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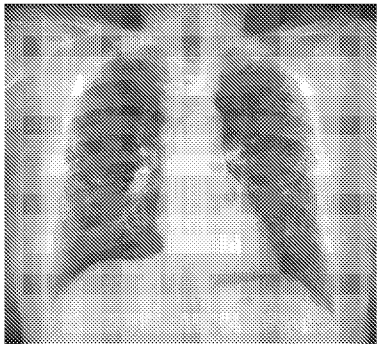
(54) Title: VIRAL TREATMENT REGIMENS

FIG. 9



(57) Abstract: Disclosed herein are methods and compositions for reducing inflammation, reversing ageing and accumulated cellular damage, and treating, preventing or reducing the ill effects of a viral infection in particular that of SARS-CoV-2, the compositions comprising a repair system activator including nicotinamide mononucleotide, nicotinamide adenine dinucleotide, nicotinamide riboside, 1-methylnicotinamide and/or cyclic adenosine monophosphate, a methyl donor including betaine, S-5'-adcnosyl-L-methioninc, methionine, choline, seine, folate and/or vitamin B12, and an antioxidant defence activator including zinc, H202, H2S, NaSH, Na2S, pterostilbene and/or resveratrol.

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VIRAL TREATMENT REGIMENS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/004,449, filed April 2, 2020 and U.S. Provisional Application No. 63/005,145, filed April 3, 2020. The contents of each of which is incorporated by reference in its entirety.

FIELD

The disclosed subject matter generally relates to compositions for defending against and repairing the effects of aging and for treating viral infections, *e.g.,* COVID-19.

BACKGROUND

Adverse effects of aging can be a result of accumulated unrepaired cellular damage. Accumulated damage to one's immune system may reduce or prevent a patient's ability to mount an effective immune response to pathogens, including viruses. New compositions and methods for repairing the effects of aging, including reversing accumulated cellular damage, and especially among cells of the immune system, are needed.

SUMMARY

The present disclosure provides methods and compositions for repairing the effects of aging, including reversing accumulated cellular damage, and especially among cells of the immune system. These methods and compositions are particularly useful in treating, preventing, and/or reducing the ill effects of a viral infection, *e.g.,* resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

An aspect of the present disclosure is a composition for administering to a subject. The composition comprises:

a repair system activator chosen from, nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, nicotinamide adenine dinucleotide (NAD+), nicotinamide riboside (NR), nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), nicotinic acid riboside (NAR), 1-methylnicotinamide (MNM), cyclic adenosine monophosphate (cAMP), and any combination thereof;

a methyl donor chosen from, betaine, S-5'-adenosyl-L-methionine (SAM), methionine, choline, serine, folate, vitamin B12, and any combination thereof; and

an antioxidant defense activator chosen from zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, NaSH, Na_2S, ROS, RNS, RCS, RSOH, $O_2^{\bullet-}$, $OH^{\bullet}$, $^1O_2$, O_3,

HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, metformin, acetaminophen, diallyl trisulfide, isothiocyanate, curcumin, sulforaphane, quercetin, isoquercetin, apigenin, luteolin, ginseng, carnosic acid, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, xanthohumol, β-lapachone, pterostilbene, resveratrol, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256, and any combination thereof.

In embodiments, the repair system activator, the methyl donor, and the antioxidant defense activator are present in a combined amount of at least 5 wt.% of the composition.

In embodiments, the repair system activator is nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, nicotinamide riboside (NR), or both.

In embodiments, the methyl donor is betaine, methionine, or both.

In embodiments, the antioxidant defense activator is Zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, or NaSH.

In embodiments, the repair system activator, methyl donor, and antioxidant defense activator are in an amount sufficient to beneficially change a surrogate marker for aging level in a human when compared to the surrogate marker level prior to administration. In embodiments, the change in the level of the surrogate marker is lowered. the surrogate marker is CMV IgG, C-Reactive Protein, Tumor Necrosis Factor-Alpha, or Interleukin-6. In embodiments, the change in the level of the surrogate marker is increased. In embodiments, the surrogate marker is DNA methylation.

In embodiments, the composition further comprises water.

In embodiments, the composition comprises at least 1 x 10^{-8} moles of the repair system activator, at least 1 x 10^{-8} moles of the methyl donor, and at least 1 x 10^{-9} moles of the antioxidant defense activator.

In embodiments, the composition comprises nicotinamide mononucleotide (NMN) or the precursor or prodrug of NMN, Betaine, and zinc (*e.g.,* as zinc sulfate).

In embodiments, the composition comprises NMN, Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

In embodiments, a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate.

In embodiments, the composition further comprises from about 25 mg to about 100 mg of NaCl. In embodiments, the composition further comprises about 50 mg of NaCl.

Any herein-disclosed composition may be used in a method for reversing aging and/or for reversing accumulated cellular damage in a subject in need thereof.

Any herein-disclosed composition may comprise or administered contemporaneously with Na+ (*e.g.,* as NaCl) to increase the absorption of NMN or Betaine.

The herein described “unit dose”, “formulation”, and/or “composition” may be referred to as an “NMN Cocktail”.

Any herein-disclosed composition may be used in a method for treating, preventing, and/or reducing the ill effects of a viral infection in a subject in need thereof. In embodiments, the viral infection is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an enterovirus A-J; a rhinovirus A-C; a rotavirus A-C; a norovirus; an influenza virus A-C and their types such as H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9; a human papillomavirus; a polyomavirus: John Cunningham virus and Merkel cell virus; a poxvirus; a herpesvirus such as human simplex virus 1, human simplex virus 2, varicella zoster virus, Epstein-Barr virus or human herpesvirus 4; a human cytomegalovirus, Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus; a hepatitis A-E virus; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; an Ebola virus; a Marburg virus; a Lassa Fever virus; a Banna virus; a rubella

virus; a measles virus; a mumps virus; a human parainfluenza virus; a rabies virus; a Hantavirus; a Dengue virus; a West Nile virus; a Zika virus; or an orbivirus.

Other aspects of the present disclosure include an injectable formulation, a tablet, a powder, and a beverage, each comprising any herein-disclosed composition.

Another aspect of the present disclosure is a method for reducing inflammation in a subject in need thereof, for reversing aging and/or for reversing accumulated cellular damage in a subject in need thereof, and/or for treating, preventing, and/or reducing the ill effects of a viral infection in a subject in need thereof. The method comprising: administering to the subject any herein-disclosed composition.

In embodiments, the composition is administered to a subject at a dosage of at least 1×10^{-6} moles /kg of the repair system activator to the subject, 1×10^{-6} moles /kg of the methyl donor to the subject, and 1×10^{-7} moles /kg of the antioxidant defense activator to the subject.

In embodiments, the composition is injected over 8-12 days.

In embodiments, the composition is in an aerosol, lyophilized, powder, or emulsion form.

In embodiments, the subject in need thereof is a human. In embodiments, the composition is administered to the human for at least two months.

In embodiments, the composition is in a tablet that is administered orally at least once daily. In embodiments, the composition further comprises water. In embodiments, the composition is administered to the subject once daily.

In embodiments, the composition comprises nicotinamide mononucleotide (NMN) or the precursor or prodrug of NMN, Betaine, and Zinc (*e.g.,* as zinc sulfate).

In embodiments, the composition comprises Na+ (*e.g.,* as NaCl) or is administered contemporaneously with Na+ (*e.g.,* as NaCl) to increase the absorption of NMN or Betaine.

In embodiments, the viral infection is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an enterovirus A-J; a rhinovirus A-C; a rotavirus A-C; a norovirus; an influenza virus A-C and their types such as H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9; a human papillomavirus; a polyomavirus: John Cunningham virus and Merkel cell virus; a poxvirus; a herpesvirus such as human simplex virus 1, human simplex virus 2, varicella zoster virus, Epstein-Barr virus or human herpesvirus 4; a human cytomegalovirus, Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus; a hepatitis A-E virus; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS

coronavirus; an Ebola virus; a Marburg virus; a Lassa Fever virus; a Banna virus; a rubella virus; a measles virus; a mumps virus; a human parainfluenza virus; a rabies virus; a Hantavirus; a Dengue virus; a West Nile virus; a Zika virus; or an orbivirus.

In embodiments, the composition comprises NMN, Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

In embodiments, a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate.

In embodiments, the unit dose further comprises from about 25 mg to about 100 mg of NaCl. In embodiments, the unit dose further comprises about 50 mg of NaCl.

In embodiments, at least one unit of the composition is administered to the subject at each dosing. In embodiments, at least two units of the composition, at least three units of the composition, at least four units of the composition, or at least five units of the composition is administered to the subject at each dosing. In embodiments, the number of units of the composition per dosing relates in part to the weight of the subject. In embodiments, when a subject weighs 100 lbs or less, the subject is administered at least one unit of the composition per dosing and/or when a subject weighs over 100 lbs, the subject is administered at least one unit, at least two units, at least three units, or at least four units or at least five units of the composition per dosing. In embodiments, the subject receives at least one dosing per day, at least two dosings per day, at least three dosings per day, or at least four dosings per day.

The herein described “unit dose”, “formulation”, and/or “composition” may be referred to as an “NMN Cocktail”.

Yet another aspect of the present disclosure is a method for reducing inflammation in a subject in need thereof, for reversing aging and/or for reversing accumulated cellular damage in a subject in need thereof, and/or for treating, preventing, and/or reducing the ill effects of a viral infection in a subject in need thereof. The method comprising administering to the subject:

a repair system activator chosen from nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, nicotinamide adenine dinucleotide (NAD+),

nicotinamide riboside (NR), nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), nicotinic acid riboside (NAR), 1-methylnicotinamide (MNM), cyclic adenosine monophosphate (cAMP), and any combination thereof;

a methyl donor chosen from, betaine, S-5'-adenosyl-L-methionine (SAM), methionine, choline, serine, folate, vitamin B12, and any combination thereof; and

an antioxidant defense activator chosen from zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, NaSH, Na_2S, ROS, RNS, RCS, RSOH, $O_2^{\bullet-}$, OH•, $^1O_2$, O_3, HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, metformin, acetaminophen, diallyl trisulfide, isothiocyanate, curcumin, sulforaphane, quercetin, isoquercetin, apigenin, luteolin, ginseng, carnosic acid, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, xanthohumol, β-lapachone, pterostilbene, resveratrol, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256, and any combination thereof.

In embodiments, the repair system activator, the methyl donor, and the antioxidant defense activator are administered at approximately the same time.

In embodiments, the repair system activator is administered within 15, 30, 60, 90, or 120 minutes of the subject's biological clock NAD+ peak.

In embodiments, the repair system activator, the methyl donor, and the antioxidant defense activator are administered at different times.

In embodiments, the subject is a human. In embodiments, the repair system activator, the methyl donor, and the antioxidant defense activator are administered to the human for at least two months.

In embodiments, the repair system activator, the methyl donor, and the antioxidant defense activator are administered to the human once daily.

In embodiments, Na+ (*e.g.*, as NaCl) is administered to increase the absorption of NMN or Betaine.

In embodiments, the viral infection is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an enterovirus A-J; a rhinovirus A-C; a rotavirus A-C; a norovirus; an influenza virus A-C and their types such as H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9; a human papillomavirus; a polyomavirus: John Cunningham virus and Merkel cell virus; a poxvirus; a herpesvirus such as human simplex virus 1, human simplex virus 2, varicella zoster virus, Epstein-Barr virus or human herpesvirus 4; a human cytomegalovirus, Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus; a hepatitis A-E virus; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; an Ebola virus; a Marburg virus; a Lassa Fever virus; a Banna virus; a rubella virus; a measles virus; a mumps virus; a human parainfluenza virus; a rabies virus; a Hantavirus; a Dengue virus; a West Nile virus; a Zika virus; or an orbivirus.

In embodiments, the repair system activator, the methyl donor, and/or the antioxidant defense activator are each independently in the form of an injectable formulation, a tablet, a powder, and/or a beverage.

In embodiments, the repair system activator, the methyl donor, and the antioxidant defense activator are respectively NMN, Betaine, and Zinc Sulfate and in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

In embodiments, a unit dose of the repair system activator, the methyl donor, and the antioxidant defense activator comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate. In embodiments, the unit dose comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate. In embodiments, the unit dose comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate.

In embodiments, the unit dose further comprises from about 25 mg to about 100 mg of NaCl. In embodiments, the unit dose further comprises about 50 mg of NaCl.

The herein described "unit dose", "formulation", and/or "composition" may be referred to as an "NMN Cocktail".

In embodiments, at least one unit of the repair system activator, the methyl donor, and the antioxidant defense activator is administered to the subject at each dosing. In embodiments, at least two units, at least three units, at least four units, or at least five units is administered to the subject at each dosing. In embodiments, the number of units per dosing relates in part to the weight of the subject. In embodiments, when a subject weighs 100 lbs or less, the subject is administered at least one unit per dosing and/or when a subject weighs over 100 lbs, the subject is administered at least one unit, at least two units, at least three units, or at least four units or at least five units per dosing. In embodiments, the subject receives at least one dosing per day, at least two dosings per day, at least three dosings per day, or at least four dosings per day.

In embodiments, the subject is at least 50 years old.

In embodiments, the subject has previously been treated with one or more of hydroxychloroquine, Zithromax, and zinc.

In embodiments, the subject is administered the composition in accordance with the subject's circadian rhythm.

In embodiments, the subject is administered the composition to a substantially empty stomach.

In yet another aspect, the present disclosure provides a composition comprising:

a precursor or prodrug of nicotinamide mononucleotide (NMN)

a methyl donor chosen from, betaine, S-5'-adenosyl-L-methionine (SAM), methionine, choline, serine, folate, vitamin B12, and any combination thereof; and

an antioxidant defense activator chosen from zinc (*e.g.*, as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, NaSH, Na_2S, ROS, RNS, RCS, RSOH, $O_2^{\bullet -}$, $OH^{\bullet}$, $^1O_2$, O_3, HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, metformin, acetaminophen, diallyl trisulfide, isothiocyanate, curcumin, sulforaphane, quercetin, isoquercetin, apigenin, luteolin, ginseng, carnosic acid, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, xanthohumol, β-lapachone, pterostilbene, resveratrol, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-

1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256, and any combination thereof.

In embodiments, the composition comprises NMN, Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

In embodiments, a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate. In embodiments, the unit dose further comprises from about 25 mg to about 100 mg of NaCl. In embodiments, the unit dose further comprises about 50 mg of NaCl.

The herein described “unit dose”, “formulation”, and/or “composition” may be referred to as an “NMN Cocktail”.

Another aspect is a disposable waterproof and/or air proof container comprising any herein-disclosed composition. In embodiments, the disposable waterproof and/or air proof container comprises instructions for use.

Yet another aspect is a kit comprising at least ten of the disposable waterproof and/or air proof containers.

Any aspect or embodiment described herein can be combined with any other aspect or embodiment as disclosed herein.

Additional advantages will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the aspects described below. The advantages described below will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic showing effects of lowered NAD+, SAM and Nrf2, which occurs as cells age. Proposed mechanisms for reversing aging and treating viral infections are shown. In the schematic, the three components NMN, Betaine, and H_2O_2 are used as illustrative of the methods and compositions for reversing aging. Other components used in the methods and compositions of the present disclosure would likewise reverse aging.

FIG. 2 is a table showing patient characteristics for patients described in Example 1.

FIG. 3 is a table showing pre-treatment clinical conditions for patients described in Example 1.

FIG. 4 is a table showing patient outcomes for patients described in Example 1.

FIG. 5 to **FIG. 9** are chest x-rays for Patient 1 described in Example 1.

FIG. 10 is a table showing vital signs of Patient 1 described in Example 1.

FIG. 11 is a table showing vital signs of Patient 2 described in Example 1.

FIG. 12 is a table showing vital signs of Patient 3 described in Example 1.

FIG. 13 to **FIG. 16** are chest x-rays for Patient 4 described in Example 1.

FIG. 17 is a table showing vital signs of Patient 4 described in Example 1.

FIG. 18 and **FIG. 19** are chest x-rays for Patient 5 described in Example 1.

FIG. 20 is a table showing vital signs of Patient 5 described in Example 1.

FIG. 21 is a chest x-ray for Patient 6 described in Example 1.

FIG. 22 is a table showing vital signs of Patient 6 described in Example 1.

FIG. 23 is a chest x-ray for Patient 6 described in Example 1.

FIG. 24 is a chest x-rays for Patient 7 described in Example 1.

FIG. 25 is a table showing vital signs of Patient 7 described in Example 1.

FIG. 26 to **FIG. 28** are chest x-rays for Patient 7 described in Example 1.

FIG. 29 is a chest x-rays for Patient 8 described in Example 1.

FIG. 30 is a table showing vital signs of Patient 8 described in Example 1.

FIG. 31 is a chest x-rays for Patient 8 described in Example 1.

FIG. 32 to **FIG. 35** are chest x-rays for Patient 10 described in Example 1.

FIG. 36 is a table showing vital signs of Patient 10 described in Example 1.

DETAILED DESCRIPTION

The materials, compounds, compositions, and methods described herein may be understood more readily by reference to the following detailed description of specific aspects of the disclosed subject matter and the Examples included therein. More specifically, the present disclosure teaches methods and compositions are particularly useful in reversing cellular consequences of aging and in treating, preventing, and/or reducing the ill effects of a viral infection, *e.g.*, resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Background information relating to cellular consequences of aging and methods for repairing the effects of aging, including reversing accumulated cellular damage are described in WO2017/062311, the contents of which is incorporated by reference in its entirety and including each reference cited in WO2017/062311.

The study of caloric restriction led to the discovery of Sirtuins, which are activated by the "depleted energy" version of NADH, which is called NAD+. NADH is not used by sirtuins enzymes and is only inhibitory at concentrations far greater that those predicted for cells. NADH is also not used for generation of NADP+ by the cytosolic NADK enzyme and this generated NADP+ is rapidly turned into NADPH. Caloric restriction induces a "nutritional stress" that results in a depletion of the cells energy stores (ATP, NADH, etc.). The "depleted energy forms" of this stored energy are cAMP and NAD+.

NAD+ activates a set of enzymes called Sirtuins as well as PARPs. What the data disclosed herein shows is that by providing NAD+ or compounds or compositions having a similar activity, immune system markers are reduced, which has been shown to be associated with anti-aging. These data are consistent with an increased activation of Sirtuins, through interaction with NAD+, or similar acting molecules. However, also disclosed herein, the positive effect of NAD+ can level off, presumably because of other reactions taking place in the organism, including in the active site of the Sirtuins themselves.

Therefore, what has been additionally shown by the disclosed methods and compositions is that by adding additional molecules along with NAD+ or similar acting molecules, the beneficial effects can be extended by, for example, a continued, enhanced, and maintained reduction in inflammation markers, which has been linked to anti-aging. This information has led to compositions and formulations, which contain three categories

of compositions, or methods where three different categories of molecules are administered, alone, in conjunction, or in combination to a subject.

Increasing lifespan and health-span by repairing cellular damage and preventing the age-related changes that can occur are disclosed. The data provided herein show that to reduce markers for inflammation three broad goals to defend against and repair deterioration from aging should be sought:

I. NAD+ should be available to turn on and be used by Sirtuins,

II. methyl donors should be available to methylate DNA and other entities needing methylation like the reaction of nicotinamide to 1-methylnicotinamide by the nicotinamide-N-methyltransferase (NNMT) enzyme, and

III. a reducing balance should be provided so that important enzymes, such as Sirtuins, can have the thiol (sulfur) groups in their reactive sites maintained in a reduced state.

Disclosed herein are compositions, formulations, and methods that reduce markers of inflammation related to aging and are consistent with enhancing these three goals.

Meeting these three goals is possible if oxidation, in the form pulsed low level H_2O_2, is available to turn on pre-conditioning of the antioxidant defense and repair system. By turning this system on, the system is protected against the down regulation of the antioxidant defense and repair system, which is an energy saving mechanism. In this way, when the antioxidant defense system is challenged with an oxidative assault from a larger oxidative burst, it is able to defend against this oxidation that would lead to cell damage and destruction.

In one embodiment, one provides enough oxidation from H_2O_2 to provide pre-conditioning from signaling to turn on the anti-oxidant defense and repair system but not enough to create oxidized damage like oxidizing the thiol groups in the Sirtuin active site that turns the Sirtuin enzymes activities off. The APE-1/ Ref-1 is a molecule that protects the thiol groups of amino acids in the Sirtuin active site from oxidation by H_2O_2. This can be kept active. It is theorized, that the same or a similar process is needed for the nicotinamide-N-methyltransferase (NNMT) enzyme to make 1-methylnicotinamide from nicotinamide and thus to stop this feedback loop from shutting off the Sirtuin enzyme by cutting off the supply of nicotinamide that can fit into the Sirtuin enzyme and stop its activity. Nrf2, thus reduction, can be turned on by other activators like Zinc (*e.g.*, as zinc sulfate), which also has additional anti-viral characteristics which makes it an appropriate Nrf2 activator in viral defense.

Disclosed is a usable solution for reversal of human aging by resetting the human endogenous defense and repair pathways and mechanisms. These mechanisms are normally set to preserve energy due to molecular settings set by and for evolutionary energy insufficiency, evolutionary sexual selection, and pathogen defense by diverting more usable energy and resources from defense and repair mechanisms. Through administration of the disclosed compounds, compositions, and formulations these pathways can be reset for increased repair and defense.

It is demonstrated herein that dietary NMN drunk by itself in water does turn into NAD+ and turns on Sirtuins in humans, but these effects are ephemeral. It is also demonstrated herein that Hormesis / feedback loops effected benefits in humans until these benefits are plateaued or reversed and even overshoot the initial beneficial effects within a three-month time frame. This discovery solves this deterioration of beneficial effect problem by turning on the beneficial effects of Sirtuin enzymes, optimizing their beneficial effects, and keeping these beneficial effects turned on.

Disclosed herein are compounds, compositions, formulations, and methods, which turn on, enhance, and in some formulations keep on, the human defense and repair mechanisms involving the Sirtuin enzymes. These compounds, compositions and formulations comprise one or more items from each of three (3) categories alone or in combination, and can be administered through ingestion, injection, inhalation, application to the skin, or any other means.

When administered, the disclosed compounds, compositions, and formulations, can perform at least one of the following activities: Protect against further cellular damage from the aging process; Repair cellular damage from the aging process; Delay the onset of the diseases of aging where aging is a causal factor; Promote weight loss / reduce hunger; and Promote more productive sleep, waking more rested.

Diseases of aging include inflammation, heart disease (including heart attack and heart failure), stroke, neurodegenerative disease such as Alzheimer's disease, diabetes, cancer, respiratory disease, systemic autoimmune disease (including arthritis) and muscle wasting.

Anti-Viral methods and compositions

The herein-disclosed methods and compositions are particularly useful in treating, preventing, and/or reducing the ill effects of a viral infection, *e.g.*, resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Death from viral attacks correlates to the speed of activation of CD-8 T-Cells. The late rise of Il-6 in a "cytokine storm" may be due to this late start, since with early start IL-6 does not seem to have the late rise. CD-8 T-cells with high CD38 expression have decreased cytotoxic capacity and higher rates of infections and increased propensity for infections. The late rise of Il-6 may be due to the low ability of the T-Cells to kill viruses. Patients with higher viral (CMV, EB, HIV) loads have more CD38+HLA-DR+ CD8 T-Cells. Likely endogenous LINE-1 as well.

Activation of CD-8 T-Cells needs CD38 and CD-38 not only is correlated to the Adaptive Immune system CD-8 T-Cells but also the Innate Immune system Toll-like Receptors.

Other correlations of CD-38 include:

NF-kB: oxidation; CD-38 active; inflammation is increased; decreased methylation (like H3K9me3 & H3K27me3); increased LINE-1; and increased Il-6 gene transcription.

Nrf2: reduction; CD-38 inactive; increased methylation; endogenous (LINE-1) viruses are inactivated.

TNF-α: modulates immune response to viral attack; an inducer of CD-38; CD-38 has a TNF receptor; lowered by compositions and methods disclosed in below working examples.

IL-6: modulates immune response to viral attack; lowered by compositions and methods disclosed in below working examples; reduction of LINE-1 leads to reduction of Il-6; basal level correlates to favorable health-span and life-span.

NAD+: CD-38 rapidly degrades NAD+ and NMN its precursor; when CD-38 is active, NAD+ is less available to Sirtuins and Defense and Repair.

Tristetraprolin (TTP): induced by CD-38 in the onset of acute inflammation; TTP-dependent degradation of CD-38 activates Sirtuin-1 at the onset of resolution; TTP controls the resolution of inflammation; Carbon monoxide (CO) inhibits inflammation by increasing TTP expression; a Phase 1 clinical trial with low dose inhaled carbon monoxide in (sepsis-induced) ARDS was successfully conducted showing it was feasible to give precise administration of CO, CO was well-tolerated and that CO was safe.

Methods and composition of the present disclosure reduced base line levels IL-6 and TNF-α in a healthy older individual was shown in below Example 3.

In anti-viral methods and compositions, using zinc (listed in category 3 compounds) as the, or one of the, Nrf2 activators may be especially desirable. Benefits of using zinc include a) Zinc (+2) inhibits Coronavirus RNA-synthesizing machinery and impairs a number of RNA viruses b) Zinc (+2) is important in regulating the immune system. Depending on the stage of the viral replication, zinc may be of benefit or harm due to its correlation to its turning on Nrf2 which correlates to the turning off of NF-kB (and vice versa) which at certain stages of certain viral replication can be of benefit. In embodiments, zinc is provided as zinc acetate, zinc arginate, zinc aspartate, zinc chloride, zinc citrate, zinc difumarate hydrate, zinc gluconate, zinc glycinate, zinc methionine, zinc monomethionine, zinc muratab, zinc orotate picolinate, zinc oxide, zinc pyrithione, or zinc sulfate. In embodiments, zinc is provided as zinc sulfate. In embodiments, a unit dose of zinc comprises about 25 mg of zinc.

Death from COVID-19 is correlated to having comorbidity. Many of these are diseases of aging. Even young 5-Day ICU patients have age type attributes like increased senescent cells. Senescent cells are most likely due to LINE-1 activation / when cytoplasmic DNA is sensed, this increases Il-6 & SASP.

Death from COVID-19 is correlated to sex with significantly more deaths in men. This correlates with death from aging being dependent on sex and that 5/6 age reversal therapies demonstrated in mice by the National Institute of Aging worked better in men and 1/6 worked better in women (this was low dose Rapamycin).

Disease fatality associated with COVID19 – like with SARS, Ebola and dengue fever - can often be attributed to cytokine storm syndrome (also referred to as “cytokine release syndrome”). It is an exaggerated pro-inflammatory response with lymphocytopenia, elevated IL-6 and CRP that gives rise complex pulmonary, cardiac and hematologic conditions. COVID-19 severity, and lethality are substantially higher in the population aged 60 and older, making this yet another “aging” disease.

Without wishing to be limited to theory, a patient experiencing a “cytokine storm syndrome” and the overwhelming oxidation and inflammation involved, will lead to an active CD-38 that breaks down all NAD+ and its precursor NMN very rapidly. Thus, supplementing a subject’s levels of NAD+ (via the methods and compositions of the present disclosure) have a beneficial effect, at least, under these oxidizing conditions. Accordingly, the methods and compositions of the present disclosure are particularly useful in treating, preventing, and/or reducing the ill effects of a viral infection, *e.g.,* resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Moreover, humans possess a circadian rhythm such that viruses are fought part time under an oxidizing state, when cells are rebuilt (those cells that have been attacked) and the other part time is under a reducing state. Accordingly, the methods of the present disclosure include administering a composition in adherence to the Circadian rhythm. Without wishing to be bound by theory, such adherence makes for a better therapeutic outcome, especially against viral attacks, *e.g.,* by SARS-CoV-2.

An advantage of the methods and compositions of the present disclosure is that they can provide a therapy against a viral attack (*e.g.,* by SARS-CoV-2) in patients who cannot receive standard treatments, *e.g.,* IL6 blockers or Remdesivir, due to sensitivity or allergy or adverse interactions with other therapies.

Although much of the present disclosure and the data presented in the Working Examples describes effectiveness of the herein-disclosed compounds, compositions, formulations, and methods for treating and/or reducing symptoms of Covid-19 infection, the herein-disclosed compounds, compositions, formulations, and methods are also effective for treating and/or reducing symptoms caused by other viral infections. Illustrative viral infections may be caused by one or more of enteroviruses A-J; rhinoviruses A-C; rotaviruses A-C; norovirus; influenza virus A-C and their several types like H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9, and their other relatives; human papillomaviruses (HPV); polyomaviruses like John Cunningham virus (JCV) and Merkel cell virus (MCV); poxviruses; herpesviruses such as human simplex virus 1 (HSV-1), human simplex virus 2 (HSV-2), varicella zoster virus, Epstein-Barr virus (human herpesvirus 4; EBV/HHV-4), human cytomegalovirus (HHV-5), Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus (HHV- 8); hepatitis A-E viruses (HAV, HBV, HCV); retroviruses like human immunodeficiency virus type 1 (HIV-1), type 2 (HIV-2) and their subtypes and endogenous LINE-1; another SARS coronavirus; Ebola virus (EBOV); Marburg virus (MARV); Lassa Fever virus; Banna virus; rubella virus; measles virus; mumps virus; human parainfluenza viruses (hPIV 1-4); rabies virus; Hantavirus; Dengue virus; West Nile virus; Zika virus; or orbivirus; as well as against other viruses that affect human or animal organism.

Illustrative diseases resulting from viral infections include (i) non-cancer diseases: enteritis (enteroviruses A-J); common cold (rhinoviruses A-C); gastroenteritis, diarrhoea (rotaviruses A-E, norovirus); gastroenteritis (norovirus); influenza (influenza virus A-C); progressive multifocal leukoencephalopathy (JCV), nephrophathy, Merkel cell cancer (MCV), smallpox (variola) (poxvirus); herpes (HSV-1, HSV-2); chicken-pox, herpes zoster

(shingles) (varicella zoster virus); infectious mononucleosis (HHV-4); hepatitis A (hepatitis A virus); hepatitis B (hepatitis B virus); hepatitis C (hepatitis C virus); acquired immunodeficiency syndrome (HIV-1, HIV-2, and their subtypes); severe acute respiratory syndrome (SARS); Ebola (EBOV); Marburg virus disease (MARV); fever and encephalitis (Banna virus); rubella (rubella virus); measles (measles virus); mumps (mumps virus); parainfluenza (hPIV 1-4); rabies (rabies virus); (ii) virus-associated cancer diseases: Hodgkin' s lymphoma, nasopharyngeal carcinoma, Burkitt's lymphoma (EBV/HHV-4); mucoepidermoid carcinoma (HHV-5); hepatocellular carcinoma (HBV, HCV); cancer of cervix, anus, penis, vagina, and oropharyngeal cancer (HPV); primary effusion lymphoma, Kaposi's sarcoma (HHV-8); as well as (iii) autoimmune diseases often associated with various viruses: dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome; and various other viral diseases of human and animals.

Compounds, Compositions, and Formulations

Also disclosed are compounds, compositions, and formulations falling into, or containing, one or more of the following three general categories:

Category 1 which are Repair System Activators

Category 2 which are Methyl Donors, and

Category 3 which are Antioxidant Defense Activators

Disclosed are compositions comprising a first compound, a second compound, and a third compound, wherein the first compound comprises nicotinamide adenine dinucleotide (NAD+), NAD+ precursor such as nicotinamide mononucleotide (NMN), a precursor or prodrug of NMN, nicotinamide riboside (NR), nicotinic acid riboside (NAR), nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), analog of NAD+ that promotes NAD+ use such as 1-methylnicotinamide (MNM), cyclic adenosine monophosphate (cAMP) wherein the second compound comprises S-5'-adenosyl-L-methionine (SAM), SAM precursor such as methionine, betaine, choline, serine, folate, vitamin B12, and wherein the third compound comprises antioxidant defense activator such as Nuclear factor erythroid 2 (Nrf2) activator, including activators that increase nuclear translocation of Nrf2, increase Nrf2 mRNA transcription, increase Nrf2 protein expression, and increase Nrf2 downstream target genes, reduce Nrf2 inhibitors (such as Bach 1, caveolae, TGF-beta)] such as zinc, calcium peroxide, N-Acetylcysteine, H_2O_2, H_2O_2 generator, hydrogen sulfide (H_2S), H_2S Donor such as, sodium hydrosulfide (NaHS), sodium sulfide (Na_2S), and optionally, a carrier.

Also disclosed are compositions, wherein the first compound, comprises NAD+ NMN, NR, NaMN, NaAD, NAR, MNM, cAMP, alone or in combination. Also disclosed are compositions wherein the first compound comprises NMN. Also disclosed are compositions wherein the first compound comprises a precursor or prodrug of NMN, *e.g.,* a compound that increases NMN production in the body.

Also disclosed are compositions wherein the composition lowers a Surrogate Marker for Aging. Also disclosed are compositions wherein the surrogate marker is CMV IgG, C-Reactive Protein, Tumor Necrosis Factor-alpha, or Interleukin-6 Serum. Also disclosed are compositions, where the composition comprises water. Also disclosed are compositions where Na (*e.g., via* NaCl) is added for increased active absorption of NMN and passive absorption of Betaine. Also, disclosed are compositions wherein the composition is formulated for injection. Also disclosed are compositions wherein the composition is in a concentrate form for dissolving in a liquid. Also disclosed are compositions wherein the composition is in tablet form or aerosol. Also disclosed are compositions wherein the composition comprises at least 1×10^{-8} moles of the first compound, at least 1×10^{-8} moles of the second compound, and at least 1×10^{-9} moles of the third compound.

The herein described "unit dose", "formulation", and/or "composition" may be referred to as an "NMN Cocktail".

Category 1, Repair System Activators

The turning on and maintaining of Sirtuin activity provides the beneficial effects disclosed herein. Sirtuins require NAD+. Providing a repair system activator can turn on the Sirtuins. Examples of a repair system activator include NAD+, NAD+ precursor such as NMN, NR, NaMN, NaAD, NAR, analog of NAD+ that promotes NAD+ use such as MNM, and cAMP, or any combination thereof. A preferred repair system activator is the NAD+ precursor NMN (to make NAD+, to turn on, and be consumed by Sirtuins, which provides the benefit from Calorie Restriction). In humans, NAD+ typically naturally peaks in the morning and the evening such as at 8 AM and 8 PM, and thus the addition of NAD+ or precursor that would turn into NAD+ would be added, for example, preferentially in the 7 AM to 8 AM and the 7 PM to 8 PM time frame. In certain aspect, preferably one wants the two daily doses 12 hours apart so as not to disrupt the natural cycle of the biological clock. Typical formulations provide greater or equal to 1.19×10^{-4} moles/kg-of-subject NMN, NAD+, or NAD+ precursor when administered (NMN is 334.22 grams / mole).

Another example of a preferred repair system activator is a precursor or prodrug of NMN, *e.g.,* a compound that increases NMN production in the body.

One can also administer, typically through injection, NAD+ or use nicotinamide riboside (NR) which can be made into NMN in some cells of the body. Typically administering of NAD+ and NR are less preferred because NAD+ is not absorbed well through the digestive system and the enzymes that make NMN from NR are not found in every cell of the body. Orally delivered NR has also been shown to largely not reach muscle.

In a specific aspect, disclosed is the administration of NMN (nicotinamide mononucleotide) to humans in preferred dosages of approximately 0.08 grams / kg total body weight per day divided into two equal doses taken approximately 12 hours apart. In certain embodiments, the dosage can be adjusted for absorption and Na (*e.g., via* NaCl) can be added for active transport absorption. It is preferred to administer the Repair System Activator such as NMN, through water and drinking. A precursor or prodrug of NMN can also be administered, in further examples.

In certain embodiments, repair system activators are administered for reducing inflammation markers related to aging. As used herein, repair system activators are any compound, composition, formulation, molecule, biologic, or substance, which activates sirtuin enzymes. These types of enzymes prefer a redox balance near or at reducing to be optimized. Examples of such molecules that activate Sirtuin are NAD+, NAD+ precursor such as NMN, NR, NaMN, NaAD, NAR, analog of NAD+ that promotes NAD+ use such as MNM, and cAMP.

Category 2, Methyl Donors

When adding a methyl donor for methylation, adding betaine is preferred. Betaine can bypass the need (with the use of choline) for extra NAD+ if used to make S-5'-adenosyl-L-methionine (SAM). SAM can provide the methyl group for nicotinamide, which has aging properties by stopping Sirtuin enzymes from working. This methylation of nicotinamide occurs *via* N-methyltransferase (NNMT) N-methylation to 1-methylnicotinamide. This nicotinamide with a methyl group attached provides competition to the available nicotinamide molecules that can get into the Sirtuin enzyme and decrease the Sirtuin enzyme's reactive ability; thus, preventing this process from happening in proportion to the concentration of each of the two competitors. Typically, the timing for giving would be with the Repair System Activator, such as NAD+ or NAD+ precursor.

SAM also provides the methyl groups to reduce the hypo-methylation seen in aging and in the right context it can to be used beneficially to combat aging, example: the need for H3K4me3 methylation of DNA found especially in older people.

Methyl Donors in addition to betaine, which can be used include SAM, methionine, choline, serine, folate, and B12. Typically, these alternatives are less preferred because only about 2% of SAM get into the body when ingested; choline needs extra NAD+ to be made into betaine, which is in short supply in the body. Serine helps make SAM from Methionine in two ways.

Dosages of betaine (trimethyl glycine) can be at least 0.03 grams/kg (3 x 10^{-4} mole/kg) of total body weight of the subject (calculated by 0.08 grams (from above NMN calculation) times 0.35 (for molecular weight ratio of betaine / NMN) = 0.03 grams / kg total body weight). This dose can be given over 24 hours and can be divided into two approximately equal doses taken approximately 12 hours apart. The dose can be dissolved in water and drunk by the subject. The administration can be along with the administration of the category 1 compound or composition.

In certain embodiments, the methylation donors are administered to a subject, and these methylation donors are molecules, substances, compositions, compounds, and formulations, which increase the methylation of molecules or methylate molecules themselves. Typically, methyl donors prefer a Redox balance to be near reduction for optimal activity. S-5'Adenosyl –L- methionine (SAM) precursors include methionine, betaine, choline (a precursor of betaine), serine, folate, Vitamin B12 alone or in combination.

Category-3 Antioxidant Defense Activators

When providing a category 3 compound, composition, or formulation the antioxidant defense is turned on. Having the antioxidant defense enzymes working increases the reduction of the thiol (sulfur) groups in the reactive site of Sirtuin enzymes and others with similar regulation. This prevents the Sirtuin enzymes from turning off due to thiol oxidation.

Hydrogen peroxide (H_2O_2)

One way to create a generally reducing environment is to "shock" the organism by a pulsed burst of oxidants, such as H_2O_2. To keep the antioxidant enzymes being made and keeping them working one uses pre-conditioning with oxidants to shock on the system, and one keeps them on by additional timed shock pulses of oxidants prior to the antioxidant enzymes turning off due to their feedback loops that turn them off or down when they are not challenged by oxidants. In doing the pulse of oxidants for the preconditioning one uses a sufficient level of oxidants to turn on and keep on the antioxidant enzymes. The preferred choice for an oxidant to do the preconditioning is hydrogen peroxide (H_2O_2) due to its

centrality in the redox signaling pathways and its relative stability for an oxidant and its low level of potential harmful effects compared to other oxidants that the cell deals with in its life cycle. H_2O_2 can oxidize thiol groups on proteins / enzymes thereby changing their enzymatic properties.

This pre-conditioning low level oxidation by H_2O_2 can be given in a pulsed, time controlled, and dose-controlled fashion to turn on enzymes and processes without providing oxidation in excess of what is needed to turn on enzymes including anti-oxidant defense and repair systems enzymes, because excess oxidation causes cellular damage and harm. Any small molecule (non-enzyme) antioxidants should be taken at other time periods (other than the time period of the oxidative pulse) so as not to diminish this temporal effect of the oxidative pulse.

Hydrogen peroxide (H_2O_2) oxidation and redox signaling

Hydrogen peroxide (H_2O_2) is a ubiquitous oxidant present in all aerobic organisms. H_2O_2 is now appreciated as a messenger molecule and it provides sensitivity to redox signaling. H_2O_2 provides oxidative modification of amino acid side chains in proteins; in decreasing order of reactivity and biological reversibility, cysteine, methionine, proline, histidine and tryptophan. Thiol modification is key in H_2O_2 sensing and perception in proteins. Hydrogen peroxide has been found to mimic insulin activity, elicit arterial pulmonary relaxation, stimulate cell proliferation, and activate NF-κB and AP-1. The functional consequences of H_2O_2 signaling concern fundamental biological processes. With recognition of the role of low-level oxidants stimuli for altering the set point of gene expression for batteries of enzymes, known as Hormesis. Transcriptional factors effected by H_2O_2 include AP-1, Nrf2, CREB, HSF1, HIF-1, TPSS, NF-κB, NOTCH, SP1, and SCREB-1 most involved in regulation of cell damage response, cell proliferation (cell cycle regulation) differentiation and apoptosis.

Protein acetylation is regulated by H_2O_2. Protein deacetylation is regulated by Sirtuins. H_2O_2 increase acetylation and Sirtuins decrease acetylation, so H_2O_2 and Sirtuins effects are in pushing acetylation reaction pathways in the opposite directions. Sirt1 is very sensitive to H_2O_2 inhibition of 1 μmol of extracellular H_2O_2. Sirt1 is protected by thiol oxidation from (APE1 / Ref-1). It governs the redox state and activity of Sirt1. It reduces the thiol groups in the active site of Sirt1, H_2O_2 oxidizes the thiols in Sirt1's active site. Sirt1 is also regulated by redox-dependent phosphorylation.

Need for pulsing of signaling oxidants

Low levels of H_2O_2 increase defenses by preconditioning and thus can ultimately protect against increase of oxidized thiols in Sirtuin's active site and Sirt1's decrease in activity by an oxidative challenge. Adaptation to H_2O_2 decrease H_2O_2 permeability of plasma membranes. Different cell membranes have a full range of permeability to H_2O_2. Aquaporins also regulate H_2O_2 transport across bio-membranes.

Common drugs that change H_2O_2 levels

Metformin, the most widely prescribed antidiabetic drug in the world, increases hydrogen peroxide (H_2O_2); this upregulates peroxiredoxin-2 (PRDX-2). Metformin increases lifespan in *C. elegans* and taking away the PRDX-2 gene takes away this effect. PRDX-2 appears to have the role of translating oxidative stress into a downstream pro-longevity signal. Treatment with N-acetylcysteine (NAC) and butylated hydroxyanisole (BHA), which are small molecule antioxidants, abolished the positive effect of metformin on lifespan. Pharmaceuticals that increase hydrogen peroxide in the body can also be used for this category either in addition to H_2O_2 or as a substitute for adding hydrogen peroxide itself. Pharmaceuticals that increase H_2O_2 in the body include metformin and acetaminophen.

Pharmaceuticals that increase H_2O_2 in the body need also to be included in the calculation of the oxidative pulse given in category #3. An example is Acetaminophen (the ingredient in Tylenol), which is a pharmaceutical that is known to increase H_2O_2 in the body. N-acetyl-l-cysteine (NAC) is a compound that is known to counter many effects of H_2O_2 in the body.

Timing, duration, and levels of H_2O_2

Enough oxidation to provide pre-conditioning to signal to the turn on the antioxidant defense and repair systems is desired; but not enough to create oxidized damage like oxidizing the thiol groups in the Sirtuin active site that turns the enzymes activities off. This level has been referred to as the "Goldilocks zone". The APE-1/ Ref-1 is a molecule that protects the thiol groups of the Sirtuin enzymes, which should remain active. The same or similar process for the nicotinamide-N-methyltransferase (NNMT) enzyme is theorized.

In certain embodiments, one can add pulsed low levels of hydrogen peroxide (H_2O_2) transiently to humans to pre-condition the antioxidant defense and repair systems to turn on and stay on. In certain preferred embodiments, approximately 100 μM concentration of food grade (commercial grade has acetanilide in it as a stabilizer) H_2O_2 in the 400 to 500 mL of water per individual dose is preferred, which can be taken alone or with Category 1 and

Category 2 compounds or compositions. 1 mole of H_2O_2 = 1+1+16+16 = approximately 34 grams. 50% of H_2O_2 is estimated to be absorbed by the gut so a more preferred concentration to take is approximately 200 μM (in the 500 mL). For example, in certain embodiments, one drop of H_2O_2 is 0.05 mL. Food grade H_2O_2 comes in 35% concentrations. Taking 2 drops of 35% H_2O_2 in 500 mL distilled water (with each dose / day), gives approximately 200 μM. H_2O_2 degrades at about 10% / year if no light and no contaminants in deionized / distilled H_2O. H_2O_2 freezes at -11 °C. In certain embodiments, taking 4 drops / day or 0.2 mL of 35% H_2O_2 / day in 1 liter of water. 35 grams / 100 mL = 0.07 grams / 0.2 mL. In certain embodiments, a quantity of approximately 0.0008 grams of H_2O_2 /kg total body weight dosages can be used.

A preferred method of administration is to ingest H_2O_2 by dissolving H_2O_2 in deionized / distilled water and drinking. A preferred timing of dosage concentration, time taken and length of time taking is to use the same timing as #1 and #2 when in water. In certain embodiments, if H_2O_2 is partially enhanced from endurance exercise do exercise directly before or after.

Administration of metformin can come in liquid form, Riomet, as well as tablets. In liquid form 5 mL is equal to a 500 mg tablet. It reaches peak plasma concentrations in 1 to 3 hours in immediate release form and a steady state in one to two days. It is typically 50 to 60% bioavailable under fasting conditions. One would need to use this data to time and dose appropriately with Metformin.

Calcium peroxide ($CaCO_2$)

Calcium peroxide turns into hydrogen peroxide when in water. An advantage of using this compound is that it exists as a solid and can be combined with other dry compounds useful in compositions of the present disclosure. As an example, a composition may be stored, shipped, and/or provided in a product sachet.

Calcium peroxide naturally decomposes very slowly to form calcium hydroxide and oxygen. Depending upon the environment, the decomposition proceeds according to the reactions below:

$$2CaO_2 + 2H_2O \rightarrow 2Ca(OH)_2 + O_2$$

or

$$CaO_2 + 2H_2O \rightarrow Ca(OH)_2 + H_2O_2$$

$$2H_2O_2 \rightarrow 2H_2O + O_2.$$

In any of the herein described compositions, methods, and examples, H_2O_2 can be replaced with calcium peroxide.

Hydrogen Sulfide (H_2S)

Another way to change the redox potential of oxidation-sensitive protein thiols besides using hydrogen peroxide (H_2O_2) to pre-condition the antioxidant defense system as discussed previously, is by directly augmenting the antioxidant defense system with hydrogen sulfide (H_2S). NaSH (a H_2S donor) (0.025-0.1 millimolar /liter) treatment dose dependently countered H_2O_2 treatment. Plasma H_2S levels decrease in humans over 50 to 80 years of age and plasma levels of H_2S in patients with cardiovascular disease (CHD) show a significant inverse correlation with severity of CHD and changes in the coronary artery. NaSH decreases ROS and enhances SOD, GPx and GST expression. Lipid and protein oxidation products decrease significantly in plasma samples of healthy volunteers with H_2S rich water (500 mL / day for 2 weeks). A 0.1 mM NaSH / Liter can increase Sirt1 in a time dependent manner. Exogenous H_2S has a protective effect on maintaining the circadian rhythm of clock genes by changing the NAD+/NADH ratio and enhancing the Sirt1 protein. H_2S is also an important endogenous inhibitor of key elements of acute inflammatory reactions by down regulating NF-kB or upregulating heme oxygenase 1 expression. H_2S can activate ATP-sensitive, intermediate-conductance and small-conductance potassium channels through cysteine S-sulfhydration causing endothelial and smooth muscle cell hyperpolarization which intern causes vasorelaxation of vascular endothelium and lowering of blood pressure. H_2S has a direct inhibitory effect on angiotensin-converting enzyme (ACE) activity. NaSH increases the expression of eNOS and PGC-1Alpha, which both play a role in mitochondria biogenesis and function. H_2S upregulates the MAPK pathway. It has been inferred that calorie restriction may help maintain H_2S signaling. GYY4237 a slow releasing H_2S donor can kill seven different human cancer cell lines in a concentration-dependent manner. Sulforaphane, also a H_2S donor, has dose-dependent antiprostate cancer (PC-3) properties.

H_2S is a gasotransmitter. Gasotransmitters are endogenously produced at low levels and are able to freely diffuse through cell membranes to invoke cellular signaling. The three gasotransmitters are nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S).

Hydrogen sulfide is synthesized from L-cysteine. Cystathionine gamma-lyase (CSE), cystathionine beta-synthase (CBS), cysteine aminotransferase (CAT), and 3-mercaptopyruvate sulfurtransferase (MST) are endogenous enzymatic sources of hydrogen sulfide (H_2S). Liver production of H_2S to different extents has been shown by these enzymes and showed H_2S regulates lipid peroxidation and antioxidant enzyme (GPx, T-SOD, Cu/Zn-SOD, and Mn-SOD) activities in the liver, by administration of H_2S donor

NaSH to the mice by injection of 0.05 mM of NaSH / kg body weight /day dissolved in 10 mL / kg body weight saline. Mitochondria are able to use H_2S under hypoxia and stress conditions to produce ATP.

Initial reports of H_2S's antioxidant ability were that H_2S can scavenge superoxide and H_2S can upregulate glutathione. Later came more detailed reports of its activation of antioxidant enzymes. H_2S has been shown to activate Nuclear factor-erythroid 2-related factor 2 (Nfr2), which turns on antioxidant genes. Daily administration of Na_2S for 7 days increased Nrf2 expression in both cytosolic and nuclear fractions. Nrf2, which up regulates expression of antioxidant response element-regulated genes, is upregulated by H_2S. H_2S activation causes Nrf2 to separate itself from its adherent inhibitor, Kelch-like ECH-associated protein 1 in the cytosol then translocate to the nucleus and bind to a specific enhancer sequence, known as the antioxidant responsive element, in the promoter region of antioxidant genes, including HO-1 and thioredoxin 1. H_2S exhibits effects on mitochondria function antioxidant stress apoptosis, inflammation angiogenesis, sepsis and shock and blood pressure.

H_2S protects against NO_3^-, as does glutathione. H_2S also significantly reduces the toxic effects of HOCl. H_2S enhances the antioxidant effects of N-acetyl-l-cysteine (NAC).

H_2S's therapeutic effects have been most studied to date in regard to heart disease. H_2S effects on heart disease include macrophages are able to produce H_2S endogenously. NaHS (a H_2S donor) inhibited pro-atherogenic oxidized low-density lipoproteins induced foam cell formation in macrophages. H_2S is able to down regulate ROS at the mitochondria, providing protection through reduced respiration. H_2S production (10-100 nM) enhanced mitochondrial electron transport and cellular bioenergetics however at high concentrations H_2S is toxic. H_2S in the diet decreased adverse left ventricle (LV) remodeling during heart failure. H_2S can upregulate endothelial nitric oxide synthase which makes NO and NO can upregulate the H_2S synthesis enzyme CSE. Mice treated with a H_2S donor significantly increase phosphorylation effecting eNOS suggesting active cross talk between H_2S and NO. There also appears to be cross talk between CO and H_2S. H_2S induces vasodilation, leading to reduced blood pressure. H_2S in the form of Na_2S (10 minutes prior) prevents reperfusion injury. Exogenous H_2S also led to improved renal function.

H_2S under in vivo conditions has an extremely short half-life which is estimated to be between seconds and minutes. Plasma concentrations of H_2S is in the range of 0.034 to 0.065 mM, in the brain it is three-fold higher than the plasma. H_2S concentration are inversely related to O_2 concentration and H_2S decrease cellular O_2 consumption. H_2S

concentrations of between 0.030 and 0.300 have also been reported in the blood and plasma. H_2S donors NaHS and Na_2S increase H_2S concentration within seconds to minutes.

The physiological range of H_2S is widely variable from 0.005 to 0.300 mM. Endogenous levels of H_2S in the brains of humans have been detected at from 0.05 to 0.16 mM; in the brains of Alzheimer's patients, the H_2S concentration is lower. Diallyl trisulfide (DATS) is a stable H_2S donor and shows effects 30 minutes after injection and is longer lasting. NaHS can be taken in drinking water. NaHS (H_2S donor), in aqueous solution releases H_2S, in drinking water for 6 weeks. There was an increase in plasma H_2S concentration with exogenous supplementation. There was no difference in the consumption of water among the groups of mice treated with NaHS and untreated groups. Other H_2S donors include GYY 4137 (CAS# 106740-09-4) a water soluble H_2S donor that slowly releases H_2S over the course of hours and SG 1002 from Sulfagenix, Inc. AP97, AP39, AP67, and AP105 are also H_2S donors with slower release. H_2S can be ingested with foods containing organosulfides, who's polysulfides can be H_2S donors.

In addition to ingesting H_2S dissolved in water, H_2S can be inhaled and inhalation increases blood H_2S levels (40 ppm for 8 hours for 7 days was used with mice). Inhalation can also be combined with ingestible H_2S donors such as Na_2S and NaHS. Measurement of H_2S in blood and tissue has been done with a sensitive and reliable means.

H_2S can also be stored in cells in the form of sulfane sulfur and transported and released in response to physiological stimulus.

FW1256

FW1256 is a phenyl analogue and a slow-releasing hydrogen sulfide (H_2S) donor. FW1256 inhibits NF-κB activity and induces cell apoptosis. FW1256 exerts potent anti-inflammatory effects and has the potential for cancer and cardiovascular disease treatment.

NRF2 Activators

The transcription factor NF-E2 p45-related factor 2 (Nrf2: gene name NFE212) regulates the expression of networks of genes encoding proteins with diverse cytoprotective activities. Nrf2 itself is controlled primarily at the level of protein stability. Nrf2 is a short-lived protein subjected to continuous ubiquitination and protease degradation. There are three known ubiquitin ligase systems that contribute to the degradation of Nrf2 a) Keap-1, a substrate adaptor protein for Cullin-3, b) glycogen synthase kinase, and c) E3 ubiquitin ligase Hrd1. Keap-1 is also a sensor for a wide array of small-molecule activators also called inducers. When Nrf2 is not degraded and is translocated to the nucleus it forms a heterodimer with a small Maf protein, binds to antioxidant-response elements which are the

upstream regulatory regions of its target genes and initiates transcription. Nrf2 is a master regulator of cellular redox homeostasis. Over 50 genes are regulated by Nrf2 in humans. In a direct effect of inflammation genes, without a Redox mechanism, Nrf2 also binds to the upstream region of the IL6 gene and when bound can significantly disrupt the recruitment of RNA polymerase II to regulate the transcription of IL6 in human macrophage cells.

Nrf2 signaling is regulated by transcriptional, translational, posttranslational, and epigenetic mechanisms as well as by other protein partners including p62, p21 and IQ motif containing GTPase activating protein 1. Nuclear factor erythroid 2 (Nrf2) activators include classes of activators with activities that: induce nuclear translocation of Nrf2, increase Nrf2 mRNA transcription, increase protein expression of Nrf2 and increase Nrf2 downstream target genes. There are also Nrf2 inhibitors (Bach 1, caveolae, TGF-beta). The Keap1-Nrf2 pathway acts in concert with autophagy to combat proteotoxicity.

Keap-1 is a zinc metalloprotein that is localized near the plasma membrane. It has three functional domains, at least 25 reactive thiols most of which are found in the intervening linker region. Keap-1 has an Nrf2 binding site on each dimer subunit forming a "latch and hinge." Keap-1 is highly sensitive to oxidation and its different thiol groups have different redox potentials. These different cysteine residues create a sensor system.

Nrf2 is a 605 amino acid transcription factor composed of six domains. The N-terminal Neh2 domain is the binding site for the inhibitory protein Keap-1. The half-life of Nrf2 when separated from Keap-1 is 20 minutes. Keap-1 is exported out of the nucleus in 0.5 hours. Nrf2 activations enhances Sirt1 activity in mice fibroblasts cell culture.

When Nrf2 releases Keap-1 it is available to capture IKKBeta thus inhibiting NF-κB target genes. This interaction correlates the expression of antioxidant enzymes by NrF2 and the turning on and off of the immune system by NF-κB. Nrf2 and NF-kB compete for CREB-binding protein (CBP). There are many phytochemicals that have Nrf2 activation abilities by interacting with Keap-1 in different ways. Immediate alkylators are fast activating. "Michael acceptors", which are acetylene compounds conjugated to an electron-withdrawing group, form reversible alkylating reactions with Keap-1 sensor thiols.

Phenolics that appear to act most directly on Nrf2 are ortho- or para-dihydroxyphenols which can be oxidized to quinones. Quinones are oxidized derivatives of aromatic compounds and are often readily made from reactive aromatic compounds with electron-donating substituents such as phenols and catechols, which increase the nucleophilicity of the ring and contributes to the large redox potential needed to break aromaticity. Quinones are conjugated but not aromatic. Quinones are electrophilic Michael

acceptors stabilized by conjugation. Depending on the quinone and the site of reduction, reduction can either re-aromatize the compound or break the conjugation. Conjugate addition nearly always breaks the conjugation.

H_2O_2 and H_2S are Nrf2 activators (listed separately above). Everything mentioned that is a Nrf2 activator, is also an antioxidant defense system activator although some things activated by Nrf2 may be seen as additional to antioxidant defense system activation. The activation comes from the multiple ways listed above of keeping the Nrf2 system on. One form of regulation of Nrf2 is reversible phosphorylation. Sirt1 and PARP1 as discussed before can also be reversibly phosphorylated.

Nrf2 activation and the turning on of the antioxidant defense system needs to be correlated in timing to NAD+ availability and methylation availability and be synced with the biological clock NAD+ peaks of the person. The Nrf2 system does need to turn off (example: around 2 pm when NAD+ concentrations normally are at their daily biological clock low) so one's body can do the things it needs to do under a redox balance when that leans towards oxidation.

Category 3 compounds

Antioxidant defense activators such as Nuclear factor erythroid 2 (Nrf2) activators (including activities such as: nuclear translocation of Nrf2, increasing Nrf2 mRNA transcription, increasing protein expression of Nrf2 and increasing Nrf2 downstream target genes), zinc, calcium peroxide, N-Acetylcysteine, H_2O_2, ROS, RNS, RCS, RSOH, O_2^1, O_2, H_2S, O_3, HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, H_2O_2 generator, such as metformin or acetaminophen, ortho hydroxyphenols which can be oxidized to quinones, para dihydroxyphenols which can be oxidized to quinones, quinones (are oxidized derivatives of aromatic compounds), hydrogen sulfide (H_2S), H_2S Donor (such as), sodium hydrosulfide (NaHS), sodium sulfide (Na_2S), diallyl trisulfide (DATS), GYY4137 (a water soluble H_2S donor (patent # WO2014018569 A1)), SG-1002 (a H_2S synthetic donor from SulfaGENEX), penicillamine-based H_2S donors, polyorganosulfides, 2-mercaptothanol, dithiothreitol, isothiocyanates, sulforaphane (in broccoli), glucoraphanin (broccoli), curcumin (in turmeric), Pyrrolidone (water soluble), Theracumin (nanoparticle), Zerumbone, Cinnamate analogs that have thioketone-conjugated-Alpha-Beta-unsaturated moiety like, cinamic aldehyde, quercetin (in onions, apples, tea), isoquercetin (2 to 6 fold better absorption), kaempferol, ginseng (Panax ginseng and Panax quinquefolius), carnosic acid, xanthohumol, Dh404, (R)-alpha–lipoic acid, Isothiocyanate, benzyl isothiocyanate,

Neoglucobrasssicin, Glucosinolates, Hydrophilic oxidized derivatives of Lycopene, (HNE) 4-hydroxynonenal, (15-dPGJ2) 15-deoxydelta prostaglandin J2, Falcarindiol, Hydroxytyrosol, Barley beta-glucan, Spermidine, Spermine, luteolin, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, pyrroloquinoline quinone, Mangafodipir trisodium (MnDPDP) (a contrast agent currently used in magnetic resonance imaging), ATB-346 from Antibe Therapeutics, NBS-1120 from City College of New York, GIC-101 from GI care Pharma, AP39 patent number WO2013045951A1 University of Exeter, Alos AP67, AP 97 and AP105, WO2014018569A1, Sialor, Sulfarlem, and Anethole trithione, DHEA, coal tar, garlic (via H_2S), β-lapachone (from tree bark of a South American tree: it produces oxidation by cycling cellular NADH into NAD+), pterostilbene, apigenin (in parsley), zinc, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol (from ginger), Acetyl-11-keto-β-boswellic acid, Acteoside, Allicin, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin (in green tea), Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Fistetin, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Quercetin, Resveratrol, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), and Triptolide; Fenofibrate, Melatonin, Vinblastin (artichokes), Cyanoside-3-O-glucoside (anthocyanins), calcium peroxide, FW1256 and compounds 1 to 51 described in Li *et al.* "Reasonably activating Nrf2: A long-term, effective and controllable strategy for neurodegenerative diseases." European Journal of Medicinal Chemistry, 07 Nov 2019, 185:111862; and optionally, a carrier.

Specific Compositions

In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise nicotinamide adenine dinucleotide (NAD+), Betaine, and Zinc (*e.g.,* as zinc sulfate). In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), folate + Vitamin B12, and Zinc (*e.g.,* as zinc sulfate). In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise

nicotinamide adenine dinucleotide (NAD+), Methionine, and Zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and Zinc (*e.g.,* as zinc sulfate). In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Choline, and Zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise nicotinamide adenine dinucleotide (NAD+), Betaine, and H_2O_2. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), folate + Vitamin B12, and H_2O_2. In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise nicotinamide adenine dinucleotide (NAD+), Methionine, and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and H_2O_2. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Choline, and H_2O_2.

In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise nicotinamide adenine dinucleotide (NAD+), Betaine, and NaHS. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Folate + Vitamin B12, and NaHS. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Methionine, and NaHS. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Choline, and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Betaine, and Na_2S. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Folate + Vitamin B12, and Na_2S. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Methionine, and Na_2S. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Choline, and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me),

Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-

boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In specific examples, the disclosed composition can comprise nicotinamide adenine dinucleotide (NAD+), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR),

with Betaine, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and zinc (*e.g.*, as zinc sulfate). Also disclosed are compositions wherein the first compound comprises NMN. Also disclosed are compositions wherein the first compound comprises a precursor or prodrug of NMN, *e.g.*, a compound that increases NMN production in the body.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, folate + Vitamin B12, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), folate + Vitamin B12, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), folate + Vitamin B12, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), folate + Vitamin B12, and zinc (*e.g.*, as zinc sulfate).

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine + Vitamin B12, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and zinc (*e.g.*, as zinc sulfate).

In specific examples, the disclosed compositions (*e.g.*, nutritional compositions) can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Methionine, and zinc (*e.g.*, as zinc sulfate). In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and zinc (*e.g.*, as zinc sulfate).

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Choline, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed compositions (*e.g.,* nutritional compositions) can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine, and H_2O_2. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Betaine, and H_2O_2. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and H_2O_2. Also disclosed are compositions wherein the first compound comprises NMN. Also disclosed are compositions wherein the first compound comprises a precursor or prodrug of NMN, *e.g.,* a compound that increases NMN production in the body.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, folate + Vitamin B12, and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), folate + Vitamin B12, and H_2O_2. In other examples, the disclosed composition can

comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), folate + Vitamin B12, and H_2O_2. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), folate + Vitamin B12, and H_2O_2.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine + Vitamin B12, and H_2O_2. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and H_2O_2. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and H_2O_2.

In specific examples, the disclosed compositions (*e.g.*, nutritional compositions) can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and H_2O_2. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Methionine, and H_2O_2. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and H_2O_2.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Choline, and H_2O_2. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and H_2O_2. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and H_2O_2.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and H_2O_2. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and H_2O_2. In other examples, the disclosed

composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and H_2O_2. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and H_2O_2.

In any of the herein described compositions, methods, and examples, H_2O_2 can be replaced with calcium peroxide or N-Acetylcysteine.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and NaHS. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine, and NaHS. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine, and NaHS. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Folate + Vitamin B12, and NaHS. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Folate + Vitamin B12, and NaHS. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Folate + Vitamin B12, and NaHS. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Folate + Vitamin B12, and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and NaHS. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine + Vitamin B12, and NaHS. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and NaHS. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and NaHS. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and NaHS. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Methionine, and NaHS. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and NaHS. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Choline, and NaHS. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and NaHS. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and NaHS. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and NaHS. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and NaHS. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and NaHS.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and Na_2S. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine, and Na_2S. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine, and Na_2S. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Folate + Vitamin B12, and Na_2S. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Folate + Vitamin B12, and Na_2S. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Folate + Vitamin B12, and Na_2S. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Folate + Vitamin B12, and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and Na_2S. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine + Vitamin B12, and Na_2S. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and Na_2S. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and Na_2S. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and Na_2S. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Methionine, and Na_2S. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and Na_2S. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Choline, and Na_2S. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and Na_2S. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and Na_2S. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and Na_2S. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and Na_2S. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and Na_2S.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of

bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2,

3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng,

(R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise 1-

methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its

analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-

glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester,

and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine,

Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol,

3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene,

resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine

(SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed

composition can comprise one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed composition can comprise 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin,

Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In the disclosed compositions, the combined amounts of compounds of category 1, 2, and 3 in the composition can be at least 5 wt.% of the composition. For example, the repair system activator, the methyl donor, and the antioxidant defense activator can be at least 5 wt.% of the composition. In other example, the combined amount of compounds of category 1, 2, and 3 in the composition can be at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 95, or 100 wt.% of the composition, where any of the stated values can form an upper or lower endpoint of a range.

The herein described "unit dose", "formulation", and/or "composition" may be referred to as an "NMN Cocktail".

Delivery system for ingredients of category 1, 2, and 3

Formulations, which can be packaged in a powder or lyophilized form, which can then have either hot or cold liquid added to them for reconstituting into a solution are disclosed. For example, the disclosed compositions could be mixed with compositions, such as is done in personal beverage systems, which make hot or cold coffee or tea or hot chocolate from individually packaged components and the addition of water. The disclosed compositions can be administered in vivo either alone or in a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, *i.e.,* the material can be administered to a subject, along with the composition disclosed herein, without causing any undesirable biological effects. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The materials can be in solution, suspension (for example, incorporated into microparticles, liposomes, or cells).

Microbiome interaction with delivery via digestive tract or skin

The mammalian intestinal microbiota is composed of up to 100 trillion microbes from over 500 genera of bacteria from two main phyla, namely *Bacteroidetes* and *Firmicutes*. A well-studied mammalian probiotic *Lactobacillus rhamnosus* GG is a potent inducer of ROS. Redox signaling mediates symbiosis between the gut microbiota and the intestine. In flies, increase in life span is correlated to increase formation of the oxidant H_2O_2 in the gut. H_2S protects the mucosal lining of the gastrointestinal tract against

oxidative stress as well as regulates various functions including fluid transport, inflammation, acid induced HCO_3^- secretion. Gut microbiota composition in the elderly has been correlated to plasma Il-6 levels.

A fasting molecule Crtc enhances immunity by making the gut barrier less permeable to bacteria. Gut bacteria that get across the gut barrier cause inflammation. This Crtc is a genetic switch in the brain that controls energy balance. This constant communication between the brain and the GI tract allows the body to keep tract of energy expenditures and stores. Crtc interacts with CREB (cAMP response element-binding protein). A partner of Crtc in the human brain is neuropeptide Y, which causes mammals to search for food. CREB activity is regulated by energy sensing Sirt1 and its ability to deacetylate CREB. This links the level of NAD+ and the feeling of hunger. The glucose-regulated antagonism between (yet coordinated with) CREB and Sirt1 for Hes-1 transcription participates in the metabolic regulation of neurogenesis, this is important since a decline in neurogenesis accompanies brain aging and CREB transcription factor is activated by nutrient deprivation which is correlated to Sirtuin enzyme activity.

TNF in the circulation of humans that occurs as part of the aging process impairs inflammatory monocyte development function and is detrimental to anti-pneumococcal immunity. This is reversed with pharmacological reduction of TNF.

The formulation could have organisms such as bacteria in the microbiome extrude any or all of these three categories of compounds that are desired and add them directly into the gut. These organisms could extrude the desired compounds in the quantity and with the timing desired. These organisms could be introduced to the microbiome either from a selection of organisms that naturally occur in the microbiome or by the engineering of organisms that naturally occurs in the microbiome. The engineered organisms could be engineered to extrude these compounds in accordance to the introduced organism's and or the host's biological clock. The introduced organism could be engineered to extrude the desired amount of compound or compounds. Gene-drive could be used to switch all of the species in the gut of this type used to the introduced organism's gene type desired. A kill switch could be engineered into this introduced species as well to allow an elimination of these engineered species if they were not desired later.

Pharmaceutically Acceptable Carriers

The compositions disclosed herein can be used therapeutically in combination with a pharmaceutically acceptable carrier.

Suitable carriers and their formulations are described in Remington: The Science and Practice of Pharmacy (22nd ed.) ed. L.V. Loyd Jr., CBS Publishers & Distributors Grandville MI USA 2012. Typically, an appropriate amount of a pharmaceutically acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers, which matrices are in the form of shaped articles, *e.g.,* films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers can be more preferable depending upon, for instance, the route of administration and concentration of composition being administered.

Pharmaceutical carriers are known to those skilled in the art. These most typically would be standard carriers for administration of drugs to humans, including solutions such as sterile water, saline, and buffered solutions at physiological pH. The compositions can be administered intramuscularly or subcutaneously. Other compounds will be administered according to standard procedures used by those skilled in the art.

Pharmaceutical compositions can include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the molecule of choice. Pharmaceutical compositions can also include one or more active ingredients such as antimicrobial agents, anti-inflammatory agents, anesthetics, and the like.

The pharmaceutical composition can be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated. Administration can be topically (including ophthalmically, vaginally, rectally, intranasally), orally, by inhalation, or parenterally, for example by intravenous drip, subcutaneous, intraperitoneal or intramuscular injection. The disclosed compounds can be administered intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer’s dextrose, dextrose and sodium chloride, lactated Ringer’s, or

fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives can also be present such as, for example, antimicrobials, chelating agents, and inert gases and the like.

Formulations for topical administration can include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable.

Some of the compositions can be administered as a pharmaceutically acceptable acid- or base- addition salt, formed by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, and phosphoric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, and fumaric acid, or by reaction with an inorganic base such as sodium hydroxide, ammonium hydroxide, potassium hydroxide, and organic bases such as mono-, di-, trialkyl and aryl amines and substituted ethanolamines.

The various compounds and compositions of categories 1, 2, and 3, can be taken at the same time or in proximity, such as within 1, 5, 10, 30, 60, 90, or 120 minutes.

Dosages of each item or items from category 1, 2, and 3 that is sufficient but not in excess (described in molar terms to body weight) and the ingredients are such that the interrelationship of these doses is balanced.

In specific examples, the disclosed composition can comprise nicotinamide mononucleotide (NMN), Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1. In embodiments, the composition further comprises about a ratio of NaCl (to the other components) of from about 0.25 and about 1.25.

In specific examples, a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate. In embodiments, the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate. In embodiments, the unit dose

further comprises from about 25 mg to about 100 mg of NaCl. In embodiments, the unit dose further comprises about 50 mg of NaCl.

The herein described "unit dose", "formulation", and/or "composition" may be referred to as an "NMN Cocktail".

In specific examples, at least one unit of a composition is administered to the subject at each dosing. In embodiments, at least two units of the composition, at least three units of the composition, at least four units of the composition, or at least five units of the composition is administered to the subject at each dosing. In embodiments, the number of units of the composition per dosing relates in part to the weight of the subject. In embodiments, when a subject weighs 100 lbs or less, the subject is administered at least one unit of the composition per dosing and/or when a subject weighs over 100 lbs, the subject is administered at least one unit, at least two units, at least three units, or at least four units or at least five units of the composition per dosing. In embodiments, the subject receives at least one dosing per day, at least two dosings per day, at least three dosings per day, or at least four dosings per day.

A delivery system in water is preferable if the preferred ingredient of category 1, 2 and 3 are used. This will help elicit the correct timing (all 3 preferred ingredients are easily absorbed and soluble in water). For some other less preferred ingredients, which are not as water soluble or are not as easily absorbed their delivery would result in a reduced benefit with respect to the pulse timing of these three categories of ingredients.

Disclosed are methods of reducing inflammation in a subject in need thereof, reversing aging and/or reversing accumulated cellular damage in a subject in need thereof, and/or for treating, preventing, and/or reducing the ill effects of a viral infection (*e.g.*, caused by SARS-CoV-2) in a subject in need thereof comprising administering to the subject compounds, compositions, or formulations, and optionally, a carrier as described herein.

Although much of the present disclosure and the data presented in the Working Examples describes effectiveness of the herein-disclosed compounds, compositions, formulations, and methods for treating and/or reducing symptoms of Covid-19 infection, the herein-disclosed compounds, compositions, formulations, and methods are also effective for treating and/or reducing symptoms caused by other viral infections. Illustrative viral infections may be caused by one or more of enteroviruses A-J; rhinoviruses A-C; rotaviruses A-C; norovirus; influenza virus A-C and their several types like H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9, and their other relatives;

human papillomaviruses (HPV); polyomaviruses like John Cunningham virus (JCV) and Merkel cell virus (MCV); poxviruses; herpesviruses such as human simplex virus 1 (HSV-1), human simplex virus 2 (HSV-2), varicella zoster virus, Epstein-Barr virus (human herpesvirus 4; EBV/HHV-4), human cytomegalovirus (HHV-5), Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus (HHV- 8); hepatitis A-E viruses (HAV, HBV, HCV); retroviruses like human immunodeficiency virus type 1 (HIV-1), type 2 (HIV-2) and their subtypes; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; Ebola virus (EBOV); Marburg virus (MARV); a Lassa Fever virus; Banna virus; rubella virus; measles virus; mumps virus; human parainfluenza viruses (hPIV 1-4); rabies virus; Hantavirus; Dengue virus; West Nile virus; Zika virus; or orbivirus; as well as against other viruses that affect human or animal organism.

Also disclosed are methods, wherein the first compound, the second compound, and the third compound are administered at approximately the same time.

Also disclosed are methods, wherein the first compound is administered within 15, 30, 60, 90, or 120 minutes of the subject's biological clock NAD+ peak.

Also disclosed are methods, wherein the subject is administered the composition in accordance with the subject's circadian rhythm.

Also disclosed are methods, wherein the compositions are administered to a subject a dosage of at least 1 x 10^{-8} moles of the first compound to the subject, 1 x 10^{-8} moles of the second compound to the subject, and 1 x 10^{-9} moles of the third compound to the subject.

Also disclosed are methods, wherein the composition is injected over 8-12 days.

Also disclosed are methods, wherein the composition is an aerosol, lyophilization, powder, or emulsion.

Also disclosed are methods, wherein the subject is a human.

Also disclosed are methods, wherein the subject is at least 50 years old.

Also disclosed are methods, wherein the human is treated for at least two months.

Also disclosed are methods, wherein the composition is a tablet that is administered orally at least once daily.

Also disclosed are methods, wherein the composition is administered once daily.

Also disclosed are methods, wherein the subject has previously been treated with one or more of hydroxychloroquine, Zithromax, and zinc.

Also disclosed are methods, wherein the subject is administered the composition to a substantially empty stomach.

The disclosed compositions can be administered at a variety of dosages. For example, category 1 compounds like Nicotinamide Mononucleotide (NMN), can be at dosages per day of 1 x 10^{-6} moles/kg to 1 x 10^{-2} moles/kg or 1 x 10^{-5} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-4} moles/kg to 1 x 10^{-3} moles/kg or 2 x 10^{-4} moles/kg to 7 x 10^{-4} moles/kg. In certain embodiments, the dosages per day of the category 1 molecule can be at least 1 x 10^{-6} moles/kg, 1 x 10^{-5} moles/kg, 1 x 10^{-4} moles/kg, 1 x 10^{-3} moles/kg or 1 x 10^{-2} moles/kg. The dosages can also be at least 2.38 moles/kg per day. The same dosages are contemplated herein for other category 1 compounds NAD+, NR, NaMN, NaAD, NAR, MNM, and cAMP.

The dosage of category 2 compounds, such as betaine, can be at dosages per day of 1 x 10^{-6} moles/kg to 1 x 10^{-2} moles/kg or 1 x 10^{-5} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-4} moles/kg to 1 x 10^{-3} moles/kg or 2 x 10^{-4} moles/kg to 7 x 10^{-4} moles/kg. In certain embodiments, the dosages per day of the category 2 compound can be at least 1 x 10^{-6} moles/kg, 1 x 10^{-5} moles/kg, 1 x 10^{-4} moles/kg, 1 x 10^{-3} moles/kg or 1 x 10^{-2} moles/kg. The dosages can also be at least 5.82 x 10^{-4} moles / kg body weight / day.

The dosages of category 3 compounds, such as zinc (*e.g.*, as zinc sulfate), can be at dosages per day of 1 x 10^{-7} moles/kg to 1 x 10^{-2} moles/kg or 1 x 10^{-6} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-5} moles/kg to 1 x 10^{-4} moles/kg or 1 x 10^{-5} moles/kg to 7 x 10^{-5} moles/kg. In certain embodiments, the dosages per day of the category 3 compound can be at least 1 x 10^{-7} moles/kg, 1 x 10^{-6} moles/kg, 1 x 10^{-5} moles/kg, 1 x 10^{-4} moles/kg or 1 x 10^{-3} moles/kg. The dosages can also be at least dosage 2.34 x 10^{-5} moles / kg body weight / day.

The dosages of category 3 compounds, such as Calcium peroxide, can be at dosages per day of 1 x 10^{-7} moles/kg to 1 x 10^{-2} moles/kg or 1 x 10^{-6} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-5} moles/kg to 1 x 10^{-4} moles/kg or 1 x 10^{-5} moles/kg to 7 x 10^{-5} moles/kg. In certain embodiments, the dosages per day of the category 3 compound can be at least 1 x 10^{-7} moles/kg, 1 x 10^{-6} moles/kg, 1 x 10^{-5} moles/kg, 1 x 10^{-4} moles/kg or 1 x 10^{-3} moles/kg. The dosages can also be at least dosage 2.34 x 10^{-5} moles / kg body weight / day.

The dosages of category 3 compounds, such as N-Acetylcysteine, can be at dosages per day of 1 x 10^{-7} moles/kg to 1 x 10^{-2} moles/kg or 1 x 10^{-6} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-5} moles/kg to 1 x 10^{-4} moles/kg or 1 x 10^{-5} moles/kg to 7 x 10^{-5} moles/kg. In certain embodiments, the dosages per day of the category 3 compound can be at least 1 x 10^{-7} moles/kg, 1 x 10^{-6} moles/kg, 1 x 10^{-5} moles/kg, 1 x 10^{-4} moles/kg or 1 x 10^{-3} moles/kg. The dosages can also be at least dosage 2.34 x 10^{-5} moles / kg body weight / day.

The dosages of category 3 compounds, such as H_2O_2, can be at dosages per day of 1 x 10^{-7} moles/kg to 1 x 10^{-2} moles/kg or 1 x 10^{-6} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-5} moles/kg to 1 x 10^{-4} moles/kg or 1 x 10^{-5} moles/kg to 7 x 10^{-5} moles/kg. In certain embodiments, the dosages per day of the category 3 compound can be at least 1 x 10^{-7} moles/kg, 1 x 10^{-6} moles/kg, 1 x 10^{-5} moles/kg, 1 x 10^{-4} moles/kg or 1 x 10^{-3} moles/kg. The dosages can also be at least dosage 2.34 x 10^{-5} moles / kg body weight / day.

The dosages of category 3 compounds, such as NaSH, can be at dosages per day of 1 x 10^{-8} moles/kg to 1 x 10^{-3} moles/kg or 1 x 10^{-7} moles/kg to 1 x 10^{-4} moles/kg or 1 x 10^{-6} moles/kg to 1 x 10^{-5} moles/kg or 1 x 10^{-6} moles/kg to 7 x 10^{-6} moles/kg. In certain embodiments, the dosages per day of the category 3 compound can be at least 1 x 10^{-8} moles/kg, 1 x 10^{-7} moles/kg, 1 x 10^{-6} moles/kg, 1 x 10^{-4} moles/kg or 1 x 10^{-3} moles/kg. In certain embodiments, the dosages can also be at least 3.02 x 10^{-6} moles / Kg body weight / day.

Methods

Disclosed are methods of resetting biological pathways for defending against and repairing deterioration from human aging. These methods reduce inflammation in a subject in need thereof, reverse aging and/or reverse accumulated cellular damage in a subject in need thereof, and/or for treat, prevent, and/or reduce the ill effects of a viral infection (*e.g.*, caused by SARS-CoV-2) in a subject in need thereof.

Although much of the present disclosure and the data presented in the Working Examples describes effectiveness of the herein-disclosed compounds, compositions, formulations, and methods for treating and/or reducing symptoms of Covid-19 infection, the herein-disclosed compounds, compositions, formulations, and methods are also effective for treating and/or reducing symptoms caused by other viral infections. Illustrative viral infections may be caused by one or more of enteroviruses A-J; rhinoviruses A-C; rotaviruses A-C; norovirus; influenza virus A-C and their several types like H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9, and their other relatives; human papillomaviruses (HPV); polyomaviruses like John Cunningham virus (JCV) and Merkel cell virus (MCV); poxviruses; herpesviruses such as human simplex virus 1 (HSV-1), human simplex virus 2 (HSV-2), varicella zoster virus, Epstein-Barr virus (human herpesvirus 4; EBV/HHV-4), human cytomegalovirus (HHV-5), and Herpesvirus 6 (A&B), herpesvirus 7, Kaposi's sarcoma-associated herpesvirus (HHV- 8); hepatitis A-E viruses (HAV, HBV, HCV); retroviruses like human immunodeficiency virus type 1 (HIV-1), type 2 (HIV-2) and their subtypes; Retroviruses like human immunodeficiency virus type 1, 2,

the endogenous LINE-1; another SARS coronavirus; Ebola virus (EBOV); Marburg virus (MARV); Lassa Fever virus; Banna virus; rubella virus; measles virus; mumps virus; human parainfluenza viruses (hPIV 1-4); rabies virus; Hantavirus; Dengue virus; West Nile virus; Zika virus; or orbivirus; as well as against other viruses that affect human or animal organism.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), S-Adenosyl-methionine (SAM), and zinc (*e.g.*, as zinc sulfate). In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), S-Adenosyl-methionine (SAM), and H_2O_2. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), S-Adenosyl-methionine (SAM), and NaSH. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), S-Adenosyl-methionine (SAM), and Na_2S. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Betaine, and zinc (*e.g.*, as zinc sulfate). In

specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), folate + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Methionine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Methionine, and zinc (*e.g.,* as zinc sulfate). In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Choline, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Betaine, and H_2O_2. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), folate + Vitamin B12, and H_2O_2. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Methionine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Methionine, and H_2O_2. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Choline, and H_2O_2.

In any of the herein described compositions, methods, and examples, H_2O_2 can be replaced with calcium peroxide or N-Acetylcysteine.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Betaine, and NaHS. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Folate + Vitamin B12, and NaHS. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Methionine, and NaHS. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Choline, and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Betaine, and Na_2S. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Folate + Vitamin B12, and Na_2S. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Methionine, and Na_2S. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Choline, and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β),

gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In specific examples, the disclosed methods can comprise administering to a subject nicotinamide adenine dinucleotide (NAD+), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic

acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Betaine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, folate + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), folate + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), folate + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), folate + Vitamin B12, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Methionine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Methionine, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Choline, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate). In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and zinc (*e.g.,* as zinc sulfate).

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject

nicotinamide riboside (NR), Betaine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Betaine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and H_2O_2.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, folate + Vitamin B12, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), folate + Vitamin B12, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), folate + Vitamin B12, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), folate + Vitamin B12, and H_2O_2.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine + Vitamin B12, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and H_2O_2.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Methionine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), with Methionine, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and H_2O_2.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Choline, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and H_2O_2.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and H_2O_2. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and H_2O_2.

In any of the herein described compositions, methods, and examples, H_2O_2 can be replaced with calcium peroxide or N-Acetylcysteine.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and NaHS. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine, and NaHS. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine, and NaHS. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Folate + Vitamin B12, and NaHS. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Folate + Vitamin B12, and NaHS. In other examples,

the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Folate + Vitamin B12, and NaHS. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Folate + Vitamin B12, and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and NaHS. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine + Vitamin B12, and NaHS. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and NaHS. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and NaHS. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Methionine, and NaHS. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Methionine, and NaHS. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and NaHS. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Choline, and NaHS. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and NaHS. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and NaHS. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and NaHS. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and NaHS. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and NaHS.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Folate + Vitamin B12, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Folate + Vitamin B12, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Folate + Vitamin B12, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Folate + Vitamin B12, and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine + Vitamin B12, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide

(NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Methionine, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Methionine, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Choline, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and Na_2S. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and Na_2S. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and Na_2S. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and Na_2S. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and Na_2S.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine, and any

one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can

comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin,

Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives,

Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Folate + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin,

Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole

derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Betaine + Vitamin B12, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic

acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a

subject nicotinamide riboside (NR), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β),

gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Methionine, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-

glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and

analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), Choline, and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

In specific examples, the disclosed methods can comprise administering to a subject nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me),

Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject nicotinamide riboside (NR), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.*, caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject one or more of nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and nicotinic acid riboside (NAR), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-

D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256. In other examples, the disclosed methods can comprise administering to a subject 1-methylnicotinamide (MNM) and/or cyclic adenosine monophosphate (cAMP), S-Adenosyl-methionine (SAM), and any one or more of H_2S, O_3, metformin, acetaminophen, sulforaphane, glucoraphanin, curcumin, quercetin, isoquercetin, ginseng, (R)-alpha–lipoic acid, Hydrophilic oxidized derivatives of Lycopene, N-Acetylcysteine, DHEA, garlic, β-lapachone, pterostilbene, resveratrol, apigenin, zinc,1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256.

The herein described "unit dose", "formulation", and/or "composition" may be referred to as an "NMN Cocktail".

DEFINITIONS

The terminology used herein is for the purpose of describing particular cases only and is not intended to be limiting.

As used herein, unless otherwise indicated, the terms "a", "an" and "the" are intended to include the plural forms as well as the single forms, unless the context clearly indicates otherwise. Thus, a composition comprising "a" compound of category 3, as an example, can include more than one compound of category 3.

The terms "comprise", "comprising", "contain," "containing," "including", "includes", "having", "has", "with", or variants thereof as used in either the present disclosure and/or in the claims, are intended to be inclusive in a manner similar to the term "comprising."

By preventing is meant, at least, avoiding the occurrence of a disease and/or reducing the likelihood of acquiring the disease. By treating is meant, at least, ameliorating or avoiding the effects of a disease, including reducing a sign or symptom of the disease.

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *e.g.,* the limitations of the measurement system. For example, "about" can mean 10% greater than or less than the stated value. In another example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the given value. Where particular values are described in the application and claims, unless otherwise stated the term "about" should be assumed to mean an acceptable error range for the particular value.

"Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

As used herein, by a "subject" is meant an individual. Thus, the "subject" can include domesticated animals (*e.g.,* cats, dogs, etc.), livestock (*e.g.,* cattle, horses, pigs, sheep, goats, etc.), laboratory animals (*e.g.,* mouse, rabbit, rat, guinea pig, etc.), and birds. "Subject" can also include a mammal, such as a primate or a human.

The term "NMN cocktail" comprises any NMN containing unit dose, composition, or formulation as disclosed herein. Illustrative NMN cocktails include at least one compound from category 1, at least one compound from category 2, and at least one compound from category 3.

Any aspect or embodiment described herein can be combined with any other aspect or embodiment as disclosed herein.

EXAMPLES

The following examples are set forth below to illustrate the methods, compositions, and results according to the disclosed subject matter. These examples are not intended to be inclusive of all aspects of the subject matter disclosed herein, but rather to illustrate representative methods, compositions, and results. These examples are not intended to exclude equivalents and variations of the present invention, which are apparent to one skilled in the art.

Example 1: Dramatic clinical improvement in ten consecutive acutely ill elderly patients with presumed COVID-19 treated with a cocktail of nicotinamide mononucleotide (NMN), betaine, sodium chloride and zinc sulfate: A case series

Background: NAD+ is a critical cellular "currency", facilitating metabolism, oxidation reduction, circadian rhythm, DNA repair, control of aging and the immune system. However, as humans age, intra-cellular NAD+ drops, with 50-year-old individuals having only half the quantity of NAD+ compared to healthy young individuals. This age associated NAD+ depletion appears to be exacerbated during COVID-19 infections, especially when complicated by cytokine storm. Severe NAD+ depletion impairs our anti-viral defense systems and our ability to optimally handle inflammation. Thus, there exists a strong molecular rationale for treating elderly patients acutely infected with complicated SARS-CoV-2 with NAD+ precursors.

Methods: Ten consecutive acutely ill presumed SARS-CoV-2 infected patients in a private internal medical practice older than 50 years were treated with over-the-counter nicotinamide mononucleotide (NMN) and three OTC boosters. One patient was not included as Covid-19 was ruled out; 8 patients had positive nasopharyngeal SARS-CoV-2 PCR tests and one patient had classic Covid-19 symptoms. Seven of the nine Covid-19 patients had serial oxygen, temperatures, room air oxygen levels, cytokine determinations as well as serial chest x-rays performed.

Results: Patients 1, 4, 7, and 10 were critically ill with documented worsening oxygenation, increasing levels of inflammation biomarkers, and worsening chest x-ray appearance immediately prior to administration of the NMN cocktail. These patients exhibited prompt post treatment clinical improvement, namely 2-3 days till temperature resolution (4 out of 4 patients), ~5 days until discharge (3 out of 3 patients), prompt chest x-ray improvement (4

out of 4 patients) and dramatic drops in cytokine levels (3 out of 4 patients) within 3 days. Patients 5 and 8 had double pneumonia but no prior films or inflammation tests. Patients 2 and 3 were severely symptomatic outpatient status post failed hydroxychloroquine (HC), Zithromax (Z) and Zinc (Zc) with no chest x-rays performed. In these four patients, there was a strong temporal relationship between NMN cocktail use and rapid clinical improvement. Patient 6, a severely symptomatic 79-year-old man with multiple comorbidities but no pneumonia clinically improved at day 8 post onset of symptoms with resolved fever less symptoms with lowered inflammation markers. He stopped the NMN cocktail after just three days, then on day12 post symptom onset had a relapse of symptoms (recurrent fever and dizziness) and new bilateral inflammatory infiltrates.

Summary: The clinical data presented here evidences an effective method for treating elderly patients infected with SARS-CoV-2 with NAD+ precursors. A cocktail of NMN and boosters repeatedly resulted in prompt clinical improvement of ill elderly persons with complicated Covid-19 infections with dramatic drops in inflammatory markers. NAD+ precursors with and without boosters deserve further placebo-controlled study in elderly individuals with complicated COVID-19 infections.

Introduction: The last century of scientific endeavor is marked by two truly transformative discoveries – nuclear fission and age reversal. Although everyone has heard of radioactive isotopes that fuel explosive nuclear reactions, only a few academic biologists are aware of the eight proven paths to reverse aging in mammals. One of the most practical and promising anti-aging agents is NMN, an orally absorbed NAD+-boosting compound with remarkable abilities to reverse age-associated kidney, liver, brain, vascular and immune system decline in mice. This food supplement, found in small amounts in breast milk, tomatoes and avocados, has its own specific transmembrane transporter, and in Phase I and II human clinical trials, larger doses were found to be safe, well tolerated and able to raise NAD^+ levels in whole blood. NAD+, the cell's hydrogen carrier, is well known for its role in oxidation-reduction (redox) reactions. More recently, it has emerged as a signaling molecule through its role as a substrate for several different families of enzymes, most notably the sirtuins. By modulating sirtuins, NAD+ controls hundreds of key processes from energy metabolism to cell survival, rising and falling depending on food intake, exercise, and the time of day. Sirtuins have been shown to play a major regulatory role in almost all cellular functions. At the physiological level, sirtuins impact inflammation, cell growth, circadian rhythm, energy metabolism, neuronal function, stress resistance, DNA repair and immune functions. The addition of other food supplements known to block the nicotinamide

feedback loop, facilitate transmembrane absorption and enable Nrf2 enzyme activity for maximal sirtuin enzyme function, are also safe and well tolerated and along with other NAD+ precursors lower human cytokine levels in healthy elderly subjects.

Patient 1 was a rapidly deteriorating SARS-CoV-2 positive woman who needed hospitalization. Her room air (RA) O_2 saturation suddenly dropped, her pulmonary infiltrates increased and cytokine levels spiked. The experimental remdesivir or any experimental anti-IL6 drug was unavailable for what appeared to be an obvious cytokine storm. With no other treatment available, after signed informed consent from the patient and family, oral NMN was administered with three additional OTC food supplement boosters (the NMN cocktail). Patient 1 dramatically improved within 48 hours. Based on this surprisingly prompt and dramatic result, these OTC products were further studied in the next nine consecutive patients who were over 50 years old and with presumptive diagnosis of COVID-19.

Methods: Ten consecutive individuals over the age of 50 with presumptive diagnosis of COVID-19 were identified and treated with NMN with three additional boosters (the NMN cocktail, EGA®).

Data was collected prospectively from each patient. Additional longitudinal information was entered based on review of hospital records and patient diaries of home temperature, O_2 saturation and the presence or absence of other COVID-19 associated symptoms (cough, sore throat, SOB, chest sensation, headache, diarrhea or anosmia) and activity (*i.e.* bedridden vs walking). Timely chest x-rays availability proved challenging as all local outpatient radiologic facilities refused service for Covid-19 patients during the duration of this study.

Acute respiratory distress syndrome (ARDS) was defined as bilateral pulmonary opacities on chest radiograph, arterial hypoxemia (partial pressure of arterial oxygen [PaO_2] to fraction of inspired oxygen [FiO_2] ratio <300), and exclusion of cardiac failure - at time of treatment (See, Bernard *et al.* The American-European Consensus Conference on ARDS. Am J Respir Crit Care Med. 1994; 149: 818-824).

Results:

Patient characteristics: Eight patients (FIG. 2) had positive PCR-based diagnosis from nasal swabs for SARS-CoV-2, Patient 3 had classic Covid-19 clinic presentation (cough, daily fevers to 102°F, severe fatigue and anosmia) and Patient 9 was ruled out for COVID-19 based on three negative PCR-based nasal swabs for SARS-CoV-2, one negative

serologic test for antibodies directed against the virus (day 18 post symptom onset) together with a normal chest x-ray and chest computerized tomography (CT) scan.

The nine Covid-19 infected patients were on average 65 years old with frequent co-morbidities -two with diabetes, five with pre-diabetes, two with known significant Coronary Artery Disease (CAD), three on baseline meds for Hypertension (HTN), and six with body mass index (BMI) in the overweight category. Nine of nine patients presented with fever, cough and lethargy leaving them for the most part bedridden; six of nine patients reported anosmia with five of nine patients initially complaining of diarrhea.

Patients 1, 2, and 3 previously were administered hydroxychloroquine plus Zithromax and zinc. Patient 10 took a six-day course of hydroxychloroquine. Patient 4 received an experimental course of convalescent plasma.

All patients were ill when treatment with the NMN cocktail was begun; treatment began from 5 to 34 days after the onset of Covid-19 symptoms (FIG. 3). Treatment was recommended for at least 6 days. Two patients took treatment for only three days.

At time of treatment, seven patient had chest x-rays done - six patients had bilateral pulmonary opacities (Patients 1, 4, 5, 7, 8, and 10) - four patients (Patients 1, 4, 8, and 10) had ARDS (FIG. 3, blue). Patient 6 had a normal chest x-ray.

Serial chest x-rays from prior to the time of treatment were available in four patients (Patients 1, 4, 7 and 10) - every case revealed worsening chest x-ray appearance (FIG. 3, yellow). Oxygenation status and inflammation markers in these critically ill cases were also deteriorating immediately prior to the initiation of treatment.

Patient Outcomes:

All nine patients fully recovered following NMN cocktail treatment and with no discernable lasting symptoms.

Fevers ran continuously an average of nine continuous days before NMN cocktail administration, then resolved in all nine patients in 2-3 days (FIG. 4). All six patients with bilateral opacities (including the four patients who met ARDS criteria) exhibited prompt post treatment clinical improvement, namely 2-3 days until temperature resolution (six out of six patients), ~5 days until discharge (three out of three patients/*) and dramatic drops in cytokine levels (five out of six patients) within 3-10 days with elevated absolute lymphocyte numbers (six out of six patients), within in a day. Chest x-ray improvement was noted in every patient with pneumonia at the onset of treatment (six out of six patients), specifically those with worsening bilateral pulmonary infiltrates (Patients 1, 4, 7 and 10)

and bilateral pulmonary infiltrates of unknown onset (Patients 5 and 8) with significant improvement at the first follow-up film (4, 4, 10, 17, 10 and 9 days respectively).

In the two severely symptomatic outpatients with no chest x-ray, there was a strong temporal relationship between NMN cocktail use and prompt clinical improvement.

Patient 6, a 79-year-old man with multiple comorbidities was severely symptomatic but had no pneumonia initially; he clinically improved after three days of treatment (resolved fever, symptoms better and inflammation biomarkers lowered). Due to a miscommunication, he stopped the NMN cocktail after just three days. Three days after treatment was stopped, he relapsed, complaining of recurrent fever and dizziness together with increased cytokines and new bilateral inflammatory infiltrates.

Patient-reported toxicity

Seven patients reported no adverse effects. Patients 1 and 2 complained of jitteriness temporally associated with NMN cocktail ingestion that attenuated with repeated use (Patient 1) and dose discontinuation at day 3 (Patient 2).

No other adverse symptoms or lab changes were noted.

Disease fatality associated with COVID19 – like with SARS, Ebola and dengue fever - can often be attributed to cytokine storm: an exaggerated pro-inflammatory response with lymphocytopenia, elevated IL-6 and CRP that gives rise complex pulmonary, cardiac and hematologic conditions. COVID-19 severity, and lethality are substantially higher in the population aged 60 and older, making this yet another “aging” disease.

Possibly effective anti- SARS-CoV-2 drugs (chloroquine, Zithromax, Zinc) - though perhaps to be credited in some patients for dropping the nasal viral load to negligible levels - are not enough to prevent this overexuberant anti-SARS-CoV-2 immune response resulting in persistent fevers and a swift pulmonary decline.

The patients’ dramatic clinical “reversal” was temporally related to the administration of NMN. Safe and well tolerated doses of NMN - with nicotinamide feedback loop blockers and Nrf2 boosters including Zinc - markedly lowers human cytokine levels (CRP-hs, Il-6 and TNF-α) in healthy elderly subjects to younger healthier levels (preliminary clinical data). Yet these individuals still spiked their inflammatory markers when they were under viral attack (*i.e.* influenza) – perhaps supporting the critical balance between virus attack on one hand and tolerable collateral tissue damage on the other hand.

In conclusion, oral administration of a composition of the present disclosure, which included nicotinamide mononucleotide/betaine/Zinc Sulfate (with NaCl to aid absorption),

possesses important immune "anti-aging" properties vital in reversing cytokine storm associated with COVID-19.

Individual Case Summaries:

Patient 1: A 55-year-old white female presented with a one-day history of body aches, choking cough and fever to 100.2ºF. The SARS-CoV-2 PCR test was positive.

On day 3, she complained of new myalgias and chest aching. On day 7, she was bedridden with chest pain, shortness of breath, cough and high fevers (T max 102° F). Her room air (RA) O_2 % sat was 93-95. A chest x-ray (CXR) taken on day 7 was normal (FIG. 5).

On day 8 her fever increased to 102.5° F. She was prescribed Zithromax, hydroxychloroquine and zinc sulfate. On day 11, despite hydroxychloroquine triple therapy, she deteriorated; her temp increased to 103° F, she had debilitating body aches, dyspnea at rest, a RA O_2 % sat of 90 and chest x-ray with bilateral patchy infiltrates throughout both lungs (FIG. 6) consistent with new onset acute respiratory distress syndrome (ARDS).

When admitted to the hospital, her body mass index (BMI) was 30 and her history was positive for a recent uneventful elective arm plastic surgery and a past history of episodic hives and allergic reactions to Ivermectin and Keflex. Admission labs suggested poor prognosis (CRP (217 mg/L), Il-6 (56 pg/mL), TNF-alpha (7.4 ng/mL) and myoglobin (>500 ng/mL) with absolute lymphopenia (490 cells/μL)). On day 13, she complained of worsening dyspnea at rest. She had lowered RA % saturation (84) and worsening ARDS (FIG. 7), with her Chest x-ray showing an interval increase in the bilateral patchy pulmonary opacities (36 hours after hospital admission).

A repeat nasopharyngeal SARS-CoV-2 test revealed negligible (<4 copies/μl) nasopharyngeal virus.

Tocilizumab – a humanized monoclonal antibody that inhibits ligand binding to the human interleukin-6 receptor (IL-6R) – was requested for presumptive cytokine storm, however, strict hospital protocol prohibited the use of this intravenous drug outside of the ICU – and because her O_2 % sat on high flow nasal O_2 was still $\geq$ 90, she did not meet criteria for ICU transfer. She therefore agreed to continue Zinc Sulfate and begin NMN, Betaine, Sodium Chloride and zinc (the NMN cocktail) twice a day diluted in 500cc water and timed in sync with the her presumed diurnal circadian rhythm peaks. (Table 4).

Quite unexpectedly, 12 hours later, her absolute lymphocyte count increased by 85%. Then, after two weeks of continuous fever, the patient turned afebrile at 5 am on day 14, 36 hours after the NMN cocktail was begun. On day 17 she was discharged home on oral NMN, betaine, NaCl and Zinc Sulfate twice a day; her clinical signs (fever, shortness

of breath, body aches) were remarkably better, her room air % O_2 sat (up from 84 to 96) and chest x-ray (FIG. 8) also dramatically improved over just 4 days, and showing improved interstitial and alveolar opacities compared with the chest x-ray of day 13. Her laboratory markers (CRP and IL6) simultaneously dropped approximately 80% during the 5 days of in hospital NMN cocktail administration.

On day 20, her third day home, she felt stronger and walked multiple times a day. Her nasopharyngeal SARS-CoV-2 test was negative. Her CRP and IL-6 decreased to 7.4 and 3.2 respectively. On day 23, she was asymptomatic; her COVID-19 IgG/IgM rapid serology was positive for both IgG and IgM. Her CXR revealed a small amount of residual peripheral infiltrates (FIG. 9) but had dramatically improved interstitial and alveolar opacities

FIG. 10 lists Patient 1's medical history over the course the study.

Patient 2: A 60-year-old SARS-CoV-2 NAA positive man with cough, chest tightness, dyspnea, diarrhea and HA was prescribed HCQ, AZ and Zn as an outpatient on his 15th consecutive day of fever. At the completion of the 6-day course he became afebrile and his chest pressure and headache improved, however his cough and insomnia continued. Three days later, his fever, HA and chest pressure recurred. He was begun on the NMN cocktail and experienced a prompt response:

- His recurrent 2-day fever resolved within 24 hours
- His clinical condition improved in 2-3 days (resolved cough, chest pain, headache)
- Improved oxygenation in three days (RA O_2 sat 95 to 96%)
- Anti-inflammatory action in 3 days (CRP dropped from 2.6 to undetectable and absolute lymphocytes increased from 1100 to 1300)
- Probable side effect: patient complained of shaky hands and a "too much caffeine" edginess. These symptoms resolved after 1-2 days off the NMN cocktail.

FIG. 11 lists Patient 2's medical history over the course the study.

Patient 3: A 72-year-old woman complained of fever, fatigue, sore throat, cough, HA, anosmia and diarrhea approximately 5 days after her personal assistant came down with a similar constellation of symptoms. She was clinically diagnosed as SARS-COV-2 infected. On symptom day 3, she was seen at her home and begun on HCQ, AZ and Zn. However, despite the "triple therapy" course, her O2 sat dropped from 96 to 94% and her symptoms intensified. She was then treated with the NMN cocktail. She experienced a prompt

response: Her 15-day fever resolved within 2 days. Her clinical condition improved in 3 days (resolution of cough, fatigue, and headache).

FIG. 12 lists Patient 3's medical history over the course the study.

Patient 4: A 79-year-old businessman was admitted to the intensive care unit (ICU) on symptom day 22 with ARDS, renal failure (Cr 4.6), diabetes, liver failure (AST/ALT 2878/1598) with possible pulmonary embolism and myocarditis. His chest x-ray on day 22 showed bilateral infiltrates consistent with ARDS (FIG. 13)

He tested positive for SARS-COV-2 RT-PCR, received high flow nasal O_2, empiric antibiotics, anticoagulants and was placed in a convalescent plasma trial on symptom day 24 (Remdesivir was contraindicated given his liver failure). Post convalescent plasma, his high-flow nasal O_2 needs, liver failure, renal failure and inflammatory profile improved allowing transfer from the ICU to a floor bed on symptom day 27.

However, over the subsequent six days, his condition consistently deteriorated; he became febrile for the first time on day 27 and the fever persisted while all his inflammatory markers increased in lockstep. Finally, on day 32, his oxygenation and chest x-ray (FIG. 14, showing increasing bilateral infiltrates, especially in the left lung) worsened to the point his family was told by the hospital Covid-19 pulmonary and infectious disease physicians that ICU transfer was imminent - they recommended Tocilizumab plus Remdesivir (AST/ALT 52/91) be started as soon as possible.

The family requested a second opinion consultation. A nasal PCR test was conducted which revealed no virus, making cytokine storm the likely cause of his week-long post convalescent plasma deterioration and rendering the Remdesivir recommendation moot. Given the patient's and the patient's family's fear of possible severe Tocilizumab side effects, after signed consent, the patient opted to first try the NMN cocktail beginning the evening of day 34.

After eight continuous days of fever, he became afebrile within 36 hours of beginning the NMN cocktail. After being bed ridden for 5 weeks, he was able to sit in 3 days, walk in 5 days. In the first 72 hours, his inflammatory markers CRP, IL-6 and D-Dimer were -43, -67 and -24% respectively. Most significantly, his oxygenation quickly normalized (RA O2 sat increased from <74 to 90% in just 6 days, with chest x-ray improvement in 5 days (FIG. 15, showing interval improvement of the extensive bilateral pulmonary infiltrates)) and near normalization in 10 days (FIG. 16), with diffuse infiltrates dramatically resolved.

The patient was discharged on day 40 and had a full, uneventful recovery at home. On Day 47 his diffuse infiltrates had dramatically resolved and his RA O_2 sat was 95.

FIG. 17 lists Patient 4's medical history over the course the study.

Patient 5: A 52-year female chef (known SARS-CoV-2 NAA positive) was first seen on symptom day 10 complaining of persistent fever, shortness of breath, headache and loss of smell and taste. Her presenting chest x-ray revealed bilateral pneumonia (FIG. 18, showing irregular marginated parenchymal opacities in the R mid and lower lobes and possibly in the left retrocardiac region).

She was begun on the NMN cocktail with a prompt and dramatic response:

- Resolution temperature (afebrile within 48 hours)
- Improved clinical condition (cough, SOB and headache improved "90%" in just 3 days)
- Potent anti-inflammatory action (CRP and IL-6 were -49 and -90% respectively in 6 days)
- Improved oxygenation (RA O2 sat from 95 to 97% in 3 days)
- Decreased chest x-ray parenchymal opacities in 10 days (FIG. 19)

FIG. 20 lists Patient 5's medical history over the course the study.

Patient 6: A 78-year-old Latino man, regularly employed in a physically demanding job, presented after prolonged contact with known SARS-COV-2 NAA positive family members and 5 days after the onset of suspicious symptoms (new fever, cough, sore throat and diarrhea). He was a past smoker on medication for hypertension, coronary heart disease and diabetes type 2. His CXR was normal (FIG. 21).

Given his high probability of having Covid-19, his symptoms (weakness and dizziness requiring him to use a walker - baseline normal ambulation) together with risk factors predicting a heighten chance of a poor outcome, he was empirically placed on the NMN cocktail treatment. His SARS-COV-2 NAA test subsequently returned positive; his CRP was normal, his IL-6 was moderately elevated. He noted a prompt response to NMN cocktail treatment:

- His 1-2-day fever resolved in two days
- His clinical condition partially improved - less cough - but he was still weak, lightheaded and nauseous and needing a cane (no longer walker) to ambulate.
- His oxygenation improved (RA O2 sat 95 to 97% in 3 days)
- In 3 days, his IL-6 dropped (-49%) and his absolute lymphocytes increased 8%.

His examination on day 8 revealed orthostatic hypotension, positional dizziness and fasting glucose 129. He was asked to discontinue his blood pressure medication. On day 10, the family reported his fever had returned, he was feeling worse and was unable to get out of bed.

His examination on day 11 revealed new fever and persistent nausea with benign positional vertigo. Laboratory tests revealed increasing inflammation markers (FIG. 22). *via* interpreters, he revealed when told on day 8 to stop his blood pressure medications, he had also prematurely stopped his NMN cocktail. He felt better over the next several days with the exception of persistent nausea.

On day 15 he was afebrile but still complained of positional vertigo and persistent N but was noted to walk without assistance. A chest x-ray was performed (FIG. 23) revealing new L mid to upper lung zone peripheral and sub pleural opacifications. His metformin was discontinued. Over the next 1-2 days the patient's nausea resolved. The patient felt progressively better such that on day 21 he felt essentially "100%" and returned to his physically demanding full time job.

Patient 7: A 61-year-old female first presented to a local ER on symptom day 5 for fever, shortness of breath (SOB), muscle cramps, cough, nausea and diarrhea. Chest x-ray (FIG. 24) was normal but a CT chest revealed several patchy peripheral regions of ground glass opacification bilaterally suspicious for viral pneumonia. She tested positive for SARS-COV-2 RT-PCR and was discharged home with no treatment.

Her SOB, cough and fever worsened and I first saw her in consultation on symptom day 7 with T=102 and an O_2 sat of 95% (FIG. 25). Chest x-ray revealed new bilateral pneumonia (FIG. 26).

She was begun on the NMN cocktail with a prompt response:

- She became afebrile within 3 days.
- Her clinical symptoms (cough, chest pressure, SOB and nausea) improved markedly in the first three days with her diarrhea nearly gone in 6 days
- Improved oxygenation (RA O_2 sat 95 to 98 % in 3 days)
- Chest x-ray on day 17 (FIG. 27, showing opacities in the mid to lower lung zone are decreased but increased parenchymal opacification without cavitation R lower lung zone was in part better, in part worse than day 7 CXR (FIG. 26).
- Normalization of chest x-ray by day 24 (FIG. 28) with decreased parenchymal opacification within the R mid to lower lung zone since day 17, irregular

marginated parenchymal opacities consistent with bilateral Covid-19 pneumonias.

- Over the first three days her CRP and IL6 both increased. They were next tested on day 17 and were both markedly decreased

Patient 8: A 60-year-old cab driver was first seen on symptom day 12 complaining of 10 days of fever, fatigue, and cough and chest pressure. A chest x-ray revealed irregular marginated bilateral parenchymal opacities L>R consistent with bilateral viral pneumonia (FIG. 29). His nasopharynx SARS-COV-2 NAA test returned positive the following day (FIG. 30).

He was begun on the NMN cocktail with a prompt response:

- Resolved temperature (afebrile within 48 hours)
- Improved clinical condition (fatigue, SOB, cough and abnormal chest sensation were 75% better in 2-3 days)
- Potent anti-inflammatory action (CRP, IL-6 and absolute lymphocytes changed -60, -41 and 36% respectively in just 3 days)
- Improved oxygenation (RA O_2 sat 93 to 94% in 3 days)
- Modest improvement of chest x-ray in 10 days (FIG. 31, showing decreased parenchymal opacification present compared with day 12).

Patient 10: A 62-year-old SARS-CoV-2 RT-PCR positive businessman was admitted to an outlying hospital on symptom day 14 for spiking fever to 104° F, dropping O_2 sats and bilateral pneumonia. His admission chest x-ray (FIG. 32) showed scattered infiltrates predominately within the periphery of bilateral lung fields. On the second day of his hospitalization, he was told there was no treatment for his condition. His interactions with hospital staff doctor and nursing staff was less than a collective 5-10 minutes per day and his wife was not allowed in the hospital or able to speak with the assigned doctor. He requested admission to the hospital but the "lateral" Covid-19 positive patient transfer was denied based on hospital protocol. He then left the hospital against medical advice.

He later presented to the clinic ill with fever to 102° F, cough, diarrhea, extreme exhaustion and hypoxia with O_2 sat 92/93%. He was immediately begun on the NMN cocktail with a prompt response:

- Resolved 17-day persistent fever (afebrile within 48 hours)
- Improved clinical condition (fatigue, SOB, cough and abnormal chest sensation were 75% better in 2-3 days)
- Improved oxygenation (RA O_2 sat 93 to 96% in 3 days)

- However, the chest x-ray day 19 (after 3 days of NMN cocktail) showed progression of infiltrates compared to the hospital admission chest x-ray (taken 2 days prior to the start of NMN cocktail administration). (FIG. 33, showing numerous bilateral ill-defined parenchymal opacities, worse since day 14 chest x-ray, consistent with viral pneumonia).

On day 26 the patient returned for a follow-up. He noted continued improvement:

- He remained afebrile and symptomatically far improved only noting some coughing and profuse night sweats
- His CRP after 9 days of treatment dropped about 50% from baseline but his IL-6 increased dramatically from 59 to 269.
- Improved oxygenation (RA O2 sat 92/93 to 98% after 9 days of treatment)
- Improved CXR (FIG. 34, showing significant decrease in bilateral parenchymal opacities).

On day 33 the patient returned for another follow-up. He was completely asymptomatic.

- Potent anti-inflammatory effect – Day 33 CRP and IL-6 were - 90 and -79% respectively.
- Near normalization of CXR at day 33 (FIG. 35, showing further decreases in bilateral parenchymal opacities).

FIG. 36 lists Patient 10's medical history over the course the study.

Summary: The ill elderly patients in this case study exhibit a compelling temporal relationship between NAD+ precursor cocktail administration and clinical improvement - more remarkably these cases document unusually rapid and thorough clinical turnarounds in just 3-6 days - markedly different than the expected course of ill Covid-19 patients, especially those with worsening hypoxemia and ARDS.

Example 2: Illustrative formulations for treating at least "Cytokine Storm Syndrome" associated with a viral infection, including COVID-19

In this example, illustrative formulations of compositions for treating a viral infection are disclosed.

Illustrative formulations of an NMN cocktail include Nicotinamide mononucleotide (NMN), Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1. Certain formulations further comprise about a ratio of NaCl (to the other

components) of from about 0.25 and about 1.25. Sodium helps absorption of components of the compositions.

Certain formulations of NMN cocktail have a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate. As examples, a unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate. In a formulation, the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate. In any of these formulations, the unit dose further may further comprise from about 25 mg to about 100 mg of NaCl. In embodiments, the unit dose further comprises about 50 mg of NaCl.

A formulation may further comprise additional components that contribute to color, stability, flavor, sweetness, and/or stability.

At least one unit of compositions of these formulations are administered to a subject at each dosing. The subject thus administered may have a viral infection, *e.g.,* caused by the SARS-CoV-2. For some subjects, at least two units of the composition, at least three units of the composition, at least four units of the composition, or at least five units of the composition is administered to the subject at each dosing.

The number of units of the composition per dosing may relate in part to the weight of the subject. For example, when a subject weighs 100 lbs or less, the subject is administered at least one unit of the composition per dosing. When a subject weighs over 100 lbs, the subject is administered at least one unit, at least two units, at least three units, or at least four units or at least five units of the composition per dosing.

In certain subjects, the subject receives at least one dosing per day, at least two dosings per day, at least three dosings per day, or at least four dosings per day.

These compositions may be obtained by a subject or by a healthcare provider in powdered form. The powder can be mixed with water or another suitable liquid. For example, a unit dose of the composition may be sufficiently soluble in at least about 100 ml of water. If solubility or preference is otherwise, more water/liquid may be mixed. Or less water if at the subject's preference.

These compositions may be obtained by the subject or the healthcare provider in a sealed air proof, waterproof package, *i.e.,* sachet. The sachet may have an inner lining to help protect the composition. The sachet may have a tear line, so composition does not spill when the sachet's top is opened. The sachet may have printed instructions on one surface.

Illustrative instructions may include: "Take as directed by a physician Dissolve the contents of each sachet completely in a minimum of 100 ml of pure water. Dose in proportion to your body weight. Take on an empty stomach in the morning and/or evening 12 hours apart. Store any unused liquid portion in refrigerator if possible. Freeze unused sachets for long term storage." Multiple (10 or more) sachets may come in a kit.

Example 3

A 61-year-old Caucasian male weighing 88 kg at the beginning of the treatment was treated with a regimen of an NMN cocktail comprising category 1, category 2, and category 3 molecules as noted below.

Nicotinamide mononucleotide (NMN) (MW=334.22)

Betaine (trimethyl glycine) (MW =117.14)

H_2O_2 (MW=34.01)

NaSH (MW=56.06)

Solutions of various compounds were produced for administering to the subject by mixing a set number of grams with 500 mL of water.

Typical final concentrations of NMN taken by subject were 3.5 grams in 500 mL H_2O, betaine were 3 grams in 500 mL H_2O, H_2O_2 were (2 drops of 35% concentration in 500 mL H_2O), and NaSH were (drops of 2 at 66uM per drop concentration in 500 mL H_2O).

The amounts of each composition were set so that by the subject drinking the full 500 mL a final dosage approximately 1.19×10^{-4} moles NMN/ kg body weight per dose, 2.91×10^{-4} moles betaine / kg body weight per dose, 1.17×10^{-5} moles of H_2O_2 / kg of body weight per dose, and 1.51×10^{-6} moles of NaSH / kg of body weight per dose was given to the subject through drinking the 500 mL solution.

By taking two similar dosages per day, the sum of the two daily equal doses was

- Nicotinamide Mononucleotide (NMN) dosage -- 2.38×10^{-4} moles / Kg body weight / day
- The betaine dosage -- 5.82×10^{-4} moles / Kg body weight / day
- The Hydrogen Peroxide (H_2O_2) dosage -- 2.34×10^{-5} moles / Kg body weight / day
- The Sodium Hydrogen Sulfide (NaSH) dosage -- 3.02×10^{-6} moles / Kg body weight / day

The subject was weighed each day.

The subject self-administered the formulations orally through drinking the solution at approximately 7AM and 7 PM each day. These times were chosen because they

approximated the subjects' biological clock peaks of NAD+ as determined by Ramsey K 2009. This had the effect of pulsing the ingredients into the body twice a day, approximately timed with the biological clock of the subject.

LabCor Inc. performed the marker testing using standard protocols on a monthly basis. Blood draw times ranged between 8:19 am and 8:54 am. Inflammatory measurements are correlated to the biological clock. LabCor tested levels of CMV IgG, C-Reactive Protein, Tumor Necrosis Factor-Alpha, and Interleukin-6 in Serum.

The subject also had the following data collected monthly at LabCorp, including Serum Glucose, Serum Uric Acid, BUN, Serum Creatinine, eGRF if non-African American, BUN/Creatinine Ratio, Serum Sodium, Serum Potassium, Serum Chloride, Total Carbon Dioxide, Serum Calcium, Serum Phosphorus, Serum Total Protein, Serum Albumin, Serum, Total Globulin, A/G Ratio, Total Bilirubin, Serum Alkaline Phosphatase, LDH, AST (SGOT), ALT (SGPT), Serum Iron, Total Cholesterol, Triglycerides, HDL Cholesterol, Calculation VLDL cholesterol Calculation LDL Cholesterol, Total Cholesterol/ HDL ratio, Estimated CHD risk, White Blood Cells, Red Blood Cells, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Platelets, Neutrophils, Lymphs, Monocytes, Eos, Basos, Immature Cells, Neutrophils (Absolute). Lymphs (Absolute), Monocytes (Absolute), Eos (Absolute), Baso (Absolute), Immature Granulocytes, Immature Grans (Absolute), NRBC, VAP Cholesterol Profile, LDL Cholesterol, HDL Cholesterol, VLDL Cholesterol, Cholesterol total, Triglycerides, Non HDL Cholesterol (LDL+VLDL), ApoB100=Calculation, LDL-R (Real)-C, Lp(a) Cholesterol, IDL Cholesterol, Remnant Lipo (IDL+VLDL3), Probable Metabolic Syndrome, HDL-2 (most Protective), HDL-3 (Less Protective), VLDL-3 (Small Remnant), LDL1 Pattern A, LDL2 Pattern A, LDL3 Pattern B, LDL4 Pattern B, LDL Density Pattern, Glucose Tolerance (4 Sp Blood), Glucose Fasting, Glucose 1 hour, Glucose 2 hours, Glucose 3 hours, Insulin Fasting, Insulin 1 hour, Insulin 2 hours, Insulin 3 hours, Cortisol AM, Cortisol PM, IL-1b (Serum), Hemoglobin A1c, Rheumatoid Arthritis Factor, IGF-1, Cardiac, Tumor Interleukin-8 (Serum), Homocyst(e)ine (Plasma), Antinuclear Antibodies direct, Sedimentation Rate-Westergren Cortisol, (Urinary Free), Cortisol, F, ug, L, U, Cortisol, Fug, 24hr,U, Serum Immunoglobulin G, Qn, Serum Immunoglobulin A, Qn, Serum Immunoglobulin M, Qn, oxLDL, CMV IgM, Ferritin, and H. pylori IgG.

University of California, San Diego measured:

a. Spectral 3 tesla MRI of right calf leg muscle before, during, and after exercise
b. Spectral 3 tesla MRI of Liver
c. Structural 3 tesla MRI of Liver

d. Spectral 3 tesla MRI of Brain (front and back)
e. A structural 3 tesla MRI of Brain
f. A structural 3 tesla MRI of the right knee (showing Arthritis)
g. 3-Nitrotyrosine (a marker for oxidative / nitrative stress)
h. Coagulation Tests (a marker for oxidative stress)
i. F2-isoprostanes (a marker for oxidative / nitrative stress,)
j. GSH: GSSH (a marker for and protection from oxidative / nitrative stress)
k. Urine Organic Acids
l. 8-hydroxydeooxyguanosine (8-OHDG) (a marker for oxidative / nitrative stress)
m. Malondialdehyde (a marker for oxidative / nitrative stress)
n. hsCRP (a marker that can be adversely affected by oxidative stress)
o. Proteomic profile (a marker for oxidative / nitrative stress)

A list of medical history questions (UCSD) were answered. Body fat and mineral testing was performed at private MD's office. Treadmill testing was performed at private MD's office. 4 tissue biopsy types (liver (needle biopsy), skin; adipose, muscle) were obtained (stored at -80 C at UCLA). A log of daily exercise and weight was obtained. Also weekly glucose monitoring before and after NMN and BP monitoring before and after NMN was obtained.

Results

Table 1.

						61-year-old Male Caucasian				
With the additions of										
NMN					X	X	X	X	X	X
Betaine								X	X	X
H_2O_2									X	
NaSH										X
		Normal Range Low	Normal Range High	Baseline						
CMV IgG		0	0	0	0	0	0	0	0	0
C-Reactive Protein	mg/L	0	3	2.77	3.25	0.43	0.53	0.85	0.21	0.40
Tumor Necrosis Factor-Alpha	pg/mL	0	8.1	1.1	0.9	1.1	1.1	1	0.5	0.3
Interleukin-6 Serum	pg/mL	0	15.5	1.3	4.4	<0.7	0.9	3.1	<0.7	<0.7
Inflammation Score		0	26.6	5.17	8.55	2.23	2.53	4.95	1.41	1.40

The results of the monthly administration schedule and testing for the subject are presented in Table 1. Table 1 shows that the subject was provided a formulation on a monthly basis, where the formulation included NMN alone for 3 months, NMN+ betaine for one month, NMN+ betaine + H_2O_2 for one month and NMN+ betaine +NaSH for one month.

Other observations of interest during study are that the subject was healthy during the full duration of the study. Photos depicted that aged skin cells on hand became youthful in appearance. The subject's complexion of facial skin improved during study. The subject had significant weight loss and apatite was lowered during study. The subject had an elimination of pain from arthritis in right knee during study. The subject had more restful sleep during study. The subject had increased energy during study. The subject had better vision at eye exam.

Discussion

The age of 61 correlates to the age of unrelated and offspring families in the Arai Y 2015 study detailed herein. The results of this study, in light of the Arai Y 2015 study, show that the triple therapy with the three categories of compounds change the predicted outcome, as identified by Arai 2015, of this 61 year old 88 kg Caucasian male from unsuccessful aging to a prediction of successful aging. In the baseline condition for the subject, both C-reactive Protein (2.77 mg/L) and Interleukin-6 (1.3 pg/mL) measurements were above the "unrelated family" level (0.7 mg/l and 1.13 pg/mL) (Arai Y 2015, Table 1) as well as the "offspring" level (0.7 mg/l and 1.03 pg/mL) (Arai Y. 2015, Table 1) respectively. The 61-male subject of this study has a similar age to the "offspring" group and the "unrelated family" group of Arai. These two inflammation test scores effect the prediction algorithm to predict a worse aging outcome for the 61-year-old subject than the "offspring" or "unrelated family" groups of Arai at baseline.

After two months of treatment with NMN, however, the markers of the 61-year-old subject were brought to levels better than the "offspring" group of Arai (CRP, 0.43 mg/l and IL-6, less than 0.7 pg/mL). While both of these markers do rise slightly in month one, the overall effect of the NMN treatment is to reduce the levels of these markers. The lower or approximately similar levels to the "offspring" group of Arai continued to be produced by administration of NMN through months 3, but the effect seemingly plateaus in the 61-year-old male.

All three inflammatory markers drop to their lowest level with the addition of all three categories of ingredients. IL-6 drops to undetectable levels, TNF-alpha drops by over

50%, and CRP drops to about a tenth of the original value. When H_2O_2 is used for the category 3 ingredient in this example CRP drops more than when NaSH is used and when NaSH is used as the category 3 ingredient TNF-alpha dropped more than when H_2O_2 is used. In both cases of triple therapy, the results are far below the necessary levels to predict very successful aging. CMV titers were not discussed here since this 61-year-old male had no or undetectable levels of CMV IgG and this is as good as the measured value of this variable can get.

When the interventional therapy for this 61-year-old male in this experiment is compared to the results gained by one or two years of calorie restriction one can see that the results are far greater with this triple category therapy and they are far easier to obtain.

It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Example 4: Fifty patients have been administered NMN cocktails

To date fifty patients have been administered NMN cocktails. In each case, improvements in the patient's conditions and/or symptoms were observed. A list of the patients treated is included in Table 2, below.

Table 2:

Outpatients administered NMN cocktails				
Patient #	**Age**	**ethnicity**	**Sex**	**Condition at presentation**
1	61	Caucasian	Male	Low O2 sat
2	72	Caucasian	Male	Low O2 sat
3	52	Hispanic	Female	**Pneumonia**
4	79	Hispanic	Male	**No Pneumonia**
5	61	Hispanic	Male	**Pneumonia**
6	60	Hispanic	Female	**Pneumonia**
7	62	Caucasian	Male	**Pneumonia**
8	87	Caucasian	Male	Low O2 sat
9	56	Caucasian	Male	Low O2 sat
10	82	Caucasian	Female	Low O2 sat
11	56	Caucasian	Male	Low O2 sat
12	83	Caucasian	Female	Low O2 sat
13	66	Caucasian	Male	Low O2 sat
14	54	Caucasian	Female	
15	67	Caucasian	Male	
16	62	Caucasian	Female	Low O2 sat
17	82	Caucasian	Male	Low O2 sat
18	65	Caucasian	Male	Low O2 sat

19	50	Caucasian	Male	**Pneumonia**
20	65	Caucasian	Male	Low O2 sat
21	50	Caucasian	Male	Low O2 sat
22	57	Caucasian	Male	**Pneumonia**
23	87	Caucasian	Female	
24	80	Black	Male	**Pneumonia**
	was hospitalized on day #3 of treatment, x 7 days, not ICU			
25	78	Caucasian	Male	
26	62	Caucasian	Female	
27	67	Caucasian	Male	
28	68	Hispanic	Female	Low O2 sat
29	60	Caucasian	Male	**Pneumonia**
	was hospitalized on day #6 treatment, x 5 days, not ICU			
30	67	Caucasian	Male	
31	61	Caucasian	Female	
32	45	Caucasian	Female	
33	68	Caucasian	Female	
34	57	Caucasian	Male	**No Pneumonia**
35	46	Indian	Female	**Pneumonia**
36	65	Caucasian	Male	Low O2 sat
37	65	Caucasian	Female	
38	65	Caucasian	Female	
39	64	Caucasian	Female	
40	70	Caucasian	Male	
41	44	Caucasian	Male	
42	66	Black	Male	Low O2 sat
43	75	Caucasian	Female	Low O2 sat
Hospitalized patients administered NMN cocktails				
Patient #	**Age**	**ethnicity**	**Sex**	**Condition at presentation**
1	55	Caucasian	Female	**Pneumonia**
	prompt improvement hypoxia, inflammation in 1-2 d post NMN			
2	78	Caucasian	Male	**Pneumonia**
	prompt improvement hypoxia, inflammation in 1-2 d post NMN			
3	62	Caucasian	Male	**Pneumonia**
	NMN given immediaetly post discharge, stronger in days			
4	56	Caucasian	Male	**Pneumonia**
	NMN begun 12 hrs prehospital, continued inpatient. DC after 4 days			
5	68	Caucasian	Male	**Pneumonia**
	NMN given twice (in ER and next AM). Then hospital denied the patient NMN cocktail. Pt stable hypoxia x 2			

	days. Day 3 onset progressive deterioration, intubated, died one week later			
6	62	black	Female	**Pneumonia**
	NMN begun 12 hrs prehospital, continued inpatient. DC after 3 d			
NMN cocktail administered for long period in a severe post-intubation patient having diffusion defect of 50.4% of normal				
1	64	Caucasian	Male	
	after 18 days NMN cocktail use, his Diffusion capacity increased 2%, his Diffusion capacity to alveolar volume increased 9%, (his calculated alveolar volume decreased 8%) he c/o nausea and was then taken off NMN cocktail			

Example 5: Additional viral infections treated by NMN cocktails

The data presented in the above Working Examples describe effectiveness of the herein-disclosed compounds, compositions, formulations, and methods for treating and/or reducing symptoms of Covid-19 infection, the herein-disclosed compounds, compositions, formulations, and methods are also effective for treating and/or reducing symptoms caused by other viral infections. Illustrative viral infections may be caused by one or more of enteroviruses A-J; rhinoviruses A-C; rotaviruses A-C; norovirus; influenza virus A-C and their several types like H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9, and their other relatives; human papillomaviruses (HPV); polyomaviruses like John Cunningham virus (JCV) and Merkel cell virus (MCV); poxviruses; herpesviruses such as human simplex virus 1 (HSV-1), human simplex virus 2 (HSV-2), varicella zoster virus, Epstein-Barr virus (human herpesvirus 4; EBV/HHV-4), human cytomegalovirus (HHV-5), and Herpesvirus 6 (A&B), herpesvirus 7, Kaposi's sarcoma-associated herpesvirus (HHV- 8); hepatitis A-E viruses (HAV, HBV, HCV); retroviruses like human immunodeficiency virus type 1 (HIV-1), type 2 (HIV-2) and their subtypes; ; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; Ebola virus (EBOV); Marburg virus (MARV); Lassa Fever virus; Banna virus; rubella virus; measles virus; mumps virus; human parainfluenza viruses (hPIV 1-4); rabies virus; Hantavirus; Dengue virus; West Nile virus; Zika virus; or orbivirus; as well as against other viruses that affect human or animal organism.

Illustrative diseases resulting from viral infections include (i) non-cancer diseases: enteritis (enteroviruses A-J); common cold (rhinoviruses A-C); gastroenteritis, diarrhoea (rotaviruses A-E, norovirus); gastroenteritis (norovirus); influenza (influenza virus A-C);

progressive multifocal leukoencephalopathy (JCV), nephrophathy, Merkel cell cancer (MCV), smallpox (variola) (poxvirus); herpes (HSV-1, HSV-2); chicken-pox, herpes zoster (shingles) (varicella zoster virus); infectious mononucleosis (HHV-4); hepatitis A (hepatitis A virus); hepatitis B (hepatitis B virus); hepatitis C (hepatitis C virus); acquired immunodeficiency syndrome (HIV-1, HIV-2, and their subtypes); severe acute respiratory syndrome (SARS); Ebola (EBOV); Marburg virus disease (MARV); fever and encephalitis (Banna virus); rubella (rubella virus); measles (measles virus); mumps (mumps virus); parainfluenza (hPIV 1-4); rabies (rabies virus); (ii) virus-associated cancer diseases: Hodgkin' s lymphoma, nasopharyngeal carcinoma, Burkitt's lymphoma (EBV/HHV-4); mucoepidermoid carcinoma (HHV-5); hepatocellular carcinoma (HBV, HCV); cancer of cervix, anus, penis, vagina, and oropharyngeal cancer (HPV); primary effusion lymphoma, Kaposi's sarcoma (HHV-8); as well as (iii) autoimmune diseases often associated with various viruses: dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome; and various other viral diseases of human and animals.

In these methods, a subject having or suspected of having a viral infection – other than caused by SARS-CoV-2 – is administered a compound, composition, or formulation as disclosed herein and according to the methods disclosed here; thereby treating or reducing a symptom of the viral infection.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed.

CLAIMS

What is claimed is:

1. A composition for administering to a subject, composition, comprising:

a repair system activator chosen from, nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, nicotinamide adenine dinucleotide (NAD+), nicotinamide riboside (NR), nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), nicotinic acid riboside (NAR), 1-methylnicotinamide (MNM), cyclic adenosine monophosphate (cAMP), and any combination thereof;

a methyl donor chosen from, betaine, S-5'-adenosyl-L-methionine (SAM), methionine, choline, serine, folate, vitamin B12, and any combination thereof; and

an antioxidant defense activator chosen from zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, NaSH, Na_2S, ROS, RNS, RCS, RSOH, $O_2^{\bullet -}$, $OH^{\bullet}$, $^1O_2$, O_3, HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, metformin, acetaminophen, diallyl trisulfide, isothiocyanate, curcumin, sulforaphane, quercetin, isoquercetin, apigenin, luteolin, ginseng, carnosic acid, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, xanthohumol, β-lapachone, pterostilbene, resveratrol, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256, and any combination thereof.

2. The composition of claim 1, wherein the repair system activator, the methyl donor, and the antioxidant defense activator are present in a combined amount of at least 5 wt.% of the composition.
3. The composition of claim 1 or claim 2, wherein the repair system activator is nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, nicotinamide riboside (NR), or both.
4. The composition of any one of claims 1 to 3, wherein the methyl donor is betaine, methionine, or both.
5. The composition of any one of claims 1 to 4, wherein the antioxidant defense activator is zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, or NaSH.
6. The composition of any one of claims 1 to 5, wherein the repair system activator, methyl donor, and antioxidant defense activator are in an amount sufficient to beneficially change a surrogate marker for aging level in a human when compared to the surrogate marker level prior to administration.
7. The composition of claim 6 wherein the change in the level of the surrogate marker is lowered.
8. The composition of claim 7, wherein the surrogate marker is CMV IgG, C-Reactive Protein, Tumor Necrosis Factor-Alpha, or Interleukin-6.
9. The composition of claim 6, wherein the change in the level of the surrogate marker is increased.
10. The composition of claim 9, wherein the surrogate marker is DNA methylation.
11. The composition of any one of claims 1 to 10, where the composition further comprises water.
12. The composition of any one of claims 1 to 11, wherein the composition comprises at least 1×10^{-8} moles of the repair system activator, at least 1×10^{-8} moles of the methyl donor, and at least 1×10^{-9} moles of the antioxidant defense activator.
13. The composition of any one of claims 1 to 12, wherein the composition comprises nicotinamide mononucleotide (NMN) or the precursor or prodrug of NMN, Betaine, and zinc (*e.g.,* as zinc sulfate).
14. The composition of anyone of claim 1 to 13, further comprising Na^+ (*e.g.*, as NaCl) to increase the absorption of NMN or Betaine.
15. The composition of any one of claims 1 to 14 for use in a method for reversing aging and/or for reversing accumulated cellular damage in a subject in need thereof.

16. The composition of any one of claims 1 to 15 for use in a method for treating, preventing, and/or reducing the ill effects of a viral infection in a subject in need thereof.

17. The composition of claim 16, wherein the viral infection is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an enterovirus A-J; a rhinovirus A-C; a rotavirus A-C; a norovirus; an influenza virus A-C and their types such as H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9; a human papillomavirus; a polyomavirus: John Cunningham virus and Merkel cell virus; a poxvirus; a herpesvirus such as human simplex virus 1, human simplex virus 2, varicella zoster virus, Epstein-Barr virus or human herpesvirus 4; a human cytomegalovirus, Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus; a hepatitis A-E virus; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; an Ebola virus; a Marburg virus; a Lassa Fever virus; a Banna virus; a rubella virus; a measles virus; a mumps virus; a human parainfluenza virus; a rabies virus; a Hantavirus; a Dengue virus; a West Nile virus; a Zika virus; or an orbivirus.

18. The composition of any one of claims 1 to 17, wherein the composition comprises NMN, Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

19. The composition of any one of claims 1 to 17, wherein a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate.

20. The composition of claim 19, wherein the unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate.

21. The composition of claim 20, wherein the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate.

22. The composition of any one of claims 1 to 21, further comprises from about 25 mg to about 100 mg of NaCl.

23. The composition of claim 22, wherein the composition further comprises about 50 mg of NaCl.

24. An injectable formulation, comprising the composition of any one of claims 1 to 23.

25. A tablet comprising the composition of any one of claims 1 to 23.

26. A powder comprising the composition of any one of claims 1 to 23.

27. A beverage comprising the composition of any one of claims 1 to 23.

28. A method for reducing inflammation in a subject in need thereof, for reversing aging and/or for reversing accumulated cellular damage in a subject in need thereof, and/or for treating, preventing, and/or reducing the ill effects of a viral infection in a subject in need thereof comprising: administering to the subject the composition of any one of claims 1 to 27.

29. The method of claim 28, wherein the composition is administered to a subject at a dosage of at least 1 x 10^{-6} moles /kg of the repair system activator to the subject, 1 x 10^{-6} moles /kg of the methyl donor to the subject, and 1 x 10^{-7} moles /kg of the antioxidant defense activator to the subject.

30. The method of any one of claims 27 to 29, wherein the composition is injected over 8-12 days.

31. The method of any one of claims 27 to 29, wherein the composition is in an aerosol, lyophilized, powder, or emulsion form.

32. The method of any one of claims 27 to 31, wherein the subject in need thereof is a human.

33. The method of claim 32, wherein the composition is administered to the human for at least two months.

34. The method of claim 33, wherein the composition is in a tablet that is administered orally at least once daily.

35. The method of claim 33, wherein the composition further comprises water.

36. The method of claim 35, wherein the composition is administered to the subject once daily.

37. The method of any one of claims 27 to 36, wherein the composition comprises nicotinamide mononucleotide (NMN) or the precursor or prodrug of NMN, Betaine, and zinc (*e.g.,* as zinc sulfate).

38. The method of any one of claim 27 to 37, wherein Na^+ is used to increase the absorption of NMN or Betaine.

39. The method of any one of claim 27 to 38, wherein the viral infection is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an enterovirus A-J; a rhinovirus A-C; a rotavirus A-C; a norovirus; an influenza virus A-C and their types such as H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9; a human papillomavirus; a polyomavirus: John Cunningham virus and Merkel cell virus; a poxvirus; a herpesvirus such as human simplex virus 1, human simplex

virus 2, varicella zoster virus, Epstein-Barr virus or human herpesvirus 4; a human cytomegalovirus, Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus; a hepatitis A-E virus; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; an Ebola virus; a Marburg virus; a Lassa Fever virus; a Banna virus; a rubella virus; a measles virus; a mumps virus; a human parainfluenza virus; a rabies virus; a Hantavirus; a Dengue virus; a West Nile virus; a Zika virus; or an orbivirus.

40. The method of any one of claims 27 to 39, wherein at least one unit of the composition is administered to the subject at each dosing.

41. The method of claim 40, wherein at least two units of the composition, at least three units of the composition, at least four units of the composition, or at least five units of the composition is administered to the subject at each dosing.

42. The method of claim 40 or claim 41, wherein the number of units of the composition per dosing relates in part to the weight of the subject.

43. The method of claim 42, wherein a subject weighing less than 100 lbs is administered at least one unit of the composition per dosing and/or a subject weighing over 100 lbs is administered at least one unit, at least two units, at least three units, or at least four units or at least five units of the composition per dosing.

44. The method of any one of claims 40 to 43, wherein the subject receives at least one dosing per day, at least two dosings per day, at least three dosings per day, or at least four dosings per day.

45. A method for reducing inflammation in a subject in need thereof, for reversing aging and/or for reversing accumulated cellular damage in a subject in need thereof, and/or for treating, preventing, and/or reducing the ill effects of a viral infection in a subject in need thereof, comprising: administering to the subject

a repair system activator chosen from nicotinamide mononucleotide (NMN) or a precursor or prodrug of NMN, nicotinamide adenine dinucleotide (NAD+), nicotinamide riboside (NR), nicotinic acid adenine mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), nicotinic acid riboside (NAR), 1-methylnicotinamide (MNM), cyclic adenosine monophosphate (cAMP), and any combination thereof;

a methyl donor chosen from, betaine, S-5'-adenosyl-L-methionine (SAM), methionine, choline, serine, folate, vitamin B12, and any combination thereof; and

an antioxidant defense activator chosen from zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, NaSH, Na_2S, ROS, RNS, RCS, RSOH, $O_2^{\bullet-}$, OH•, $^1O_2$, O_3, HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, metformin, acetaminophen, diallyl trisulfide, isothiocyanate, curcumin, sulforaphane, quercetin, isoquercetin, apigenin, luteolin, ginseng, carnosic acid, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, xanthohumol, β-lapachone, pterostilbene, resveratrol, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256, and any combination thereof.

46. The method of claim 45, wherein the repair system activator, the methyl donor, and the antioxidant defense activator are administered at approximately the same time.

47. The method of claim 45 or 46, wherein the repair system activator is administered within 15, 30, 60, 90, or 120 minutes of the subject's biological clock NAD+ peak.

48. The method of any one of claim 45 to 47, wherein the repair system activator, the methyl donor, and the antioxidant defense activator are administered at different times.

49. The method of any one of claim 45 to 48, wherein the subject is a human.

50. The method of claim 49, wherein the repair system activator, the methyl donor, and the antioxidant defense activator are administered to the human for at least two months.

51. The method of claim 49 or claim 50, wherein the repair system activator, the methyl donor, and the antioxidant defense activator are administered to the human once daily.

52. The method of anyone of any one of claims 45 to 51, wherein Na+ is used to increase the absorption of NMN or Betaine.

53. The method of any one of claim 45 to 52, wherein the viral infection is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an enterovirus A-J; a rhinovirus A-C; a rotavirus A-C; a norovirus; an influenza virus A-C and their types such as H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9; a human papillomavirus; a polyomavirus: John Cunningham virus and Merkel cell virus; a poxvirus; a herpesvirus such as human simplex virus 1, human simplex virus 2, varicella zoster virus, Epstein-Barr virus or human herpesvirus 4; a human cytomegalovirus, Herpesvirus 6 (A&B), herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus; a hepatitis A-E virus; Retroviruses like human immunodeficiency virus type 1, 2, the endogenous LINE-1; another SARS coronavirus; an Ebola virus; a Marburg virus; a Lassa Fever virus; a Banna virus; a rubella virus; a measles virus; a mumps virus; a human parainfluenza virus; a rabies virus; a Hantavirus; a Dengue virus; a West Nile virus; a Zika virus; or an orbivirus.

54. The method of any one of claim 45 to 53, wherein the repair system activator, the methyl donor, and/or the antioxidant defense activator are each independently in the form of an injectable formulation.

55. The method of any one of claim 45 to 54, wherein the repair system activator, the methyl donor, and/or the antioxidant defense activator are each independently in the form of a tablet.

56. The method of any one of claim 45 to 55, wherein the repair system activator, the methyl donor, and/or the antioxidant defense activator are each independently in the form of a powder.

57. The method of any one of claim 45 to 56, wherein the repair system activator, the methyl donor, and/or the antioxidant defense activator are each independently in the form of a beverage.

58. The method of any one of claims 45 to 57, wherein the repair system activator, the methyl donor, and the antioxidant defense activator are respectively NMN, Betaine, and Zinc Sulfate and in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

59. The method of any one of claims 45 to 58, wherein a unit dose of the repair system activator, the methyl donor, and the antioxidant defense activator comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate.

60. The method of claim 59, wherein the unit dose comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate.

61. The method of claim 60, wherein the unit dose comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate.

62. The method of any one of claims 59 to 61, wherein the unit dose further comprises from about 25 mg to about 100 mg of NaCl.

63. The method of claim 62, wherein the unit dose further comprises about 50 mg of NaCl.

64. The method of any one of claims 59 to 63, wherein at least one unit of the composition is administered to the subject at each dosing.

65. The method of claim 64, wherein at least two units of the composition, at least three units of the composition, at least four units of the composition, or at least five units of the composition is administered to the subject at each dosing.

66. The method of claim 64 or claim 65, wherein the number of units of the composition per dosing relates in part to the weight of the subject.

67. The method of claim 66, wherein a subject weighing less than or about 100 lbs is administered at least one unit of the composition per dosing and/or a subject weighing over 100 lbs is administered at least one unit, at least two units, at least three units, or at least four units or at least five units of the composition per dosing.

68. The method of any one of claims 64 to 67, wherein the subject receives at least one dosing per day, at least two dosings per day, at least three dosings per day, or at least four dosings per day.

69. The method of any one of claims 28 to 68, wherein the subject is at least 50 years old.

70. The method of any one of claims 28 to 69, wherein the subject has previously been treated with one or more of hydroxychloroquine, Zithromax, and zinc.

71. The method of any one of claims 28 to 70, wherein the subject is administered the composition in accordance with the subject's circadian rhythm.

72. The method of any one of claims 28 to 71, wherein the subject is administered the composition to a substantially empty stomach.

73. A composition comprising:

a precursor or prodrug of nicotinamide mononucleotide (NMN)

a methyl donor chosen from, betaine, S-5'-adenosyl-L-methionine (SAM), methionine, choline, serine, folate, vitamin B12, and any combination thereof; and

an antioxidant defense activator chosen from zinc (*e.g.,* as zinc sulfate), calcium peroxide, N-Acetylcysteine, H_2O_2, H_2S, NaSH, Na_2S, ROS, RNS, RCS, RSOH, $O_2^{\bullet-}$, OH•, $^1O_2$, O_3, HOCl, HOBr, HOI, ROOH, where R is alkyl, cycloalkyl, heteralkyl, heterocycloalkyl, alkenyl, heteroalkenyl, cycloalkenyl, or hetercycloalkenyl, metformin, acetaminophen, diallyl trisulfide, isothiocyanate, curcumin, sulforaphane, quercetin, isoquercetin, apigenin, luteolin, ginseng, carnosic acid, 4-methylalkylcatechol, 4 vinylcatechol, 4-ethlycatechol, xanthohumol, β-lapachone, pterostilbene, resveratrol, 1,4-diphenyl-1,2,3-triazoles, 15-deoxy-D12,14-prostaglandin J2, 3,4-dihyfroxyphenylethanol, 3-alkylamino-1H-indole acrylates, 4-phenyl-1,2,4-triazole derivatives, 6-Shogaol, Acetyl-11-keto-β-boswellic acid, Acteoside, Astaxanthin, Bardoxolone (CDDO), Methyl ester of bardoxolone (CDDO-Me), Benfotiamine, Berberine, Butein, tert-butylhydroquinone (tBHQ), Caffeine, Cardamonin, Carnosol, Catechin, Cinnamic acid and its derivatives (*e.g.,* caffeic acid phenethyl ester, ferulic acid ethyl ester, and trans-Cinnamaldehyde), Curcumin and its derivatives and analogues, Dimeric derivative of ferulic acid, Dimethyl fumarate (DMF, Tecfidera), Diterpenoid derivatives, Epicatechin, Epigallocatechin, Epigallocatechin gallate (EGCG), Eriodictyol-7-O-glucoside, Genistein, Licochalcone E, Naphthazarin, Naringenin, Nordihydroguaia retic acid (NDGA), Phenethyl isothiocyanate (PEITC), Phloretin, Piperlongumine and its analogs, Pyrrolidine dithiocarbamate, Silybin, Alpha (α), beta (β), gamma (γ), and delta (δ) Tocotrienols (T3), Triptolide, Fenofibrate, Melatonin, Vinblastin, Cyanoside-3-O-glucoside, and FW1256, and any combination thereof.

74. The composition of claim 73, wherein the composition comprises NMN, Betaine, and Zinc Sulfate in a ratio of from about 7 and 20: to from about 4 and 10; to about 1.

75. The composition of claim 73 or claim 74, wherein a unit dose of the composition comprises from about 0.8 grams and about 2.0 grams of NMN, from about 0.4 grams and 0.8 grams of Betaine, and from about 0.09 and 0.25 grams of Zinc Sulfate.

76. The composition of claim 75, wherein the unit dose of the composition comprises from about 0.9 grams and about 1.1 grams of NMN, from about 0.45 grams and 0.55 grams of Betaine, and from about 0.1 and 0.12 grams of Zinc Sulfate.

77. The composition of claim 76, wherein the unit dose of the composition comprises about 1 gram of NMN, 0.5 grams of Betaine, and about 0.11 grams of Zinc Sulfate.

78. The composition of any one of claims 73 to 77, wherein the unit dose further comprises from about 25 mg to about 100 mg of NaCl.

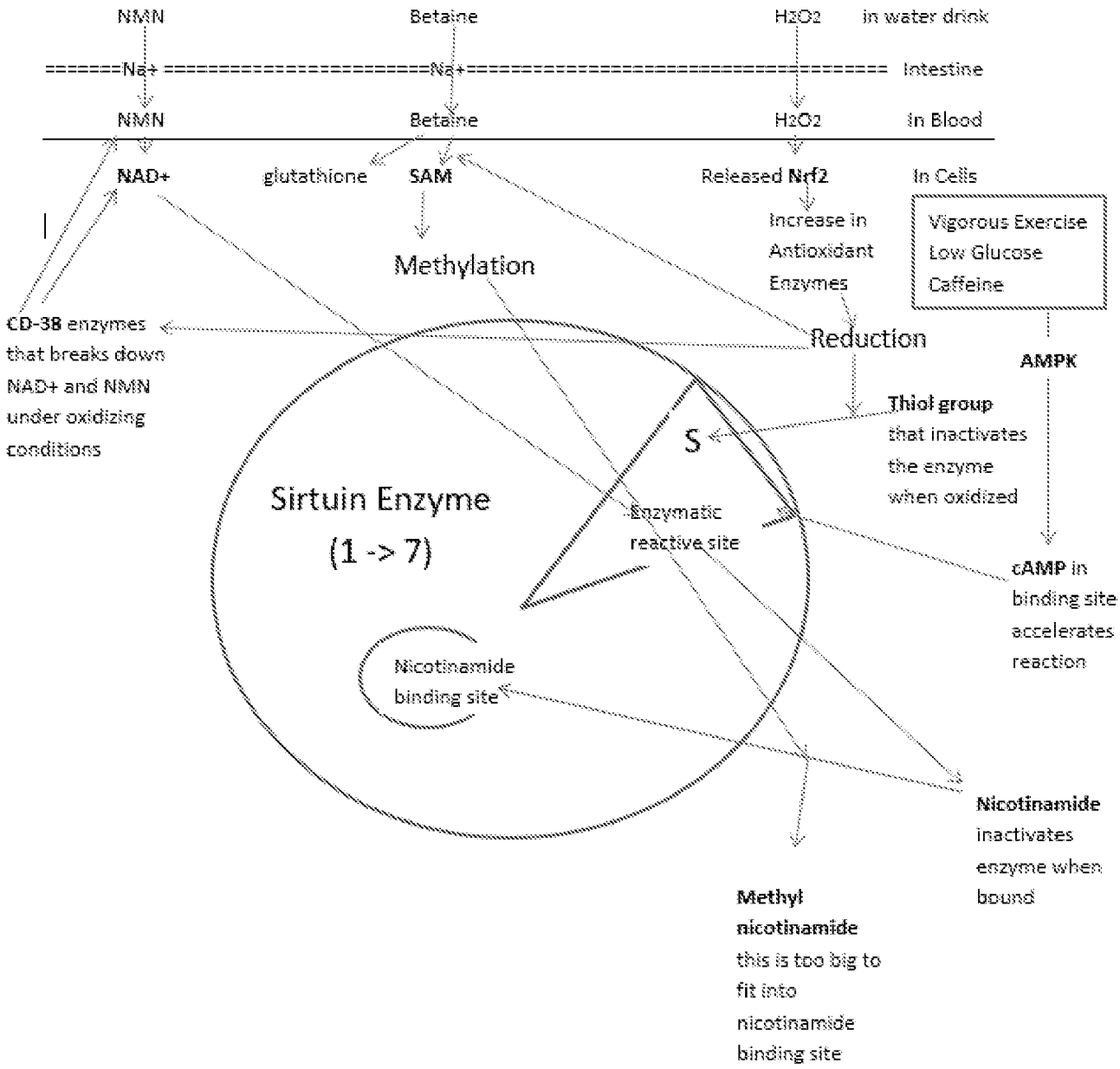
79. The composition of claim 78, wherein the unit dose further comprises about 50 mg of NaCl.

80. A disposable waterproof and/or air proof container comprising the composition of any one of claims 73 to 79.

81. The disposable waterproof and/or air proof container of claim 80, wherein the container comprises instructions for use.

82. A kit comprising at least ten of the containers of claim 80 or claim 81.

FIG. 1


NMN
Betaine
H2O2
in water drink
Na+
Na+
Intestine
NMN
Betaine
H2O2
In Blood
NAD+
glutathione
SAM
Released Nrf2
In Cells
Increase in Antioxidant Enzymes
Vigorous Exercise
Low Glucose
Caffeine
Methylation
CD-38 enzymes that breaks down NAD+ and NMN under oxidizing conditions
Reduction
AMPK
Thiol group that inactivates the enzyme when oxidized
S
Sirtuin Enzyme
(1 -> 7)
Enzymatic reactive site
cAMP in binding site accelerates reaction
Nicotinamide binding site
Nicotinamide inactivates enzyme when bound
Methyl nicotinamide this is too big to fit into nicotinamide binding site

Patient Characteristics										
Patient #	1	2	3	4	5	6	7	8	10	9
Covid-19 Test	(+) PCR	(+) PCR	na	(+) PCR	(+) PCR	(+) PCR	(+) PCR	(+) PCR	(+) PCR	(-) PCR x 3
Age	55.1	60.6	72.2	79.3	52.4	78.7	61.4	59.6	62.0	56.7
Gender	F	M	F	M	F	M	F	M	M	M
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Hispanic	Hispanic	Hispanic	Hispanic	Caucasian	Caucasian
Exercise/Week	0	0	0	4	0	0	0	0	0	5
Job Physicality	0	0	0	0	1	1	0	0	0	0
Comorbidities										
BMI	30	26	24	24	29	29	26	28	24	25
Smoking Hx		past		past		past		current		
Diabetes			pre-DM2	DM2	pre-DM2	DM2	pre-DM2	pre-DM2	pre-DM2	
CAD			CAD	OSA		CAD, CABG				
HTN			HTN	HTN		HTN				
Medication		lipitor	diazide	metformin		metformin				
			crestor	lipitor		metropolol				
				lisinopril		benicar				
				allopurinol		lipitor				
Symptom onset	3/15/20	3/6/20	4/1/20	4/12/20	5/17/20	5/22/20	5/20/20	5/18/20	5/24/20	5/27/20
Symptoms	fever	fever	fever	fever	fever	fever	fever	fever	fever	fever
	cough	cough	cough	cough	cough	cough	cough	cough	cough	cough
		diarrhea	diarrhea			diarrhea	diarrhea		diarrhea	hoarseness
		HA	HA	Fatigue		nausea	nausea		Fatigue	
	chest tight	chest tight	chest tight		chest tight	dizzyness	chest tight	chest tight		
			anosmia	anosmia	anosmia	anosmia	anosmia		anosmia	
	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden
Prior treatment	HC, A, Zinc	HC, A, Zinc	HC, A, Zinc	Convalescent plasma					HC	

FIG. 2

Pre-Treatment Clinical Condition										
Patient #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**
Why treatment begun:	Worsening pulm infiltrates and hypoxia, increasing cytokine levels	Recurrent fever, severe headache and chest pressure several days after apparent recovery	Persistent fever, cough, abnormal O2 sat, lethargy	Worsening pulm infiltrates and hypoxia, increasing cytokine levels , new fever s/p convalescent plasma therapy	**Double pneumonia, risk factors for poor outcome**	**Severe Covid-19 symptoms, risk factors for poor outcome**	Worsening pulm infiltrates, risk factors for poor outcome	**Double pneumonia, risk factors for poor outcome**	Worsening pulm infiltrates and hypoxia, increasing cytokine levels
Days of Symptoms	12	24	9	34	8	5	7	12	16
Consecutive days fever	12	1	14	8	10	2	7	9	15
Bilateral pulmonary infiltrates	yes	unknown	suspected	yes	yes	no	yes	yes	yes
ARDS	yes	unknown	unknown	yes	no	no	no	yes	yes
Worsening Infiltrates	yes	unknown	unknown	yes	unknown	no	yes	unknown	yes
Pre-Treatment Lab Values									
RA O2 sat %	84	95	94	<74	95	98	97	93	93
CRP	201	2.6	na	211	5.7	<0.2	3.1	25	14.9
IL6	54	na	na	19	23.1	13.3	17.4	29.7	59.2
Absolute lymphocytes	291	1100	na	920	1200	1300	1700	1400	1000

FIG. 3

FIG. 4

Patient Outcomes									
Patient #	1	2	3	4	5	6	7	8	10
Days of Rx till T< 99.3	2	1	2	2	3	2	3	3	2
Treatment (d)	11	3	6	13	6	3	6	6	9
CRP 3 d post	134	0.1		121	6.8	<0.2	5.8	10.1	12.1
% change	-33%	-96%		-43%	19%	0%	87%	-60%	-19%
CRP 6 d post	26			32	2.9	2			
change	-87%			-85%	-49%				
CRP 10 d post	7.4			0.7	0.1	1.3	0.3	1.5	7
change	-96%			-100%	-98%		-90%	-94%	-53%
IL6 3 d post	38			18.4	14.7	6.8	41.1	17.6	73.4
change	-30%			-3%	-36%	-49%	136%	-41%	24%
IL6 6 d post	17			6.2	2.4	19.6			
change	-69%			-67%	-90%	47%			
Il6 10 d post	3.2			4.3	2.9	12.3	5.3	6.2	269.0
change	-94%			-77%	-87%	-8%	-70%	-79%	354%
Abs lymphocye 3 d post	785	1300		1450	1200	1400	2100	1900	900
change	170%	18%		58%	0%	8%	24%	36%	-31%
Abs lymphocye 6 d post	1092			1230	1200	1100			
change	275%			34%	0%	-15%			
Abs lymphocye 10 d post	1218			1900	1500	1800	3500	1800	1100
change	319%			107%	25%	38%	106%	29%	10%

Six cases with documented bilateral infiltrates at time of treatment

Decreasing inflamation markers or increasing absolute lyphoctye count

Increasing inflamation markers or decreasing absolute lyphoctye count

FIG. 5

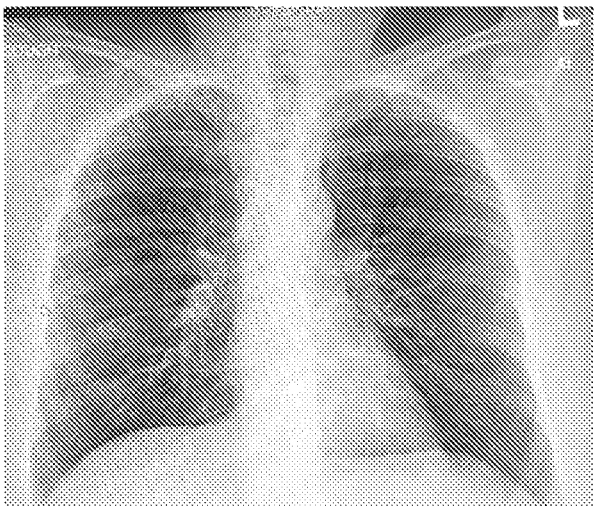


FIG 6

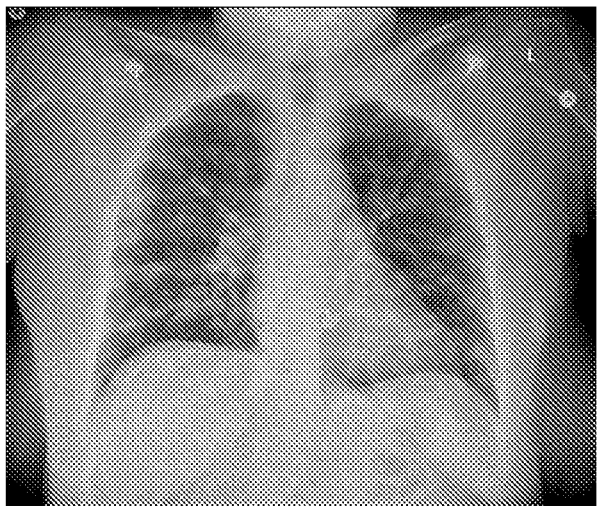


FIG. 7

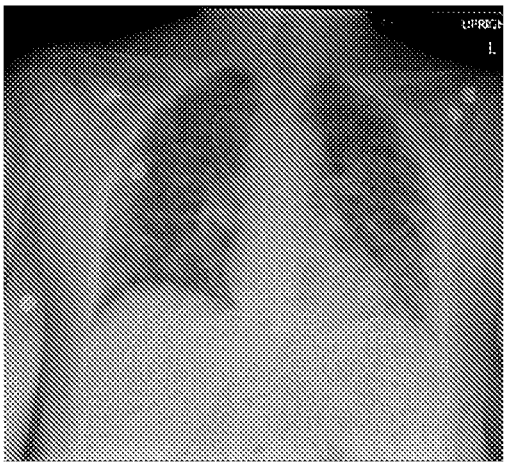


FIG 8

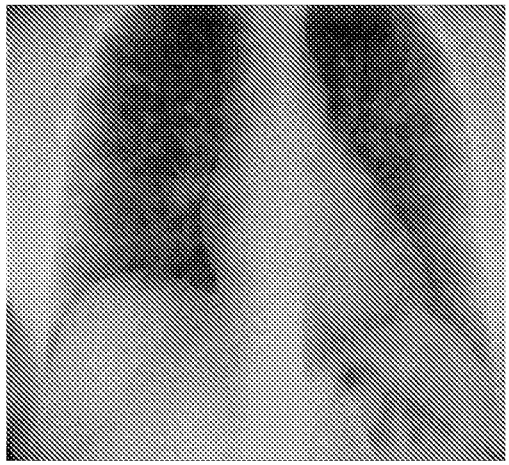


FIG. 9

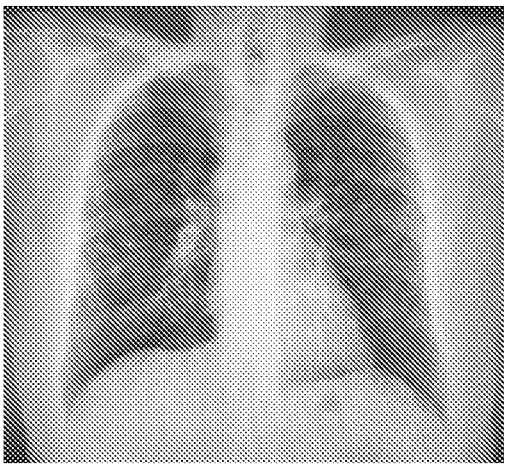


FIG. 10

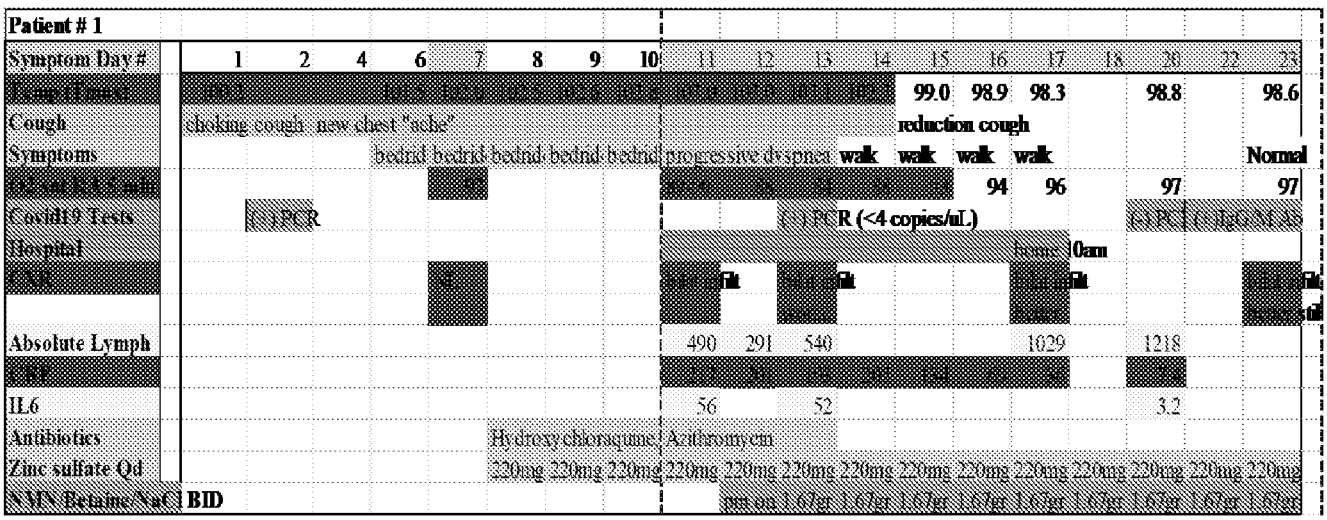


FIG. 11

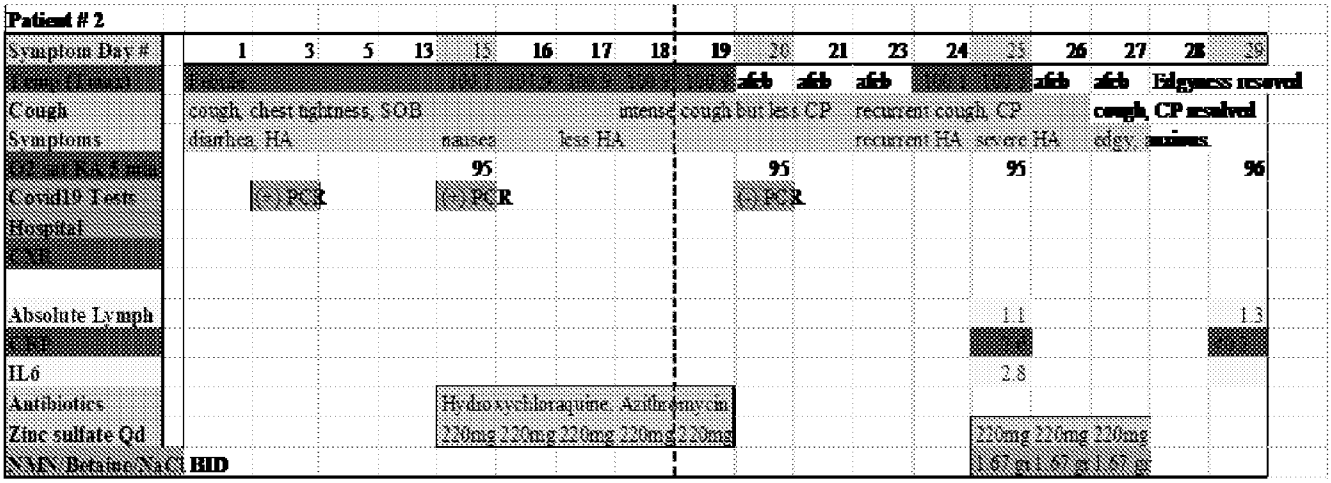


FIG. 12

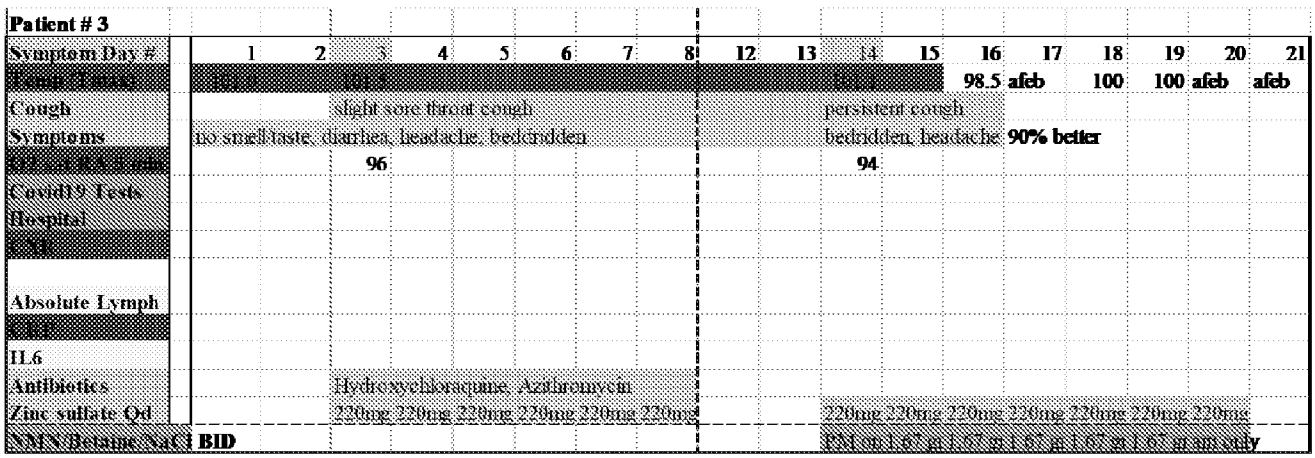


FIG. 13

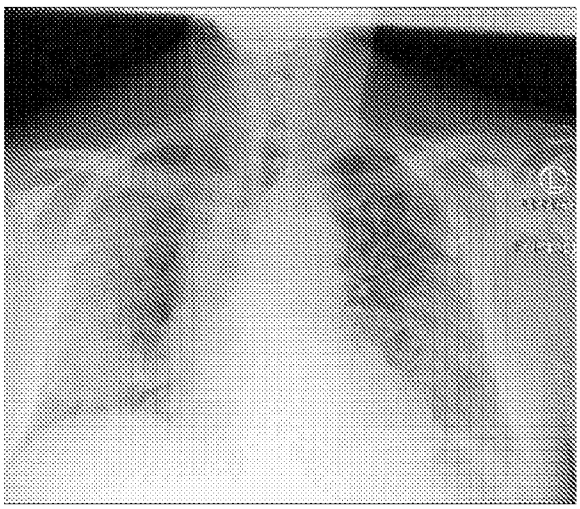


FIG. 14

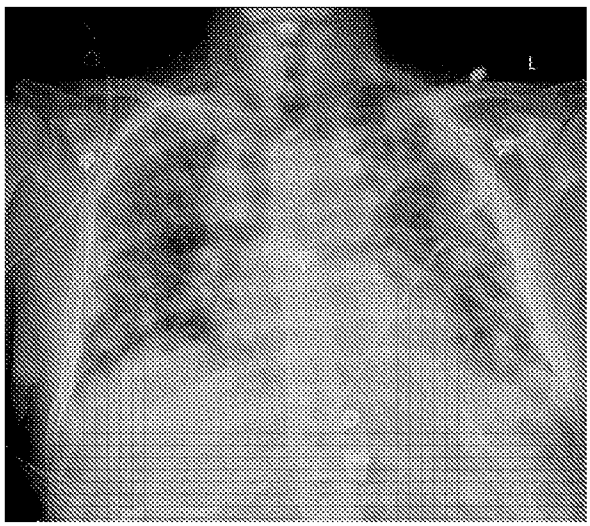


FIG. 15

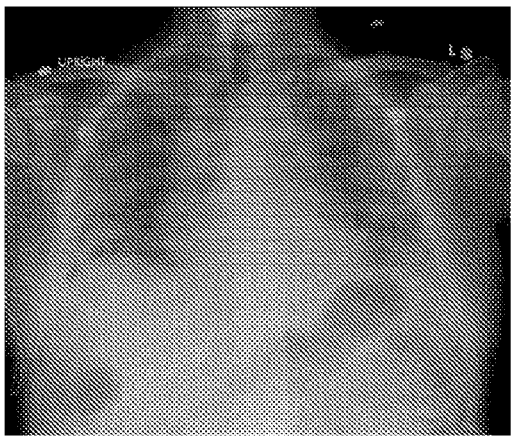


FIG. 16

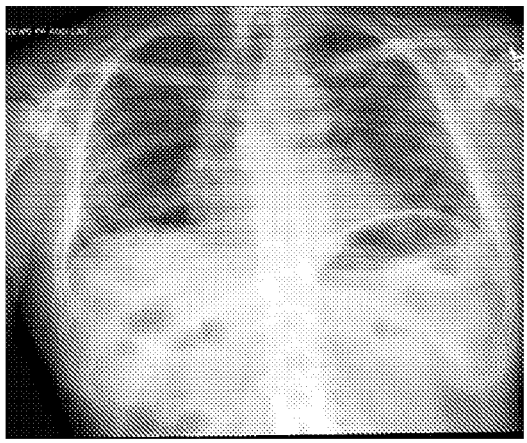


FIG. 17

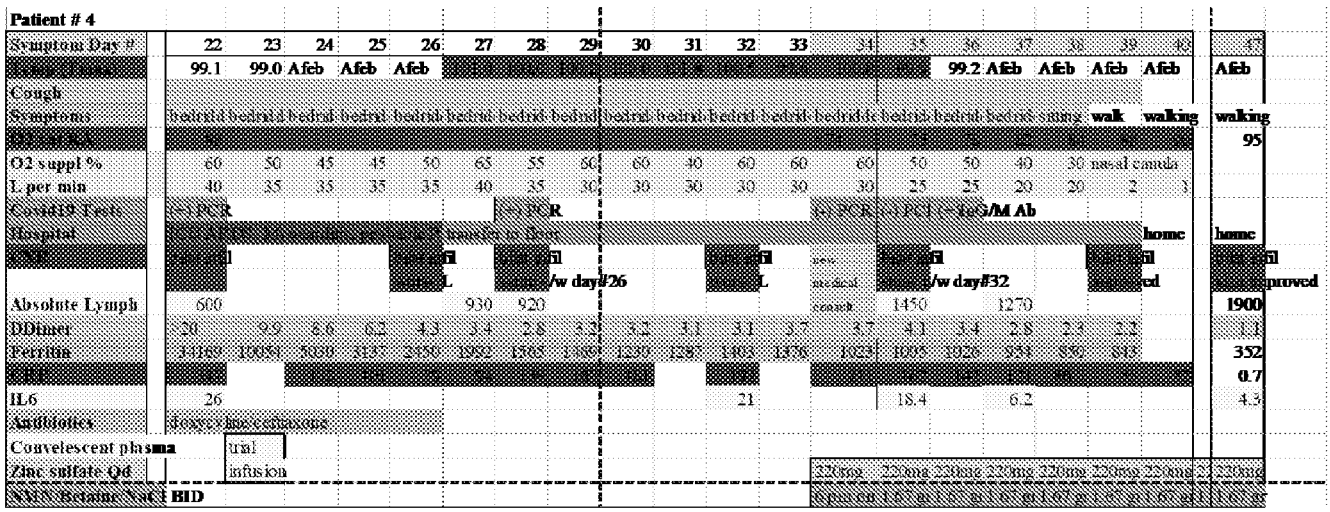


FIG. 18

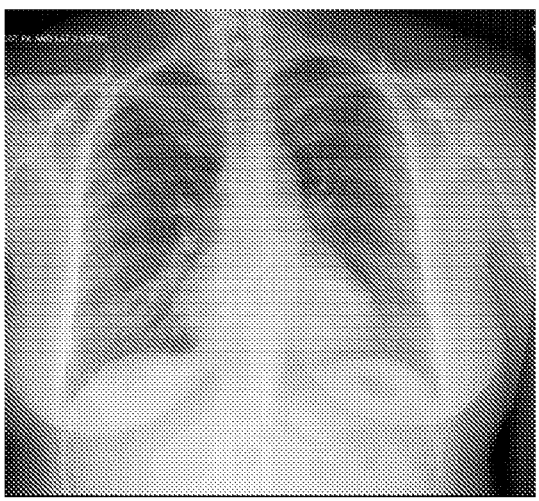


FIG. 19

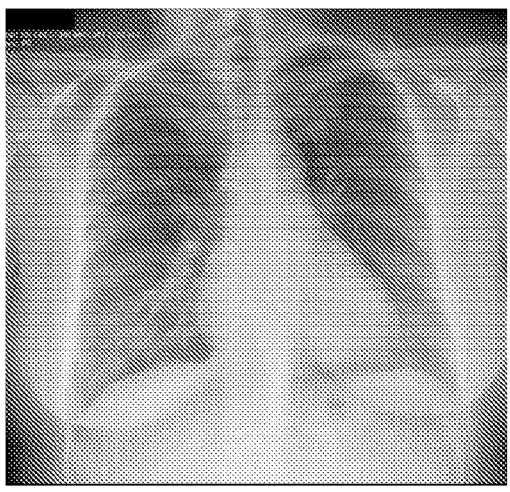


FIG. 20

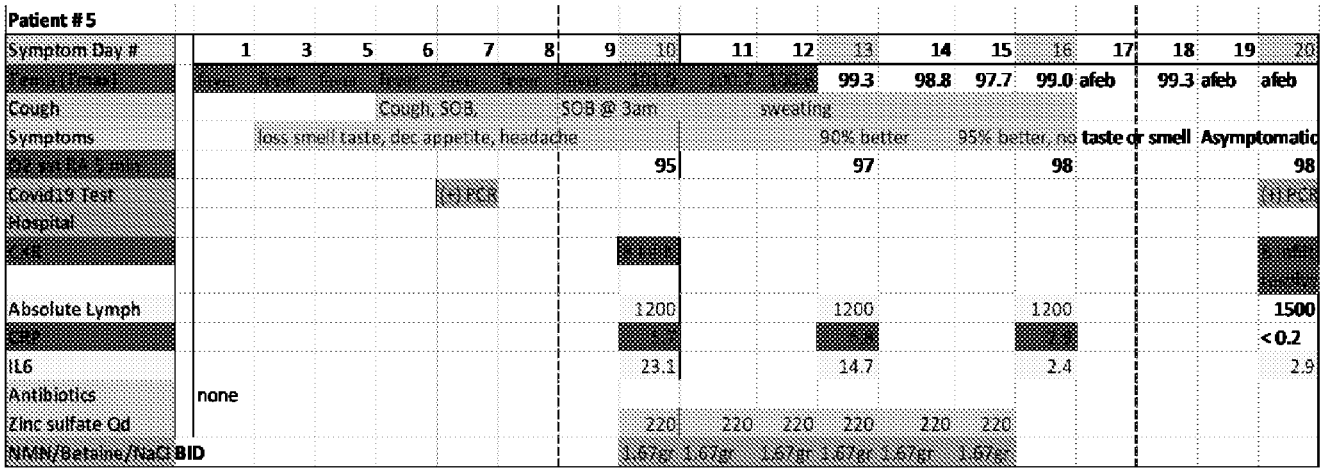


FIG. 21

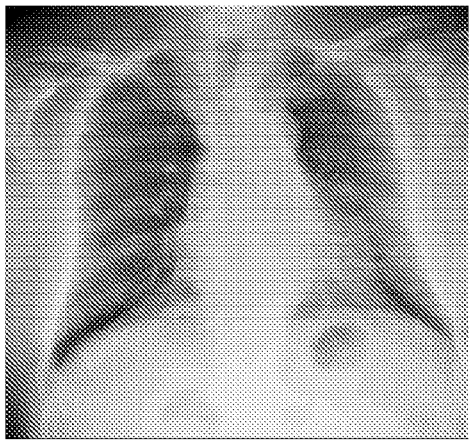


FIG. 22

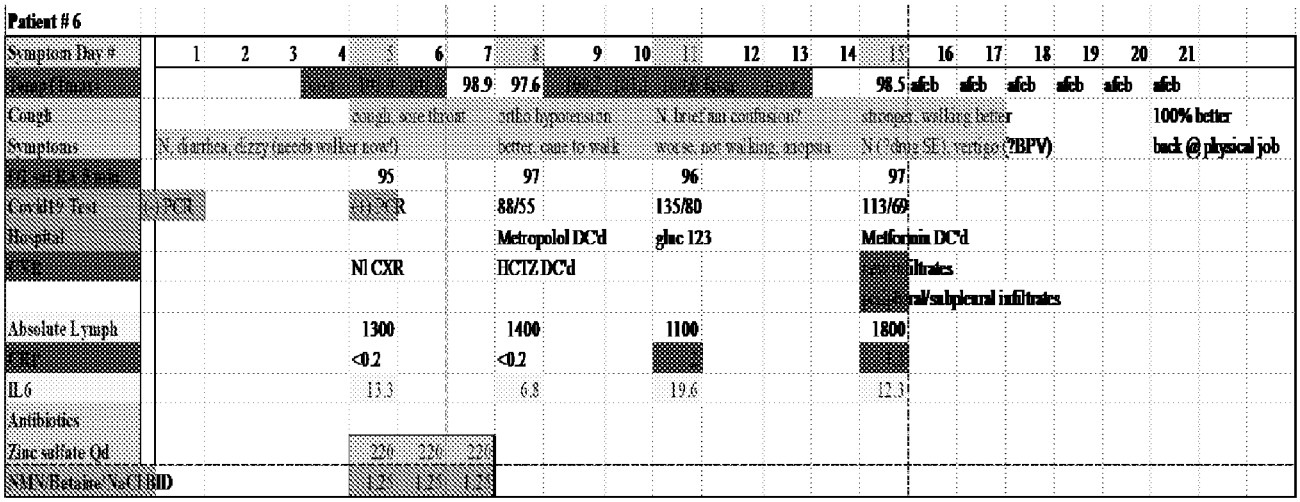


FIG. 23

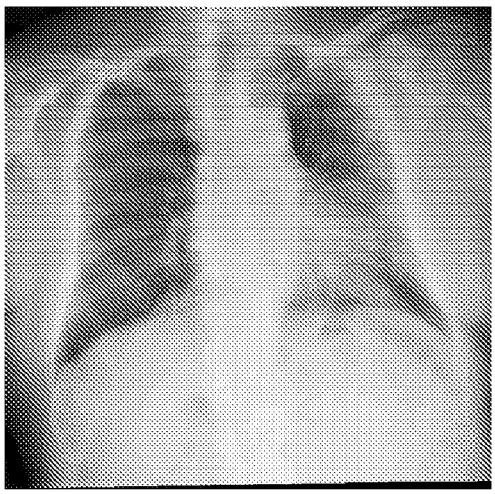


FIG. 24

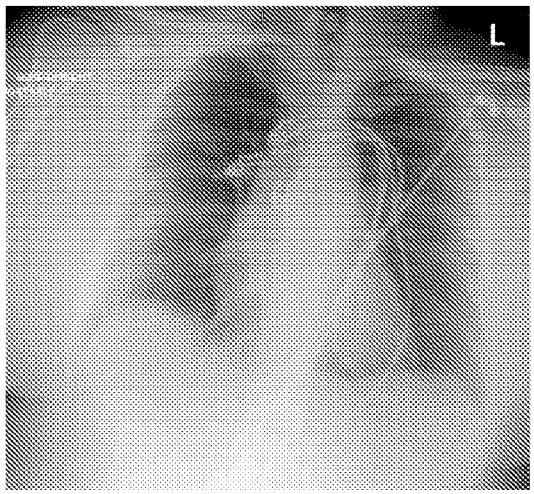


FIG. 25

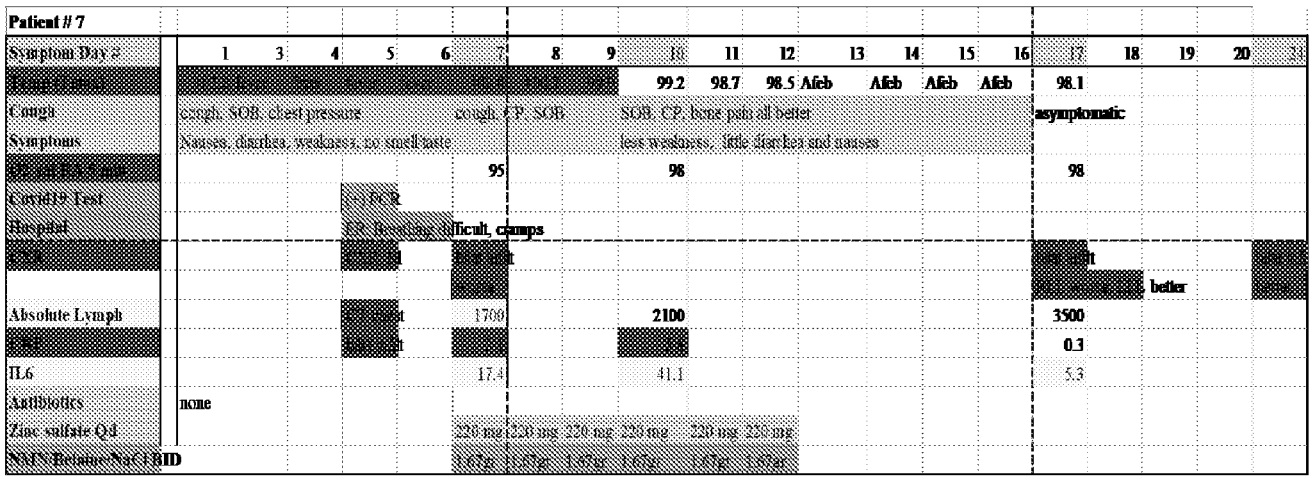


FIG. 26

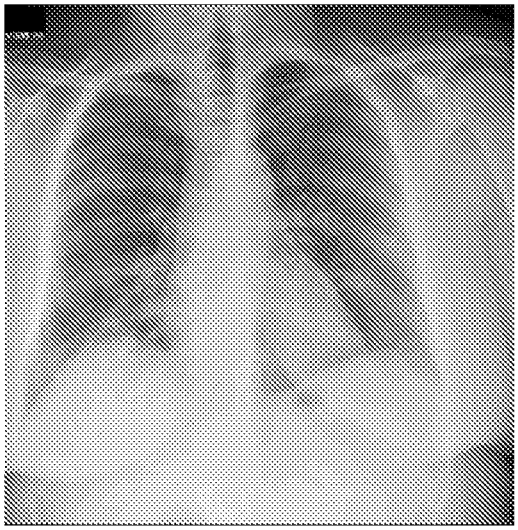


FIG. 27

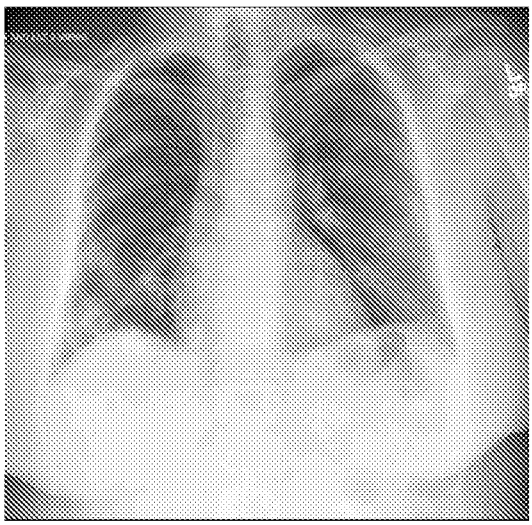


FIG. 28

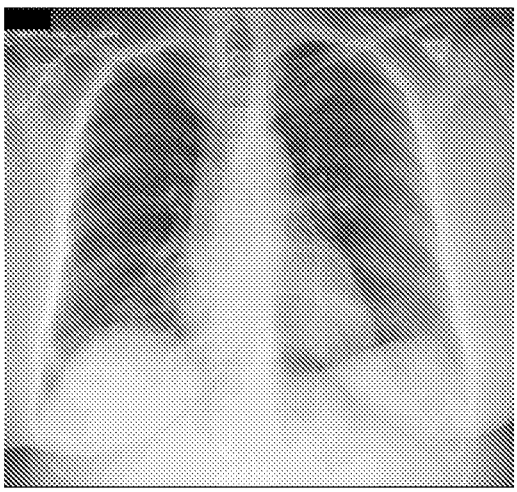


FIG. 29

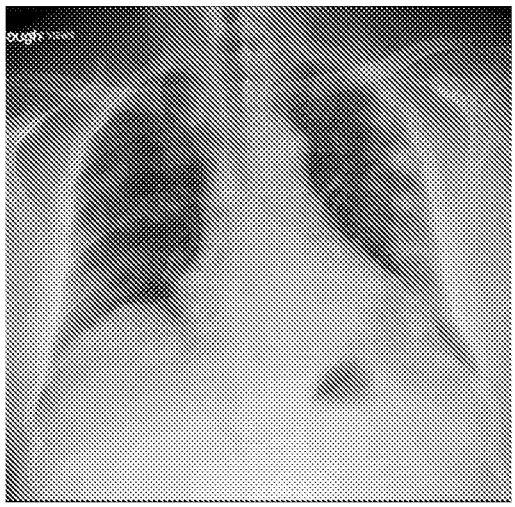


FIG. 30

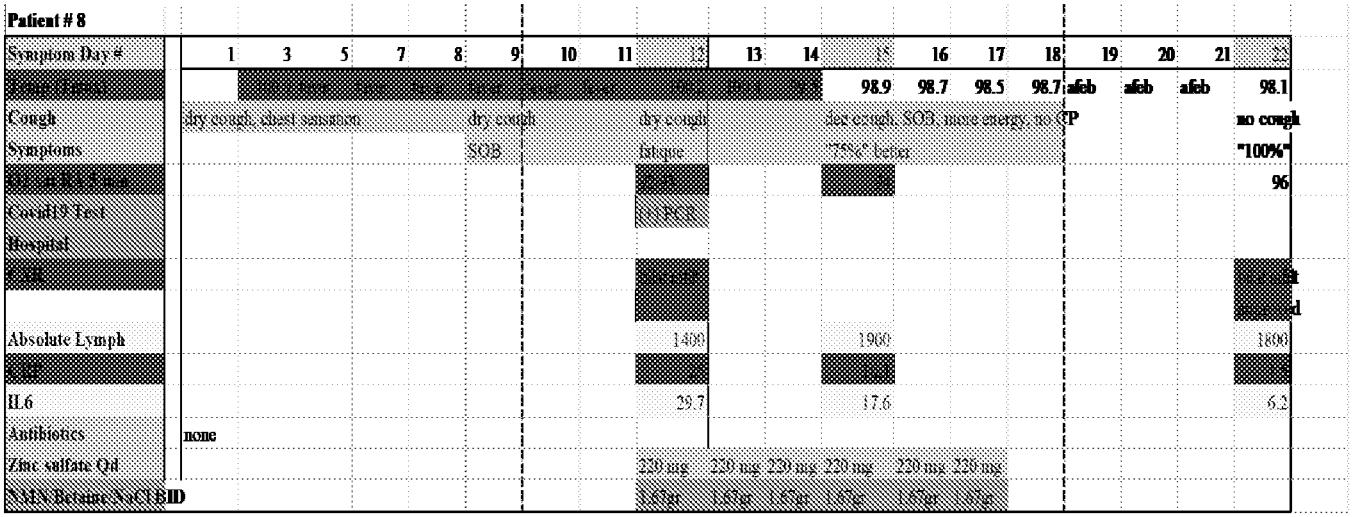


FIG. 31

FIG. 32

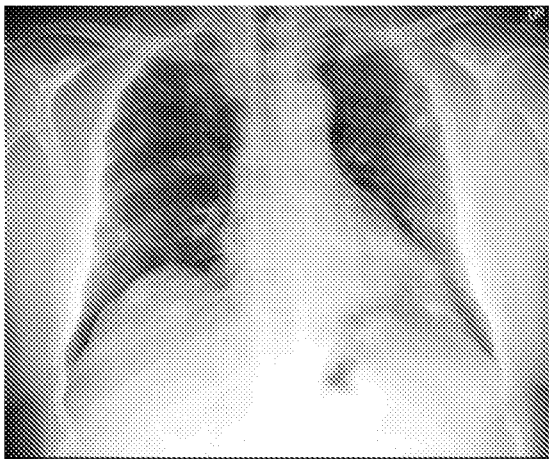


FIG. 33

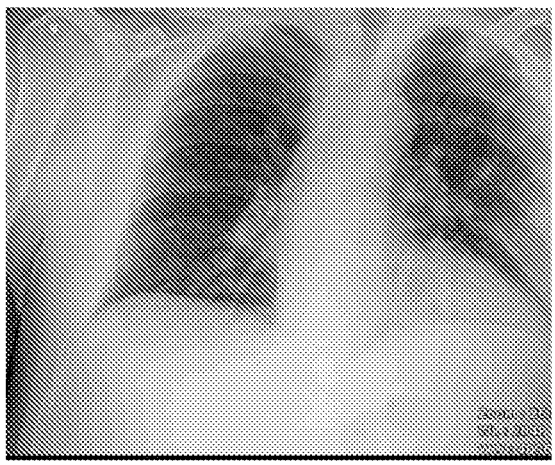
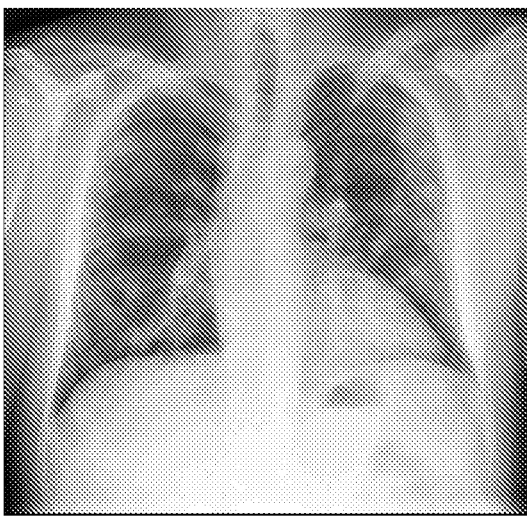


FIG. 34



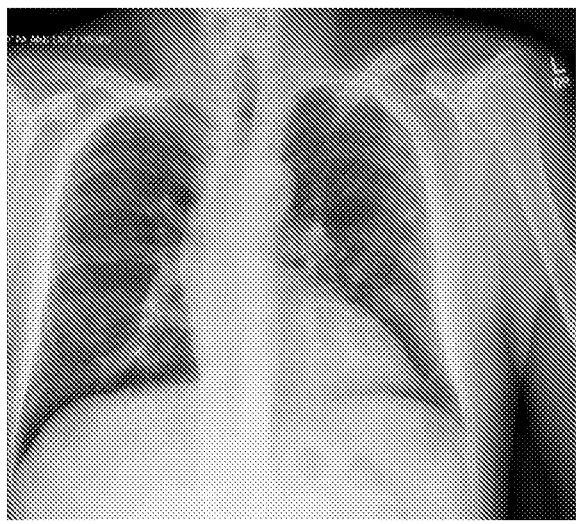


FIG. 35

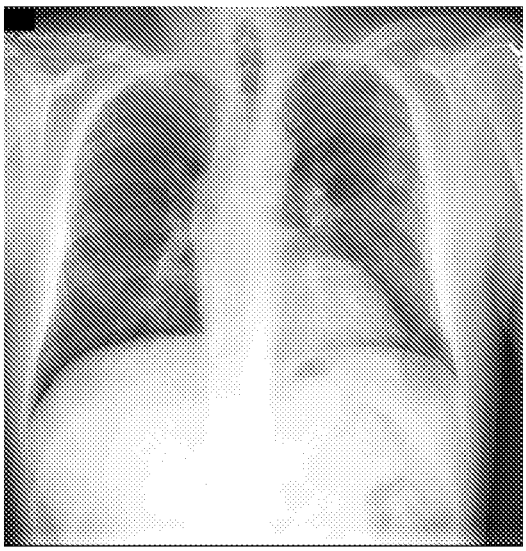
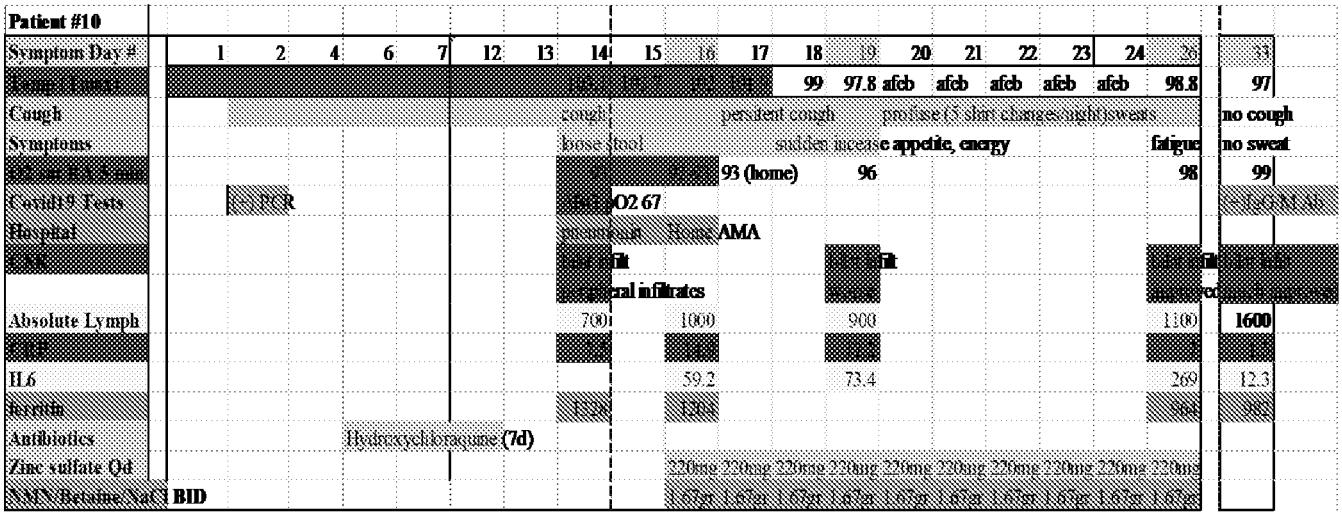


FIG. 36


Patient #10
Symptom Day #
1 2 4 6 7 12 13 14 15 16 17 18 19 20 21 22 23 24 26 33
99 97.8 afeb afeb afeb afeb afeb 98.8 97
Cough
cough persistent cough profuse (5 shirt changes/night)/sweats no cough
Symptoms
loose stool sudden increase appetite, energy fatigue no sweat
93 (home) 96 98 99
Covid19 Tests
PCR O2 67 IgG/IgM Ab
Hospital
AMA
CXR
clear infiltrates
Absolute Lymph
700 1000 900 1100 1600
CRP
59.2 73.4 269 12.3
H6
Ferritin
1328 1200 868 382
Antibiotics
Hydroxychloroquine (7d)
Zinc sulfate Qd
220mg 220mg 220mg 220mg 220mg 220mg 220mg 220mg 220mg 220mg
NAC
BID
1.67gm 1.67gm 1.67gm 1.67gm 1.67gm 1.67gm 1.67gm 1.67gm 1.67gm 1.67gm

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/024207

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/205 (2006.01) A61K 31/706 (2006.01) A61K 33/04 (2006.01) A61K 33/30 (2006.01) A61K 33/40 (2006.01) A61K 47/02 (2006.01) A61K 9/00 (2006.01) A61P 29/00 (2006.01) A61P 31/14 (2006.01) A61P 39/06 (2006.01)

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)

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)

Epoque, STN; Databases: Epodoc, WPIAP, Medline, TXTE, Registry, CAplus, Biosis, Embase; websites: Google.com, clinicaltrials.gov, clients.mintel.com; Keywords: repair system activator, nicotinamide mononucleotide, adenine, riboside, NMN, nicotinic acid mononucleotide, adenine, riboside, methyl nicotinamide, trigonellamide, methyl donor, betaine, trimethylglycine, oxyneurine, adenosyl methionine, SAM, methionine, choline, serine, folate, folic acid, vitamin B12, cobalamin, zinc, zinc sulphate, Zn2+, ZnSO4, white vitriol, goslarite, zinc oxide, acetate, gluconate, antioxidant, hydrogen peroxide, hydrogen sulphide, sodium sulphide, ageing, aging, cellular damage, viral infection, virus, corona virus, COVID, SARS-CoV, severe acute respiratory syndrome, NCOV-2019, MERS, middle east respiratory syndrome, camel flu, coronaviridae, coronavirinae, spike protein, treatment, therapy, prophylaxis, ameliorate, medicament, pharmaceutical, drug & like terms including Registry numbers; IPC: A61K2300/00;
Name and Applicant searches conducted on PatentScope, Espacenet, AusPat, PubMed and IP Australia internal databases.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
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"D" document cited by the applicant in the international application
"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)
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2021	21 June 2021
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Ross Heisey AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262833185

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2021/024207**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20190060336 A1 (HUIZENGA, JOEL) 28 February 2019 Abstract; para. 0121-0127, 0182, 0186, 0205-0212, 0223, 0248, 0267-0272; Examples; Table 1; claims 1-33	1-17, 22-37-51-57, 69-73, 80-82
X	US 20170316487 A1 (MAZED, MOHAMMAD A.) 02 November 2017 Abstract; para. 0050, 0173, 0177; Tables 3E, 13Y and 13Z1-13Z4; claims 1-33	1-12, 14-17, 22-23, 25-29, 31-36, 38-53, 55-57, 69-73, 78-82
X	CN 109045059 A (HOBOOM LIFE TECH SHENZHEN CO LTD) 21 December 2018 Abstract; Examples 2-4; Experimental cases 1, 3; claims 4, 10	1-3, 5-12, 14-17, 22-36, 38-57, 69-73, 78-82
X	CN 108651993 A (HOBOOM LIFE TECH SHENZHEN CO LTD) 16 October 2018 Abstract; Examples 2-4; Experimental cases 2-3; claims 4, 10	1-3, 5-12, 14-17, 22-36, 38-57, 69-73, 78-82
X	US 9629846 B1 (ARGENT DEVELOPMENT GROUP, LLC) 25 April 2017 Abstract; Examples 1, 4-5, 10-16; claims 1-11	1-3, 5-12, 14-17, 22-26, 73, 78-82
X	US 9492421 B1 (GREATHOUSE et al.) 15 November 2016 Abstract; Examples 1, 4-5, 10-16; claims 1-11	1-3, 5-12, 14-17, 22-26, 73, 78-82
X	Caddy Bar™, specialty chocolate bar, Golf Nutrition, USA, GNPD Mintel Record ID 10082139 (Feb 2001) Whole document; Section: Product Information	1-3, 5-12, 14-17, 25-27, 73, 80-82
A	READ, S.A., et al., "The Role of Zinc in Antiviral Immunity", Advances in Nutrition (2019) vol. 10, pages 696-710 Whole document, in particular, Table 1; page 701; Fig. 1	
P,X	HUIZENGA, R., "Dramatic Cytokine Storm Reversal with an Over the Counter NMN Cocktail", SSRN (20 April 2020) [retrieved from Internet on 19 May 2021] <URL: https://ssrn.com/abstract=3581388> Epub 20 April 2020 Whole document	1-82
P,X	HUIZENGA, R., "Dramatic Clinical Improvement in Nine Consecutive Acutely Ill Elderly COVID-19 Patients Treated with a Nicotinamide Mononucleotide Cocktail: A Case Series, SSRN (August 17, 2020) [retrieved from Internet on 19 May 2021] <URL: https://ssrn.com/abstract=3677428> Epub 17 August 2020 Whole document	1-82
P,X	CN 112206237 A (WEIJIA et al.) 12 January 2021 Abstract; Examples 1-4; Table 2; Fig. 1; claims 1-6	1-17, 24-27, 28-37, 40-51, 54-57, 64-69, 71-73, 80-82

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2021/024207**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 20190060336 A1	28 February 2019		
US 20170316487 A1	02 November 2017	US 2017316487 A1	02 Nov 2017
		US 10529003 B2	07 Jan 2020
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		US 8017147 B2	13 Sep 2011
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		US 10841673 B2	17 Nov 2020

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2021/024207**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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		US 10945054 B2	09 Mar 2021
		US 2020374608 A1	26 Nov 2020
		US 10945055 B2	09 Mar 2021
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US 9492421 B1	15 November 2016		
CN 112206237 A	12 January 2021	CN 112206237 A	12 Jan 2021

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.