use of the hands or an applicator such as a wipe, a contact lens, a dropper or a spray.

[0223] In other embodiments the compounds may be administered by the oral route. Oral administration is advantageous due to its ease of implementation and patient (or caretaker) compliance. Introduction of medicine via feeding tube, feeding syringe, or gastrostomy can be employed in order to accomplish enteric administration. The active compound (and, if present, other co-administered agents) can be enterally administered in sesame oil, or any other pharmaceutically acceptable carrier suitable for formulation for administration via feeding tube, feeding syringe, or gastrostomy.

[0224] The compounds described for use herein can be administered in solid form, in liquid form, in aerosol form, or in the form of tablets, pills, powder mixtures, gums, jellies, gelatin confections, soft gels, capsules, granules, injectables, creams,

solutions, suppositories, enemas, colonic irrigations, emulsions, dispersions, food premixes, and in other suitable forms. The compounds can also be administered in liposome formulations. The compounds can also be administered as prodrugs, where the prodrug undergoes transformation in the treated subject to a form which is therapeutically effective. Additional methods of administration are known in the art.

[0225] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to methods known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in propylene glycol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0226] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[0227] Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents. Alternatively, the compound may also be administered in neat form if suitable.

[0228] The compounds for use in the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming

liposomes can be used. The present compositions in liposome form can contain, in addition to a compound for use in the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidylcholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 et seq (1976).

[0229] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form can vary depending upon the patient to which the active ingredient is administered and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed; the age, body weight, body area, body mass index (BMI), general health, sex, and diet of the patient; the time of administration and route of administration used; the rate of excretion; drug combination, if any, used; and the progression, and severity of the disease in the patient undergoing therapy. The pharmaceutical unit dosage chosen is usually fabricated and administered to provide a defined final concentration of drug in the blood, cerebrospinal fluid, brain tissues, spinal cord tissues, other tissues, other organs, or other targeted region of the body.

[0230] Compounds for use in the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided dosage of two, three or four times daily.

EXAMPLES

Example A

Screening Compounds of the Invention in Human Dermal Fibroblasts from Friedreich's Ataxia Patients

[0231] An initial screen was performed to identify compounds effective for the amelioration of mitochondrial disorders. Reference samples and solvent controls were tested for their ability to rescue FRDA fibroblasts stressed by addition of L-buthionine-(S,R)-sulfoximine (BSO), as described in Jauslin, ML *et al.*, *Hum. Mol. Genet.* 2002, 11(24):3055, Jauslin, ML *et al.*, *FASEB J.* 2003, 17:1972-4, and International Patent Application WO 2004/003565. Human dermal fibroblasts from Friedreich's Ataxia patients have been shown to be hypersensitive to inhibition of the

de novo synthesis of glutathione (GSH) with L-buthionine-(S,R)-sulfoximine (BSO), a specific inhibitor of GSH synthetase (Jauslin, ML et al., *Hum. Mol. Genet.* 2002, 11(24):3055). This specific BSO-mediated cell death can be prevented by administration of antioxidants or molecules involved in the antioxidant pathway, such as alpha-tocopherol, selenium, or small molecule glutathione peroxidase mimetics. However, antioxidants differ in their potency, i.e. the concentration at which they are able to rescue BSO-stressed FRDA fibroblasts.

[0232] MEM (a medium enriched in amino acids and vitamins, catalog no. 1-31F24-I) and Medium 199 (M199, catalog no. 1-21F22-I) with Earle's Balanced Salts, without phenol red, were purchased from Bioconcept. Fetal Calf Serum was obtained from PAA Laboratories. Basic fibroblast growth factor and epidermal growth factor were purchased from PeproTech. Penicillin-streptomycin-glutamine mix, L-buthionine (S,R)-sulfoximine, Vitamin K1, Vitamin K2 and insulin from bovine pancreas were purchased from Sigma. Idebenone was obtained from Chemo Iberica. Calcein AM was purchased from Molecular Probes. Cell culture medium was made by combining 125 ml M199 EBS, 50 ml Fetal Calf Serum, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM glutamine, 10 µg/ml insulin, 10 ng/ml EGF, and 10 ng/ml bFGF; MEM EBS was added to make the volume up to 500 ml. A 10 mM BSO solution was prepared by dissolving 444 mg BSO in 200 ml of medium (Invitrogen, Carlsbad, Ca.) with subsequent filter-sterilization. During the course of the experiments, this solution was stored at +4°C. The cells were obtained from the Coriell Cell Repositories (Camden, NJ; repository number GM04078) and grown in 10 cm tissue culture plates. Every third day, they were split at a 1:3 ratio.

[0233] The test samples were supplied in 1.5 ml glass vials. The compounds were diluted with DMSO, ethanol or PBS to result in a 5 mM stock solution. Once dissolved, they were stored at -20°C.

[0234] Test samples were screened according to the following protocol:

[0235] A culture with FRDA fibroblasts was started from a 1 ml vial with approximately 500,000 cells stored in liquid nitrogen. Cells were propagated in 10 cm cell culture dishes by splitting every third day in a ratio of 1:3 until nine plates were available. Once confluent, fibroblasts were harvested. For 54 micro titer plates (96 well-MTP) a total of 14.3 million cells (passage eight) were re-suspended in 480 ml medium, corresponding to 100 µl medium with 3,000 cells/well. The remaining cells were distributed in 10 cm cell culture plates (500,000 cells/plate) for

propagation. The plates were incubated overnight at 37°C in an atmosphere with 95% humidity and 5% CO₂ to allow attachment of the cells to the culture plate.

[0236] MTP medium (243 µl) is added to a well of the microtiter plate. The test compounds were unfrozen, and 7.5 µl of a 5 mM stock solution was dissolved in the well containing 243 µl medium, resulting in a 150 µM master solution. Serial dilutions from the master solution were made. The period between the single dilution steps was kept as short as possible (generally less than 1 second).

[0237] Plates were kept overnight in the cell culture incubator. The next day, 10 µl of a 10 mM BSO solution were added to the wells, resulting in a 1 mM final BSO concentration. Forty-eight hours later, three plates were examined under a phase-contrast microscope to verify that the cells in the 0% control (wells E1-H1) were clearly dead. The medium from all plates was discarded, and the remaining liquid was removed by gently tapping the plate inversed onto a paper towel.

[0238] 100 µl of PBS containing 1.2 µM Calcein AM were then added to each well. The plates were incubated for 50-70 minutes at room temperature. After that time the PBS was discarded, the plate gently tapped on a paper towel and fluorescence (excitation/emission wavelengths of 485 nm and 525 nm, respectively) was read on a Gemini fluorescence reader. Data was imported into Microsoft Excel (EXCEL is a registered trademark of Microsoft Corporation for a spreadsheet program) and used to calculate the EC₅₀ concentration for each compound and each combination of compounds.

[0239] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof were tested three times, i.e., the experiment was performed three times, the passage number of the cells increasing by one with every repetition.

[0240] The solvents (DMSO, ethanol, PBS) neither have a detrimental effect on the viability of non-BSO treated cells nor did they have a beneficial influence on BSO-treated fibroblasts even at the highest concentration tested (1%). None of the compounds showed auto-fluorescence. The viability of non-BSO treated fibroblasts was set as 100%, and the viability of the BSO- and compound-treated cells was calculated as relative to the value of the control.

[0241] Table 1 shows the increase of viability effected by the addition of vitamin K2 at a concentration where it did not exhibit viability (40nM) to compounds at a concentration where they did show any viability.

Table 1

Compound (Cpd.)	0 % Viability Cpd. Conc.	% Viability Cpd. +40nM Vit.K2
Vitamin K2	40nM	0
idebenone	10nM	33.9
2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione	100nM	61.3
alpha-tocotrienol quinone	10nM	33.9
Coenzyme Q2	100nM	20.5
Coenzyme Q4	100nM	56.8

[0242] Table 2 shows the changes to the EC₅₀'s of certain quinones when combined with Vitamin K2. They exhibit a synergistic effect.

Table 2

Compound (Cpd)	EC ₅₀ Cpd	EC ₅₀ Cpd +40nM Vit. K2
idebenone	-	111nM
2,3,5-trimethyl-6-nonylcyclohexa-2,5-diene-1,4-dione	100nM	61nM
alpha-tocotrienol quinone	26nM	9nM
Coenzyme Q2	-	144nM
Coenzyme Q4	396nM	59nM

[0243] Table 3 shows the synergism effected to the EC₅₀'s of Vitamin K1 and Vitamin K2 when combined with 10 nM alpha-tocotrienol quinone or with 10 nM 2,3,5-trimethyl-6-(12- hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone in the assay with fibroblasts of FRDA patients.

Table 3

		+ 10 nM alpha-tocotrienol quinone	+ 10 nM 2,3,5-trimethyl-6-(12- hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone
	EC ₅₀	EC ₅₀	EC ₅₀
Vitamin K1	750	399	600
Vitamin K2	34	11	25

*Example B*Screening Compounds of the Invention in Fibroblasts from Huntington's Patients

[0244] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof were tested using a screen similar to the one described in Example A, but substituting FRDA cells with Huntington's cells obtained from the Coriell Cell Repositories (Camden, NJ; repository number GM 04281). The individual compounds and combinations thereof were tested for their ability to rescue human dermal fibroblasts from Huntington's patients from oxidative stress.

[0245] Table 4 shows the synergism effected to the EC₅₀'s of Vitamin K1 and Vitamin K2 when combined with a non active concentration of 10 nM alpha-tocotrienol quinone in the assay with fibroblasts of Huntington's patients.

Table 4

		+ 10 nM alpha-tocotrienol quinone
	EC ₅₀	EC ₅₀
Vitamin K1	297	125.8
Vitamin K2	40	17

Example C

Screening Compounds of the Invention in Fibroblasts from Leber's Hereditary Optic Neuropathy Patients (LHON)

[0246] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested using a screen similar to the one described in Example A, but substituting FRDA cells with Leber's Hereditary Optic Neuropathy (LHON) cells obtained from the Coriell Cell Repositories (Camden, NJ; repository number GM03858). The individual compounds and combinations thereof are tested for their ability to rescue human dermal fibroblasts from LHON patients from oxidative stress.

Example D

Screening Compounds of the Invention in Fibroblasts from Parkinson's Disease Patients

[0247] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested using a screen similar to the one described in Example A described in Example A, but substituting FRDA cells with Parkinson's Disease (PD) cells obtained from the Coriell Cell Repositories (Camden, NJ; repository number AG20439). The individual compounds and combinations thereof are tested for their ability to rescue human dermal fibroblasts from Parkinson's disease patients from oxidative stress.

Example E

Screening Compounds of the Invention in Fibroblasts from CoQ₁₀ deficient Patients

[0248] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested using a screen similar to the one described in Example A, but substituting FRDA cells with cells obtained from CoQ₁₀ deficient patients harboring a CoQ2 mutation. The individual compounds and combinations thereof are tested for their ability to rescue human dermal fibroblasts from CoQ₁₀ deficient patients from oxidative stress.

Example F

Screening Compounds of the Invention in Human Dermal Fibroblasts from Autistic Patients

[0249] A screen is performed to identify compounds effective for the amelioration of ASD. Test samples, and solvent controls are tested for their ability to rescue ASD fibroblasts stressed by addition of L-buthionine-(S,R)-sulfoximine (BSO).

[0250] MEM (a medium enriched in amino acids and vitamins, catalog no. Gibco 11965) and Fetal Calf Serum are obtained from Invitrogen. Basic fibroblast growth factor and epidermal growth factor are purchased from PeproTech. Penicillin-streptomycin-glutamine mix, L-buthionine (S,R)-sulfoximine, and insulin from bovine pancreas are purchased from Sigma. Calcein AM is purchased from Molecular Probes. Cell culture medium (ATP) is made by combining 75 ml Fetal Calf Serum, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM glutamine, 10 ng/ml EGF, and 10 ng/ml bFGF; MEM EBS is added to make the volume up to 500 ml. A 10 mM BSO solution is prepared by dissolving 444 mg BSO in 200 ml of medium with

subsequent filter-sterilization. During the course of the experiments, this solution is stored at +4°C. The cells obtained from Dr. J.M. Shoffner, Medical Neurogenetics, Atlanta, Ga. are grown in 10 cm tissue culture plates. Every week, they are split at a 1:3 ratio.

[0251] The samples are supplied in 1.5 ml glass vials. Alpha-Tocotrienol quinone, EPO and different combinations of both alpha tocotrienol and EPO are diluted with DMSO, ethanol or PBS to result in a 5 mM stock solution. Once dissolved, they are stored at -20°C.

[0252] The samples are screened according to the following protocol:

[0253] A culture with ASD fibroblasts is started from a 1 ml vial with approximately 500,000 cells stored in liquid nitrogen. Cells are propagated in 10 cm cell culture dishes by splitting every week in a ratio of 1:3 until nine plates are available. Once confluent, fibroblasts are harvested. For 54 micro titer plates (96 well-MTP) a total of 14.3 million cells (passage eight) are re-suspended in 480 ml medium, corresponding to 100 µl medium with 3,000 cells/well. The remaining cells are distributed in 10 cm cell culture plates (500,000 cells/plate) for propagation. The plates are incubated overnight at 37°C in an atmosphere with 95% humidity and 5% CO₂ to allow attachment of the cells to the culture plate.

[0254] MTP medium (243 µl) is added to a well of the microtiter plate. The test compounds are unfrozen, and 7.5 µl of a 5 mM stock solution is dissolved in the well containing 243 µl medium, resulting in a 150 µM master solution. Serial dilutions from the master solution are made. The period between the single dilution steps is kept as short as possible (generally less than 1 second).

[0255] Plates are kept overnight in the cell culture incubator. The next day, 10 µl of a 10 mM BSO solution are added to the wells, resulting in a 1 mM final BSO concentration. Forty-eight hours later, three plates are examined under a phase-contrast microscope to verify that the cells in the 0% control (wells E1-H1) are clearly dead. The medium from all plates is discarded, and the remaining liquid is removed by gently tapping the plate inverted onto a paper towel.

[0256] 100 µl of PBS containing 1.2 µM Calcein AM are then added to each well. The plates are incubated for 50-70 minutes at room temperature. After that time the PBS is discarded, the plate gently tapped on a paper towel and fluorescence (excitation/emission wavelengths of 485 nm and 525 nm, respectively) is read on a

Gemini fluorescence reader. Data is imported into Microsoft Excel® and used to calculate the EC₅₀ concentration for each compound. The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested for their ability to rescue human dermal fibroblasts from autistic patients from oxidative stress.

Example G

Screening Compounds of the Invention in Surf1-1 (SURF1) Cell Line Fibroblasts from Patients

[0257] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested for their ability to rescue cells from SURF-1 fibroblasts of a patient diagnosed with SURF-1, when the cells are stressed by addition of L-buthionine-(S,R)-sulfoximine (BSO), as described in Jauslin, ML *et al.*, Hum. Mol. Genet. 2002, 11(24):3055, Jauslin, ML *et al.*, FASEB J. 200317:1972-4, and International Patent Application WO 2004/003565. EC₅₀ concentrations of test compounds are determined and compared.

[0258] MEM (a medium enriched in amino acids and vitamins, catalog no. 1-31F24-I) and Medium 199 (M199, catalog no. 1-21F22-I) with Earle's Balanced Salts, without phenol red, were purchased from Bioconcept. Fetal Calf Serum was obtained from PAA Laboratories. Basic fibroblast growth factor and epidermal growth factor were purchased from PeproTech. Penicillin-streptomycin-glutamine mix, L-buthionine (S,R)-sulfoximine, and insulin from bovine pancreas were purchased from Sigma. Calcein AM was purchased from Molecular Probes. Cell culture medium was made by combining 125 mL M199 EBS, 50 ml Fetal Calf Serum, 100 U/mL penicillin, 100 µg/ml streptomycin, 2 mM glutamine, 10 µg/mL insulin, 10 ng/mL EGF, and 10 ng/mL bFGF. MEM EBS was added to make the volume up to 500 mL. A 10 mM BSO solution was prepared by dissolving 444 mg BSO in 200 mL of medium with subsequent filter-sterilization. During the course of the experiments, this solution was stored at +4°C. The cells were obtained from the SURF-1 patient and grown in 10 cm tissue culture plates. Every third day, they were split at a 1:3 ratio.

[0259] The test samples are supplied in 1.5 mL glass vials. The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are diluted with DMSO, ethanol or PBS to result in a 5 mM stock solution. Once dissolved, they were stored at -20 °C.

[0260] Test samples are screened according to the following protocol: A culture with FRDA fibroblasts is started from a 1 mL vial with approximately 500,000 cells stored in liquid nitrogen. Cells are propagated in 10 cm cell culture dishes by splitting every third day in a ratio of 1:3 until nine plates were available. Once confluent, fibroblasts are harvested. For 54 micro titer plates (96 well-MTP) a total of 14.3 million cells (passage eight) are re-suspended in 480 mL medium, corresponding to 100 μ L medium with 3,000 cells/well. The remaining cells are distributed in 10 cm cell culture plates (500,000 cells/plate) for propagation. The plates are incubated overnight at 37°C in an atmosphere with 95% humidity and 5% CO₂ to allow attachment of the cells to the culture plate.

[0261] MTP medium (243 μ L) is added to a well of the microtiter plate. The test compounds are unfrozen, and 7.5 μ L of a 5 mM stock solution is dissolved in the well containing 243 μ L medium, resulting in a 150 μ M master solution. Serial dilutions from the master solution are made. The period between the single dilution steps is kept as short as possible (generally less than 1 second).

[0262] Plates are kept overnight in the cell culture incubator. The next day, 10 μ L of a 10 mM BSO solution are added to the wells, resulting in a 1 mM final BSO concentration. Forty-eight hours later, three plates are examined under a phase-contrast microscope to verify that the cells in the 0% control (wells E1-H1) were clearly dead. The medium from all plates is discarded, and the remaining liquid is removed by gently tapping the plate inversed onto a paper towel.

[0263] 100 μ L of PBS containing 1.2 μ M Calcein AM are then added to each well. The plates are incubated for 50-70 minutes at room temperature. After that time the PBS is discarded, the plate gently tapped on a paper towel and fluorescence (excitation/emission wavelengths of 485 nm and 525 nm, respectively) is read on a Gemini fluorescence reader. Data is imported into Microsoft Excel (EXCEL is a registered trademark of Microsoft Corporation for a spreadsheet program) and used to calculate the EC₅₀ concentration for each compound.

[0264] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested three times, i.e., the experiment is performed three times, the passage number of the cells increasing by one with every repetition.

[0265] The solvents (DMSO, ethanol, PBS) neither have a detrimental effect on the viability of non-BSO treated cells nor do they have a beneficial influence on BSO-

treated fibroblasts even at the highest concentration tested (1%). The compounds show no auto-fluorescence. The viability of non-BSO treated fibroblasts is set as 100%, and the viability of the BSO- and compound-treated cells is calculated as relative to this value.

[0266] The individual quinones and naphthoquinones compounds of the invention as well as combinations thereof are tested for their ability to rescue human dermal fibroblasts from Surfeit 1 (SURF1) deficient patients from oxidative stress.

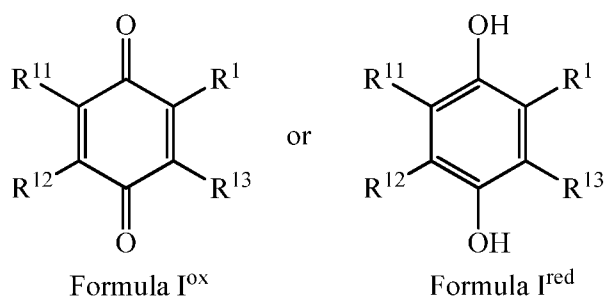
[0267] The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

[0268] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

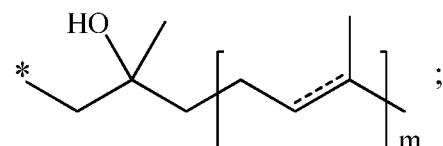
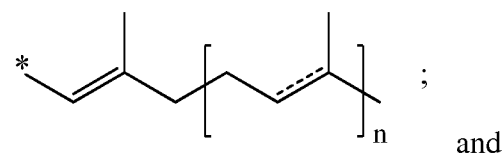
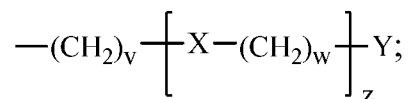
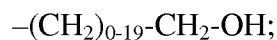
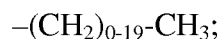
What is claimed is:

1. A method for treating a mitochondrial disorder in a subject in need of such treatment, comprising administering a therapeutically effective amount of one or more quinones of Formula I^{ox} or their reduced form of Formula I^{red} and one or more naphthoquinones of Formula II^{ox} or their reduced form of Formula II^{red} to an individual suffering from a mitochondrial disorder; wherein the amount of one or one or more quinones of Formula I^{ox} or their reduced form of Formula I^{red} and one or more naphthoquinones of Formula II^{ox} or their reduced form of Formula II^{red} are selected to produce a synergistic effect; and wherein Formulas I^{ox} and I^{red} are:



where,

R^1 is selected from the group consisting of



the * indicates the point of attachment to R¹;

the bond indicated by a dashed line can be double or single;

R¹¹, R¹² and R¹³ are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or

$-O(C_1-C_6)alkyl$;

X is $-CH=CH-$ or $-C\equiv C-$;

Y is hydrogen, $-OR^{14}$, $-CN$ or $-COOR^{15}$;

R¹⁴ and R¹⁵ are independently of each other selected from hydrogen,

$-(C_1-C_6)alkyl$, and $-(C_1-C_6)haloalkyl$;

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the same or different;

m is 1-12, with the proviso that when m is an integer from 2 to 12, each unit can be the same or different;

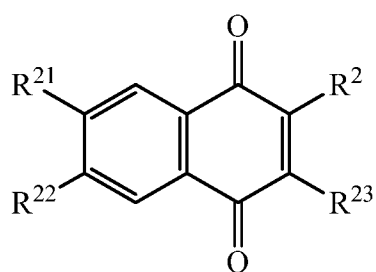
v is 1-10;

w is 1-5; and

z is 1-3, with the proviso that when z is an integer of 2 to 3, w is optionally variable from 1-5 in each occurrence of the group;

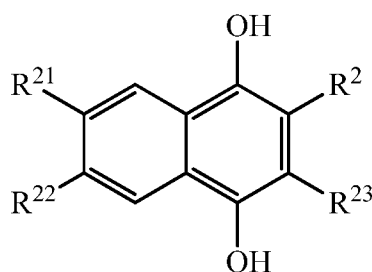
and

wherein Formulas II^{ox} and II^{red} are:



Formula II^{ox}

or



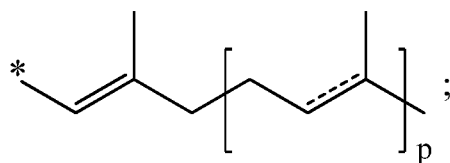
Formula II^{red}

where,

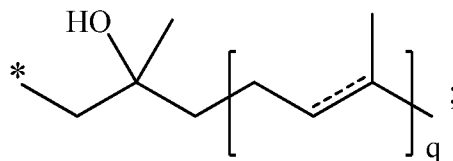
R² is selected from the group consisting of:

$-(CH_2)_{0-19}-CH_3$;

$-((CH_2)_2-CH(CH_3))_{1-20}-CH_3$;



and



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or

$-O(C_1-C_6)alkyl$;

R^{23} is hydrogen; $-(C_1-C_6)alkyl$; $-OH$; or $-O(C_1-C_6)alkyl$;

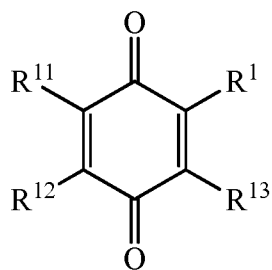
p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different; and

q is 1-12, with the proviso that when q is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, crystalline form, non-crystalline form, hydrate or solvate of formulas I^{ox} , I^{red} , II^{ox} or II^{red} .

2. The method according to claim 1, comprising administering a therapeutically effective amount of one or more quinones of Formula I and one or more naphthoquinones of Formula II to an individual suffering from a mitochondrial disorder wherein the amount of one or more quinones of Formula I and one or more naphthoquinones of Formula II are selected to produce a synergistic effect;

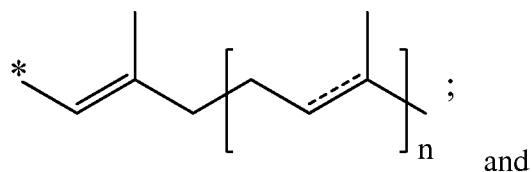
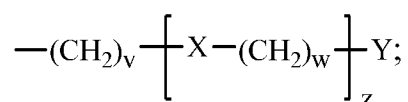
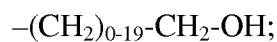
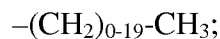
and wherein Formula I is:



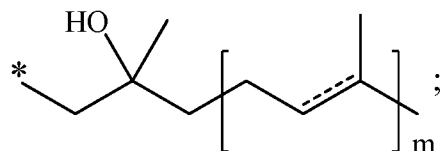
Formula I

where,

R^1 is selected from the group consisting of:



and



the * indicates the point of attachment to R^1 ;

the bond indicated by a dashed line can be double or single;

R^{11} , R^{12} and R^{13} are independently of each other hydrogen; $-(C_1-C_6)$ alkyl; or

$-O(C_1-C_6)$ alkyl;

X is $-CH=CH-$ or $-C\equiv C-$;

Y is hydrogen, $-OR^{14}$, $-CN$ or $-COOR^{15}$;

R^{14} and R^{15} are independently of each other selected from hydrogen,

$-(C_1-C_6)$ alkyl, and $-(C_1-C_6)$ haloalkyl;

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the same or different;

m is 1-12, with the proviso that when m is an integer from 2 to 12, each unit can be the same or different;

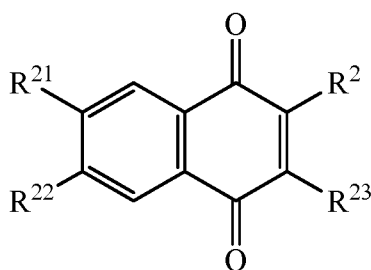
v is 1-10;

w is 1-5; and

z is 1-3, with the proviso that when z is an integer of 2 to 3, w is optionally variable from 1-5 in each occurrence of the group;

and

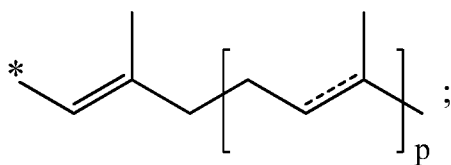
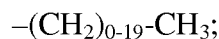
wherein Formula II is:



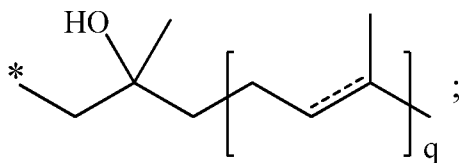
Formula II

where,

R^2 is selected from the group consisting of:



and



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(C_1-C_6)$ alkyl; or

$-O(C_1-C_6)$ alkyl;

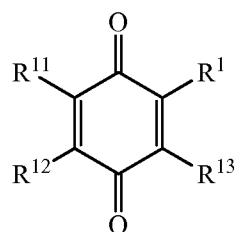
R^{23} is hydrogen; $-(C_1-C_6)alkyl$; $-OH$; or $-O(C_1-C_6)alkyl$;

p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different; and

q is 1-12, with the proviso that when q is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, crystalline form, non-crystalline form, hydrate or solvate of Formulas I or II.

3. The method according to claim 2, wherein the one or more quinones of Formula I are selected from quinones of Formula Ia:



Formula Ia

where,

R^1 is selected from the group consisting of :

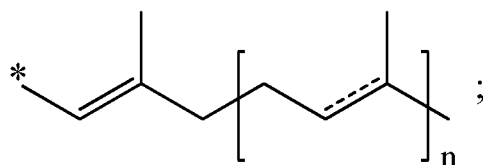
$-(CH_2)_{0-19}-CH_3$;

$-(CH_2)_{0-19}-CH_2-OH$;

$-((CH_2)_2-CH(CH_3))_{1-20}-CH_3$;

$-(CH_2)_v \left[X-(CH_2)_w \right]_z Y$;

and



the * indicates the point of attachment to R^1 ;

the bond indicated by a dashed line can be double or single;

R^{11} , R^{12} and R^{13} are independently of each other hydrogen; $-(C_1-C_6)alkyl$; or

$-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$;

X is $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

Y is hydrogen, $-\text{OR}^{14}$, $-\text{CN}$ or $-\text{COOR}^{15}$;

R^{14} and R^{15} are independently of each other selected from hydrogen,

$-\text{C}_1\text{-C}_6)\text{alkyl}$, and $-(\text{C}_1\text{-C}_6)\text{haloalkyl}$

n is 0-12, with the proviso that when n is an integer from 2 to 12, each unit can be the same or different;

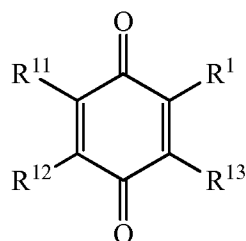
v is 1-10;

w is 1-5; and

z is 1-3, with the proviso that when z is an integer of 2 to 3, w is optionally variable from 1-5 in each occurrence of the group;

or any stereoisomer, mixture of stereoisomers, crystalline form, non-crystalline form, hydrate or solvate thereof.

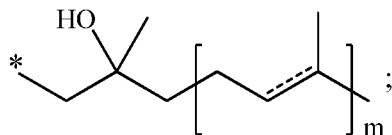
4. The method according to claim 2, wherein the one or more quinones of Formula I are selected from quinones of Formula Ib



Formula Ib

where,

R^1 is:



the * indicates the point of attachment to R^1 ;

the bond indicated by a dashed line can be double or single;

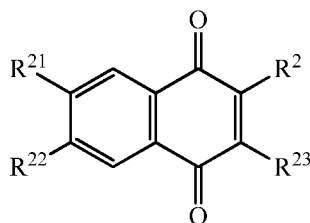
R^{11} , R^{12} and R^{13} are independently of each other hydrogen; $-(\text{C}_1\text{-C}_6)\text{alkyl}$; or

$-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$; and

m is 1-12, with the proviso that when m is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, crystalline form, non-crystalline form, hydrate or solvate thereof.

5. The method according to claim 2, wherein the one or more naphthoquinones of Formula II are selected from naphthoquinones of Formula IIa:



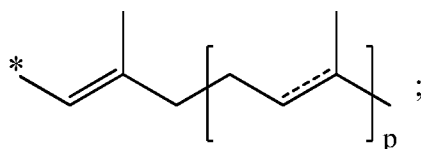
Formula IIa

where,

R^2 is independently selected from the group consisting of:

$-(\text{CH}_2)_{0-19}\text{-CH}_3$;

$-((\text{CH}_2)_2\text{-CH}(\text{CH}_3))_{1-20}\text{-CH}_3$; and



the * indicates the point of attachment to R^2 ;

the bond indicated by a dashed line can be double or single;

R^{21} and R^{22} are independently of each other hydrogen; $-(\text{C}_1\text{-C}_6)\text{alkyl}$; or

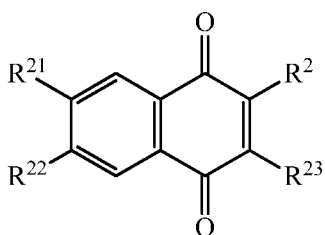
$-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$;

R^{23} is hydrogen; $-(\text{C}_1\text{-C}_6)\text{alkyl}$; $-\text{OH}$; or $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$; and

p is 0-12, with the proviso that when p is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, crystalline form, non-crystalline form, hydrate or solvate thereof.

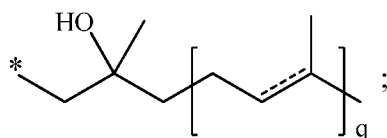
6. The method according to claim 2, wherein the one or more naphthoquinones of Formula II are selected from naphthoquinones of Formula IIb:



Formula IIb

where,

R^2 is independently selected from:



the $*$ indicates the point of attachment to $\mathbb{R}^2$;

the bond indicated by a dashed line can be double or single;

R²¹ and R²² are independently of each other hydrogen; -(C₁-C₆)alkyl; or

—O(C₁-C₆)alkyl;

R²³ is hydrogen; -(C₁-C₆)alkyl; -OH; or -O(C₁-C₆)alkyl; and

q is 1-12, with the proviso that when q is an integer from 2 to 12, each unit can be the same or different;

or any stereoisomer, mixture of stereoisomers, crystalline form, non-crystalline form, hydrate or solvate thereof.

7. The method according to claim 1, wherein said subject has a mitochondrial disorder selected from the group consisting of inherited mitochondrial diseases; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, and Stroke (MELAS); Leber's Hereditary Optic Neuropathy (LHON); Optic Dominant Atrophy (DOA); Leigh syndrome or Leigh-like syndrome; SURF1; Kearns-Sayre syndrome (KSS); Friedreich's Ataxia (FRDA); overlap syndromes; other myopathies; cardiomyopathy; encephalomyopathy; renal tubular

acidosis; neurodegenerative diseases; Parkinson's Disease; Alzheimer's Disease; Amyotrophic Lateral Sclerosis (ALS); motor neuron diseases; other neurological diseases; epilepsy; genetic diseases; Huntington's disease; mood disorders; schizophrenia; bipolar disorder; age-associated diseases; cerebral vascular accidents, macular degeneration; diabetes; and cancer.

8. The method according to claim 1, wherein said subject has a mitochondrial disorder selected from the group consisting of inherited mitochondrial diseases; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, and Stroke (MELAS); Leber's Hereditary Optic Neuropathy (LHON); Optic Dominant Atrophy (DOA); Leigh syndrome or Leigh-like syndrome; SURF1; Kearns-Sayre syndrome (KSS); and Friedreich's Ataxia (FRDA).
9. A composition comprising one or more quinones of Formula I^{ox} or Formula I^{red} and a pharmaceutically acceptable carrier, and one or more naphthoquinones of Formula II^{ox} or Formula II^{red} and a pharmaceutically acceptable carrier, wherein Formulas I^{ox}, I^{red}, II^{ox}, and II^{red} are as described in Claim 1.
10. The composition according to claim 9, comprising a tocopherol quinone or a tocotrienol quinone and a pharmaceutically acceptable carrier, and a Vitamin K and a pharmaceutically acceptable carrier.
11. The composition according to claim 9, comprising a tocopherol quinone or a tocotrienol quinone and a pharmaceutically acceptable carrier, and a Vitamin K1 and a pharmaceutically acceptable carrier.
12. The composition according to claims 9, comprising a tocopherol quinone or a tocotrienol quinone and a pharmaceutically acceptable carrier, and a Vitamin K2 and a pharmaceutically acceptable carrier.
13. The composition according to claim 10, 11, or 12, wherein said composition is a pharmaceutical composition for the treatment of mitochondrial diseases.

14. A composition comprising one or more quinones of Formula I^{ox} or Formula I^{red}; one or more naphthoquinones of Formula II^{ox} or Formula II^{red}; and a pharmaceutically acceptable carrier, wherein Formulas I^{ox}, I^{red}, II^{ox}, and II^{red}, are as described in Claim 1.
15. The composition according to claim 12, comprising a tocopherol quinone or a tocotrienol quinone; a Vitamin K and a pharmaceutically acceptable carrier.
16. The composition according to claim 12, comprising a tocopherol quinone or a tocotrienol quinone; a Vitamin K1 and a pharmaceutically acceptable carrier
17. The composition according to claim 12, comprising a tocopherol quinone or a tocotrienol quinone; a Vitamin K2 and a pharmaceutically acceptable carrier
18. The composition according to claim 15, 16, or 17, wherein said composition is a pharmaceutical composition for the treatment of mitochondrial diseases.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/041486

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/122 (2012.01)

USPC - 514/682

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/05, 31/122; A61P 25/02, 25/08 25/18, 25/28 (2012.01)

USPC - 514/678, 681, 682, 688, 689, 731, 732, 733

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Orbit, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0107472 A1 (WISCHIK et al) 19 May 2005 (19.05.2005) entire document	1-18
A	US 2002/0040011 A1 (BROWN) 04 April 2002 (04.04.2002) entire document	1-18
A	US 2005/0148521 A1 (BEN-SASSON et al) 07 July 2005 (07.07.2005) entire document	1-18
A	US 2010/0056625 A1 (MILLER et al) 04 March 2010 (04.03.2010) entire document	1-18

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2012

Date of mailing of the international search report

07 AUG 2012

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