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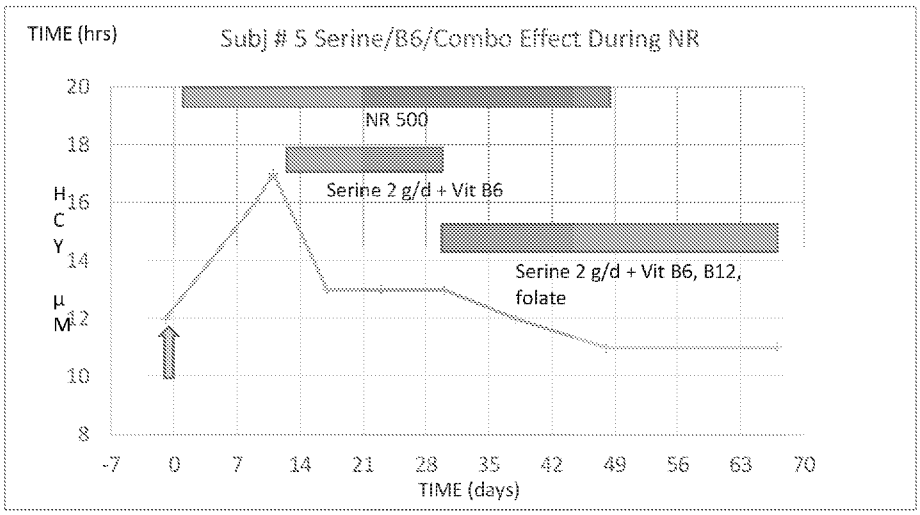

FIG. 3

(57) Abstract: The present application provides compositions such as pharmaceutical compositions, unit dosage forms, food product and dietary supplements, kits and methods for treatment or prevention of hyperhomocysteinemia, including high levels of total plasma homocysteine caused by administration of a nicotinamide adenine dinucleotide pathway agent and homocystinuria.

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COMPOSITIONS USEFUL IN THE TREATMENT OF HYPERHOMOCYSTEINEMIA

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 62/753,599, filed on October 31, 2018, and U.S. Provisional Application No. 62/819,354, filed on March 15, 2019, the contents of which are hereby incorporated by reference in their entireties.

FIELD OF INVENTION

[0002] The present disclosure relates generally to compositions and methods for the treatment or prevention of diseases and conditions characterized by high levels of homocysteine, including hyperhomocysteinemia associated with administration of a nicotinamide adenine dinucleotide pathway agent.

BACKGROUND

[0003] Hyperhomocysteinemia is a condition characterized by an abnormally high level of the amino acid homocysteine in the blood. Nearly two thirds of hyperhomocysteinemia cases are acquired hyperhomocysteinemia, caused by inadequate levels of vitamins B_6 and B_{12} and/or folate (vitamin B_9) in the diet. In some cases, high levels of homocysteine in the blood plasma are caused by the hereditary disease homocystinuria.

[0004] A high level of homocysteine in the blood is a known risk factor for various diseases, including cardiovascular, cerebrovascular and peripheral vascular disease. The risk of thrombosis and stroke is increased for patients with hyperhomocysteinemia. It is thought that the role of homocysteine in degrading and inhibiting the formation of collagen, elastin and proteoglycans, which are essential components for healthy arterial function, leads to the increased cardiovascular risk.

[0005] In addition, hyperhomocysteinemia has been linked to neurological conditions such as Alzheimer's disease, mild cognitive impairment, dementia and schizophrenia. There is also a recognized link between hyperhomocysteinemia and bone health, with higher levels of blood homocysteine increasing the risk of bone fracture in elderly people, thought to arise from inhibition of collagen crosslinking by homocysteine.

[0006] Hyperhomocysteinemia is diagnosed with a blood test, which detects the level of total plasma homocysteine, *i.e.*, the concentration of homocysteine in its three most commonly occurring forms in the blood plasma: protein (albumin)-bound, free circulating

and sulfhydryl. At present, the standard treatment for hyperhomocysteinemia is the administration of supplements containing vitamins B_6, B_9 and B_{12}. We have discovered that administration of nicotinamide riboside causes hyperhomocysteinemia in humans. There is a need for safe and effective alternative treatments of hyperhomocysteinemia, including hyperhomocysteinemia associated with administration of a nicotinamide adenine dinucleotide pathway agent ("NPA"), including commonly consumed forms of vitamin B_3 such as nicotinamide, nicotinic acid, and/or nicotinamide riboside.

[0007] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF SUMMARY

[0008] The present application provides compositions, kits, articles of manufacture and methods for treating or preventing diseases or conditions characterized by high levels of homocysteine, including elevated levels of total homocysteine ("tHcy"), hyperhomocysteinemia (Hhcy), homocystinuria (or hyperhomocystinuria), elevated levels of homocysteine associated with (including caused by) administration of a nicotinamide adenine dinucleotide pathway agent ("NPA"), such as nicotinamide riboside (NR). In some embodiments, the compositions and methods are useful for raising NAD levels in a subject while preventing high levels of homocysteine in the subject.

[0009] One aspect of the present application provides a composition comprising the active agents: (a) serine; and (b) vitamin B_6. In some embodiments, the composition further comprises: (c) vitamin B_9. In some embodiments, the composition further comprises (d) vitamin B_{12}. In some embodiments, the composition further comprises vitamin B_2. In some embodiments, the composition further comprises an NPA such as vitamin B_3. In some embodiments, the composition further comprises trimethylglycine. In some embodiments, the composition does not comprise trimethylglycine. In some embodiments, the composition further comprises dimethylglycine. In some embodiments, the composition further comprises monomethylglycine. In some embodiments, the composition further comprises glycine. In some embodiments, the composition further comprises choline. In some embodiments, the composition further comprises phosphatidylcholine. In some embodiments, the composition further comprises vitamin D (*e.g.*, vitamin D_3). In some embodiments, the composition further comprises one or more agents selected from the group consisting of vitamin B_1, quercetin, fisetin, fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant

extracts (*e.g.*, green tea and/or rosemary extracts), *N*-acetylcysteine, and *S*-adenosylmethionine (SAM).

[0010] One aspect of the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}. In some embodiments, the composition further comprises: (g) vitamin B_2. In some embodiments, the composition further comprises: (j) trimethylglycine. In some embodiments, the composition further comprises: (k) a nicotinamide adenine dinucleotide (NAD+) pathway agent selected from the group consisting of nicotinamide riboside (NR), nicotinic acid riboside (NAR), nicotinamide mononucleotide (NMN), nicotinic acid adenine dinucleotide (NAAD), nicotinamide adenine dinucleotide (NAD+), nicotinic acid (NA), and mixtures thereof. In some embodiments, the composition further comprises NR. In some embodiments, the composition further comprises one or more agents selected from the group consisting of vitamin B_1, vitamin D (*e.g.*, vitamin D_3), vitamin B_2, quercetin, fisetin, fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), *N*-acetylcysteine, *S*-adenosylmethionine (SAM), and trimethylglycine (betaine). In some embodiments, the composition further comprises glycine.

[0011] One aspect of the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin. In some embodiments, the composition further comprises: (g) vitamin B_2. In some embodiments, the composition further comprises: (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) *S*-adenosylmethionine (SAM). In some embodiments, the composition further comprises: (j) trimethylglycine.

[0012] One aspect of the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; (f) *N*-acetylcysteine; and (j) trimethylglycine. In some embodiments, the composition further comprises: (l) vitamin D (*e.g.*, vitamin D_3).

[0013] One aspect of the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA (*e.g.*, NA); and vitamin B_1.

[0014] One aspect of the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate).

[0015] The specific combinations of active agents described herein may be useful in the treatment of hyperhomocysteinemia and related diseases, including high levels of total plasma homocysteine caused by administration of an NPA or homocystinuria. For example, a combination described herein may be useful in reducing the level of total plasma homocysteine in a patient.

[0016] In some embodiments according to any one of the compositions described above, the composition further comprises one or more additional active agents independently selected from the group consisting of fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), dimethylglycine, monomethylglycine, glycine, choline, phosphatidylcholine, and mixtures thereof. These one or more additional active agents may increase the effectiveness of the composition in treating hyperhomocysteinemia.

[0017] In some embodiments according to any one of the compositions described above, at least one of the active agents is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier. In some embodiments, the composition is sterilized. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier, excipient, binder, or diluent. In some embodiments, the composition further comprises a wax matrix.

[0018] A second aspect of the present application provides a pharmaceutical composition comprising a therapeutically effective amount of the composition according to any one of the compositions described above, and a pharmaceutically acceptable carrier, excipient, binder, or diluent.

[0019] Also provided is a food product or dietary supplement comprising any one of the compositions or pharmaceutical compositions described above.

[0020] A third aspect of the present application provides a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; and (b) vitamin B_6, provided that each of the active agents (a)-(b) are contained within the kit. In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}, provided that each of the active agents (a)-(d) are contained within the kit. In some embodiments, each component comprises one or more active agents independently selected

from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA (*e.g.*, NA); and vitamin B_1, provided that each of the active agents are contained within the kit. In some embodiments, each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate), provided that each of the active agents are contained within the kit. In some embodiments, each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin, provided that each of the active agents (a)-(f) are contained within the kit. In some embodiments, each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2, provided that each of the active agents (a)-(g) are contained within the kit. In some embodiments, each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM, provided that each of the active agents (a)-(i) are contained within the kit. In some embodiments, each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and glycine, provided that each of the active agents are contained within the kit. In some embodiments, one or more components of the kit further comprises (j) trimethylglycine.

[0021] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; (f) *N*-acetylcysteine; and (g) trimethylglycine, provided that each of active agents (a)-(g) are contained within the kit.

[0022] In some embodiments according to any one of the kits described above, the kit further comprises an NPA, such as NR, NAR, NAAD, NAD+, NA, and/or NMN. In some embodiments, the kit further comprises (l) vitamin D (*e.g.*, vitamin D_3). In some embodiments, the kit further comprises one or more additional active agents independently selected from the group consisting of fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), dimethylglycine, monomethylglycine, glycine, choline, phosphatidylcholine, and mixtures thereof. In some embodiments, the additional active agents are provided in additional components of the kit.

In some embodiments, at least one of the active agents is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier. In some embodiments, at least one of the components is sterilized.

[0023] A fourth aspect of the present application provides a method of reducing the level of total plasma homocysteine or treating or preventing a disease or condition characterized by high levels of homocysteine in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; and (b) vitamin B_6. In some embodiments, there is provided a method of reducing the level of total plasma homocysteine or treating or preventing a disease or condition characterized by high levels of homocysteine in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}. In some embodiments, the method comprises co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin. In some embodiments, the method comprises co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2. In some embodiments, the method comprises co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM. In some embodiments, the method comprises co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA (*e.g.*, NA); and vitamin B_1. In some embodiments, the method comprises co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate). In some embodiments, the method comprises co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and glycine. In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of (j) trimethylglycine. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of (j) trimethylglycine. In some embodiments, the method does not comprise administering to the subject (j) trimethylglycine. In some embodiments, the method further comprises

administering to the subject (k) an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the subject receives an NPA in his or her diet. In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of (l) vitamin D (*e.g.*, vitamin D_3).

[0024] In some embodiments, there is provided a method of reducing the level of total plasma homocysteine or treating or preventing a disease or condition characterized by high levels of homocysteine in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; and (j) trimethylglycine. In some embodiments, the subject is further administered with an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the subject receives an NPA in his or her diet. In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of (l) vitamin D (*e.g.*, vitamin D_3).

[0025] In some embodiments, there is provided a method of reducing the level of total plasma homocysteine, or treating or preventing hyperhomocysteinemia in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; and (k) NR.

[0026] In some embodiments, there is provided a method of reducing the level of total plasma homocysteine, or treating or preventing hyperhomocysteinemia in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B6; (c) vitamin B9; (d) vitamin B12; (e) vitamin B2; and (l) vitamin D_3.

[0027] In some embodiments, there is provided a method of reducing the level of total plasma homocysteine, or treating or preventing hyperhomocysteinemia in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA (*e.g.*, NA); and vitamin B_1.

[0028] In some embodiments, there is provided a method of reducing the level of total plasma homocysteine, or treating or preventing hyperhomocysteinemia in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate).

[0029] In some embodiments according to any one of the methods described above, the active agents are administered simultaneously. In some embodiments, the method comprises administering to the subject a composition comprising a therapeutically effective amount of the active agents. In some embodiments, the active agents are administered sequentially, in any order. In some embodiments, two or more of the active agents are administered simultaneously and the third is administered sequentially. In some embodiments, the active agents other than trimethylglycine are administered simultaneously, and trimethylglycine is administered sequentially. In some embodiments, the active agents other than NPA are administered simultaneously, and NPA is administered sequentially.

[0030] In some embodiments according to any one of the methods described above, the method further comprises administering therapeutically effective amounts of one or more additional active agents independently selected from the group consisting of fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), dimethylglycine, monomethylglycine, glycine, choline, phosphatidylcholine, and mixtures thereof. In some embodiments, at least one of the active agents is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier. In some embodiments, at least one of the active agents is sterilized.

[0031] In some embodiments according to any one of the methods described above, the subject has a high initial level of total plasma homocysteine. In some embodiments, the high initial level of total plasma homocysteine is caused by administration of an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, there is provided a method of reducing the level of total plasma homocysteine in a subject to a concentration of less than about 100 μmol/L. In some embodiments, there is provided a method of reducing the level of total plasma homocysteine in a subject to a concentration of less than about 31 μmol/L. In some embodiments, there is provided a method of reducing the level of total plasma homocysteine in a subject to a concentration of less than about 15 μmol/L. In some embodiments, there is provided is a method of reducing the level of total plasma homocysteine in a subject to a concentration of less than 12 μmol/L. In some embodiments, there is provided is a method of treating or preventing hyperhomocysteinemia in a subject. In some embodiments, there is provided is a method of treating or preventing hyperhomocysteinemia caused by administration of an NAD+ agent in a subject. In some

embodiments, there is provided a method of treating or preventing acquired hyperhomocysteinemia in a subject. In some embodiments, there is provided a method of treating or preventing homocystinuria in a subject. In some embodiments, the method further increases the levels of NAD and/or HDL, and/or decreases the levels of LDL, triglyceride, total cholesterol, plasma trimethylamine N-oxide (TMAO) and/or lipoprotein a.

[0032] In some embodiments, there is provided a method of treating or preventing a disease characterized by high levels of total plasma homocysteine in a subject. In some embodiments, there is provided a method of treating or preventing a disease in a subject characterized by total plasma homocysteine levels of at least 12 μmol/L. In some embodiments, there is provided a method of treating or preventing a disease in a subject characterized by total plasma homocysteine levels of at least 31 μmol/L. In some embodiments, there is provided is a method of treating or preventing a disease in a subject characterized by total plasma homocysteine levels of greater than 100 μmol/L. In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject selected from cardiovascular disease, cerebrovascular disease, peripheral vascular disease, thrombosis, stroke, atherothrombotic coronary artery disease (CAD), myocardial infarction (MI), Alzheimer's disease, cognitive impairment, dementia, diabetic retinopathy, intraocular lens dislocation, schizophrenia, osteoporosis, homocystinuria and hyperhomocysteinemia. In some embodiments, there is provided a method of preventing or reducing the risk of bone fracture in a subject.

[0033] Further aspects of the invention include the use of any one of the compositions described above in the preparation of a medicament for the treatment or prevention of the diseases and conditions described herein. Further aspects include any one of compositions or pharmaceutical compositions described above for use in the treatment or prevention of the diseases and conditions described herein.

[0034] Further aspects include methods of preparing the compositions and kits described herein.

BRIEF DESCRIPTION OF THE FIGURES

[0035] FIG. 1 shows daily dosages of NR, NA, Betaine, serine, vitamin B_6, vitamin B_{12}, vitamin B_9 (folic acid) and glycine received by the subject and his serum homocysteine levels as determined by the AnyLabs Inc. test or Quest Diagnostics test.

[0036] FIG. 2 shows the effect of betaine treatment on the subject's homocysteine level while the subject received NR and NA.

[0037] FIG. 3 shows the effect of serine and vitamin B_6 treatment on the subject's homocysteine level while the subject received NR.

[0038] FIG. 4 shows the effect of serine, vitamin B6, vitamin B12 and vitamin B_9 (folic acid) treatment on the subject's homocysteine level while the subject received NR, or a combination of NR and NA.

[0039] FIG. 5 shows elevated homocysteine level in subject #110 caused by NR treatment.

[0040] FIG. 6 shows elevated homocysteine level in subject #107 caused by NR treatment.

[0041] FIG. 7 shows elevated homocysteine level in subject #106 caused by NR treatment.

DETAILED DESCRIPTION

[0042] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific compositions, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

[0043] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entireties. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in a patent, application, or other publication that is herein incorporated by reference, the definition set forth in this section prevails over the definition incorporated herein by reference.

[0044] As used herein, the term "hyperhomocysteinemia," "hyperhomocysteinaemia," or "HHcy" refers to any disease or condition characterized by abnormally high levels of the amino acid homocysteine in the blood, whether acquired or inherited. According to the American Heart Association (AHA) advisory statement, normal homocysteine concentrations in the blood range from 5-15 μmol/L, although in some cases 12 μmol/L concentrations have been considered abnormal. Levels of 31-100 μmol/L are considered intermediately elevated, while levels greater than 100 μmol/L are considered severely elevated.

[0045] As used herein, "high levels of homocysteine" or "elevated levels of homocysteine" refer to a total blood plasma or serum concentration of homocysteine of at least 10 μmol/L,

for example at least 11 μmol/L, at least 12 μmol/L, at least 13 μmol/L, at least 14 μmol/L, at least 15 μmol/L, at least 16 μmol/L, at least 17 μmol/L, at least 18 μmol/L, at least 19 μmol/L, or at least 20 μmol/L. High levels of homocysteine also include intermediately elevated levels such as at least 31 μmol/L, and severely elevated levels such as greater than 100 μmol/L.

[0046] As used herein, "nicotinamide adenine dinucleotide pathway agent," or "NPA" refers to one or more agents selected from the group consisting of nicotinic acid ("NA"), niacinamide ("NAM", also known as nicotinamide), nicotinamide riboside ("NR"), nicotinamide mononucleotide ("NMN"), nicotinic acid riboside ("NAR"), nicotinic acid mononucleotide ("NAMN"), nicotinic acid adenine dinucleotide ("NAAD"), oxidized nicotinamide adenine dinucleotide ("NAD+"), reduced nicotinamide adenine dinucleotide ("NADH"), and other precursors or metabolites of NAD+ or NADH.

[0047] As used herein, the term "treat" or "treatment" refers to an approach for obtaining a beneficial or desired result, including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to: reducing the severity of or suppressing the worsening of an existing disease, symptom, or condition, alleviating a symptom and/or diminishing the extent of a symptom and/or preventing a worsening of a symptom associated with a condition, arresting the development of a disease, symptom, or condition, relieving the disease, symptom, or condition, causing regression of the disease, disorders, conditions, or symptom (in terms of severity or frequency of negative symptoms), or stopping the symptoms of the disease or condition. Beneficial or desired results can also be slowing, halting, or reversing the progressive course of a disease or condition.

[0048] "Preventing," as used herein, includes providing prophylaxis with respect to the occurrence or recurrence of a disease or condition in a subject that may be predisposed to the disease or condition but has not yet been diagnosed with the disease or condition. In some embodiments, the provided compositions are used to delay development of a disease or condition or to slow the progression of a disease or condition such as hyperhomocysteinemia.

[0049] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as an antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0050] As used herein, the terms "including," "containing," and "comprising" are used in their open, non-limiting sense. It is understood that embodiments of the invention described herein include "consisting" and/or "consisting essentially of" embodiments. The term "consists essentially of" means excluding other materials that contribute to function, unless otherwise defined herein. Nonetheless, such other materials may be present, collectively or individually, in trace amounts.

[0051] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about." It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. For example, description referring to "about X" includes description of "X".

[0052] Except as otherwise noted, the methods and techniques of the present embodiments are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification.

[0053] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to particular method steps, reagents, or conditions are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed.

[0054] Where any compound recited herein may also exist as a corresponding salt, solvate or hydrate, the use of such salts, solvates or hydrates in place of or in addition to the recited compound is also encompassed by the present invention.

[0055] A "pharmaceutically acceptable salt" is a salt form that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. *See generally* Berge et al. (1977) *J. Pharm. Sci.* 66, 1-19. Particular pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response.

[0056] The skilled person understands that in the context of compositions for administration to the human or animal body, for minerals such as magnesium, potassium, calcium and strontium, stated dosages and weights refer to the quantity of elemental metal, not to the weight of the compound containing the metal. Herein, where a weight or dosage of such a mineral is specified, this refers to the weight or dosage of the particular element and not the compound, which contains it, unless the context clearly implies otherwise, or unless explicitly stated otherwise.

I. Compositions

[0057] The present application provides various compositions useful for reducing total plasma homocysteine levels. The compositions described herein comprise various active agents. For the purpose of Sections I-VII only, exemplary active agents are referred to as active agents (a)-(m) according to the designation in sections I (a)-(m). The active agents described herein include salts or solvates thereof. Active agents may have one or more physiological effects on a subject receiving the compositions described herein. In some embodiments, the active agent changes, *e.g.*, increases or decreases, homocysteine levels in the subject. In some embodiments, the active agent does not affect the homocysteine levels in the subject.

[0058] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; and (b) vitamin B_6. In some embodiments, the composition consists of active agents (a)-(b). In some embodiments, the composition consists essentially of active agents (a)-(b). In some embodiments, the composition further comprises one or more agents selected from the group consisting of NPA, vitamin B_1, vitamin B_2, vitamin D (*e.g.*, vitamin D_3), quercetin, fisetin, fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), *N*-acetylcysteine, *S*-adenosylmethionine (SAM), trimethylglycine (betaine), dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine. In some embodiments, the composition does not comprise trimethylglycine.

[0059] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; and (c) vitamin B_9. In some embodiments, the composition consists of active agents (a)-(c). In some embodiments, the composition consists essentially of active agents (a)-(c). In some embodiments, the composition further comprises one or more agents selected from the group consisting of NPA, vitamin B_1, vitamin B_2,

vitamin D (*e.g.*, vitamin D_3), quercetin, fisetin, fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), *N*-acetylcysteine, *S*-adenosylmethionine (SAM), trimethylglycine (betaine), dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine. In some embodiments, the composition does not comprise trimethylglycine.

[0060] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}. In some embodiments, the composition further comprises one or more agents selected from the group consisting of vitamin B_1, vitamin B_2, vitamin D (*e.g.*, vitamin D_3), quercetin, fisetin, fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), *N*-acetylcysteine, *S*-adenosylmethionine (SAM), trimethylglycine (betaine), dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine. In some embodiments, the composition does not comprise trimethylglycine. In some embodiments, the composition consists of active agents (a)-(d). In some embodiments, the composition consists essentially of active agents (a)-(d).

[0061] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (k) an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. In some embodiments, the composition further comprises one or more agents selected from the group consisting of vitamin B_1, vitamin B_2, vitamin D (*e.g.*, vitamin D_3), quercetin, fisetin, fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), *N*-acetylcysteine, *S*-adenosylmethionine (SAM), trimethylglycine, dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine. In some embodiments, the composition does not comprise trimethylglycine. In some embodiments, the composition consists of active agents (a)-(d) and (k). In some embodiments, the composition consists essentially of active agents (a)-(d) and (k).

[0062] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin. In some embodiments, the composition does not comprise trimethylglycine. In

some embodiments, the composition consists of active agents (a)-(f). In some embodiments, the composition consists essentially of active agents (a)-(f). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0063] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (j) trimethylglycine. In some embodiments, the composition consists of active agents (a)-(f) and (j). In some embodiments, the composition consists essentially of active agents (a)-(f) and (j). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0064] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2. In some embodiments, the composition does not comprise trimethylglycine. In some embodiments, the composition consists of active agents (a)-(d) and (g). In some embodiments, the composition consists essentially of active agents (a)-(d) and (g). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. In some embodiments, the composition further comprises vitamin B_1. In some embodiments, the composition further comprises *N*-acetyl cysteine. In some embodiments, the composition further comprises quercetin. In some embodiments, the composition further comprises a magnesium-containing compound (*e.g.*, magnesium bisglycinate). In some embodiments, the composition further comprises fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), and/or plant extracts (*e.g.*, green tea and/or rosemary extracts).

[0065] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2, (k) an NPA (*e.g.*, NA); and vitamin B_1. In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate). In some embodiments, the composition further comprises fruit extracts (*e.g.*, blueberry, cranberry,

strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), and/or plant extracts (*e.g.*, green tea and/or rosemary extracts).

[0066] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2. In some embodiments, the composition consists of active agents (a)-(g). In some embodiments, the composition does not comprise trimethylglycine. In some embodiments, the composition consists essentially of active agents (a)-(g). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0067] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; and (j) trimethylglycine. In some embodiments, the composition consists of active agents (a)-(g) and (j). In some embodiments, the composition consists essentially of active agents (a)-(g) and (j). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0068] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) *S*-adenosylmethionine (SAM). In some embodiments, the composition does not comprise trimethylglycine. In some embodiments, the composition consists of active agents (a)-(i). In some embodiments, the composition consists essentially of active agents (a)-(i). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0069] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; (i) SAM; and (j) trimethylglycine. In some embodiments, the composition consists of active agents (a)-(j). In some embodiments, the composition consists essentially of active agents (a)-(j). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN).

In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0070] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; and (j) trimethylglycine. In some embodiments, the composition consists of active agents (a)-(d), (g)-(h) and (j). In some embodiments, the composition consists essentially of active agents (a)-(d), (g)-(h) and (j). In some embodiments, the composition further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

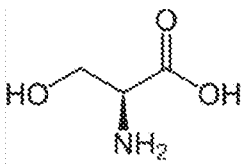
[0071] In some embodiments, the present application provides a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) N-acetylcysteine; and (l) vitamin D_3. In some embodiments, the composition consists of active agents (a)-(d), (g)-(h) and (l). In some embodiments, the composition consists essentially of active agents (a)-(d), (g)-(h) and (l). In some embodiments, the composition further comprises fruit, plant and/or vegetable extracts, such as, blueberry, cranberry, strawberry, pomegranate, grape, ginger, green tea, turmeric, black pepper and/or rosemary extracts.

[0072] The active agents described herein include pharmaceutically acceptable salts. In some embodiments, pharmaceutically acceptable salts include acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like. These salts may be derived from inorganic or organic acids. Non-limiting examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, and mandelates. In some embodiments, pharmaceutically acceptable salts are formed when an acidic proton

present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Salts derived from pharmaceutically acceptable organic non-toxic bases include, without limitation, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, trimetharnine, dicyclohexylamine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N- ethylglucamine, N-methylglucamine, theobromine, purines, piperazine, piperidine, N- ethylpiperidine, polyamine resins, amino acids such as lysine, arginine, histidine, and the like. Examples of pharmaceutically acceptable base addition salts include, without limitation, those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. In some embodiments, the organic non-toxic bases are L-amino acids, such as L-lysine and L- arginine, tromethamine, N-ethylglucamine and N-methylglucamine. Acceptable inorganic bases include, without limitation, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Lists of other suitable pharmaceutically acceptable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

(a) Serine

[0073] Active agent (a) is serine (also referred to as "L-serine"). Serine is a proteinogenic α-amino acid having the following structure:



(I).

[0074] Serine is a non-essential amino acid, which may be synthesized by human bodies. Without being bound by any theory or hypothesis, serine and vitamin B_6 may activate the trans-sulfuration pathway, which degrades homocysteine.

[0075] In some embodiments, active agent (a) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent,

excipient, or carrier within active agent (a) or any other component of the composition. Thus, purity in this context refers to the purity of the serine component *per se*.

[0076] In some embodiments, the composition comprises at least about 90 wt% active agent (a), for example at least about any one of 91 wt%, 92 wt%, 93 wt%, 94 wt%, 95 wt%, 96 wt%, 97 wt%, or 98 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises up to about 98 wt% active agent (a), for example up to about any one of 97 wt%, 96 wt%, 95 wt%, 94 wt%, 93 wt%, 92 wt%, 91 wt%, or 90 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 90 wt% to about 98 wt% active agent (a), for example about any one of 90-92 wt%, 92-94 wt%, 94-96 wt%, 96-98 wt%, 90-94 wt%, 94-98 wt%, or 92-97 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 95.2 wt%, 95.8%, or 98.4% active agent (a), based on the total weight of active agents (a)-(d) in the composition.

[0077] In some embodiments, the composition comprises at least about 70 wt% active agent (a), for example at least about any one of 71 wt%, 72 wt%, 73 wt%, 74 wt%, 75 wt%, 76 wt%, 77 wt%, or 78 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises up to about 80 wt% active agent (a), for example up to about any one of 79 wt%, 78 wt%, 77 wt%, 76 wt%, 75 wt%, 74 wt%, 73 wt%, 73 wt%, or 71 wt% based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 70 wt% to about 80 wt% active agent (a), for example about any one of 70-72 wt%, 72-74 wt%, 74-76 wt%, 76-78 wt%, 70-98 wt%, 70-75 wt%, or 75-80 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 76.9 wt% active agent (a), based on the total weight of active agents (a)-(d) and (k) in the composition.

[0078] In some embodiments, the composition comprises at least about 70 wt% active agent (a), for example at least about any one of 72 wt%, 74 wt%, 76 wt%, 78 wt%, 80 wt%, 82 wt%, 84 wt%, 86 wt%, or 88 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises up to about 90 wt% active agent (a), for example up to about any one of 88 wt%, 86 wt%, 84 wt%, 82 wt%, 80 wt%, 78 wt%, 76 wt%, 74 wt%, or 72 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 70 wt% to about 90 wt% active agent (a), for example about any one of 70-75 wt%, 75-80 wt%, 80-85 wt%, 85-

90 wt%, 75-85 wt%, 76-84 wt%, 78-82 wt%, or 79-81 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 80.8 wt% active agent (a), based on the total weight of active agents (a)-(f) in the composition.

[0079] In some embodiments, the composition comprises at least about 35 wt% active agent (a), for example at least about any one of 37 wt%, 39 wt%, 41 wt%, 43 wt%, 45 wt%, 47 wt%, 49 wt%, 51 wt%, or 53 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 55 wt% active agent (a), for example up to about any one of 53 wt%, 51 wt%, 49 wt%, 47 wt%, 45 wt%, 43 wt%, 41 wt%, 39 wt%, or 37 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 35 wt% to about 55 wt% active agent (a), for example about any one of 35-40 wt%, 40-45 wt%, 45-50 wt%, 50-55 wt%, 40-50 wt%, or 42-46 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 44.7 wt% active agent (a), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0080] In some embodiments, the composition comprises at least about 70 wt% active agent (a), for example at least about any one of 72 wt%, 74 wt%, 76 wt%, 78 wt%, 80 wt%, 82 wt%, 84 wt%, 86 wt%, or 88 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 90 wt% active agent (a), for example up to about any one of 88 wt%, 86 wt%, 84 wt%, 82 wt%, 80 wt%, 78 wt%, 76 wt%, 74 wt%, or 72 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 70 wt% to about 90 wt% active agent (a), for example about any one of 70-75 wt%, 75-80 wt%, 80-85 wt%, 85-90 wt%, 75-85 wt%, 72-84 wt%, 74-82 wt%, or 76-80 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 78.4 wt% active agent (a), based on the total weight of active agents (a)-(g) in the composition.

[0081] In some embodiments, the composition comprises at least about 35 wt% active agent (a), for example at least about any one of 37 wt%, 39 wt%, 41 wt%, 43 wt%, 45 wt%, 47 wt%, 49 wt%, 51 wt%, or 53 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 55 wt% active agent (a), for example up to about any one of 53 wt%, 51 wt%, 49 wt%, 47 wt%, 45 wt%, 43 wt%, 41 wt%, 39 wt%, or 37 wt%, based on the total weight of active

agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 35 wt% to about 55 wt% active agent (a), for example about any one of 35-40 wt%, 40-45 wt%, 45-50 wt%, 50-55 wt%, 40-50 wt%, or 42-46 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 44.0 wt% active agent (a), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0082] In some embodiments, the composition comprises at least about 20 wt% active agent (a), for example at least about any one of 22 wt%, 24 wt%, 26 wt%, 28 wt%, 30 wt%, 32 wt%, 34 wt%, 36 wt%, or 38 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (a), for example up to about any one of 38 wt%, 36 wt%, 34 wt%, 32 wt%, 30 wt%, 28 wt%, 26 wt%, 24 wt%, or 22 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 20 wt% to about 40 wt% active agent (a), for example about any one of 20-25 wt%, 25-30 wt%, 30-35 wt%, 35-40 wt%, 25-35 wt%, 27-33 wt%, or 29-31 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 30.5 wt% active agent (a), based on the total weight of active agents (a)-(i) in the composition.

[0083] In some embodiments, the composition comprises at least about 15 wt% active agent (a), for example at least about any one of 17 wt%, 19 wt%, 21 wt%, 23 wt%, 25 wt%, 27 wt%, 29%, or 31 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 32 wt% active agent (a), for example up to about any one of 30 wt%, 28 wt%, 26 wt%, 24 wt%, 22 wt%, 21 wt%, 19 wt%, 18 wt%, or 17 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 15 wt% to about 32 wt% active agent (a), for example about any one of 15-20 wt%, 20-25 wt%, 25-32 wt%, 17-30 wt%, 19-28 wt%, 21-26 wt%, or 23-24 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 23.4 wt% active agent (a), based on the total weight of active agents (a)-(j) in the composition.

[0084] In some embodiments, the composition comprises at least about 25 wt% active agent (a), for example, at least about any one of 26 wt%, 27 wt%, 28 wt%, 29 wt%, 30 wt%, or 31 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (a), for example, up to about any one of 35 wt%, 34 wt%, 33 wt%, or 32 wt%, based on

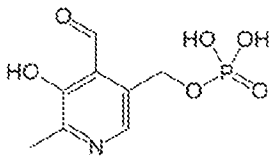
the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 25 wt% to about 40 wt% active agent (a), for example, about any one of 25-35 wt%, 25-34 wt%, 26-34 wt%, 27-34 wt%, 28-34 wt%, 29-34 wt%, or 30-34 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 32.5 wt% active agent (a), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0085] In this way, the relative quantity of active agent (a) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0086] In some embodiments, the composition comprises about 1000 mg to about 10000 mg of serine, for example, at least about any one of 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2500 mg, 3000 mg, 4000 mg, 5000 mg or 10000 mg, or about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, about 2000 mg to about 2500 mg, about 2500 mg to about 3000 mg, about 1000 mg to about 2000 mg, about 2000 mg to about 3000 mg, about 1000 mg to about 3000 mg, or about 3000 mg to about 10000 mg.

(b) Vitamin B_6

[0087] Active agent (b) of the composition is vitamin B_6. The term "vitamin B_6" refers to a group of biologically interconvertible compounds of similar chemical structure. The active form is pyridoxal 5'-phosphate, which has the following structure:



(II)

[0088] However any of the known forms (vitamers) of vitamin B_6 may be used in the present invention, including but not limited to pyridoxine, pyridoxine 5'-phosphate, pyridoxal, pyridoxal 5'-phosphate, pyridoxamine, pyridoxamine 5'-phosphate and pyritinol. Active agent (b) may comprise a single vitamer of vitamin B_6 or may comprise a mixture of two or more vitamers in any ratio. For example, active agent (b) may consist of pyridoxal 5'-phosphate. Alternatively, active agent (d) may consist of a mixture of pyridoxal 5'-phosphate and one or more other vitamin B_6 vitamers.

[0089] In some embodiments, the vitamin B_6 component of the composition comprises pyridoxal 5'-phosphate. In some embodiments, the vitamin B_6 component of the composition consists of pyridoxal 5'-phosphate. In some embodiments, the vitamin B_6 component of the composition comprises pyridoxine. In some embodiments, the vitamin B_6 component of the

composition consists of pyridoxine. In some embodiments, the vitamin B_6 component of the composition comprises pyridoxine 5'-phosphate. In some embodiments, the vitamin B_6 component of the composition consists of pyridoxine 5'-phosphate.

[0090] In some embodiments, active agent (b) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (b) or any other component of the composition. Thus, purity in this context refers to the purity of the vitamin B_6 component *per se*.

[0091] In some embodiments, the composition comprises at least about 1 wt% active agent (b), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 3.5 wt%, 4 wt%, 4.5 wt%, 5 wt%, 5.5 wt%, 6 wt%, 6.5 wt%, 7 wt%, or 7.5 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises up to about 7.5 wt% active agent (b), for example, up to about any one of 7 wt%, 6.5 wt%, 6 wt%, 5.5 wt%, 5 wt%, 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 1 wt% to about 7.5 wt% active agent (b), for example, about any one of 1-1.5 wt%, 1-2 wt%, 1-4 wt%, 1.5-5 wt%, 2.5-7.5 wt%, 2.5-5 wt%, 5-7.5 wt%, 3-4 wt%, 4-5 wt%, 5-6 wt%, or 6-7 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 1.4 wt%, 4 wt%, or 4.8 wt% active agent (b), based on the total weight of active agents (a)-(d) in the composition.

[0092] In some embodiments, the composition comprises at least about 2 wt% active agent (b), for example at least about any one of 2.5 wt%, 3 wt%, 3.5 wt%, 4 wt%, 4.5 wt%, 5 wt%, 5.5 wt%, 6 wt%, 6.5 wt%, or 7 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises up to about 7 wt% active agent (b), for example, up to about any one of 6.5 wt%, 6 wt%, 5.5 wt%, 5 wt%, 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, or 2.5 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 2 wt% to about 7 wt% active agent (b), for example, about any one of 2-3 wt%, 3-4 wt%, 4-5 wt%, 5-6 wt%, 6-7 wt%, 2-5 wt%, or 4-7 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 3.8 wt% active agent (b), based on the total weight of active agents (a)-(d) and (k) in the composition.

[0093] In some embodiments, the composition comprises at least about 1 wt% active agent (b), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 3.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (b), for example, up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (b), for example, about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, 1-4 wt%, or 2-3.5 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 3.0 wt% active agent (b), based on the total weight of active agents (a)-(f) in the composition.

[0094] In some embodiments, the composition comprises at least about 1 wt% active agent (b), for example at least about any one of 1.1 wt%, 1.2 wt%, 1.3 wt%, 1.4 wt%, 1.5 wt%, 1.6 wt%, 1.7 wt%, 1.8 wt% or 1.9 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 2 wt% active agent (b), for example, up to about any one of 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, or 1.1 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 2 wt% active agent (b), for example, about any one of 1-1.5 wt%, 1.5-2 wt%, 1.2-1.8 wt%, 1.4-1.6 wt%, 1.6-1.8 wt%, or 1.3-1.8 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 1.7 wt% active agent (b), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0095] In some embodiments, the composition comprises at least about 1 wt% active agent (b), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 3.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (b), for example, up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (b), for example, about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, 1-4 wt%, or 2-3.5 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 2.9 wt% active agent (b), based on the total weight of active agents (a)-(g) in the composition.

[0096] In some embodiments, the composition comprises at least about 1 wt% active agent (b), for example at least about any one of 1.1 wt%, 1.2 wt%, 1.3 wt%, 1.4 wt%, 1.5 wt%, 1.6 wt%, 1.7 wt%, 1.8 wt% or 1.9 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 2 wt% active agent (b), for example, up to about any one of 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, or 1.1 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 2 wt% active agent (b), for example, about any one of 1-1.5 wt%, 1.5-2 wt%, 1.2-1.8 wt%, 1.4-1.6 wt%, 1.6-1.8 wt%, or 1.3-1.8 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 1.6 wt% active agent (b), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0097] In some embodiments, the composition comprises at least about 0.5 wt% active agent (b), for example at least about any one of 0.7 wt%, 0.9 wt%, 1.1 wt%, 1.3 wt%, 1.5 wt%, 1.7 wt%, or 1.9 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 2 wt% active agent (b), for example, up to about any one of 1.8 wt%, 1.6 wt%, 1.4 wt%, 1.2 wt%, 1 wt%, 0.8 wt%, or 0.6 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 0.5 wt% to about 2 wt% active agent (b), for example, about any one of 0.5-1 wt%, 1-1.5 wt%, 1.5-2 wt%, 0.5-1.5 wt%, 0.8-1.3 wt%, or 1-1.2 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 1.1 wt% active agent (b), based on the total weight of active agents (a)-(i) in the composition.

[0098] In some embodiments, the composition comprises at least about 0.3 wt% active agent (b), for example at least about any one of 0.4 wt%, 0.5 wt%, 0.6 wt%, 0.7 wt%, 0.8 wt%, 0.9 wt%, 1 wt%, 1.1 wt%, or 1.2 wt% based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 1.3 wt% active agent (b), for example, up to about any one of 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or 0.4 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 0.3 wt% to about 1.3 wt% active agent (b), for example, about any one of 0.3-0.6 wt%, 0.6-0.9 wt%, 0.9-1.3 wt%, 0.3-1 wt%, 0.5-1.3 wt%, or 0.5-1 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 0.88 wt% active agent (b), based on the total weight of active agents (a)-(j) in the composition.

[0099] In some embodiments, the composition comprises at least about 0.5 wt% active agent (b), for example, at least about any one of 0.6 wt%, 0.7 wt%, 0.8 wt%, 0.9 wt%, 1.0 wt%, or 1.1 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 1.6 wt% active agent (b), for example, up to about any one of 1.5 wt%, 1.4 wt%, 1.3 wt%, or 1.2 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 0.5 wt% to about 1.6 wt% active agent (b), for example, about any one of 0.6-1.6 wt%, 0.7-1.6 wt%, 0.8-1.6 wt%, 0.8-1.5 wt%, 0.8-1.4 wt%, 0.9-1.4 wt%, or 1.0-1.3 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 1.2 wt% active agent (b), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0100] In this way, the relative quantity of active agent (b) with respect to the other active agents in the composition reflects the relative appropriate dosages.

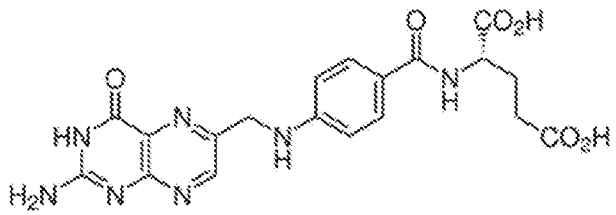
[0101] In some embodiments, the composition comprises about 100 µg to about 2 mg of vitamin B_6, for example, at least about any one of 100 µg, 200 µg, 250 µg, 300 µg, 400 µg, 500 µg, 600 µg, 700 µg, 800 µg, 900 µg, 1 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, or 1.9 mg or about 200 µg to about 500 µg, about 500 µg to about 750 µg, about 750 µg to about 1 µg, about 200 µg to about 750 µg, about 250 µg to about 1.5 mg, about 200 µg to about 1.5 mg, or about 500 µg to about 1.5 µg.

[0102] In some embodiments, the composition comprises about 10 mg to about 100 mg of vitamin B_6, for example, at least about any one of 10 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, or 100 mg, or about 20 mg to about 50 mg, about 50 mg to about 75 mg, about 75 mg to about 100 mg, about 20 mg to about 75 mg, about 25 mg to about 100 mg, about 20 mg to about 100 mg, or about 50 mg to about 100 mg.

(c) Vitamin B_9

[0103] Active agent (c) of the composition is vitamin B_9, also known as folate. The term "vitamin B_9" encompasses folic acid and its congeners, any of which may be used in the present invention, including but not limited to tetrahydrofolic acid, methyltetrahydrofolate, methenyltetrahydrofolate, folinic acid and folacin.

[0104] Folic acid has the following chemical structure:



(III)

[0105] Without being bound by any theory or hypothesis, vitamin B_9, vitamin B_{12}, and trimethylglycine may activate the methionine cycle, which degrades homocysteine. Small amounts of vitamin B_2 and vitamin B_3 may be required for the methionine cycle, which may be supplemented via the compositions described herein, or provided from dietary sources.

[0106] Active agent (c) may comprise a single congener of vitamin B_9 or may comprise a mixture of two or more congeners in any ratio. For example, active agent (c) may consist of folic acid. Alternatively, active agent (c) may consist of a mixture of folic acid and one or more other vitamin B_9 congeners, including tetrahydrofolic acid or tetrahydrofolate ("THF"). In some embodiments, active agent (c) comprises methyl folate. In some embodiments, active agent (c) is methyl folate. In some embodiments, active agent (c) comprises THF. In some embodiments, active agent (c) is THF.

[0107] In some embodiments, the vitamin B_9 component of the composition comprises folic acid or tetrahydrofolate. In some embodiments, the vitamin B_9 component of the composition consists of folic acid or tetrahydrofolate.

[0108] In some embodiments, active agent (c) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (c) or any other component of the composition. Thus, purity in this context refers to the purity of the vitamin B_9 component *per se*.

[0109] In some embodiments, the composition comprises at least about 0.01 wt% active agent (c), for example at least about any one of 0.02 wt%, 0.03 wt%, 0.04 wt%, 0.05 wt% , 0.06 wt%, 0.07 wt%, 0.08 wt%, 0.09 wt%, or 1.0 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises up to about 1.0 wt% active agent (c), for example up to about any one of 0.09 wt%, 0.08 wt%, 0.07 wt%, 0.06 wt%, 0.05 wt%, 0.04 wt%, 0.03 wt%, 0.02 wt%, or 0.01 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 0.01 wt% to about 1.0 wt% active agent (c), for example about any one of 0.01-0.08 wt%, 0.01-0.05 wt%, 0.05-1.0 wt%, 0.01-0.04 wt%, 0.04-0.08 wt%, 0.01-0.03 wt%, 0.03-0.06 wt%, 0.06-0.08 wt%, or 0.02-0.06 wt%, based on the total weight of active

agents (a)-(d) in the composition. In some embodiments, the composition comprises about , 0.038 wt%, 0.046 wt%, or 0.079 wt% active agent (c), based on the total weight of active agents (a)-(d) in the composition.

[0110] In some embodiments, the composition comprises at least about 0.01 wt% active agent (c), for example at least about any one of 0.02 wt%, 0.03 wt%, 0.04 wt%, 0.05 wt% , 0.06 wt%, 0.07 wt%, or 0.08 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises up to about 0.08 wt% active agent (c), for example up to about any one of 0.07 wt%, 0.06 wt%, 0.05 wt%, 0.04 wt%, 0.03 wt%, 0.02 wt%, or 0.01 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 0.01 wt% to about 0.08 wt% active agent (c), for example about any one of 0.01-0.04 wt%, 0.04-0.08 wt%, 0.01-0.03 wt%, 0.03-0.06 wt%, 0.06-0.08 wt%, or 0.02-0.06 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 0.031 wt% active agent (c), based on the total weight of active agents (a)-(d) and (k) in the composition.

[0111] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example at least about any one of 0.002 wt%, 0.004 wt%, 0.006 wt%, 0.008 wt% , 0.01 wt%, 0.012 wt%, 0.014 wt%, 0.016 wt%, or 0.018 wt% based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises up to about 0.02 wt% active agent (c), for example up to about any one of 0.018 wt%, 0.016 wt%, 0.014 wt%, 0.012 wt%, 0.01 wt%, 0.008 wt%, 0.006 wt%, 0.004 wt%, or 0.002 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 0.001 wt% to about 0.02 wt% active agent (c), for example about any one of 0.002-0.01 wt%, 0.005-0.015 wt%, 0.007-0.013 wt%, 0.01-0.02 wt%, 0.012-0.018 wt%, or 0.014-0.016 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 0.016 wt% active agent (c), based on the total weight of active agents (a)-(f) in the composition.

[0112] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example at least about any one of 0.002 wt%, 0.004 wt%, 0.006 wt%, 0.008 wt% , 0.01 wt%, 0.012 wt%, or 0.014 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 0.015 wt% active agent (c), for example up to about any one of 0.014 wt%, 0.012 wt%, 0.01 wt%, 0.008 wt%, 0.006 wt%, 0.004 wt%, or 0.002 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises

about 0.001 wt% to about 0.015 wt% active agent (c), for example about any one of 0.002-0.005 wt%, 0.005-0.010 wt%, 0.010-0.015 wt%, 0.002-0.010 wt%, 0.005-0.012 wt%, or 0.005-0.012 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 0.0089 wt% active agent (c), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0113] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example at least about any one of 0.002 wt%, 0.004 wt%, 0.006 wt%, 0.008 wt% , 0.01 wt%, 0.012 wt%, 0.014 wt%, 0.016 wt%, or 0.018 wt% based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 0.02 wt% active agent (c), for example up to about any one of 0.018 wt%, 0.016 wt%, 0.014 wt%, 0.012 wt%, 0.01 wt%, 0.008 wt%, 0.006 wt%, 0.004 wt%, or 0.002 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 0.001 wt% to about 0.02 wt% active agent (c), for example about any one of 0.002-0.01 wt%, 0.005-0.015 wt%, 0.007-0.013 wt%, 0.01-0.02 wt%, 0.012-0.018 wt%, or 0.014-0.016 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 0.016 wt% active agent (c), based on the total weight of active agents (a)-(g) in the composition.

[0114] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example at least about any one of 0.002 wt%, 0.004 wt%, 0.006 wt%, 0.008 wt% , 0.01 wt%, 0.012 wt%, or 0.014 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 0.015 wt% active agent (c), for example up to about any one of 0.014 wt%, 0.012 wt%, 0.01 wt%, 0.008 wt%, 0.006 wt%, 0.004 wt%, or 0.002 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 0.001 wt% to about 0.015 wt% active agent (c), for example about any one of 0.002-0.005 wt%, 0.005-0.010 wt%, 0.010-0.015 wt%, 0.002-0.010 wt%, 0.005-0.012 wt%, or 0.005-0.012 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 0.0088 wt% active agent (c), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0115] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example at least about any one of 0.002 wt%, 0.004 wt%, 0.006 wt%, 0.008 wt% , 0.01 wt%, 0.012 wt%, or 0.014 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 0.015 wt% active agent (c), for example up to about any one of 0.014 wt%, 0.012 wt%, 0.01 wt%, 0.008

wt%, 0.006 wt%, 0.004 wt%, or 0.002 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 0.001 wt% to about 0.015 wt% active agent (c), for example about any one of 0.002-0.005 wt%, 0.005-0.010 wt%, 0.010-0.015 wt%, 0.002-0.010 wt%, 0.002-0.008 wt%, or 0.005-0.012 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 0.0061 wt% active agent (c), based on the total weight of active agents (a)-(i) in the composition.

[0116] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example at least about any one of 0.002 wt%, 0.003 wt%, 0.004 wt%, 0.005 wt%, 0.006 wt%, 0.007 wt%, 0.008 wt% , or 0.009 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 0.010 wt% active agent (c), for example up to about any one of 0.009 wt%, 0.008 wt%, 0.007 wt%, 0.006 wt%, 0.005 wt%, 0.004 wt%, 0.003 wt%, or 0.002 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 0.001 wt% to about 0.010 wt% active agent (c), for example about any one of 0.001-0.005 wt%, 0.005-0.010 wt%, 0.002-0.008 wt%, 0.003-0.007 wt%, or 0.004-0.006 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 0.0046 wt% active agent (c), based on the total weight of active agents (a)-(j) in the composition.

[0117] In some embodiments, the composition comprises at least about 0.001 wt% active agent (c), for example, at least about any one of 0.002 wt%, 0.003 wt%, 0.004 wt%, 0.005 wt%, or 0.006 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 0.01 wt% active agent (c), for example, up to about any one of 0.009 wt%, 0.008 wt%, or 0.007 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 0.001 wt% to about 0.01 wt% active agent (c), for example, about any one of 0.002-0.01 wt%, 0.003-0.01 wt%, 0.003-0.009 wt%, 0.003-0.009 wt%, 0.003-0.008 wt%, 0.004-0.008 wt%, or 0.005-0.007 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 0.0065 wt% active agent (c), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

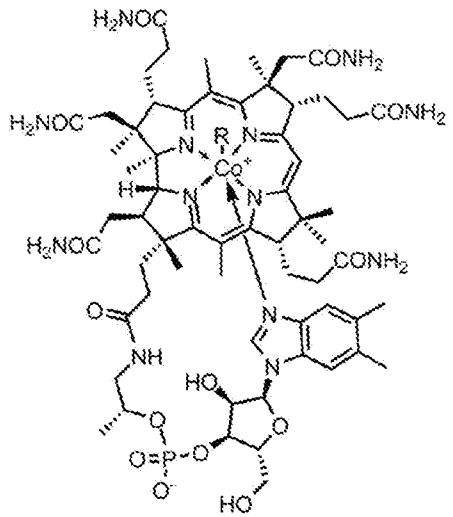
[0118] In this way, the relative quantity of active agent (c) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0119] In some embodiments, the composition comprises about 0.1 mg to about 2 mg of vitamin B_9, for example, at least about any one of 0.1 mg, 0.25 mg, 0.5 mg, 0.8 mg, 0.9 mg, 1 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 2 mg, or about 0.1 mg to 1.0 mg, about 0.1 mg to about 0.5 mg, about 0.5 mg to about 1 mg, about 1 mg to about 1.5 mg, about 1 mg to about 2 mg, about 0.5 mg to about 1.5 mg, about 0.75 mg to about 1.25 mg, or about 0.8 mg to about 1.5 mg.

(d) Vitamin B_{12}

[0120] Active agent (d) of the composition is vitamin B_{12}, also known as cobalamin. The term "vitamin B_{12}" encompasses a group of related compounds (vitamers) which are chemically related. The core structure of vitamin B_{12} compounds consists of a cobalt atom chelated by a corrin ring.

[0121] There are four commonly recognized vitamers of vitamin B_{12}, any of which may be used in the present invention. These four vitamers are represented by the varying R group in the following general structure:



R = 5'-deoxyadenosyl, Me, OH, CN (IV)

[0122] The four vitamers are cyanocobalamin (R = CN), hydroxocobalamin (R = OH), adenosylcobalamin (R = 5'-deoxyadenosyl) and methylcobalamin (R = Me).

[0123] Active agent (d) may comprise a single vitamer of vitamin B_{12} or may comprise a mixture of two or more vitamers in any ratio.

[0124] In some embodiments, active agent (d) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent,

excipient, or carrier within active agent (d) or any other component of the composition. Thus, purity in this context refers to the purity of the vitamin B_{12} component *per se*.

[0125] In some embodiments, the composition comprises at least about 0.01 wt% active agent (d), for example at least about any one of 0.015 wt%, 0.02 wt%, 0.025 wt%, 0.03 wt% , 0.035 wt%, 0.04 wt%, 0.045 wt%, 0.05 wt%, 0.06 wt%, 0.07 wt%, 0.08 wt%, 0.09 wt%, 0.10 wt%, 0.12 wt%, or 0.14 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises up to about 0.15 wt% active agent (d), for example up to about any one of 0.13 wt%, 0.11 wt%, 0.09 wt%, 0.07 wt%, 0.05 wt%, 0.045 wt%, 0.04 wt%, 0.035 wt%, 0.03 wt%, 0.025 wt%, 0.02 wt%, 0.015 wt%, or 0.01 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 0.01 wt% to about 0.15 wt% active agent (d), for example about any one of 0.01-0.02 wt%, 0.02-0.03 wt%, 0.03-0.04 wt%, 0.04-0.05 wt%, 0.01-0.03 wt%, 0.02-0.05 wt%, 0.05-0.10 wt%, or 0.10-0.15 wt%, based on the total weight of active agents (a)-(d) in the composition. In some embodiments, the composition comprises about 0.024 wt%, 0.029 wt%, or 0.040 wt% active agent (d), based on the total weight of active agents (a)-(d) in the composition.

[0126] In some embodiments, the composition comprises at least about 0.01 wt% active agent (d), for example at least about any one of 0.015 wt%, 0.02 wt%, 0.025 wt%, 0.03 wt% , 0.035 wt%, 0.04 wt%, or 0.045 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises up to about 0.05 wt% active agent (d), for example up to about any one of 0.045 wt%, 0.04 wt%, 0.035 wt%, 0.03 wt%, 0.025 wt%, 0.02 wt%, 0.015 wt%, or 0.01 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 0.01 wt% to about 0.05 wt% active agent (d), for example about any one of 0.01-0.02 wt%, 0.02-0.03 wt%, 0.03-0.04 wt%, 0.04-0.05 wt%, 0.01-0.03 wt%, or 0.02-0.05 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 0.019 wt% active agent (d), based on the total weight of active agents (a)-(d) and (k) in the composition.

[0127] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (d), for example at least about any one of 0.001 wt%, 0.002 wt%, 0.003 wt%, or 0.004 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises up to about 0.005 wt% active agent (d), for example up to about any one of 0.004 wt%, 0.003 wt%, 0.002 wt%, or 0.001 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the

composition comprises about 0.0005 wt% to about 0.005 wt% active agent (d), for example about any one of 0.0005-0.001 wt%, 0.001-0.002 wt%, 0.002-0.003 wt%, 0.003-0.004 wt%, 0.004-0.005 wt%, 0.002-0.005 wt% or 0.003-0.004 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 0.0030 wt% active agent (d), based on the total weight of active agents (a)-(f) in the composition.

[0128] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (d), for example at least about any one of 0.0006 wt%, 0.0008 wt%, 0.001 wt%, 0.0012 wt%, 0.0014 wt%, 0.0016 wt%, 0.0018 wt%, 0.002 wt%, or 0.0025 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 0.003 wt% active agent (d), for example up to about any one of 0.0025 wt%, 0.002 wt%, 0.0018 wt%, 0.0016 wt%, 0.0014 wt%, 0.0012 wt%, 0.001 wt%, 0.0008 wt%, or 0.0006 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 0.0005 wt% to about 0.003 wt% active agent (d), for example about any one of 0.0005-0.001 wt%, 0.001-0.002 wt%, 0.002-0.003 wt%, 0.001-0.003 wt%, 0.0005-0.0002 wt%, or 0.0015-0.0025 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 0.0017 wt% active agent (d), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0129] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (d), for example at least about any one of 0.001 wt%, 0.002 wt%, 0.003 wt%, or 0.004 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 0.005 wt% active agent (d), for example up to about any one of 0.004 wt%, 0.003 wt%, 0.002 wt%, or 0.001 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 0.0005 wt% to about 0.005 wt% active agent (d), for example about any one of 0.0005-0.001 wt%, 0.001-0.002 wt%, 0.002-0.003 wt%, 0.003-0.004 wt%, 0.004-0.005 wt%, 0.002-0.005 wt% or 0.003-0.004 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 0.0029 wt% active agent (d), based on the total weight of active agents (a)-(g) in the composition.

[0130] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (d), for example at least about any one of 0.0006 wt%, 0.0008 wt%, 0.001 wt%, 0.0012 wt%, 0.0014 wt%, 0.0016 wt%, 0.0018 wt%, 0.002 wt%, or 0.0025 wt%, based on the total

weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 0.003 wt% active agent (d), for example up to about any one of 0.0025 wt%, 0.002 wt%, 0.0018 wt%, 0.0016 wt%, 0.0014 wt%, 0.0012 wt%, 0.001 wt%, 0.0008 wt%, or 0.0006 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 0.0005 wt% to about 0.003 wt% active agent (d), for example about any one of 0.0005-0.001 wt%, 0.001-0.002 wt%, 0.002-0.003 wt%, 0.001-0.003 wt%, 0.0005-0.0002 wt%, or 0.0015-0.0025 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 0.0016 wt% active agent (d), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0131] In some embodiments, the composition comprises at least about 0.0001 wt% active agent (d), for example at least about any one of 0.0002 wt%, 0.0004 wt%, 0.0006 wt%, 0.0008 wt%, 0.0010 wt%, 0.0012 wt%, 0.0014 wt%, 0.0016 wt%, or 0.0018 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 0.002 wt% active agent (d), for example up to about any one of 0.0018 wt%, 0.0016 wt%, 0.0014 wt%, 0.0012 wt%, 0.0010 wt%, 0.0008 wt%, 0.0006 wt%, 0.0004 wt%, or 0.0002 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 0.0001 wt% to about 0.002 wt% active agent (d), for example about any one of 0.0001-0.0005 wt%, 0.0005-0.001 wt%, 0.001-0.0015 wt%, 0.0015-0.002 wt%, 0.0005-0.0015 wt%, or 0.0008-0.0012 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 0.0011 wt% active agent (d), based on the total weight of active agents (a)-(i) in the composition.

[0132] In some embodiments, the composition comprises at least about 0.0001 wt% active agent (d), for example at least about any one of 0.0002 wt%, 0.0004 wt%, 0.0006 wt%, 0.0008 wt%, 0.0010 wt%, 0.0012 wt%, 0.0014 wt%, 0.0016 wt%, or 0.0018 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 0.002 wt% active agent (d), for example up to about any one of 0.0018 wt%, 0.0016 wt%, 0.0014 wt%, 0.0012 wt%, 0.0010 wt%, 0.0008 wt%, 0.0006 wt%, 0.0004 wt%, or 0.0002 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 0.0001 wt% to about 0.002 wt% active agent (d), for example about any one of 0.0001-0.0005 wt%, 0.0005-0.001 wt%, 0.001-0.0015 wt%, 0.0015-0.002 wt%, 0.0005-0.0015 wt%, or 0.0008-0.0012 wt%, based on the total weight of active agents (a)-(j) in the composition. In some

embodiments, the composition comprises about 0.00088 wt% active agent (d), based on the total weight of active agents (a)-(j) in the composition.

[0133] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (d), for example, at least about any one of 0.0006 wt%, 0.0007 wt%, 0.0008 wt%, 0.0009 wt%, or 0.001 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 0.002 wt% active agent (d), for example up to about any one of 0.0015 wt%, 0.0014 wt%, 0.0013 wt%, or 0.00125 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 0.0005 wt% to about 0.002 wt% active agent (d), for example, about any one of 0.0006-0.002 wt%, 0.0007-0.002 wt%, 0.0008-0.002 wt%, 0.0008-0.0019 wt%, 0.0008-0.0015 wt%, 0.0009-0.0014 wt%, or 0.001-0.0013 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 0.0012 wt% active agent (d), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

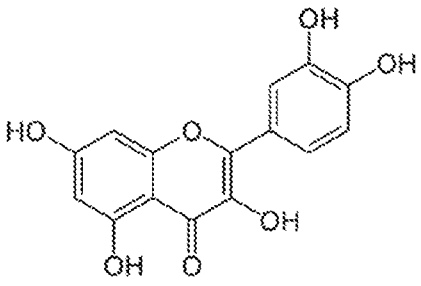
[0134] In this way, the relative quantity of active agent (d) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0135] In some embodiments, the composition comprises about 200 ng to about 3 µg of vitamin B_{12}, for example, at least about any one of 200 ng, 500 ng, 1 µg, 1.2 µg, 1.3 µg, 1.4 µg, 1.5 µg, 1.6 µg, 1.7 µg, 1.8 µg, 1.9 µg, 2 µg, 2.2 µg, 2.3 µg, 2.4 µg, 2.5 µg, 2.6 µg, 2.7 µg, 2.8 µg, or 2.9 µg, or about 200 ng to about 1 µg, about 1 µg to about 2 µg, about 2 µg to about 3 µg, about 500 ng to about 1 µg, about 1 µg to about 2.5 µg, about 800 ng to about 1.5 µg, about 2 µg to about 2.5 µg, about 1.3 µg to about 2.3 µg, or about 1.4 µg to about 2.4 µg,.

[0136] In some embodiments, the composition comprises about 20 µg to about 3 mg of vitamin B_{12}, for example, at least about any one of 20 µg, 50 µg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1 mg, 2 mg or 3 mg, or about 0.1 mg to about 1 mg, about 1 mg to about 2 mg, about 2 mg to about 3 mg, about 50 µg to about 0.5 mg, about 0.1 mg to about 0.5 mg, about 0.5 mg to about 1 mg, about 0.2 mg to about 1 mg, about 0.3 mg to about 1 mg, about 0.4 mg to about 1 mg, about 0.25 mg to about 0.75 mg, or about 0.4 mg to about 0.8 mg.

(e) Quercetin

[0137] Active agent (e) of the composition is quercetin. Quercetin is a flavonoid having the following structure:



(V)

[0138] In some embodiments, active agent (e) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (e) or any other component of the composition. Thus, purity in this context refers to the purity of the quercetin component *per se*.

[0139] In some embodiments, the composition comprises at least about 5 wt% active agent (e), for example at least about any one of 7 wt%, 9 wt%, 11 wt%, 13 wt%, 15 wt%, 17 wt%, or 19 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises up to about 20 wt% active agent (e), for example up to about any one of 18 wt%, 16 wt%, 14 wt%, 12 wt%, 10 wt%, 8 wt%, or 6 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 5 wt% to about 20 wt% active agent (e), for example about any one of 5-10 wt%, 10-15 wt%, 15-20 wt%, 10-20 wt%, 5-15 wt%, or 7-14 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 12.1 wt% active agent (e), based on the total weight of active agents (a)-(f) in the composition.

[0140] In some embodiments, the composition comprises at least about 1 wt% active agent (e), for example at least about any one of 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, 9 wt%, 10 wt%, or 11 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 12 wt% active agent (e), for example up to about any one of 11 wt%, 10 wt%, 9 wt%, 8 wt%, 7 wt%, 6 wt%, 5 wt%, 4 wt%, 3 wt%, or 2 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 12 wt% active agent (e), for example about any one of 1-4 wt%, 4-8 wt%, 8-10 wt%, 2-10 wt%, or 4-6 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 6.7 wt% active agent (e), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0141] In some embodiments, the composition comprises at least about 5 wt% active agent (e), for example at least about any one of 7 wt%, 9 wt%, 11 wt%, 13 wt%, 15 wt%, 17 wt%, or 19 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 20 wt% active agent (e), for example up to about any one of 18 wt%, 16 wt%, 14 wt%, 12 wt%, 10 wt%, 8 wt%, or 6 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 5 wt% to about 20 wt% active agent (e), for example about any one of 5-10 wt%, 10-15 wt%, 15-20 wt%, 10-20 wt%, 5-15 wt%, or 7-14 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 11.8 wt% active agent (e), based on the total weight of active agents (a)-(g) in the composition.

[0142] In some embodiments, the composition comprises at least about 1 wt% active agent (e), for example at least about any one of 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, 9 wt%, 10 wt%, or 11 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 12 wt% active agent (e), for example up to about any one of 11 wt%, 10 wt%, 9 wt%, 8 wt%, 7 wt%, 6 wt%, 5 wt%, 4 wt%, 3 wt%, or 2 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 12 wt% active agent (e), for example about any one of 1-4 wt%, 4-8 wt%, 8-10 wt%, 2-10 wt%, or 4-6 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 6.6 wt% active agent (e), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0143] In some embodiments, the composition comprises at least about 1 wt% active agent (e), for example at least about any one of 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, or 9 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 10 wt% active agent (e), for example up to about any one of 9 wt%, 8 wt%, 7 wt%, 6 wt%, 5 wt%, 4 wt%, 3 wt%, or 2 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 1 wt% to about 10 wt% active agent (e), for example about any one of 1-5 wt%, 5-10 wt%, 2-8 wt%, 3-7 wt%, or 4-6 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 4.6 wt% active agent (e), based on the total weight of active agents (a)-(i) in the composition.

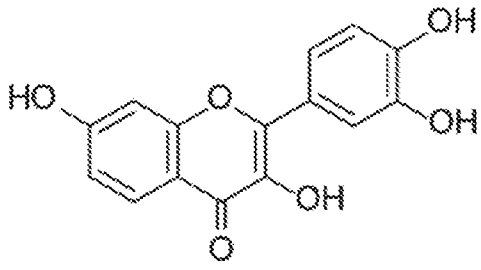
[0144] In some embodiments, the composition comprises at least about 1 wt% active agent (e), for example at least about any one of 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, or 9 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 10 wt% active agent (e), for example up to about any one of 9 wt%, 8 wt%, 7 wt%, 6 wt%, 5 wt%, 4 wt%, 3 wt%, or 2 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 10 wt% active agent (e), for example about any one of 1-5 wt%, 5-10 wt%, 2-8 wt%, 3-7 wt%, or 4-6 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 3.5 wt% active agent (e), based on the total weight of active agents (a)-(j) in the composition.

[0145] In this way, the relative quantity of active agent (e) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0146] In some embodiments, the composition comprises about 50 mg to about 500 mg of quercetin, for example, at least about any one of 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, or 500 mg, or about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, about 400 mg to about 500 mg, about 100 mg to about 500 mg, or about 100 mg to about 300 mg.

(f) Fisetin

[0147] Active agent (f) of the composition is fisetin, also known as 7, 3', 4'-flavon-3-ol. Fisetin is a flavonoid having the following structure:



(VI)

[0148] In some embodiments, active agent (f) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (f) or any other component of the composition. Thus, purity in this context refers to the purity of the fisetin component *per se*.

[0149] In some embodiments, the composition comprises at least about 1 wt% active agent (f), for example at least about any one of 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, or 9 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises up to about 10 wt% active agent (f), for example up to about any one of 9 wt%, 8 wt%, 7 wt%, 6 wt%, 5 wt%, 4 wt%, 3 wt%, or 2 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 1 wt% to about 10 wt% active agent (f), for example about any one of 1-5 wt%, 5-10 wt%, 2-8 wt%, 3-7 wt%, or 4-6 wt%, based on the total weight of active agents (a)-(f) in the composition. In some embodiments, the composition comprises about 4.0 wt% active agent (f), based on the total weight of active agents (a)-(f) in the composition.

[0150] In some embodiments, the composition comprises at least about 1 wt% active agent (f), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 2.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (f), for example up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (f), for example about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, or 2-4 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 2.2 wt% active agent (f), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0151] In some embodiments, the composition comprises at least about 1 wt% active agent (f), for example at least about any one of 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, or 9 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 10 wt% active agent (f), for example up to about any one of 9 wt%, 8 wt%, 7 wt%, 6 wt%, 5 wt%, 4 wt%, 3 wt%, or 2 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 1 wt% to about 10 wt% active agent (f), for example about any one of 1-5 wt%, 5-10 wt%, 2-8 wt%, 3-7 wt%, or 4-6 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 3.9 wt% active agent (f), based on the total weight of active agents (a)-(g) in the composition.

[0152] In some embodiments, the composition comprises at least about 1 wt% active agent (f), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 2.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (f), for example up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (f), for example about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, or 2-4 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 2.2 wt% active agent (f), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0153] In some embodiments, the composition comprises at least about 1 wt% active agent (f), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 2.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (f), for example up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (f), for example about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, or 2-4 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 1.5 wt% active agent (f), based on the total weight of active agents (a)-(i) in the composition.

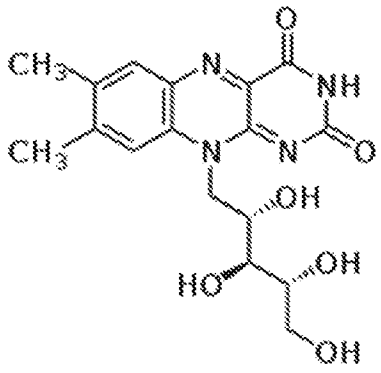
[0154] In some embodiments, the composition comprises at least about 1 wt% active agent (f), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 2.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (f), for example up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (f), for example about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, or 2-4 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 1.2 wt% active agent (f), based on the total weight of active agents (a)-(j) in the composition.

[0155] In this way, the relative quantity of active agent (f) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0156] In some embodiments, the composition comprises about 20 mg to about 500 mg of fisetin, for example, at least about any one of 20 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, or 500 mg, or about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, about 400 mg to about 500 mg, about 20 mg to about 200 mg, about 20 mg to about 100 mg, about 100 mg to about 500 mg, or about 100 mg to about 300 mg.

(g) Vitamin B_2

[0157] Active agent (g) of the composition is vitamin B_2, also known as riboflavin. Vitamin B_2 has the following structure:



(VII).

[0158] In some embodiments, active agent (g) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (g) or any other component of the composition. Thus, purity in this context refers to the purity of the vitamin B_2 component *per se*.

[0159] In some embodiments, the composition comprises at least about 1 wt% active agent (g), for example at least about any one of 1.5 wt%, 2 wt%, 2.5 wt%, 3 wt%, 3.5 wt%, 4 wt%, or 4.5 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises up to about 5 wt% active agent (g), for example, up to about any one of 4.5 wt%, 4 wt%, 3.5 wt%, 3 wt%, 2.5 wt%, 2 wt%, or 1.5 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition comprises about 1 wt% to about 5 wt% active agent (g), for example, about any one of 1-2 wt%, 2-3 wt%, 3-4 wt%, 4-5 wt%, 1-4 wt%, or 2-3.5 wt%, based on the total weight of active agents (a)-(g) in the composition. In some embodiments, the composition

comprises about 2.9 wt% active agent (g), based on the total weight of active agents (a)-(g) in the composition.

[0160] In some embodiments, the composition comprises at least about 1 wt% active agent (g), for example at least about any one of 1.1 wt%, 1.2 wt%, 1.3 wt%, 1.4 wt%, 1.5 wt%, 1.6 wt%, 1.7 wt%, 1.8 wt% or 1.9 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 2 wt% active agent (g), for example, up to about any one of 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, or 1.1 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 1 wt% to about 2 wt% active agent (g), for example, about any one of 1-1.5 wt%, 1.5-2 wt%, 1.2-1.8 wt%, 1.4-1.6 wt%, 1.6-1.8 wt%, or 1.3-1.8 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 1.6 wt% active agent (g), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0161] In some embodiments, the composition comprises at least about 0.5 wt% active agent (g), for example at least about any one of 0.7 wt%, 0.9 wt%, 1.1 wt%, 1.3 wt%, 1.5 wt%, 1.7 wt%, or 1.9 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 2 wt% active agent (g), for example, up to about any one of 1.8 wt%, 1.6 wt%, 1.4 wt%, 1.2 wt%, 1 wt%, 0.8 wt%, or 0.6 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 0.5 wt% to about 2 wt% active agent (g), for example, about any one of 0.5-1 wt%, 1-1.5 wt%, 1.5-2 wt%, 0.5-1.5 wt%, 0.8-1.3 wt%, or 1-1.2 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 1.1 wt% active agent (g), based on the total weight of active agents (a)-(i) in the composition.

[0162] In some embodiments, the composition comprises at least about 0.3 wt% active agent (g), for example at least about any one of 0.4 wt%, 0.5 wt%, 0.6 wt%, 0.7 wt%, 0.8 wt%, 0.9 wt%, 1 wt%, 1.1 wt%, or 1.2 wt% based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 1.3 wt% active agent (g), for example, up to about any one of 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or 0.4 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 0.3 wt% to about 1.3 wt% active agent (g), for example, about any one of 0.3-0.6 wt%, 0.6-0.9 wt%, 0.9-1.3 wt%, 0.3-1 wt%, 0.5-1.3 wt%, or 0.5-1 wt%, based on the total weight of active agents

(a)-(j) in the composition. In some embodiments, the composition comprises about 0.88 wt% active agent (g), based on the total weight of active agents (a)-(j) in the composition.

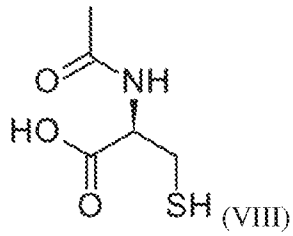
[0163] In some embodiments, the composition comprises at least about 0.5 wt% active agent (g), for example, at least about any one of 0.6 wt%, 0.7 wt%, 0.8 wt%, 0.9 wt%, 1.0 wt%, or 1.1 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 1.6 wt% active agent (g), for example, up to about any one of 1.5 wt%, 1.4 wt%, 1.3 wt%, or 1.2 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 0.5 wt% to about 1.6 wt% active agent (g), for example, about any one of 0.6-1.6 wt%, 0.7-1.6 wt%, 0.8-1.6 wt%, 0.8-1.5 wt%, 0.8-1.4 wt%, 0.9-1.4 wt%, or 1.0-1.3 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 1.2 wt% active agent (g), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0164] In this way, the relative quantity of active agent (g) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0165] In some embodiments, the composition comprises about 0.1 mg to about 2 mg of vitamin B_2, for example, at least about any one of 0.1 mg, 0.25 mg, 0.5 mg, 0.8 mg, 0.9 mg, 1 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 2 mg, or about 0.1 mg to about 0.5 mg, about 0.5 mg to about 1 mg, about 1 mg to about 1.5 mg, about 1 mg to about 2 mg, about 0.5 mg to about 1.5 mg, about 0.75 mg to about 1.25 mg, or about 0.8 mg to about 1.5 mg. In some embodiments, the composition comprises about 20 mg to about 400 mg of vitamin B_2, for example, at least about any one of 20 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 400 mg, or about 20 mg to about 50 mg, about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 400 mg, or about 20 mg to about 200 mg.

(h) *N*-acetylcysteine

[0166] Active agent (h) of the composition is *N*-acetylcysteine, which has the following structure:



(VIII)

[0167] In some embodiments, active agent (h) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (h) or any other component of the composition. Thus, purity in this context refers to the purity of the *N*-acetylcysteine component *per se*.

[0168] In some embodiments, the composition comprises at least about 20 wt% active agent (h), for example at least about any one of 22 wt%, 24 wt%, 26 wt%, 28 wt%, 30 wt%, 32 wt%, 34 wt%, 36 wt%, or 38 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (h), for example up to about any one of 38 wt%, 36 wt%, 34 wt%, 32 wt%, 30 wt%, 28 wt%, 26 wt%, 24 wt%, or 22 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 20 wt% to about 40 wt% active agent (h), for example about any one of 20-25 wt%, 25-30 wt%, 30-35 wt%, 35-40 wt%, 25-35 wt%, 27-33 wt%, or 29-31 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 30.5 wt% active agent (h), based on the total weight of active agents (a)-(i) in the composition.

[0169] In some embodiments, the composition comprises at least about 15 wt% active agent (h), for example at least about any one of 17 wt%, 19 wt%, 21 wt%, 23 wt%, 25 wt%, 27 wt%, 29%, or 31 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 32 wt% active agent (h), for example up to about any one of 30 wt%, 28 wt%, 26 wt%, 24 wt%, 22 wt%, 21 wt%, 19 wt%, 18 wt%, or 17 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 15 wt% to about 32 wt% active agent (h), for example about any one of 15-20 wt%, 20-25 wt%, 25-32 wt%, 17-30 wt%, 19-28 wt%, 21-26 wt%, or 23-24 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 23.4 wt% active agent (h), based on the total weight of active agents (a)-(j) in the composition.

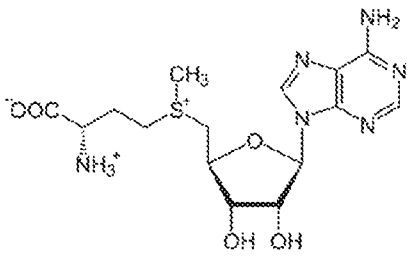
[0170] In some embodiments, the composition comprises at least about 25 wt% active agent (h), for example, at least about any one of 26 wt%, 27 wt%, 28 wt%, 29 wt%, 30 wt%, or 31 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (h), for example, up to about any one of 35 wt%, 34 wt%, 33 wt%, or 32 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 25 wt% to about 40 wt% active agent (h), for example, about any one of 25-35 wt%, 25-34 wt%, 26-34 wt%, 27-34 wt%, 28-34 wt%, 29-34 wt%, or 30-34 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 32.5 wt% active agent (h), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0171] In this way, the relative quantity of active agent (h) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0172] In some embodiments, the composition comprises about 1000 mg to about 10000 mg of *N*-acetylcysteine, for example, at least about any one of 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2500 mg, 3000 mg, 5000 mg or 10000 mg, or about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, about 2000 mg to about 2500 mg, about 2500 mg to about 3000 mg, about 1000 mg to about 2000 mg, about 2000 mg to about 3000 mg, about 1000 mg to about 3000 mg, or about 3000 mg to about 10000 mg.

(i) *S*-adenosylmethionine

[0173] Active agent (i) of the composition is *S*-adenosylmethionine, also known as SAM or SAMe, which has the following structure:



(IX)

[0174] In some embodiments, active agent (i) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (i) or any other component of the composition. Thus, purity in this context refers to the purity of the *S*-adenosylmethionine component *per se*.

[0175] In some embodiments, the composition comprises at least about 20 wt% active agent (i), for example at least about any one of 22 wt%, 24 wt%, 26 wt%, 28 wt%, 30 wt%, 32 wt%, 34 wt%, 36 wt%, or 38 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (i), for example up to about any one of 38 wt%, 36 wt%, 34 wt%, 32 wt%, 30 wt%, 28 wt%, 26 wt%, 24 wt%, or 22 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 20 wt% to about 40 wt% active agent (i), for example about any one of 20-25 wt%, 25-30 wt%, 30-35 wt%, 35-40 wt%, 25-35 wt%, 27-33 wt%, or 29-31 wt%, based on the total weight of active agents (a)-(i) in the composition. In some embodiments, the composition comprises about 30.5 wt% active agent (i), based on the total weight of active agents (a)-(i) in the composition.

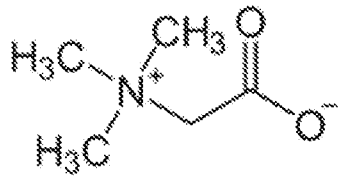
[0176] In some embodiments, the composition comprises at least about 15 wt% active agent (i), for example at least about any one of 17 wt%, 19 wt%, 21 wt%, 23 wt%, 25 wt%, 27 wt%, 29%, or 31 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 32 wt% active agent (i), for example up to about any one of 30 wt%, 28 wt%, 26 wt%, 24 wt%, 22 wt%, 21 wt%, 19 wt%, 18 wt%, or 17 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 15 wt% to about 32 wt% active agent (i), for example about any one of 15-20 wt%, 20-25 wt%, 25-32 wt%, 17-30 wt%, 19-28 wt%, 21-26 wt%, or 23-24 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 23.4 wt% active agent (i), based on the total weight of active agents (a)-(j) in the composition.

[0177] In this way, the relative quantity of active agent (i) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0178] In some embodiments, the composition comprises about 1000 mg to about 10000 mg of *S*-adenosylmethionine, for example, at least about any one of 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2500 mg, 3000 mg, 5000 mg or 10000 mg, or about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, about 2000 mg to about 2500 mg, about 2500 mg to about 3000 mg, about 1000 mg to about 2000 mg, about 2000 mg to about 3000 mg, about 1000 mg to about 3000 mg, or about 3000 mg to about 10000 mg.

(j) Trimethylglycine

[0179] Active agent (j) of the composition is trimethylglycine (TMG), also known as glycine betaine. TMG exists as a zwitterion at neutral pH, having the following structure:



(X)

[0180] In some embodiments, the composition does not comprise active agent (j). In some embodiments, the composition does not comprise a therapeutically effective amount of active agent (j).

[0181] In some embodiments, active agent (j) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (j) or any other component of the composition. Thus, purity in this context refers to the purity of the TMG component *per se*.

[0182] In some embodiments, the composition comprises at least about 35 wt% active agent (j), for example at least about any one of 37 wt%, 39 wt%, 41 wt%, 43 wt%, 45 wt%, 47 wt%, 49 wt%, 51 wt%, or 53 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises up to about 55 wt% active agent (j), for example up to about any one of 53 wt%, 51 wt%, 49 wt%, 47 wt%, 45 wt%, 43 wt%, 41 wt%, 39 wt%, or 37 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 35 wt% to about 55 wt% active agent (j), for example about any one of 35-40 wt%, 40-45 wt%, 45-50 wt%, 50-55 wt%, 40-50 wt%, or 42-46 wt%, based on the total weight of active agents (a)-(f) and (j) in the composition. In some embodiments, the composition comprises about 44.7 wt% active agent (j), based on the total weight of active agents (a)-(f) and (j) in the composition.

[0183] In some embodiments, the composition comprises at least about 35 wt% active agent (j), for example at least about any one of 37 wt%, 39 wt%, 41 wt%, 43 wt%, 45 wt%, 47 wt%, 49 wt%, 51 wt%, or 53 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises up to about 55 wt% active agent (j), for example up to about any one of 53 wt%, 51 wt%, 49 wt%, 47 wt%, 45 wt%, 43 wt%, 41 wt%, 39 wt%, or 37 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 35 wt% to about 55 wt% active agent (j), for example about any one of 35-40 wt%, 40-45 wt%, 45-50 wt%, 50-55 wt%, 40-50 wt%, or 42-46 wt%, based on the total weight of active agents (a)-(g) and (j) in the composition. In some embodiments, the composition comprises about 44.0

wt% active agent (j), based on the total weight of active agents (a)-(g) and (j) in the composition.

[0184] In some embodiments, the composition comprises at least about 15 wt% active agent (j), for example at least about any one of 17 wt%, 19 wt%, 21 wt%, 23 wt%, 25 wt%, 27 wt%, 29%, or 31 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises up to about 32 wt% active agent (j), for example up to about any one of 30 wt%, 28 wt%, 26 wt%, 24 wt%, 22 wt%, 21 wt%, 19 wt%, 18 wt%, or 17 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 15 wt% to about 32 wt% active agent (j), for example about any one of 15-20 wt%, 20-25 wt%, 25-32 wt%, 17-30 wt%, 19-28 wt%, 21-26 wt%, or 23-24 wt%, based on the total weight of active agents (a)-(j) in the composition. In some embodiments, the composition comprises about 23.4 wt% active agent (j), based on the total weight of active agents (a)-(j) in the composition.

[0185] In some embodiments, the composition comprises at least about 25 wt% active agent (j), for example, at least about any one of 26 wt%, 27 wt%, 28 wt%, 29 wt%, 30 wt%, or 31 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (j), for example, up to about any one of 35 wt%, 34 wt%, 33 wt%, or 32 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 25 wt% to about 40 wt% active agent (j), for example, about any one of 25-35 wt%, 25-34 wt%, 26-34 wt%, 27-34 wt%, 28-34 wt%, 29-34 wt%, or 30-34 wt%, based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition. In some embodiments, the composition comprises about 32.5 wt% active agent (j), based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

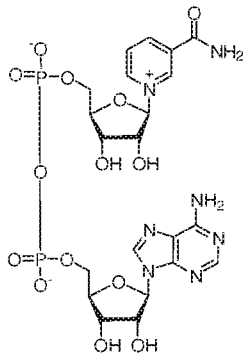
[0186] In this way, the relative quantity of active agent (j) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0187] In some embodiments, the composition comprises about 1000 mg to about 10000 mg of trimethylglycine, for example, at least about any one of 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2500 mg, 3000 mg, 5000 mg or 10000 mg, or about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, about 2000 mg to about 2500 mg, about 2500 mg to about 3000 mg, about 1000 mg to about 2000 mg, about 2000 mg to about 3000 mg, about 1000 mg to about 3000 mg, or about 3000 mg to about 10000 mg.

(k) Nicotinamide adenine dinucleotide pathway agent (NPA)

[0188] Active component (k) of the composition is a nicotinamide adenine dinucleotide (NAD) pathway agent ("NPA"). Exemplary NPAs include NAD+, NADH, NADP, NADPH, nicotinic acid adenine dinucleotide, nicotinic acid mononucleotide, nicotinamide, nicotinic acid (also known as "niacin" or vitamin B_3), nicotinamide mononucleotide, nicotinic acid riboside, a salt of any of the foregoing, and mixtures thereof. Administration of an NPA is associated with increased levels of total plasma homocysteine.

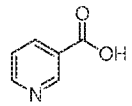
[0189] NAD+ has important functions in cellular bioenergetics and adaptive stress responses. Decreasing NAD+ levels have been associated with metabolism-related diseases, including neurodegenerative diseases, cardiovascular diseases, muscle atrophy, and age-related conditions. Maintenance of NAD+ levels is especially important for cells with higher energy demands. Therefore, molecules involved in NAD+ biosynthesis and consumption are of particular interest in modulating NAD+ level as a way to combat these diseases and conditions.



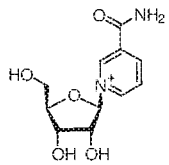
Nicotinamide adenine dinucleotide (NAD+)

[0190] NAD+ can be synthesized from a variety of sources. Major precursors for NAD+ biosynthesis include, but are not limited to, nicotinic acid (NA), nicotinamide riboside (NR), nicotinamide mononucleotide (NMN), nicotinamide (NAM), nicotinic acid adenine dinucleotide, nicotinic acid mononucleotide, and nicotinic acid riboside (NAR). Common food sources for NA include, without limitation, eggs, fish, meat, diary, certain vegetables and whole grains. NR can be found in milk, and NMN in broccoli, avocado, and beef. Downstream metabolism of ingested NAD+ can also produce these precursors. Depending on the bioavailability of these precursors, NAD+ can be biosynthesized from NA in the Preiss-Handler pathway; or it can be produced from NAM, NR, and NMN in the salvage pathway. In the Preiss-Handler pathway, NA can be converted to nicotinic acid mononucleotide, and then to nicotinic acid adenine dinucleotide, which can produce NAD+

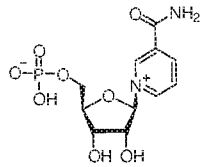
enzymatically. In the salvage pathway, NR and NAM can be converted to NMN, which can then produce NAD+ enzymatically. Fang et al. (2017) *Trends Mol. Med.* 23, 899. NAR can also be generated from NA through NMN formation and is an integral part of NAD metabolism. Kulikova et al. (2015) *J. Bio. Chem.* 290, 27124. NAD+ can be further converted to NADPH and NADP, another two major players in metabolism, especially in a multitude of redox reactions.



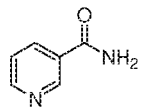
Nicotinic acid (NA);



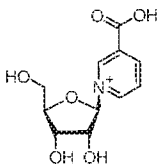
Nicotinamide riboside (NR);



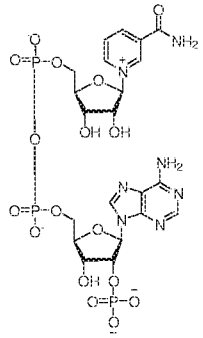
Nicotinamide mononucleotide (NMN);



Nicotinamide (NAM);

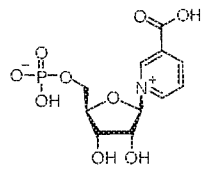


Nicotinic acid riboside (NAR);



Nicotinamide adenine dinucleotide phosphate

(NADP)



Nicotinic acid adenine dinucleotide;

nicotinic acid mononucleotide.

[0191] NMN is a direct precursor of NAD+. In common biosynthesis pathways, NR, NAM, and NA need to be converted to NMN in order to produce NAD+. As such, NMN may be a more potent NAD+ modulator compared to the other NAD+ precursors. After NMN supplementation, NMN can make its way through the liver intact and bloodstream into muscle and is metabolized to NAD+ within 30 minutes. Mills et al. (2016) *Cell Metab.* 24, 795. And NMN was shown to be retained in the body for longer than NAM. Kawamura et al. (2016) *J. Nutr. Sci. Vitaminol* 62, 272. Additionally, NMN is abundant in certain

vegetables and meat, while chemical synthesis is required to obtain large scales of NR, during which toxic organic solvents are commonly used. *See e.g.*,US2017/0121746. It has been reported that NR, unlike NMN, is unstable under certain conditions and can quickly degrade into NAM in murine plasma or fetal-bovine-serum containing culture medium. Ratajczak et al. (2016) *Nat. Commun.* 7, 13103. As such, there might be potential benefits to use NMN, NA, NAR, NAM, nicotinic acid adenine dinucleotide, nicotinic acid mononucleotide, NAD+/NADH, and NADP/NADPH to modulate NAD+ levels.

[0192] In some embodiments, the active agent (k) comprises an agent selected from the group consisting of NA, NR, NMN, NAR, NAAD, NAD+ and mixtures thereof. In some embodiments, the active agent (k) comprises NR. In some embodiments, the active agent (k) consists of or consists essentially of NR. In some embodiments, the active agent (k) comprises NA and NR. In some embodiments, the active agent (k) consists essentially of NR and NA. In some embodiments, the active agent (k) comprises NA and NMN. In some embodiments, the active agent (k) comprises NR and NMN. In some embodiments, the active agent (k) comprises NA, NR and NMN. In some embodiments, the active agent (k) comprises NR and one or more agents selected from the group consisting of NA, NMN, NAR, NAAD, and NAD+. In some embodiments, the active agent (k) does not comprise NR. In some embodiments, the active agent (k) comprises one or more agents selected from the group consisting of NA, NMN, NAR, NAAD, and NAD+.

[0193] Without being bound by any theory or hypothesis, the mixtures of two or more NAD pathway molecules (*e.g.*, NR and NA) may increase NAD levels faster and to higher levels than using single NAD pathway molecule alone (*e.g.*, NR). Some NAD pathway molecules, *e.g.*, NA, may have a less pronounced effect on increasing total homocysteine levels than NR. Additionally, NA may raise HDL level and lower LDL and triglyceride levels. NA is also less expensive than NR and easier to produce.

[0194] In some embodiments, the active agent (k) comprises salts of NAD+, NADH, NADP, NADPH, nicotinic acid adenine dinucleotide, nicotinic acid mononucleotide, nicotinamide, nicotinic acid, nicotinamide mononucleotide, and/or nicotinic acid riboside. In some embodiments, the salt is a pharmaceutically acceptable salt.

[0195] In some embodiments, the weight ratio between (a) serine and the active agent (k) (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN) is no more than about any one of 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, or 1:1. In some embodiments, the weight ratio between (a) serine and the active agent (k) (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN) is at least about any one of 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, or 8:1. In some embodiments, the weight ratio between

(a) serine and the active agent (k) (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN) is about 1:1 to about 1:8, for example at least about any one of 1:1-2:1, 2:1-4:1, 4:1-6:1, 6:1-8:1, 2:1-6:1, 3:1-5:1, 1:1-4:1 or 4:1-8:1.

[0196] In some embodiments, active agent (k) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (k) or any other component of the composition. Thus, purity in this context refers to the purity of the NAP *per se*.

[0197] In some embodiments, the composition comprises at least about 15 wt% active agent (k), for example at least about any one of 16 wt%, 17 wt%, 18 wt%, 19 wt%, 20 wt%, 21 wt%, 22 wt%, 23 wt%, 24 wt%, or 25 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises up to about 25 wt% active agent (k), for example up to about any one of 24 wt%, 23 wt%, 22 wt%, 21 wt%, 20 wt%, 19 wt%, 18 wt%, 19 wt%, or 16 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 15 wt% to about 25 wt% active agent (k), for example about any one of 15-20 wt%, 20-25 wt%, 16-24 wt%, 17-23 wt%, 18-22 wt%, or 19-21 wt%, based on the total weight of active agents (a)-(d) and (k) in the composition. In some embodiments, the composition comprises about 19.2 wt% active agent (k), based on the total weight of active agents (a)-(d) and (k) in the composition.

[0198] In this way, the relative quantity of active agent (k) with respect to the other active agents in the composition reflects the relative appropriate dosages.

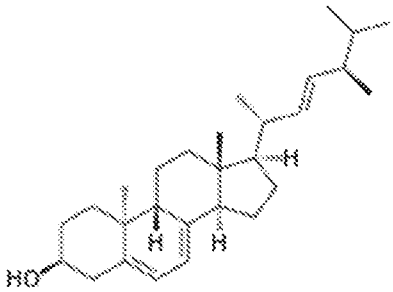
[0199] In some embodiments, the composition comprises about 10 mg to about 2000 mg of NAP (*e.g.*, NA and/or NR), for example, at least about any one of 10 mg, 20 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, or 500 mg, or about 10 mg to about 50 mg, about 10 mg to about 20 mg, about 20 mg to about 50 mg, about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, about 400 mg to about 500 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 300 mg to about 500 mg, about 500 mg to about 1000 mg, about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, or about 10 mg to about 300 mg. .

(l) Vitamin D

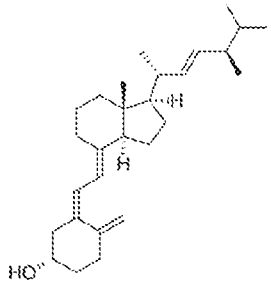
[0200] Herein, the term "vitamin D" refers to vitamin D_1 (a 1:1 mixture of ergocalciferol with lumisterol), vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), or any combination thereof. Thus active agent (l) of the composition is vitamin D_1, vitamin D_2, vitamin D_3 or a combination thereof. These compounds are known to be important for the intestinal absorption of calcium, magnesium and phosphate in humans.

[0201] The structures of chemical components of vitamins D_1, D_2 and D_3 are shown below:

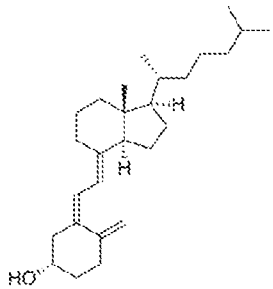
Lumisterol (in Vitamin D_1)



Ergocalciferol (Vitamin D_2 and also in Vitamin D_1)



Cholecalciferol (Vitamin D_3)



[0202] According to Moore et al., vitamin D_3 can increase betaine homocysteine methyltransferase-1 (BHMT1) enzyme activity, which can transmethylate homocysteine to replenish methionine, thereby reducing homocysteine toxicity. Moore, J. R., *et al.* (2018). Journal of neuroimmunology, 324: 100-114. Longoni et al demonstrates that calcitriol reverts the effect of homocysteine. Vitamin D_3 can improve mitochondrial function,

energy metabolism, cell viability and decrease oxidative stress and lipid peroxidation. Longoni, A., *et al.* (2017). Nutrition Research, 38, 52-63. In a clinical trial, 12 weeks of vitamin D_3 supplementation (4000IU/day) and walking training decreased homocysteine levels. Walentukiewicz, A., *et al.* (2018). International journal of environmental research and public health, 15(10), 2064.

[0203] In some embodiments, active agent (l) is vitamin D_1. In some embodiments, active agent (l) is vitamin D_2. In some embodiments, active agent (l) is vitamin D_3. In some embodiments, active agent (l) is a combination of vitamin D_2 and vitamin D_3.

[0204] In some embodiments, active agent (l) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (l) or any other component of the composition. Thus, purity in this context refers to the purity of the vitamin D component *per se*.

[0205] In some embodiments, the composition comprises about 5 μg to about 125 μg of active agent (l), for example, at least about any one of 10 μg, 20 μg, 25 μg, 50 μg, 75 μg, 100 μg, or 125 μg, or about 20 μg to about 125 μg, about 20 μg to about 100 μg, about 20 μg to about 50 μg, about 50 μg to about 100 μg, or about 25 μg to about 100 μg. In some embodiments, the composition comprises no more than about 1 mg, or no more than about 250 μg of active agent (l). In some embodiments, the composition comprises about 200 IU to about 5000 IU of active agent (l), for example, about 800 IU to about 4000 IU, or at least about 400 IU. In some embodiments, the composition comprises no more than about 40,000 IU, or no more than about 10,000 IU of active agent (l).

[0206] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (l), for example at least about any one of 0.001 wt%, 0.002 wt%, 0.003 wt%, 0.004 wt%, 0.005 wt%, 0.006 wt% or 0.007 wt%, based on the total weight of active agents (a)-(g) and (l) in the composition. In some embodiments, the composition comprises up to about 0.0075 wt% active agent (l), for example up to about any one of 0.007 wt%, 0.006 wt%, 0.005 wt%, 0.004 wt%, 0.003 wt%, 0.002 wt%, or 0.001 wt%, based on the total weight of active agents (a)-(g) and (l) in the composition. In some embodiments, the composition comprises about 0.0005 wt% to about 0.0075 wt% active agent (l), for example about any one of 0.0005-0.001 wt%, 0.001-0.002 wt%, 0.002-0.003 wt%, 0.003-0.004 wt%, 0.004-0.005 wt%, 0.002-0.005 wt%, 0.005-0.006 wt%, 0.006-0.0075 wt%, 0.001-0.005 wt%, or 0.0025-0.0075 wt%, based on the total weight of active agents (a)-(g) and (l) in the composition. In

some embodiments, the composition comprises about 0.0049 wt% active agent (l), based on the total weight of active agents (a)-(g) and (l) in the composition.

[0207] In some embodiments, the composition comprises at least about 0.0005 wt% active agent (l), for example, at least about any one of 0.001 wt%, 0.0015 wt%, 0.002 wt%, 0.0025 wt%, or 0.003 wt%, based on the total weight of active agents (a)-(d), (g)-(h), (j) and (l) in the composition. In some embodiments, the composition comprises up to about 0.003 wt% active agent (l), for example up to about any one of 0.0025 wt%, 0.002 wt%, 0.0015 wt%, or 0.001 wt%, based on the total weight of active agents (a)-(d), (g)-(h), (j) and (l) in the composition. In some embodiments, the composition comprises about 0.0005 wt% to about 0.003 wt% active agent (l), for example, about any one of 0.0005-0.001 wt%, 0.001-0.0015 wt%, 0.0015-0.002 wt%, 0.002-0.0025 wt%, 0.0025-0.003 wt%, 0.001-0.003 wt%, or 0.0015-0.0025 wt%, based on the total weight of active agents (a)-(d), (g)-(h), (j) and (l) in the composition. In some embodiments, the composition comprises about 0.0020 wt% active agent (l), based on the total weight of active agents (a)-(d), (g)-(h), (j) and (l) in the composition.

[0208] In this way, the relative quantity of active agent (j) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0209] In some embodiments, the composition comprises about 20 μg to about 125 μg of vitamin D, for example, at least about any one of 20 μg, 25 μg, 30 μg, 40 μg, 50 μg, 60 μg, 70 μg, 75 μg, 100 μg, or 125 μg, or about 20 μg to about 50 μg, about 50 μg to about 75 μg, about 75 μg to about 100 μg, about 100 μg to about 125 μg, about 25 μg to about 75 μg, about 50 μg to about 100 μg, or about 50 μg to about 125 μg.

(m) Additional Components

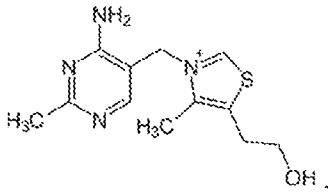
[0210] In addition to active agents (a)-(l), in some embodiments, the composition further comprises one or more additional components, such as one or more additional active agents. In some embodiments, these optional additional active agents may increase the therapeutic effect of the composition. In some embodiments, this increase in therapeutic effect is synergistic. In some embodiments, the composition further comprises one or more additional active agents selected from fruit or fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable or vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant or plant extracts (*e.g.*, green tea and/or rosemary extracts and/or quinoa), dimethylglycine, monomethylglycine, glycine, choline, lipoic acid, diindolylmethane, ribose, sulforaphane, and phosphatidylcholine. In some embodiments, the

composition further comprises one or more additional active agents selected from fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine.

[0211] In some embodiments, in addition to the active agents (a)-(d); (a)-(d) and (g); (a)-(d) and (k); (a)-(f); (a)-(g); (a)-(i); (a)-(f) and (j); (a)-(g) and (j); (a)-(j); or (a)-(d), (g)-(h) and (j) and any of the optional additional components described above, the composition further comprises one or more additional active or inactive agents including, without limitation, vitamins, minerals, amino acids, carbohydrates, proteins, or lipids. Vitamins may be water-soluble (*e.g.*, vitamin C, vitamin B_1), or they may be water-insoluble (*e.g.*, vitamin A, vitamin D, vitamin E, or vitamin K). Minerals may be essential minerals (*e.g.*, calcium, chloride, chromium, copper, iodine, iron, magnesium, molybdenum, phosphorus, phosphate, potassium, selenium, sodium, or zinc), or they may be non-essential minerals (*e.g.*, sulfur). Carbohydrates include, without limitation, monosaccharides (*e.g.*, fructose, galactose, glucose, mannose, tagatose, xylose), disaccharides (*e.g.*, isomaltose, isomaltulose, lactose, maltose, sucrose, trehalose, trehalulose), and sugar alcohols (*e.g.*, erythritol, glycerol, hydrogenated starch hydrolysates, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol). Lipids include, without limitation, saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids (*e.g.*, omega-3, alpha-linolenic acid (ALA), eicosapentaenoic (EPA), docosahexaenoic acid (DHA), omega-6, arachidonic acid (AA), anandamide (N-arachidonoylethanolamine), linoleic acid, and conjugated linoleic acid (CLA)).

[0212] In some embodiments, at least one of the active agents (a)-(l) or the additional active agents is purified. In some embodiments, an active agent is at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.1%, about 99.2%, about 99.3%, about 99.4%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9%, or about 100% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier.

[0213] In some embodiments, active agent (m) comprises vitamin B_1. The term "vitamin B_1" is also known as thiamine or thiamin. The chemical structure of vitamin B_1 is shown below:



[0214] In some embodiments, the composition comprises about 0.5 mg to about 2 mg of vitamin B_1, for example, at least about any one of 0.5 mg, 0.8 mg, 0.9 mg, 1 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 2 mg, or about 0.5 mg to about 1 mg, about 1 mg to about 1.5 mg, about 1 mg to about 2 mg, about 0.5 mg to about 1.5 mg, about 0.75 mg to about 1.25 mg, or about 0.8 mg to about 1.5 mg.

[0215] In some embodiments, active agent (m) comprises a magnesium -containing compound. In some embodiments, the magnesium-containing compound is one or more pharmaceutically acceptable magnesium-containing compounds. In some embodiments, the magnesium-containing compound is one or more pharmaceutically acceptable magnesium salts. In some embodiments, active agent (m) comprises one or more magnesium-containing compounds selected from magnesium citrate, magnesium oxide, magnesium oxalate, magnesium gluconate, magnesium hydroxide, magnesium glycinate, magnesium orotate, magnesium threonate, magnesium borate, magnesium salicylate, magnesium sulfate, magnesium chloride, magnesium aspartate and magnesium lactate. In some embodiments, active agent (m) comprises a single magnesium-containing compound selected from magnesium oxide, magnesium oxalate, magnesium gluconate, magnesium hydroxide, magnesium glycinate, magnesium orotate, magnesium threonate, magnesium borate, magnesium salicylate, magnesium sulfate, magnesium citrate, magnesium chloride, magnesium aspartate and magnesium lactate. In some embodiments, active agent (m) comprises magnesium bisglycinate.

[0216] In some embodiments, the composition comprises about 10 mg to about 500 mg of elemental magnesium provided by a magnesium-containing compound, for example, at least about any one of 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg, or about 10 mg to about 50 mg, about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 500 mg, about 10 mg to about 100 mg, or about 20 mg to about 80 mg. In some embodiments, the composition comprises about 100 mg to about 500 mg of magnesium bisglycinate, for example, at least about any one of 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg, or about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 200 mg to about 500 mg, or about 250 mg to about 500 mg.

[0217] In some embodiments, active agent (m) comprises fruit extracts. In some embodiments, active agent (m) comprises one or more fruit extracts selected from the group consisting of blueberry extract, cranberry extract, strawberry extract, pomegranate extract, and grape extract. In some embodiments, fruit extracts may be obtained from whole fruit, seeds of fruit, or juice of fruit. For example, strawberry extract may be whole fruit powder; pomegranate extract may be pomegranate juice powder; and grape extract may be grape juice powder. In some embodiments, active agent (m) comprises grape seed extract, such as resveratrol. In some embodiments, active agent (m) comprises vegetable extracts. In some embodiments, active agent (m) comprises ginger extract. In some embodiments, active agent (m) comprises turmeric extract. In some embodiments, active agent (m) comprises black pepper extract. In some embodiments, active agent (m) comprises turmeric extract and black pepper extract. In some embodiments, active agent (m) comprises plant extracts. In some embodiments, active agent (m) comprises green tea extract. In some embodiments, active agent (m) comprises rosemary extract. In some embodiments, active agent (m) comprises quinoa or quinoa extract.

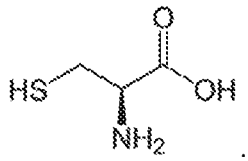
[0218] In some embodiments, the composition comprises about 2.5 mg to about 500 mg of a fruit and/or fruit extract, vegetable and/or vegetable extract, and/or plant and/or plant extract (*e.g.*, blueberry extract, cranberry extract, strawberry extract, pomegranate extract, grape extract, ginger extract, green tea extract, turmeric extract, black pepper extract, and/or rosemary extract) or combinations thereof, for example, at least about any one of 5mg, 10 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg, or about 2.5 mg to about 10 mg, about 2.5 mg to about 100 mg, about 5 mg to about 500 mg, about 5 mg to about 100 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, about 400 mg to about 500 mg, about 20 mg to about 200 mg, about 100 mg to about 300 mg, about 200 mg to about 400 mg, about 50 mg to about 250 mg, or about 250 mg to about 500 mg. In some embodiments, the composition comprises about 2.5 mg to about 10 mg of each fruit extract. In some embodiments, the composition comprises about 2.5 mg to about 10 mg (*e.g.*, 5 mg) of each vegetable extract. In some embodiments, the composition comprises about 2.5 mg to about 10 mg (*e.g.*, 5 mg) of each plant extract. In some embodiments, the composition comprises about 5 mg to about 50 mg (*e.g.*, about 25 mg) of total fruit extracts. In some embodiments, the composition comprises about 5 mg to about 50 mg (*e.g.*, about 10 mg) of total vegetable extracts. In some embodiments, the composition comprises about 5 mg to about 50 mg (*e.g.*, about 10 mg) of total plant extracts. In some embodiments, the

composition comprises about 5 mg to about 100 mg (*e.g.*, about 35 mg) of total fruit, vegetable and plant extracts.

[0219] In some embodiments, the composition is sterile. Sterile pharmaceutical formulations are compounded or manufactured according to pharmaceutical-grade sterilization standards (*e.g.*, United States Pharmacopeia Chapters 797, 1072, and 1211; California Business & Professions Code 4127.7; 16 California Code of Regulations 1751, 21 Code of Federal Regulations 211) known to those of skill in the art.

(n) Cysteine

[0220] Active agent (n) is cysteine (also referred to as "L-cysteine"). Cysteine is a proteinogenic α-amino acid having the following structure:



[0221] Cysteine is a non-essential amino acid, which may be synthesized by human bodies.

[0222] In some embodiments, active agent (n) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (n) or any other component of the composition. Thus, purity in this context refers to the purity of the cysteine component *per se*.

[0223] In some embodiments, the composition comprises at least about 35 wt% active agent (n), for example at least about any one of 37 wt%, 39 wt%, 41 wt%, 43 wt%, 45 wt%, 47 wt%, 49 wt%, 51 wt%, or 53 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises up to about 55 wt% active agent (n), for example up to about any one of 53 wt%, 51 wt%, 49 wt%, 47 wt%, 45 wt%, 43 wt%, 41 wt%, 39 wt%, or 37 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 35 wt% to about 55 wt% active agent (n), for example about any one of 35-40 wt%, 40-45 wt%, 45-50 wt%, 50-55 wt%, 40-50 wt%, or 42-46 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 44 wt% active agent (n), based on the total weight of active agents (a)-(o) in the composition.

[0224] In some embodiments, the composition comprises at least about 15 wt% active agent (n), for example at least about any one of 17 wt%, 19 wt%, 21 wt%, 23 wt%, 25 wt%,

27 wt%, 29%, or 31 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises up to about 32 wt% active agent (n), for example up to about any one of 30 wt%, 28 wt%, 26 wt%, 24 wt%, 22 wt%, 21 wt%, 19 wt%, 18 wt%, or 17 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 15 wt% to about 32 wt% active agent (n), for example about any one of 15-20 wt%, 20-25 wt%, 25-32 wt%, 17-30 wt%, 19-28 wt%, 21-26 wt%, or 23-24 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 23 wt% active agent (n), based on the total weight of active agents (a)-(o) in the composition.

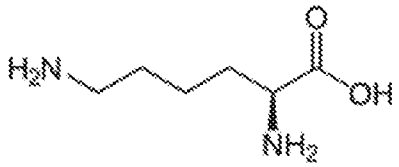
[0225] In some embodiments, the composition comprises at least about 25 wt% active agent (n), for example, at least about any one of 26 wt%, 27 wt%, 28 wt%, 29 wt%, 30 wt%, or 31 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (n), for example, up to about any one of 35 wt%, 34 wt%, 33 wt%, or 32 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 25 wt% to about 40 wt% active agent (n), for example, about any one of 25-35 wt%, 25-34 wt%, 26-34 wt%, 27-34 wt%, 28-34 wt%, 29-34 wt%, or 30-34 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 32 wt% active agent (n), based on the total weight of active agents (a)-(o) in the composition.

[0226] In this way, the relative quantity of active agent (n) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0227] In some embodiments, the composition comprises about 1000 mg to about 10000 mg of cysteine, for example, at least about any one of 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2500 mg, 3000 mg, 5000 mg or 10000 mg, or about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, about 2000 mg to about 2500 mg, about 2500 mg to about 3000 mg, about 1000 mg to about 2000 mg, about 2000 mg to about 3000 mg, about 1000 mg to about 3000 mg, or about 3000 mg to about 10000 mg.

(o) Lysine

[0228] Active agent (o) is lysine (also referred to as "L-lysine"). Lysine is a basic α-amino acid having the following structure:



[0229] Lysine is an essential amino acid, which is not synthesized by human bodies.

[0230] In some embodiments, active agent (o) is at least about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% pure. In this context, the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier within active agent (o) or any other component of the composition. Thus, purity in this context refers to the purity of the lysine component *per se*.

[0231] In some embodiments, the composition comprises at least about 35 wt% active agent (o), for example at least about any one of 37 wt%, 39 wt%, 41 wt%, 43 wt%, 45 wt%, 47 wt%, 49 wt%, 51 wt%, or 53 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises up to about 55 wt% active agent (o), for example up to about any one of 53 wt%, 51 wt%, 49 wt%, 47 wt%, 45 wt%, 43 wt%, 41 wt%, 39 wt%, or 37 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 35 wt% to about 55 wt% active agent (o), for example about any one of 35-40 wt%, 40-45 wt%, 45-50 wt%, 50-55 wt%, 40-50 wt%, or 42-46 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 44 wt% active agent (o), based on the total weight of active agents (a)-(o) in the composition.

[0232] In some embodiments, the composition comprises at least about 15 wt% active agent (o), for example at least about any one of 17 wt%, 19 wt%, 21 wt%, 23 wt%, 25 wt%, 27 wt%, 29%, or 31 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises up to about 32 wt% active agent (o), for example up to about any one of 30 wt%, 28 wt%, 26 wt%, 24 wt%, 22 wt%, 21 wt%, 19 wt%, 18 wt%, or 17 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 15 wt% to about 32 wt% active agent (o), for example about any one of 15-20 wt%, 20-25 wt%, 25-32 wt%, 17-30 wt%, 19-28 wt%, 21-26 wt%, or 23-24 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 23 wt% active agent (o), based on the total weight of active agents (a)-(o) in the composition.

[0233] In some embodiments, the composition comprises at least about 25 wt% active agent (o), for example, at least about any one of 26 wt%, 27 wt%, 28 wt%, 29 wt%, 30 wt%,

or 31 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises up to about 40 wt% active agent (o), for example, up to about any one of 35 wt%, 34 wt%, 33 wt%, or 32 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 25 wt% to about 40 wt% active agent (o), for example, about any one of 25-35 wt%, 25-34 wt%, 26-34 wt%, 27-34 wt%, 28-34 wt%, 29-34 wt%, or 30-34 wt%, based on the total weight of active agents (a)-(o) in the composition. In some embodiments, the composition comprises about 32 wt% active agent (o), based on the total weight of active agents (a)-(o) in the composition.

[0234] In this way, the relative quantity of active agent (o) with respect to the other active agents in the composition reflects the relative appropriate dosages.

[0235] In some embodiments, the composition comprises about 1000 mg to about 10000 mg of lysine, for example, at least about any one of 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, 2500 mg, 3000 mg, 5000 mg or 10000 mg, or about 1000 mg to about 1500 mg, about 1500 mg to about 2000 mg, about 2000 mg to about 2500 mg, about 2500 mg to about 3000 mg, about 1000 mg to about 2000 mg, about 2000 mg to about 3000 mg, about 1000 mg to about 3000 mg, or about 3000 mg to about 10000 mg.

II. Exemplary Compositions

[0236] In some embodiments, there is provided a composition comprising 2 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 2 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), and (o). In some embodiments, there is provided a composition comprising 3 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 4 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 5 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 6 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 7 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 8 or more active

agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 9 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 10 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 11 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 12 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 13 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising 14 or more active agents selected from (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, there is provided a composition comprising active agents (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (n), (m), and (o). In some embodiments, the composition comprise more than one active agent (m).

[0237] In some embodiments, there is provided a composition comprising (a) serine, (n) cysteine, and (o) lysine. In some embodiments, the composition comprising (a) serine, (n) cysteine, and (o) lysine further comprises one or more active agents selected from (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), and (m), such as 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8, or more, 9 or more, 10 or more, or 11 active agents selected from (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), and (m). In some embodiments, the composition comprises (a) serine, (n) cysteine, (o) lysine, and one or more of (j) trimethylglycine, lipoic acid, diindolylmethane, ribose, quinoa, and sulforaphane. In some embodiments, the composition comprises (a) serine, (n) cysteine, (o) lysine, and (j) trimethylglycine. In some embodiments, the composition comprises (a) serine, (n) cysteine, (o) lysine, and one or more of lipoic acid, diindolylmethane, ribose, quinoa, and sulforaphane. In some embodiments, the composition comprises (a) serine, (n) cysteine, (o) lysine, (j) trimethylglycine, lipoic acid, diindolylmethane, ribose, quinoa, and sulforaphane.

[0238] In some embodiments, there is provided a composition comprising: (a) about 90 wt% to 98 wt% serine; and (b) about 2 wt% to about 10 wt% vitamin B_6.

[0239] In some embodiments, there is provided a unit dosage composition comprising: (a) about 1000 mg to about 3000 mg serine; and (b) about 20 mg to about 150 mg (*e.g.*, about 20 mg to about 100 mg) vitamin B_6.

[0240] In some embodiments, there is provided a unit dosage composition comprising: (a) about 2000 mg serine; and (b) about 75 mg vitamin B_6.

[0241] In some embodiments, there is provided a unit dosage composition comprising: (a) about 2000 mg serine; and (b) about 100 mg vitamin B_6.

[0242] In some embodiments, there is provided a unit dosage composition comprising: (a) about 2000 mg serine; and (b) about 150 mg vitamin B_6.

[0243] In some embodiments, there is provided a composition comprising: (a) about 90 wt% to 99 wt% serine; (b) about 1 wt% to about 7.5 wt% vitamin B_6; (c) about 0.01 wt% to about 0.10 wt% vitamin B_9; and (d) about 0.01 wt% to about 0.05 wt% vitamin B_{12}, wherein wt% is based on the total weight of active agents (a)-(d) in the composition.

[0244] In some embodiments, there is provided a composition comprising: (a) about 95.2 wt% serine; (b) about 4.8 wt% vitamin B_6; (c) about 0.038 wt% vitamin B_9; and (d) about 0.024 wt% vitamin B_{12}, wherein wt% is based on the total weight of active agents (a)-(d) in the composition.

[0245] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 1000 mg to about 5000 mg (*e.g.*, about 1000 mg to about 3000 mg) serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 2.0 mg vitamin B_9; and (d) about 100 μg to about 3 mg (*e.g.*, about 100 μg to about 1 mg) vitamin B_{12}. In some embodiments, the unit dosage further comprises (j) about 1000 mg to about 3000 mg trimethylglycine. In some embodiments, the unit dosage further comprises (g) about 10 mg to about 200 mg vitamin B_2. In some embodiments, the unit dosage further comprises about 1000 mg to about 5000 mg glycine. In some embodiments, the unit dosage further comprises about 10 mg to 2000 mg of the NPA (*e.g.*, NR, or NR and NA).

[0246] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; and (d) about 0.5 mg vitamin B_{12}. In some embodiments, the unit dosage further comprises (j) about 1000 mg trimethylglycine. In some embodiments, the unit dosage further comprises (g) about 10 mg vitamin B_2. In some embodiments, the unit dosage further comprises about 500 mg NR, or about 500 mg NR and about 500 mg NA.

[0247] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; and (d) about 3 mg vitamin B_{12}. In some embodiments, the unit dosage further comprises (g) about 10 mg vitamin B_2. In some embodiments, the unit dosage further comprises about 500 mg NR, or about 500 mg NR and about 500 mg NA.

[0248] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 4000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; and (d) about 0.5 mg vitamin B_{12}. In some embodiments, the unit dosage further comprises about 4000 mg glycine. In some embodiments, the unit dosage further comprises (g) about 10 mg vitamin B_2. In some embodiments, the unit dosage further comprises about 500 mg NR, or about 500 mg NR and about 500 mg NA.

[0249] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 2.0 mg vitamin B_9; (d) about 100 µg to about 1 mg vitamin B_{12}; (g) about 0.10 mg to about 2.0 mg vitamin B_2; (h) about 1000 mg to about 3000 mg *N*-acetylcysteine; (k) about 10 mg to about 500 mg NA; about 0.10 mg to about 2.0 mg vitamin B_1, and about 100 mg to about 500 mg magnesium bisglycinate.

[0250] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 1200 mg serine; (b) about 50 mg vitamin B_6; (c) about 1 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; (g) about 1.3 mg vitamin B_2; (h) about 1500 mg *N*-acetylcysteine; (k) about 16 mg NA; about 1.2 mg vitamin B_1, and about 300 mg magnesium bisglycinate.

[0251] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 2.0 mg vitamin B_9; (d) about 100 µg to about 1 mg vitamin B_{12}; (e) about 50 mg to about 300 mg quercetin; (g) about 0.10 mg to about 2.0 mg vitamin B_2; (k) about 10 mg to about 500 mg NA; and about 0.10 mg to about 2.0 mg vitamin B_1.

[0252] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 1700 mg serine; (b) about 25 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; (e) about 100 mg quercetin; (g) about 1.3 mg vitamin B_2; (k) about 50 mg NA; and about 1.2 mg vitamin B_1.

[0253] In some embodiments, there is provided a composition comprising: (a) about 70 wt% to 90 wt% serine; (b) about 1 wt% to about 5 wt% vitamin B_6; (c) about 0.001 wt% to about 0.02 wt% vitamin B_9; (d) about 0.0005 wt% to about 0.005 wt% vitamin B_{12}; (e) about 5 wt% to about 20 wt% quercetin; and (f) about 1 wt% to about 10 wt% fisetin, wherein wt% is based on the total weight of active agents (a)-(f) in the composition.

[0254] In some embodiments, there is provided a composition comprising: (a) about 75 wt% to 85 wt% serine; (b) about 2 wt% to about 4 wt% vitamin B_6; (c) about 0.01 wt% to

about 0.02 wt% vitamin B_9; (d) about 0.001 wt% to about 0.005 wt% vitamin B_{12}; (e) about 10 wt% to about 15 wt% quercetin; and (f) about 2 wt% to about 6 wt% fisetin, wherein wt% is based on the total weight of active agents (a)-(f) in the composition.

[0255] In some embodiments, there is provided a composition comprising: (a) about 80.8 wt% serine; (b) about 3.0 wt% vitamin B_6; (c) about 0.016 wt% vitamin B_9; (d) about 0.0030 wt% vitamin B_{12}; (e) about 12.1 wt% quercetin; and (f) about 4.0 wt% fisetin, wherein wt% is based on the total weight of active agents (a)-(f) in the composition.

[0256] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 200 µg vitamin B_{12}; (e) about 100 mg to about 500 mg quercetin; and (f) about 20 mg to about 200 mg fisetin.

[0257] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (e) about 300 mg quercetin; and (f) about 100 mg fisetin.

[0258] In some embodiments, there is provided a composition comprising: (a) about 70 wt% to 90 wt% serine; (b) about 1 wt% to about 5 wt% vitamin B_6; (c) about 0.001 wt% to about 0.02 wt% vitamin B_9; (d) about 0.0005 wt% to about 0.005 wt% vitamin B_{12}; (e) about 5 wt% to about 20 wt% quercetin; (f) about 1 wt% to about 10 wt% fisetin, and (g) about 1 wt% to about 5 wt% vitamin B_2, wherein wt% is based on the total weight of active agents (a)-(g) in the composition.

[0259] In some embodiments, there is provided a composition comprising: (a) about 75 wt% to 85 wt% serine; (b) about 2 wt% to about 4 wt% vitamin B_6; (c) about 0.01 wt% to about 0.02 wt% vitamin B_9; (d) about 0.001 wt% to about 0.005 wt% vitamin B_{12}; (e) about 10 wt% to about 15 wt% quercetin; (f) about 2 wt% to about 6 wt% fisetin; and (g) about 2 wt% to about 4 wt% vitamin B_2, wherein wt% is based on the total weight of active agents (a)-(g) in the composition.

[0260] In some embodiments, there is provided a composition comprising: (a) about 78.4 wt% serine; (b) about 2.9 wt% vitamin B_6; (c) about 0.016 wt% vitamin B_9; (d) about 0.0029 wt% vitamin B_{12}; (e) about 11.8 wt% quercetin; (f) about 3.9 wt% fisetin; and (g) about 2.9 wt% vitamin B_2, wherein wt% is based on the total weight of active agents (a)-(g) in the composition.

[0261] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 200 µg vitamin B_{12}; (e)

about 100 mg to about 500 mg quercetin; (f) about 20 mg to about 200 mg fisetin; and (g) about 20 mg to about 200 mg vitamin B_2. In some embodiments, the unit dosage further comprises (j) about 1000 mg to about 5000 mg (*e.g.*, about 1000 mg to about 3000 mg) trimethylglycine.

[0262] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (e) about 300 mg quercetin; (f) about 100 mg fisetin; and (g) about 30 mg vitamin B_2. In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (e) about 300 mg quercetin; (f) about 100 mg fisetin; and (g) about 75 mg vitamin B_2. In some embodiments, the unit dosage further comprises (j) about 1000 mg trimethylglycine.

[0263] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 200 µg vitamin B_{12}; (e) about 100 mg to about 500 mg quercetin; (f) about 20 mg to about 200 mg fisetin; (g) about 20 mg to about 200 mg vitamin B_2; and (l) about 20 µg to about 125 µg vitamin D_3.

[0264] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (e) about 300 mg quercetin; (f) about 100 mg fisetin; (g) about 75 mg vitamin B_2; and (l) about 125 µg vitamin D_3.

[0265] In some embodiments, there is provided a composition comprising: (a) about 20 wt% to 40 wt% serine; (b) about 0.5 wt% to about 2 wt% vitamin B_6; (c) about 0.001 wt% to about 0.015 wt% vitamin B_9; (d) about 0.0001 wt% to about 0.002 wt% vitamin B_{12}; (e) about 1 wt% to about 10 wt% quercetin; (f) about 1 wt% to about 5 wt% fisetin; (g) about 0.5 wt% to about 2 wt% vitamin B_2; (h) about 20 wt% to about 40 wt% *N*-acetylcysteine; and (i) about 20 wt% to about 40 wt% SAM, wherein wt% is based on the total weight of active agents (a)-(i) in the composition.

[0266] In some embodiments, there is provided a composition comprising: (a) about 25 wt% to 35 wt% serine; (b) about 1 wt% to about 1.5 wt% vitamin B_6; (c) about 0.002 wt% to about 0.01 wt% vitamin B_9; (d) about 0.0005 wt% to about 0.0015 wt% vitamin B_{12}; (e) about 2.5 wt% to about 7 wt% quercetin; (f) about 1 wt% to about 2 wt% fisetin; (g) about 1 wt% to about 1.5 wt% vitamin B_2; (h) about 25 wt% to about 35 wt% *N*-acetylcysteine; and

(i) about 25 wt% to about 35 wt% SAM, wherein wt% is based on the total weight of active agents (a)-(i) in the composition.

[0267] In some embodiments, there is provided a composition comprising: (a) about 30.5 wt% serine; (b) about 1.1 wt% vitamin B_6; (c) about 0.0061 wt% vitamin B_9; (d) about 0.0011 wt% vitamin B_{12}; (e) about 4.6 wt% quercetin; (f) about 1.5 wt% fisetin; (g) about 1.1 wt% vitamin B_2; (h) about 30.5 wt% *N*-acetylcysteine; and (i) about 30.5 wt% SAM, wherein wt% is based on the total weight of active agents (a)-(i) in the composition.

[0268] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 100 mg to about 10000 mg serine; (b) about 10 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 3000 µg vitamin B_{12}; (e) about 100 mg to about 500 mg quercetin; (f) about 20 mg to about 200 mg fisetin; (g) about 20 mg to about 400 mg vitamin B_2; (h) about 1000 mg to about 10000 mg *N*-acetylcysteine; and (i) about 1000 mg to about 10000 mg SAM.

[0269] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 200 µg vitamin B_{12}; (e) about 100 mg to about 500 mg quercetin; (f) about 20 mg to about 200 mg fisetin; (g) about 20 mg to about 200 mg vitamin B_2; (h) about 1000 mg to about 3000 mg *N*-acetylcysteine; and (i) about 1000 mg to about 3000 mg SAM.

[0270] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (e) about 300 mg quercetin; (f) about 100 mg fisetin; (g) about 75 mg vitamin B_2; (h) about 2000 mg *N*-acetylcysteine; and (i) about 2000 mg SAM.

[0271] In some embodiments, the present application provides a composition comprising the active agents: (a) about 25 wt% to about 40 wt% serine; (b) about 0.5 wt% to about 1.6 wt% vitamin B_6; (c) about 0.001 wt% to about 0.01 wt% vitamin B_9; (d) about 0.0005 wt% to about 0.002 wt% vitamin B_{12}; (g) about 0.5 wt% to about 1.6 wt% vitamin B_2; (h) about 25 wt% to about 40 wt% *N*-acetylcysteine; and (j) about 25 wt% to about 40 wt% trimethylglycine, wherein wt% is based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0272] In some embodiments, the present application provides a composition comprising the active agents: (a) about 30 wt% to about 35 wt% serine; (b) about 1 wt% to about 1.5 wt% vitamin B_6; (c) about 0.005 wt% to about 0.007 wt% vitamin B_9; (d) about 0.0009 wt% to about 0.0013 wt% vitamin B_{12}; (g) about 1 wt% to about 1.5 wt% vitamin B_2; (h) about 30

wt% to about 35 wt% *N*-acetylcysteine; and (j) about 30 wt% to about 35 wt% trimethylglycine, wherein wt% is based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0273] In some embodiments, the present application provides a composition comprising the active agents: (a) about 32.5 wt% serine; (b) about 1.2 wt% vitamin B_6; (c) about 0.0065 wt% vitamin B_9; (d) about 0.0012 wt% vitamin B_{12}; (g) about 1.2 wt% vitamin B_2; (h) about 32.5 wt% *N*-acetylcysteine; and (j) about 32.5 wt% trimethylglycine, wherein wt% is based on the total weight of active agents (a)-(d), (g)-(h) and (j) in the composition.

[0274] In some embodiments, provided herein is a unit dosage composition comprising: (a) about 100 mg to about 10000 mg serine; (b) about 10 mg to about 100 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 3000 µg vitamin B_{12}; (e) about 100 mg to about 500 mg quercetin; (f) about 20 mg to about 200 mg fisetin; (g) about 20 mg to about 400 mg vitamin B_2; (h) about 1000 mg to about 10000 mg *N*-acetylcysteine; (i) about 1000 mg to about 10000 mg SAM; and (j) about 1000 mg to about 3000 mg trimethylglycine.

[0275] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 200 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 200 µg vitamin B_{12}; (g) about 20 mg to about 200 mg vitamin B_2; (h) about 1000 mg to about 3000 mg *N*-acetylcysteine; and (j) about 1000 mg to about 10000 mg trimethylglycine.

[0276] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (g) about 75 mg vitamin B_2; (h) about 2000 mg *N*-acetylcysteine; and (j) about 2000 mg trimethylglycine.

[0277] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 1000 mg to about 3000 mg serine; (b) about 20 mg to about 200 mg vitamin B_6; (c) about 0.10 mg to about 1.0 mg vitamin B_9; (d) about 20 µg to about 200 µg vitamin B_{12}; (g) about 20 mg to about 200 mg vitamin B_2; (l) about 20 µg to about 125 µg vitamin D_3.

[0278] In some embodiments, the present application provides a unit dosage composition comprising the active agents: (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 75 µg vitamin B_{12}; (g) about 75 mg vitamin B_2; (l) about 125 µg vitamin D_3.

[0279] In some embodiments according to any one of the compositions described herein, the composition further comprises one or more additional active agents selected from the group consisting of fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts). In some embodiments, the composition comprises about 2.5 mg to 500 mg (*e.g.*, 5 mg) of each additional active agent. In some embodiments, the composition comprises about 5 mg blueberry extract, about 5 mg ginger extract, about 5 mg cranberry extract, about 5 mg turmeric extract with black pepper extract, about 5mg strawberry extract, about 5 mg pomegranate extract, and about 5 mg grape extract. In some embodiments, the composition comprises about 500 mg to 2500 mg of total additional active agents.

[0280] In some embodiments according to any one of the compositions described herein, the composition further comprises one or more additional active agents selected from the group consisting of trimethylglycine, dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine. In some embodiments, the composition comprises about 500 mg to 5000 mg of each additional active agent. In some embodiments, the composition comprises about 500 mg to 5000 mg of total additional active agents. In some embodiments, the composition comprises about 4000 mg of glycine.

[0281] In some embodiments according to any one of the compositions described herein, the composition further comprises an NPA selected from the group consisting of NA, NR, NMN, NAR, NAAD, NAD+ and mixtures thereof. In some embodiments, the composition comprises about 10 mg to 2000 mg of the NPA. In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

III. Pharmaceutical Compositions

[0282] The present application also provides pharmaceutical compositions comprising any one of the compositions as described herein and a pharmaceutically acceptable carrier, excipient, binder, or diluent.

[0283] In some embodiments, the pharmaceutical compositions comprise one or more pharmaceutically acceptable excipients. A pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject. Such excipients facilitate administration of the compositions described herein and are compatible with the active ingredient. Examples of pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, anti-oxidants, binders, coloring agents,

bulking agents, emulsifiers, or taste-modifying agents. In some embodiments, pharmaceutical compositions according to the embodiments are sterile compositions. Pharmaceutical compositions may be prepared using compounding techniques known or that become available to those skilled in the art. Sterile compositions are also contemplated by the embodiments, including compositions that are in accord with national and local regulations governing such compositions.

[0284] The pharmaceutical compositions and compositions described herein may be formulated as solutions, emulsions, suspensions, dispersions, or inclusion complexes such as cyclodextrins in suitable pharmaceutical solvents or carriers, or as pills, tablets, lozenges, bars, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. Pharmaceutical compositions provided herein may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, or topical route, or by inhalation. In some embodiments, the compositions are formulated for intravenous or oral administration.

[0285] For oral administration, the pharmaceutical composition may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension. To prepare the oral compositions, the pharmaceutical composition may be formulated to yield a dosage of the composition, *e.g.*, from about 0.01 to about 200 mg/kg daily, or from about 20 to about 50 mg/kg daily or from about 50 to about 200 mg/kg daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0286] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an

oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0287] Liquids for oral administration may be in the form of suspensions, solutions, emulsions, or syrups, or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, *e.g.*, oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

[0288] The compositions described herein may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, intranasal, or subcutaneous routes, the agents provided herein may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms may be presented in unit-dose form such as ampoules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 2000 µg/kg/minute of the composition admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[0289] For nasal, inhaled, or oral administration, the compositions or pharmaceutical compositions described herein may be administered using, for example, a spray formulation also containing a suitable carrier.

[0290] In some embodiments, for topical applications, the compositions of the present embodiments are formulated as creams or ointments or a similar vehicle suitable for topical administration. For topical administration, the pharmaceutical compositions described herein may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to 1%, 1% to 5%, 5% to 10%, 10% to 20%, 20% to 30%, 0.1 % to 0.5%, 0.5% to 1%, 1% to 1.5%, 1.5% to 2%, 2% to 2.5%, 2.5% to 5%, 5% to 7.5%, or 7.5% to 10% of drug to vehicle. Another mode of administering the compositions provided herein may utilize a patch formulation to effect transdermal delivery.

[0291] In another aspect, the pharmaceutical composition further comprises a matrix. In some embodiments, the matrix is a hydrophilic matrix, including, without limitation, non-ionic soluble cellulose ether (*e.g.*, hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxylethylcellulose), non-ionic homopolymers of ethylene oxide (*e.g.*, poly(ethylene oxide)), water soluble natural gums of polysaccharides (*e.g.*, xanthum gum, alginate, and locust bean gum), water swellable, but insoluble, high molecular weight homopolymers and copolymers of acrylic acid optionally crosslinked with polyalkenyl alcohols, polyvinyl acetate, povidone mixture, cross-linked high amylose starch, and ionic methacrylate copolymers. In some embodiments, the matrix is a hydrophobic matrix, including, without limitation, fatty acids, fatty acid esters, fatty alcohols, waxes of natural and synthetic origins with differing melting points, and hydrophobic polymers. In some embodiments, the hydrophobic matrix comprises stearic acid, lauryl, cetyl or cetostearyl alcohol, carnauba wax, beeswax, candelilla wax, microcrystalline wax, low molecular weight polyethylene, ammoniomethacrylate copolymers, ethyl cellulose, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate or latex dispersions of insoluble polymers. In some embodiments, the matrix is a lipid type matrix, biodegradable type matrix, or mineral type matrix. In some embodiments, the matrix is part of the outer layer of a tablet. In some embodiments, the wax matrix comprises a polymer. In some embodiments, the polymer is selected from acrylic polymer.

[0292] In some embodiments, the pharmaceutical composition is formulated for extended release or slow release. In some embodiments, the pharmaceutical composition is formulated with a matrix. In some embodiments, the pharmaceutical composition is formulated with a wax matrix. In some embodiments, the wax matrix is vegetable-based. In some embodiments, the wax matrix comprises an acrylic polymer.

IV. Food Products and Dietary Supplements

[0293] The present application also provides compositions in the form of a food product or a dietary supplement.

[0294] A food product comprises a substance that can be used or prepared for use as food. A food product may be in a solid or a liquid (*e.g.*, beverage) form. A food product may contain fruits, plants, vegetables, nuts, seeds, or juice, extracts, jam, concentrate, wheat, or alcohol thereof. A food product may also contain milk, yogurt, meat, fish, or processed products thereof. A food product may be flowers, leaves or bark of a plant. A food product may be a product prepared from a natural food. A food product may be a medical food, a

functional food, a food additive or a nutritional food. A medical food comprises foods that are specially formulated and intended for dietary management of a disease or condition that has distinctive nutritional needs that cannot be met by normal diet alone. Medical foods can be for oral ingestion or tube feeding. A functional food comprises foods that have a potentially positive effect on health beyond basic nutrition. A food additive comprises any substance added to food and its intended use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food. The addition of food additives may be during production, processing, treatment, packaging, or transportation or storage of food. A nutritional food comprises foods that provide a high amount of nutrients. In some embodiments, the nutritional foods also comprise few calories. In some embodiments, the food product is a therapeutic food bar.

[0295] A dietary supplement comprises a manufactured product intended to supplement the diet. A dietary supplement can be synthetic or natural. A dietary supplement can comprise one component or more than one component in combination. A dietary supplement may comprise vitamins, amino acids, probiotics, minerals, fiber, fatty acids, pigments, polyphenols, lipids, or proteins. In some embodiments, the dietary supplement may be formulated as a pharmaceutical composition as discussed herein. In some embodiments, the dietary supplement is intended to be taken by mouth as a pill, capsule, tablet, or liquid. In some embodiments, the dietary supplement comprises a label as being a dietary supplement. In some embodiments, the dietary supplement comprises non-dietary ingredients such as fillers, artificial colors, sweeteners, flavors, or binders.

[0296] In some embodiments, the food product or dietary supplement comprises an effective amount of the composition for the treatment or prevention of diseases characterized by low bone density or brittle bones, such as osteoporosis.

V. Kits

[0297] Also provided herein are kits comprising two or more active agents or compositions described herein.

[0298] In some embodiments, there is provided a kit comprising: (a) serine; and (b) vitamin B_6. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA.

[0299] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from:

(a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}, provided that each of active agents (a)-(d) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(d), and the remaining three of (a)-(d) are contained within one or more additional components of the kit. In some embodiments, the kit comprises four or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, and a fourth component comprises vitamin B_{12}. Any additional active agents present may be provided in one or more of the first to fourth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0300] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}, and (k) an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN), provided that each of active agents (a)-(d) and (k) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(d) and (k), and the remaining four of (a)-(d) and (k) are contained within one or more additional components of the kit. In some embodiments, the kit comprises five or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, and a fifth component comprises an NPA. In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to fifth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3). In some embodiments, the kit further comprises vitamin B_1. In some embodiments, the kit further comprises a magnesium-containing compound (*e.g.*, magnesium bisglycinate). In some embodiments, the kit further comprises (e) quercetin.

[0301] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin, provided that each of active agents (a)-(f) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(f), and the remaining five of (a)-(f) are contained within one or more additional components of the kit. In some embodiments, the kit comprises six or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth

component comprises vitamin B_{12}, a fifth component comprises quercetin, and a sixth component comprises fisetin. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to sixth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0302] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (j) trimethylglycine, provided that each of active agents (a)-(f) and (j) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(f) and (j), and the remaining six of (a)-(f) and (j) are contained within one or more additional components of the kit. In some embodiments, the kit comprises seven or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises quercetin, a sixth component comprises fisetin, and a seventh component comprises trimethylglycine. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to seventh components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0303] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2, provided that each of active agents (a)-(d) and (g) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(d) and (g), and the remaining four of (a)-(d) and (g) are contained within one or more additional components of the kit. In some embodiments, the kit comprises seven or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises vitamin B_2. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NA. In some embodiments, the

NPA is NR and NA. In some embodiments, the composition further comprises vitamin B_1. Any additional active agents present may be provided in one or more of the first to fifth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3). In some embodiments, the kit further comprises *N*-acetyl cysteine. In some embodiments, the kit further comprises quercetin. In some embodiments, the kit further comprises a magnesium-containing compound (*e.g.*, magnesium bisglycinate).

[0304] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2, provided that each of active agents (a)-(g) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(g), and the remaining six of (a)-(g) are contained within one or more additional components of the kit. In some embodiments, the kit comprises seven or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises quercetin, a sixth component comprises fisetin, and a seventh component comprises vitamin B_2. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to seventh components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0305] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; and (j) trimethylglycine, provided that each of active agents (a)-(g) and (j) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(g) and (j), and the remaining seven of (a)-(g) and (j) are contained within one or more additional components of the kit. In some embodiments, the kit comprises eight or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises quercetin, a sixth component comprises fisetin, a seventh component comprises vitamin B_2, and an eighth component comprises trimethylglycine. In

some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to eighth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0306] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM, provided that each of active agents (a)-(i) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(i), and the remaining eight of (a)-(i) are contained within one or more additional components of the kit. In some embodiments, the kit comprises nine or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises quercetin, a sixth component comprises fisetin, a seventh component comprises vitamin B2, an eighth component comprises *N*-acetylcysteine, and a ninth component comprises SAM. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to ninth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0307] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; (i) SAM; and (j) trimethylglycine, provided that each of active agents (a)-(j) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(j), and the remaining nine of (a)-(j) are contained within one or more additional components of the kit. In some embodiments, the kit comprises ten or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises quercetin, a sixth component comprises fisetin, a seventh component comprises vitamin B2, an eighth component comprises *N*-acetylcysteine, a ninth

component comprises SAM, and a tenth component comprises trimethylglycine. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to tenth components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0308] In some embodiments, there is provided a kit comprising two or more components, wherein each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; and (j) trimethylglycine, provided that each of active agents (a)-(d), (g)-(h) and (j) are contained within the kit. In some embodiments, a first component of the kit comprises one of (a)-(d), (g)-(h) and (j), and the remaining six of (a)-(d), (g)-(h) and (j) are contained within one or more additional components of the kit. In some embodiments, the kit comprises seven or more components, wherein a first component comprises serine, a second component comprises vitamin B_6, a third component comprises vitamin B_9, a fourth component comprises vitamin B_{12}, a fifth component comprises vitamin B2, a sixth component comprises *N*-acetylcysteine, and a seventh component comprises trimethylglycine. In some embodiments, the kit further comprises an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the NPA is NR. In some embodiments, the NPA is NA. In some embodiments, the NPA is NR and NA. Any additional active agents present may be provided in one or more of the first to seventh components of the kit, or in one or more further components of the kit. In some embodiments, the kit further comprises vitamin D (*e.g.*, vitamin D_3).

[0309] In some embodiments, one or more additional active agents are provided in one or more components of the kit. In some embodiments, additional active agents are provided in a component of the kit which is the same or different to the component(s) containing (a)-(d); (a)-(d) and (k); (a)-(d) and (g); (a)-(f); (a)-(g); (a)-(i); (a)-(f) and (j); (a)-(g) and (j); (a)-(j); or (a)-(d), (g)-(h) and (j). In some embodiments, further components of the kit are provided which comprise one or more additional active agents. In some embodiments, the additional active agents are selected from fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine.

[0310] In some embodiments, at least one active agent is purified. In some embodiments, an active agent is at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.1%, about 99.2%, about 99.3%, about 99.4%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9%, or about 100% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier.

[0311] In some embodiments of the disclosure, at least one active agent is sterile. Sterile components are compounded or manufactured according to pharmaceutical-grade sterilization standards (United States Pharmacopeia Chapters 797, 1072, and 1211; California Business & Professions Code 4127.7; 16 California Code of Regulations 1751, 21 Code of Federal Regulations 211) known to those of skill in the art.

[0312] In one aspect, the kits may contain instructions for use in the treatment or prevention of hyperhomocysteinemia (including high levels of total plasma homocysteine caused by administration of an NPA, or homocystinuria) or any other disease or condition described herein in a subject in need thereof. In some embodiments, the condition is bone loss, low bone density or osteoporosis. A kit may additionally contain any materials or equipment that may be used in the administration of the active agents or composition, such as vials, syringes, or IV bags. A kit may also contain sterile packaging.

[0313] In another aspect, the kit may contain any composition described herein. In another aspect, the kit may contain any pharmaceutical composition described herein. In some embodiments, the kit contains one or more active agents formulated in any manner described herein. In some embodiments, the kit contains two or more active agents formulated in any manner described herein.

[0314] In some embodiments, the kit comprises a dosage form (*e.g.*, a unit dosage form) comprising the composition according to any one of the compositions described herein at greater than about 20%, or greater than about 25%, or greater than about 30%, or greater than about 35%, or greater than about 40%, or greater than about 45%, or greater than about 50%, or greater than about 55%, or greater than about 60%, or greater than about 65%, or greater than about 70%, or greater than about 75%, or greater than about 80%, or greater than about 85%, or greater than about 90%, or greater than 95% by weight. In some embodiments, the kit comprises a dosage form (*e.g.*, a unit dosage form) comprising the composition according to any one of the compositions described herein at less than about 20%, or less than about

25%, or less than about 30%, or less than about 35%, or less than about 40%, or less than about 45%, or less than about 50%, or less than about 55%, or less than about 60%, or less than about 65%, or less than about 70%, or less than about 75%, or less than about 80%, or less than about 85%, or less than about 90%, or less than about 95% by weight.

[0315] In some embodiments, the kit further comprises one or more additional active or inactive agents including, without limitation, vitamins, minerals, amino acids, carbohydrates, proteins, or lipids (*e.g.*, as described herein).

[0316] In another aspect, the kit comprises a pharmaceutical composition comprising one or more active agents and a pharmaceutically acceptable carrier, excipient, binder or diluent. In another aspect, the kit comprises a pharmaceutical composition comprising two or more active agents and a pharmaceutically acceptable carrier, excipient, binder or diluent.

[0317] The active agents described herein may be formulated as solutions, emulsions, suspensions, dispersions, or inclusion complexes such as cyclodextrins in suitable pharmaceutical solvents or carriers, or as pills, tablets, lozenges, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. The active agents provided herein may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. In some embodiments, the active agents are formulated for intravenous or oral administration.

[0318] The active agents in the pharmaceutical composition can be formulated separately in multiple formulations or together in one formulation. In some embodiments, the active agents are formulated together as a solution, emulsion, suspension, dispersion, or inclusion complex such as with cyclodextrins in suitable pharmaceutical solvents or carriers, or as pills, tablets, bars, lozenges, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. In some embodiments, the active agents are formulated separately. In some embodiments, the active agents are formulated in different dosage forms. In some embodiments, at least one active agent is formulated as a liquid, and at least one active agent is formulated as a solid. In some embodiments, at least one active agent is formulated as a solution or suspension, and at least one active agent is formulated as a pill or tablet. The active agents of the kit can be formulated, together or separately, in any manner and with any excipients or other ingredients described herein. In some embodiments, the active agents are all formulated as solids. In some embodiments, the active agents are all formulated as liquids.

[0319] In some embodiments, the active agents are formulated for simultaneous administration. In some embodiments, the active agents are formulated for sequential administration. In some embodiments, the active agents (a)-(d), (a)-(d) and (g), (a)-(f), (a)-(g), (a)-(i) or (a)-(d) and (g)-(h) are formulated for simultaneous administration, *e.g.*, as a single formulation, and trimethylglycine (*i.e.*, active agent (j)) and/or the NPA (*i.e.*, active agent (k)) is formulated for sequential administration as a separate formulation. In some embodiments, the active agents are formulated for administration via different routes. In some embodiments, the active agents are administered via the same route (*e.g.*, oral administration). In some embodiments, the administration of at least one active agent and the administration of the other active agents are 1-60 mins, 60-120 mins, 120-240 mins, 240-480 mins, 480-1440 mins, 1-2 days, 2-5 days, or 5-10 days apart.

[0320] In another aspect, at least one active agent may be in the form of a food product or a dietary supplement. In some embodiments, at least one active agent is administered in the form of a natural food, including fruits, vegetables, plants, meat, milk, nuts, or seeds. In some embodiments, at least one active agent is administered in the form of a processed food product, including juice, extract, concentrate, jam, or alcohol.

[0321] In some embodiments, at least one active agent may be formulated for extended release or slow release. In some embodiments, the active agent is formulated with a matrix. In some embodiments, the active agent is formulated with a wax matrix. In some embodiments, the wax matrix is vegetable-based. In some embodiments, the wax matrix comprises an acrylic polymer.

[0322] In other aspects, the kits may be used for any of the methods described herein, including, for example, treat or prevent a disease or condition characterized by high levels of total plasma homocysteine and/or to reduce the level of total plasma homocysteine in a subject, or to treat or prevent hyperhomocysteinemia (such as high levels of homocysteine caused by administration of an NPA) or homocystinuria.

[0323] In another aspect, articles of manufacture or kits for treating a subject who suffers from or is susceptible to the conditions described herein are provided, comprising a first container comprising a dosage amount of the active agents as disclosed herein, and instructions for use. The container may be any of those known in the art and appropriate for storage and delivery of intravenous formulation. In certain embodiments, the article of manufacture or kit further comprises a second container comprising a pharmaceutically acceptable carrier, diluent, adjuvant, *etc.* for preparation of the formulation to be administered to the subject.

[0324] Kits may optionally include appropriate instructions for preparation and administration of the formulation, side effects of the formulation, and any other relevant information. The instructions may be in any suitable format, including, but not limited to, printed matter, videotape, computer readable disk, optical disc or directions to internet-based instructions.

[0325] Kits may also be provided that contain sufficient dosages of the active agents described herein (including pharmaceutical compositions thereof) to provide effective treatment or prevention for a subject for an extended period, such as 1-3 days, 1-5 days, a week, 2 weeks, 3, weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or more.

[0326] Kits may also include multiple doses of the active agents and instructions for use and may be packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies. In certain embodiments, the kits may include a dosage amount of the active agents as disclosed herein.

[0327] Kits may include the composition as described herein packaged in either a unit dosage form or in a multi-use form. Kits may also include multiple units of the unit dose form.

[0328] Kits may also comprise a means for the delivery of the composition thereof.

VI. Methods of Treatment

[0329] One aspect of the present application provides a method of reducing a level of homocysteine (*e.g.*, total plasma homocysteine level and/or urine homocysteine level) in a subject. The methods can be used for treating hyperhomocysteinemia or homocystinuria. The methods can be combined with administration of an NPA to increase NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, plasma trimethylamine N-oxide (TMAO) and/or lipoprotein a levels in the tissue or blood of a subject, while reducing or preventing elevated homocysteine levels (*e.g.*, total plasma homocysteine level and/or urine homocysteine level) in the subject caused by the administration of an NPA.

[0330] In some embodiments, there is provided a method of treating or preventing hyperhomocysteinemia or a disease or condition characterized by high levels of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of any one of the compositions or pharmaceutical compositions described herein. In some embodiments, wherein the composition or pharmaceutical composition does not comprise trimethylglycine, the method further comprises administering to the subject a

therapeutically effective amount of trimethylglycine (*e.g.*, at about 1000 mg/day or 2000 mg/day). In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA (*e.g.*, NR at about 500 mg/day). In some embodiments, the subject has a high level of total plasma homocysteine caused by consumption of an NPA (*e.g.*, vitamin B_3) from his or her diet. In some embodiments, the subject receives vitamin B_6 and/or vitamin B_3 in his or her diet. In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has homocystinuria.

[0331] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising serine. In some embodiments, the subject receives vitamin B_6 and/or vitamin B_3 from his or her diet.

[0332] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; and (b) vitamin B_6. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0333] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of

trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0334] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA (*e.g.*, NA); and vitamin B_1. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0335] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate). In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0336] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0337] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (j) trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0338] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise

administering to the subject trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0339] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0340] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; and (j) trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In

some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0341] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine. In some embodiments, the method does not comprise administering to the subject trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0342] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; (i) SAM; and (j) trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0343] In some embodiments, there is provided a method of treating or preventing a disease or condition in a subject characterized by characterized by high levels of homocysteine or reducing the level of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising the active agents: (a)

serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; and (j) trimethylglycine. In some embodiments, the method further comprises administering to the subject an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method further comprises administering to the subject a therapeutically effective amount of vitamin D (*e.g.*, vitamin D_3). In some embodiments, the method increases NAD and/or HDL levels, and/or decrease LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of the subject. In some embodiments, the subject has a high level of total plasma homocysteine caused by administration of an NPA.

[0344] In some embodiments, the method further comprises administering one or more additional active agents. In some embodiments, the method further comprises administering one or more additional active agents selected from fruit extracts (*e.g.*, blueberry, cranberry, strawberry, pomegranate, and/or grape extracts), vegetable extracts (*e.g.*, ginger, turmeric and/or black pepper extracts), plant extracts (*e.g.*, green tea and/or rosemary extracts), dimethylglycine, monomethylglycine, glycine, choline, and phosphatidylcholine. Preferences for these additional active agents are as specified in the composition section above.

[0345] The methods described herein are useful for treating all forms of elevated homocysteine levels in subjects, including idiopathic hyperhomocysteinemia, *e.g.*, hyperhomocysteinemia caused by consumption of excessive amount of dietary methionine such as egg whites, or hyperhomocysteinemia due to other unknown causes; and high levels of total plasma homocysteine caused by administration of an NPA (*e.g.*, NR). NA and NAM are taken by many people as vitamins. Sustained release NA, e.g., NIASPAN®, is also taken by millions of people. The compositions and methods described herein are useful to treat or prevent elevated total homocysteine levels associated with or caused by administration of an NPA, such as NR, NA, and/or NAM. The compositions and methods described herein may or may not comprise trimethylglycine (TMG).

[0346] In some embodiments, the active agents are formulated and administered as one composition. In some embodiments, the composition further comprises a pharmaceutically acceptable salt. In some embodiments, at least one active agent is in the form of a food product or a dietary supplement. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier, excipient, binder or diluent. The active agents provided herein may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. In some embodiments, the active agents are formulated for intravenous or oral administration. For oral administration, the active agents

may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension.

[0347] In some embodiments, the active agents are formulated as two or more compositions (*e.g.*, each formulated individually) and administered simultaneously. In some embodiments, the active agents are formulated as two or more formulations (*e.g.*, each formulated individually) and administered sequentially. In some embodiments, the active agents are formulated as two or more pharmaceutical compositions comprising at least one active agent and a pharmaceutically acceptable carrier, excipient, binder or diluent. In some embodiments, the active agents are formulated as a first composition, and trimethylglycine is formulated as a second composition, and the first composition and the second composition are administered simultaneously or sequentially. In some embodiments, the active agents except for active agent (k) are formulated as a first composition, the active agent (k) is formulated as a second composition, and the first composition and the second composition are administered simultaneously or sequentially. In some embodiments, the active agents are formulated individually and administered sequentially.

[0348] In some embodiments, the active agents are administered via different routes. In some embodiments, the active agents are administered via the same route. In some embodiments, the administration of at least one active agent and the administration of the other active agents are about 1-60 mins, 60-120 mins, 120-240 mins, 240-480 mins, 480-1440 mins, 1-2 days, 2-5 days, or 5-10 days apart. In some embodiments, at least one active agent is formulated as a pill, tablet, or capsule, while at least one active agent is formulated as a solution or suspension. In some embodiments, at least one active agent is formulated as a food product, while at least one active agent is formulated as a food additive. In some embodiments, at least one active agent is formulated as a dietary supplement, while at least one active agent is formulated as a food product.

[0349] In some embodiments, at least one active agent is purified. In some embodiments, an active agent is at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.1%, about 99.2%, about 99.3%, about 99.4%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9%, or about 100% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier.

[0350] In some embodiments, the formulations and preparations used in the methods of the disclosure are sterile. Sterile pharmaceutical formulations are compounded or manufactured according to pharmaceutical-grade sterilization standards (*e.g.*, United States Pharmacopeia Chapters 797, 1072, and 1211; California Business & Professions Code 4127.7; 16 California Code of Regulations 1751, 21 Code of Federal Regulations 211) known to those of skill in the art. In some embodiments, at least one active agent is sterilized.

[0351] In some embodiments, the active agents can be formulated as any pharmaceutical composition described herein. In some embodiments, the active agents are provided as a kit.

[0352] In some embodiments, the dosage regimen provides about 1000-5000 mg/day of serine; for example, 1000-3000 mg/day, 1000-2900 mg/day, 1000-2800 mg/day, 1000-2700 mg/day, 1000-2600 mg/day, 1000-2500 mg/day, 1100-2500 mg/day, 1200-2500 mg/day, 1300-2500 mg/day, 1400-2500 mg/day, 1500-2500 mg/day, 1500-2400 mg/day, 1600-2500 mg/day, 1600-2400 mg/day, 1700-2400 mg/day, 1700-2300 mg/day, 1800-2300 mg/day, 1800-2200 mg/day, or 1900-2100 mg/day. In some embodiments, the dosage regimen provides about 1200 mg/day, 1700 mg/day or 2000 mg/day of serine. In some embodiments, the dosage regimen provides about 4000 mg/day of serine.

[0353] In some embodiments, the dosage regimen provides about 20-100 mg/day of vitamin B_6; for example, about any one of 20-100 mg/day, 20-80 mg/day, 20-70 mg/day, 20-60 mg/day, 25-80 mg/day, 30-80 mg/day, 30-70 mg/day, 30-70 mg/day, 30-65 mg/day, 30-60 mg/day, 30-50 mg/day, 35-100 mg/day, 40-100 mg/day, 45-100 mg/day, 50-100 mg/day, 50-90 mg/day, or 65-85 mg/day. In some embodiments, the dosage regimen provides about 25 mg/day, 50 mg/day, or 75 mg/day of vitamin B_6. In some embodiments, the dosage regimen provides about 100 mg/day of vitamin B_6. In some embodiments, the dosage regimen provides about 150 mg/day of vitamin B_6.

[0354] In some embodiments, the dosage regimen provides about 0.10-2.0 mg/day of vitamin B_9; for example, about any one of 0.10-1.0 mg/day, 1.0 mg/day-2.0 mg/day, 0.50 mg/day-1.5 mg/day, 1.0-1.5 mg/day, 1.5-2.0 mg/day, 0.10-0.95 mg/day, 0.10-0.90 mg/day, 0.10-0.85 mg/day, 0.10-0.80 mg/day, 0.10-0.75 mg/day, 0.10-0.70 mg/day, 0.15-0.70 mg/day, 0.20-0.70 mg/day, 0.20-0.65 mg/day, 0.20-0.60 mg/day, 0.25-0.60 mg/day, 0.25-0.55 mg/day, 0.30-0.55 mg/day or 0.30-0.50 mg/day. In some embodiments, the dosage regimen provides about 0.4 mg/day or 1 mg/day of vitamin B_9. In some embodiments, the dosage regimen provides about 0.8 mg/day of vitamin B_9.

[0355] In some embodiments, the dosage regimen provides about 20 μg-3mg/day of vitamin B_{12}; for example, about any one of 20-190 μg/day, 20-180 μg/day, 20-170 μg/day,

20-160 μg/day, 25-160 μg/day, 30-160 μg/day, 30-150 μg/day, 30-140 μg/day, 30-130 μg/day, 30-120 μg/day, 30-110 μg/day, 30-100 μg/day, 35-100 μg/day, 40-100 μg/day, 45-100 μg/day, 50-100 μg/day, 50-90 μg/day, 65-85 μg/day, 100-200 μg/day, 200-300 μg/day, 300-400 μg/day, 400-500 μg/day, 500-1000 μg/day, 1000-2000 μg/day, or 2000-3000 μg/day. In some embodiments, the dosage regimen provides about 75 μg/day of vitamin B_{12}. In some embodiments, the dosage regimen provides about 500 μg/day of vitamin B_{12}. In some embodiments, the dosage regimen provides about 3000 μg/day of vitamin B_{12}.

[0356] In some embodiments, the dosage regimen provides 50-500 mg/day of quercetin; for example, about any one of 50-100 mg/day, 100-200 mg/day, 100-300 mg/day, 100-400 mg/day, 200-300 mg/day, 200-400 mg/day, 200-500 mg/day, 250-400 mg/day, 250-500 mg/day, 150-400 mg/day, 150-250 mg/day, 200-350 mg/day, or 250-350 mg/day. In some embodiments, the dosage regimen provides about 100 mg/day or 300 mg/day of quercetin.

[0357] In some embodiments, the dosage regimen provides 20-200 mg/day of fisetin; for example, about any one of 20-190 mg/day, 20-180 mg/day, 20-170 mg/day, 20-160 mg/day, 25-160 mg/day, 30-160 mg/day, 30-150 mg/day, 30-140 mg/day, 30-130 mg/day, 30-120 mg/day, 30-110 mg/day, 30-100 mg/day, 35-100 mg/day, 40-100 mg/day, 45-100 mg/day, 50-100 mg/day, 50-90 mg/day, or 65-85 mg/day. In some embodiments, the dosage regimen provides about 100 mg/day of fisetin.

[0358] In some embodiments, the dosage regimen provides about 0.10-2.0 mg/day of vitamin B_2; for example, about any one of 0.10-1.0 mg/day, 1.0 mg/day-2.0 mg/day, 0.50 mg/day-1.5 mg/day, 1.0-1.5 mg/day, or 1.5-2.0 mg/day. In some embodiments, the dosage regimen provides about 1.3 mg/day of vitamin B_2.

[0359] In some embodiments, the dosage regimen provides 20-200 mg/day of vitamin B_2; for example, about any one of 20-190 mg/day, 20-180 mg/day, 20-170 mg/day, 20-160 mg/day, 25-160 mg/day, 30-160 mg/day, 30-150 mg/day, 30-140 mg/day, 30-130 mg/day, 30-120 mg/day, 30-110 mg/day, 30-100 mg/day, 35-100 mg/day, 40-100 mg/day, 45-100 mg/day, 50-100 mg/day, 50-90 mg/day, or 65-85 mg/day. In some embodiments, the dosage regimen provides about 75 mg/day of vitamin B_2.

[0360] In some embodiments, the dosage regimen provides about 0.10-2.0 mg/day of vitamin B_1; for example, about any one of 0.10-1.0 mg/day, 1.0 mg/day-2.0 mg/day, 0.50 mg/day-1.5 mg/day, 1.0-1.5 mg/day, or 1.5-2.0 mg/day. In some embodiments, the dosage regimen provides about 1.2 mg/day of vitamin B_1.

[0361] In some embodiments, the dosage regimen provides 1000-3000 mg/day of *N*-acetylcysteine; for example, about any one of 1000-2900 mg/day, 1000-2800 mg/day,

1000-2700 mg/day, 1000-2600 mg/day, 1000-2500 mg/day, 1100-2500 mg/day, 1200-2500 mg/day, 1300-2500 mg/day, 1400-2500 mg/day, 1500-2500 mg/day, 1500-2400 mg/day, 1600-2500 mg/day, 1600-2400 mg/day, 1700-2400 mg/day, 1700-2300 mg/day, 1800-2300 mg/day, 1800-2200 mg/day, or 1900-2100 mg/day. In some embodiments, the dosage regimen provides about 1500 mg/day or 2000 mg/day of *N*-acetylcysteine.

[0362] In some embodiments, the dosage regimen provides 1000-3000 mg/day of SAM; for example, about any one of 1000-2900 mg/day, 1000-2800 mg/day, 1000-2700 mg/day, 1000-2600 mg/day, 1000-2500 mg/day, 1100-2500 mg/day, 1200-2500 mg/day, 1300-2500 mg/day, 1400-2500 mg/day, 1500-2500 mg/day, 1500-2400 mg/day, 1600-2500 mg/day, 1600-2400 mg/day, 1700-2400 mg/day, 1700-2300 mg/day, 1800-2300 mg/day, 1800-2200 mg/day, or 1900-2100 mg/day. In some embodiments, the dosage regimen provides about 2000 mg/day of SAM.

[0363] In some embodiments, the dosage regimen provides about 1000-5000 mg/day of trimethylglycine; for example, about any one of 1000-3000 mg/day, 1000-2900 mg/day, 1000-2800 mg/day, 1000-2700 mg/day, 1000-2600 mg/day, 1000-2500 mg/day, 1100-2500 mg/day, 1200-2500 mg/day, 1300-2500 mg/day, 1400-2500 mg/day, 1500-2500 mg/day, 1500-2400 mg/day, 1600-2500 mg/day, 1600-2400 mg/day, 1700-2400 mg/day, 1700-2300 mg/day, 1800-2300 mg/day, 1800-2200 mg/day, 1900-2100 mg/day or 3000-5000 mg/day. In some embodiments, the dosage regimen provides about 1000 mg/day or 2000 mg/day of trimethylglycine. In some embodiments, the method does not comprise administering to the subject a therapeutically effective amount of trimethylglycine.

[0364] In some embodiments, the dosage regimen provides about 1000-5000 mg/day of glycine; for example, about any one of 1000-2000 mg/day, 2000-3000 mg/day, 3000-4000 mg/day, 4000-5000 mg/day, 1000-2500 mg/day, 2500-5000 mg/day, 1500-2500 mg/day, or 3000-5000 mg/day. In some embodiments, the dosage regimen provides about 4000 mg/day of glycine.

[0365] In some embodiments, the dosage regimen provides about 800-5000 IU/day of vitamin D_3,for example, about any one of 800-4800 IU/day, 1000-4600 IU/day, 1200-4400 IU/day, 1400-4200IU/day, 1600-4000IU/day, 1800-3800IU/day,2000-3600IU/day,2200-3400 IU/day, 2400-3200IU/day, or 2600-3000 IU/day.

[0366] In some embodiments, the dosage regimen provides about 10-2000 mg/day of NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN, such as NR or NR and NA); for example 200-500 mg/day, 500-1000 mg/day, 1000-1500 mg/day, 1500-2000 mg/day, 1000-2000 mg/day, 200-2000 mg/day, 10 -50 mg/day, 50-100 mg/day, 100-200 mg/day, 200-1000

mg/day, 250-750 mg/day, 200-300 mg/day, 300-400 mg/day, 400-500 mg/day, 500-600 mg/day, 600-700 mg/day, 700-800 mg/day, 800-900 mg/day, 900-1000 mg/day, or 500-1500 mg/day. In some embodiments, the dosage regimen provides about 500 mg/day of NR. In some embodiments, the dosage regimen provides about 16 mg/day or 50 g/day of NA, such as about 500 mg or about 1000 mg/day of NA.

[0367] The above dosage regimens provide levels of active agents, which may offer improved therapeutic benefit while reducing the risk of any toxicity-related side-effects. In some embodiments, the active agents or composition are administered to the subject at a suitable frequency, such as once daily, twice daily, three times daily, or once every other day. In some embodiments, the active agents or composition are administered to the subject once daily. In some embodiments, different active agents are administered to the subject at the same frequency. In some embodiments, different active agents are administered to the subject at different frequencies.

[0368] In some embodiments, an effective amount of the active agents is administered to a subject in need thereof. In some embodiments, the subject is a mammalian patient. In some embodiments, the subject is a human or an animal (*e.g.*, cat, dog, cow, rat, mouse, horse, sheep, pig, goat, buffalo, chicken, duck, goose or other domesticated mammal). In some embodiments, the subject is a human patient.

[0369] In some embodiments, an effective amount of the active agents is administered to an experimental subject for research purposes. In some embodiments, the subject is a mammalian patient. In some embodiments, the subject is a human or an animal (*e.g.*, mouse, rat, monkey, ape, worm, fly, fruit fly, fish, Zebrafish, frog, Xenopus, cat, dog, cow, pig, horse, sheep, goat, buffalo, chicken, duck, goose or other domesticated mammal)), a nematode, a fungus, a eukaryotic cell or a bacterium. In some embodiments, the subject is a cell line, cell strain, animal organ, group of cells, yeast.

[0370] In some embodiments, the administration of the active agents exhibits synergistic effect toward reduction of the level of total plasma homocysteine, or treatment or prevention of hyperhomocysteinemia or a disease or condition characterized by high levels of total plasma homocysteine.

[0371] One aspect of the present application provides a composition as described herein for use in a method of treatment of the human or animal body by therapy. In some embodiments, the method of treatment is a method of treatment of a disease or condition characterized by high levels of total plasma homocysteine. In some embodiments, the method of treatment is a method of reducing the level of total plasma homocysteine in a subject. In some

embodiments, the method of treatment is a method of treating or preventing hyperhomocysteinemia. In some embodiments, the method of treatment is a method of treating or preventing idiopathic hyperhomocysteinemia. In some embodiments, the method of treatment is a method of treating or preventing hyperhomocysteinemia associated with administration of an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the method of treatment is a method of treating or preventing homocystinuria. In some embodiments, the method of treatment is a method of treating a disease or condition selected from cardiovascular disease, cerebrovascular disease, peripheral vascular disease, thrombosis, stroke, atherothrombotic coronary artery disease (CAD), myocardial infarction (MI), Alzheimer's disease, cognitive impairment, dementia, diabetic retinopathy, intraocular lens dislocation, schizophrenia and osteoporosis.

[0372] In some embodiments, the methods described herein reduce a homocysteine level (*e.g.*, total plasma or serum homocysteine level, or urine homocysteine level) of the subject by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or more relative to the homocysteine level prior to the treatment. In some embodiments, the methods described herein reduce the total plasma homocysteine level of the subject to no more than 12 μmol/L, no more than 11 μmol/L, no more than 10 μmol/L, no more than 9 μmol/L, no more than 8 μmol/L, no more than 7 μmol/L, no more than 6 μmol/L, or lower. Homocysteine levels can be can be measured using routine homocysteine test kits, such as immunoassays for determining total homocysteine levels in a plasma, serum or urine sample of a subject.

[0373] One aspect of the present application provides use of a composition as described herein in the manufacture of a medicament for the treatment of hyperhomocysteinemia or a disease or condition characterized by high levels of homocysteine (*e.g.*, plasma, serum, or urine homocysteine levels). In some embodiments, the medicament is for reducing the level of total plasma homocysteine in a subject. In some embodiments, the medicament is for reducing the level of urine homocysteine in a subject. In some embodiments, the medicament is for the treatment or prevention of hyperhomocysteinemia. In some embodiments, the medicament is for the treatment or prevention of hyperhomocysteinemia caused by administration of an NPA. In some embodiments, the medicament is for the treatment or prevention of idiopathic hyperhomocysteinemia. In some embodiments, the medicament is for the treatment or prevention of homocystinuria. In some embodiments, the medicament is for the treatment or prevention of a disease or condition selected from cardiovascular disease, cerebrovascular disease, peripheral vascular disease, thrombosis, stroke, atherothrombotic coronary artery disease (CAD), myocardial infarction (MI), Alzheimer's disease, cognitive

impairment, dementia, diabetic retinopathy, intraocular lens dislocation, schizophrenia and osteoporosis.

[0374] One aspect of the present application provides a method of treating a disease or condition in a subject characterized by high levels of homocysteine (*e.g.*, plasma, serum and/or urine homocysteine levels) and/or reducing homocysteine levels (*e.g.*, plasma, serum and/or urine homocysteine level) in a subject, comprising administering to the subject an effective amount of any one of the compositions described herein. In some embodiments, the present application provides a method of reducing a high level of total plasma homocysteine caused by administration of an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN) in a subject, comprising administering to the subject an effective amount of any one of the compositions described herein. In some embodiments, the present application provides a method of reducing a high level of total plasma homocysteine in a subject, comprising administering to the subject an effective amount of any one of the compositions described herein, wherein the subject is further administered an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN). In some embodiments, the present application provides a method of treating or preventing high levels of homocysteine caused by administration of an NPA (*e.g.*, NR, NA, NAR, NAAD, NAD+ and/or NMN), and increasing NAD and/or HDL levels, and/or lowering LDL, triglyceride, total cholesterol, TMAO and/or lipoprotein a levels in the tissue or blood plasma of a subject, comprising administering to the subject an effective amount of any one of the compositions described herein. In some embodiments, the present application provides a method of treating or preventing hyperhomocysteinemia, comprising administering to the subject an effective amount of any one of the compositions described herein. In some embodiments, the present application provides a method of treating or preventing homocystinuria in a subject, comprising administering to the subject an effective amount of any one of the compositions described herein. In some embodiments, the method of treatment is a method of treating a disease or condition selected from cardiovascular disease, cerebrovascular disease, peripheral vascular disease, thrombosis, stroke, atherothrombotic coronary artery disease (CAD), myocardial infarction (MI), Alzheimer's disease, cognitive impairment, dementia, diabetic retinopathy, intraocular lens dislocation, schizophrenia and osteoporosis.

VII. Methods of Preparation

[0375] Another aspect of the present application provides a method of preparing any one of the compositions described herein.

[0376] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; and optionally (k) an NPA.

[0377] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and optionally (k) an NPA.

[0378] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; glycine; and optionally (k) an NPA.

[0379] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and optionally (k) an NPA.

[0380] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (j) trimethylglycine; and optionally (k) an NPA.

[0381] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; and optionally (k) an NPA.

[0382] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (j) trimethylglycine; and optionally (k) an NPA.

[0383] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; (i) SAM; and optionally (k) an NPA.

[0384] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; (i) SAM; (j) trimethylglycine; and optionally (k) an NPA.

[0385] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (j) trimethylglycine; and optionally (k) an NPA.

[0386] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (l) vitamin D_3; and optionally (k) an NPA.

[0387] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (l) vitamin D_3; and optionally (k) an NPA.

[0388] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA (*e.g.*, NA); and vitamin B_1.

[0389] In some embodiments, there is provided a method of preparing a composition, comprising the step of mixing the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA (*e.g.*, NA); vitamin B_1, and a magnesium-containing compound (*e.g.*, magnesium bisglycinate).

[0390] The ingredients may be mixed in any order. In some embodiments, the method comprises mixing the active agents to provide a homogeneous mixture. In some embodiments, the method further comprises the step of mixing a pharmaceutically acceptable carrier, excipient, binder or diluent with the active agents. In some embodiments, the method further comprises formulating the ingredients as a capsule, an extended-release tablet, a liquid, a powder, granules, a dragee or a lozenge. Some embodiments provide a method of preparing a pharmaceutical composition.

VIII. EXEMPLARY EMBODIMENTS

[0391] Among the embodiments provided herein are:

1. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}.
2. The composition of embodiment 1, wherein the composition comprises about 90 wt% to about 99 wt% serine, based on the total weight of active agents (a)-(d) in the composition.
3. The composition of embodiment 1 or 2, wherein the composition comprises about 1 wt% to about 7.5 wt% vitamin B_6, based on the total weight of active agents (a)-(d) in the composition.
4. The composition of any one of embodiments 1-3, wherein the composition comprises about 0.01 wt% to about 0.10 wt% vitamin B_9, based on the total weight of active agents (a)-(d) in the composition.

5. The composition of any one of embodiments 1-4, wherein the composition comprises about 0.01 wt% to about 0.05 wt% vitamin B_{12}, based on the total weight of active agents (a)-(d) in the composition.
6. The composition of any one of embodiments 1-5, further comprising vitamin B_1, a magnesium-containing compound, and *N*-acetyl cysteine.
7. The composition of any one of embodiments 1-5, further comprising vitamin B_1 and quercetin.
8. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}; (e) quercetin; and (f) fisetin.
9. The composition of embodiment 8, wherein the composition comprises about 70 wt% to about 90 wt% serine, based on the total weight of active agents (a)-(f) in the composition.
10. The composition of embodiment 8 or 9, wherein the composition comprises about 1 wt% to about 5 wt% vitamin B_6, based on the total weight of active agents (a)-(f) in the composition.
11. The composition of any one of embodiments 8-10, wherein the composition comprises about 5 wt% to about 20 wt% quercetin, based on the total weight of active agents (a)-(f) in the composition.
12. The composition of any one of embodiments 8-11, wherein the composition comprises about 1 wt% to about 10 wt% fisetin, based on the total weight of active agents (a)-(f) in the composition.
13. The composition of any one of embodiments 8-12, wherein the composition comprises about 0.001 wt% to about 0.02 wt% vitamin B_9, based on the total weight of active agents (a)-(f) in the composition.
14. The composition of any one of embodiments 8-13, wherein the composition comprises about 0.0005 wt% to about 0.005 wt% vitamin B_{12}, based on the total weight of active agents (a)-(f) in the composition.
15. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2.
16. The composition of embodiment 15, wherein the composition comprises about 70 wt% to about 90 wt% serine, based on the total weight of active agents (a)-(g) in the composition.
17. The composition of embodiment 15 or 16, wherein the composition comprises about 1 wt% to about 5 wt% vitamin B_6, based on the total weight of active agents (a)-(g) in the composition.

18. The composition of any one of embodiments 15-17, wherein the composition comprises about 5 wt% to about 20 wt% quercetin, based on the total weight of active agents (a)-(g) in the composition.
19. The composition of any one of embodiments 15-18, wherein the composition comprises about 1 wt% to about 10 wt% fisetin, based on the total weight of active agents (a)-(g) in the composition.
20. The composition of any one of embodiments 15-19, wherein the composition comprises about 0.001 wt% to about 0.02 wt% vitamin B_9, based on the total weight of active agents (a)-(g) in the composition.
21. The composition of any one of embodiments 15-20, wherein the composition comprises about 0.0005 wt% to about 0.005 wt% vitamin B_{12}, based on the total weight of active agents (a)-(g) in the composition.
22. The composition of any one of embodiments 15-21, wherein the composition comprises about 1 wt% to about 5 wt% vitamin B_2, based on the total weight of active agents (a)-(g) in the composition.
23. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) *S*-adenosylmethionine (SAM).
24. The composition of embodiment 23, wherein the composition comprises about 20 wt% to about 40 wt% serine, based on the total weight of active agents (a)-(i) in the composition.
25. The composition of embodiment 23 or 24, wherein the composition comprises about 0.5 wt% to about 2 wt% vitamin B_6, based on the total weight of active agents (a)-(i) in the composition.
26. The composition of any one of embodiments 23-25, wherein the composition comprises about 1 wt% to about 10 wt% quercetin, based on the total weight of active agents (a)-(i) in the composition.
27. The composition of any one of embodiments 23-26, wherein the composition comprises about 1 wt% to about 5 wt% fisetin, based on the total weight of active agents (a)-(i) in the composition.
28. The composition of any one of embodiments 23-27, wherein the composition comprises about 0.001 wt% to about 0.015 wt% vitamin B_9, based on the total weight of active agents (a)-(i) in the composition.

29. The composition of any one of embodiments 23-28, wherein the composition comprises about 0.0001 wt% to about 0.002 wt% vitamin B_{12}, based on the total weight of active agents (a)-(i) in the composition.
30. The composition of any one of embodiments 23-29, wherein the composition comprises about 0.5 wt% to about 2 wt% vitamin B_2, based on the total weight of active agents (a)-(i) in the composition.
31. The composition of any one of embodiments 23-30, wherein the composition comprises about 20 wt% to about 40 wt% *N*-acetylcysteine, based on the total weight of active agents (a)-(i) in the composition.
32. The composition of any one of embodiments 23-31, wherein the composition comprises about 20 wt% to about 40 wt% SAM, based on the total weight of active agents (a)-(i) in the composition.
33. The composition of any one of embodiments 1-32, further comprising: (j) trimethylglycine.
34. The composition of embodiment 33, wherein the weight ratio between serine and trimethylglycine is about 1:1.
35. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; (f) *N*-acetylcysteine; and (g) trimethylglycine.
36. The composition according to embodiment 35, wherein the composition comprises about 25 wt% to about 40 wt% serine, based on the total weight of active agents (a)-(g) in the composition.
37. The composition of embodiment 35 or 36, wherein the composition comprises about 25 wt% to about 40 wt% *N*-acetylcysteine, based on the total weight of active agents (a)-(g) in the composition.
38. The composition of any one of embodiments 35-37, wherein the composition comprises about 0.5 wt% to about 1.6 wt% vitamin B_2, based on the total weight of active agents (a)-(g) in the composition.
39. The composition of any one of embodiments 35-38, wherein the composition comprises about 0.5 wt% to about 1.6 wt% vitamin B_6, based on the total weight of active agents (a)-(g) in the composition.
40. The composition of any one of embodiments 35-39, wherein the composition comprises about 0.001 wt% to about 0.01 wt% vitamin B_9, based on the total weight of active agents (a)-(g) in the composition.

41. The composition of any one of embodiments 35-40, wherein the composition comprises about 0.0005 wt% to about 0.002 wt% vitamin B_{12}, based on the total weight of active agents (a)-(g) in the composition.
42. The composition of any one of embodiments 35-41, wherein the composition comprises about 25 wt% to about 40 wt% trimethylglycine, based on the total weight of active agents (a)-(g) in the composition.
43. The composition of any one of embodiments 1-42, further comprising: (k) a nicotinamide adenine dinucleotide pathway agent (NPA) selected from the group consisting of nicotinamide riboside (NR), nicotinic acid (NA), nicotinic acid riboside (NAR), nicotinamide mononucleotide (NMN), nicotinic acid adenine dinucleotide (NAAD), nicotinamide adenine dinucleotide (NAD+), and mixtures thereof.
44. The composition of embodiment 43, wherein the NPA is NR, NA, or NR and NA.
45. The composition of embodiment 44, wherein the NPA is NR and NA, and wherein weight ratio between serine and NR is about 4:1.
46. The composition of any one of embodiments 1-45, wherein at least one of the active agents is at least about 80% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier.
47. The composition of any one of embodiments 1-46, wherein vitamin B_6 comprises pyridoxal 5'-phosphate.
48. The composition of any one of embodiments 1-47, wherein vitamin B_9 comprises folic acid or tetrahydrofolate.
49. The composition of any one of embodiments 1-48, further comprising a wax matrix.
50. The composition of any one of embodiments 1-49, further comprising vitamin D_3, fruit extracts, plant extracts, vegetable extracts, dimethylglycine, monomethylglycine, glycine, choline, and/or phosphatidylcholine.
51. A pharmaceutical composition comprising a therapeutically effective amount of the composition of any one of embodiments 1-50, and a pharmaceutically acceptable carrier, excipient, binder, or diluent.
52. The pharmaceutical composition of embodiment 51, formulated for oral, topical, intramuscular, intravenous, intrabuccal or sublingual administration to a subject.
53. The pharmaceutical composition of embodiment 51 or 52, in the form of a tablet, a capsule, an extended-release tablet, a liquid, a powder, granules, a dragee or a lozenge.
54. The pharmaceutical composition of embodiment 51 or 52, in unit dosage form, comprising:

1) (a) about 2000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12};
2) (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 0.075 mg vitamin B_{12}; (e) about 75 mg quercetin; and (f) about 300 mg fisetin;
3) (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 0.075 mg vitamin B_{12}; (e) about 75 mg quercetin; (f) about 300 mg fisetin; and (g) about 75 mg vitamin B_2;
4) (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 0.075 mg vitamin B_{12}; (e) about 75 mg quercetin; (f) about 300 mg fisetin; (g) about 75 mg vitamin B_2; (h) about 2000 mg *N*-acetylcysteine; and (i) about 2000 mg SAM;
5) (a) about 1700 mg serine; (b) about 25 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; (e) about 100 mg quercetin; (g) about 1.3 mg vitamin B_2; (k) about 50 mg NA; and about 1.2 mg vitamin B_1;
6) (a) about 1200 mg serine; (b) about 50 mg vitamin B_6; (c) about 1 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; (g) about 1.3 mg vitamin B_2; (h) about 1500 mg *N*-acetylcysteine; (k) about 16 mg NA; about 1.2 mg vitamin B_1, and about 300 mg magnesium bisglycinate;
7) (a) about 2000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 3 mg vitamin B_{12}; or
8) (a) about 4000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; and about 4000 mg glycine.

55. The pharmaceutical composition of embodiment 54, in unit dosage form, further comprising: (j) about 1000 mg or about 2000 mg trimethylglycine.
56. A food product or dietary supplement comprising the composition of any one of embodiments 1-55.
57. A method of reducing the level of total plasma homocysteine in a subject or treating or preventing a disease or condition characterized by high levels of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of the composition of any one of embodiments 1-50, the pharmaceutical composition of any one of embodiments 51-55 or the food product or dietary supplement of embodiment 56.
58. The method of embodiment 57, further comprising administering to the subject a therapeutically effective amount of trimethylglycine.

59. The method of embodiment 58, wherein trimethylglycine is administered at about 1000 mg/day or 2000 mg/day.
60. The method of embodiment 58 or 59, wherein the composition and trimethylglycine are administered to the subject simultaneously.
61. The method of embodiment 58 or 59, wherein the composition and trimethylglycine are administered to the subject sequentially.
62. The method of any one of embodiments 57-61, wherein the subject has a high initial level of total plasma homocysteine caused by administration of an NPA to the subject.
63. The method of embodiment 62, wherein NPA is NR, NA, or NR and NA.
64. The method of embodiment 63, wherein NR is administered at about 500 mg/day.
65. The method of any one of embodiments 62-64, wherein the initial level of total plasma homocysteine in the subject is at least 12 μmol/L.
66. The method of any one of embodiments 62-64, wherein the initial level of total plasma homocysteine in the subject is at least 31 μmol/L.
67. The method of any one of embodiments 62-64, wherein the initial level of total plasma homocysteine in the subject is greater than 100 μmol/L.
68. The method of any one of embodiments 62-67, wherein the composition and the NPA are administered to the subject simultaneously.
69. The method of any one of embodiments 62-67, wherein the composition and the NPA are administered to the subject sequentially.
70. The method of any one of embodiments 57-69, wherein the disease or condition is selected from the group consisting of hyperhomocysteinemia, homocystinuria, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, thrombosis, stroke, atherothrombotic coronary artery disease (CAD), myocardial infarction (MI), Alzheimer's disease, cognitive impairment, dementia, diabetic retinopathy, intraocular lens dislocation, schizophrenia and osteoporosis.
71. A method of treating or preventing hyperhomocysteinemia in a subject, comprising administering to the subject a therapeutically effective amount of the composition of any one of embodiments 1-50, the pharmaceutical composition of any one of embodiments 51-55 or the food product or dietary supplement of embodiment 56.
72. A kit comprising two or more components, wherein:

1) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}; provided that each of active agents (a)-(d) are contained within the kit;

2) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin, provided that each of active agents (a)-(f) are contained within the kit;
3) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2, provided that each of active agents (a)-(g) are contained within the kit;
4) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2, provided that each of active agents (a)-(d) and (g) are contained within the kit;
5) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM, provided that each of active agents (a)-(i) are contained within the kit;
6) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; (f) *N*-acetylcysteine; and (g) trimethylglycine, provided that each of active agents (a)-(g) are contained within the kit;
7) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA; and vitamin B_1;
8) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA; vitamin B_1, and a magnesium-containing compound; or
9) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and glycine.

73. The kit of embodiment 72 (1)-(4), wherein one or more components of the kit further comprises trimethylglycine.
74. The kit of embodiment 72 or 73, wherein at least one of the active agents is at least about 80% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier.
75. The kit of embodiment 74, wherein each of the active agents is at least about 80% pure, wherein the % purity excludes the weight of any other active agent and any added counter-ion, vehicle, diluent, excipient, or carrier.

76. The kit of any one of embodiments 72-75, wherein at least one of the components is sterilized.
77. The kit of any one of embodiments 72-76, wherein at least one of the components further comprises a pharmaceutically acceptable carrier, excipient, binder, or diluent.
78. The kit of any one of embodiments 72-77, wherein at least one of the two or more components further comprises a wax matrix.
79. The kit of any one of embodiments 72-78, wherein one or more components are formulated for oral, topical, intramuscular, intravenous, intrabuccal, or sublingual administration to a subject.
80. The kit of any one of embodiments 72-79, wherein one or more components are in the form of a tablet, a capsule, an extended-release tablet, a liquid, a powder, granules, a dragee, or a lozenge.
81. The kit of any one of embodiments 72-80, wherein one or more components are in the form of a food product or dietary supplement.
82. The kit of any one of embodiments 72-81, wherein the components are formulated for simultaneous administration to a subject.
83. The kit of any one of embodiments 72-81, wherein the components are formulated for sequential administration to a subject.
84. A method of reducing the level of total plasma homocysteine in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents:

1) (a) serine; and (b) vitamin B_6;
2) (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12};
3) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin;
4) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2;
5) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2;
6) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM;
7) (a) serine; (b) vitamin B_6; (c) vitamin B9; (d) vitamin B12; (e) vitamin B2; and (f) *N*-acetylcysteine;
8) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA; and vitamin B_1;
9) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA; vitamin B_1, and a magnesium-containing compound; or

10) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and glycine.

85. The method of embodiment 84, further comprising administering to the subject a therapeutically effective amount of trimethylglycine.

86. The method of embodiment 84 or 85, wherein the subject has a high initial level of total plasma homocysteine caused by administration of an NPA to the subject.

87. A capsule comprising the composition of any one of embodiments 1-50.

EXAMPLES

[0392] The following examples are offered to illustrate but not to limit the invention. One of skill in the art will recognize that the following procedures may be modified using methods known to one of ordinary skill in the art.

Example 1 – Preparation of anti-hyperhomocysteinemia compositions

[0393] Eight anti-hyperhomocysteinemia ("anti-HHcy") compositions were prepared containing the ingredients set out in Table 1 below:

Table 1. Anti-HHcy formulations.

Ingredient	*Formulations—Quantity/dose (mg)*							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Serine	2000	2000	2000	2000	2000	2000	2000	2000
Vitamin B_2	0	75	75	75	0	10	30	75
Vitamin B_6 (pyridoxine)	75	75	75	75	100	100	75	75
Quercetin	300	300	300	0	0	0	300	300
Fisetin	100	100	100	0	0	0	100	100
N-acetylcysteine	0	0	2000	2000	0	0	0	2000
S-adenosylmethionine (SAM)	0	0	2000	0	0	0	0	2000
Vitamin B_9 (folic acid)	0.4	0.4	0.4	0.4	0.8	0.8	0.4	0.4
Vitamin B_{12} (cobalamin)	0.075	0.075	0.075	0.075	0.5	0.5	0.075	0.075
Trimethylglycine	0	0	0	2000	0	1000	0	1000
Vitamin D_3	0	0.125	0	0.125	0	0	0	0

[0394] The compositions were made according to the following method. A batch of a composition set out in Table 1 was produced by weighing out and mixing together one hundred times the quantities from Table 1 (*i.e.* 200 g serine, *etc.*). The ingredients were combined and mixed until homogeneous.

[0395] Size 1 capsules were then loaded into an encapsulation tray by separating the two halves of a capsule, placing the bottom half into the tray and placing the top half in the

detachable tray. The mixture of active ingredients was poured over the capsules and smoothed flat with a scraper. The powder was compressed and the step of pouring, smoothing and compressing was repeated until no further compression was possible. Once the capsules were full, the top halves of the capsules were attached to the bottom haves by pressing the detachable tray into place. The capsules were removed from the tray and transferred into an airtight bottle.

Example 2 – Assessment of Safety, Pharmacokinetics and Pharmacodynamics of anti-HHcy compositions

[0396] In this study, safety, pharmacokinetics and pharmacodynamics of each of anti-HHcy composition of Formula 5 of Example 1 in combination with nicotinamide riboside (NR) as dietary supplements are studied. Each subject receives the following treatment: oral administration of 500 mg nicotinamide riboside (NR) once daily (QD) for 3 months without anti-HHcy composition; followed by 1 month of washout period with no administration of NR or anti-HHcy composition; and followed by oral administration of 500 mg NR QD with oral administration of anti-HHcy composition (*e.g.*, 4 capsules of the anti-HHcy composition of Formula 5) for 3 months. The primary endpoints of this study include: (1) safety profile, including serum homocysteine levels; (2) pharmacokinetics and pharmacodynamics of the anti-HHcy composition in combination with NR; and (3) biomarker levels, including NAD, HDL, LDL, triglyceride, lipoprotein a, and homocysteine.

[0397] The inclusion criteria of this study are as follows: (1) subjects are healthy male or female, and older than 18 years; (2) subjects have signed, informed consent; (3) subjects who are female of childbearing potential must have negative urine pregnancy test result and must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) during the study and one month thereafter; (4) subjects are healthy as determined by laboratory results and medical history, including serum homocysteine level lower than 12 μM; (5) subjects agree to maintain current level of physical activity throughout the study; (6) subjects agree to avoid study compounds for 30 days prior to enrollment and during the study; (7) subjects agree to avoid nutritional yeast, whey proteins, energy drinks, pomegranate, pomegranate juice, grapefruit, grapefruit juice and alcohol 7 days prior to enrollment and during study; and (8) subjects are willingness and ability to comply with scheduled visits, cell phone calls, treatment plans, laboratory tests, and completion of other study procedures as specified in the protocol.

[0398] The exclusion criteria of this study are as follows: (1) women who are pregnant, breastfeeding, or planning to became pregnant during the course of the trial; (2) subjects who re smokers; (3) subjects who have unstable medical conditions as determined by the Investigator; (4) immunocompromised individuals such as subjects that had undergone organ transplantation or subjects diagnosed with human immunodeficiency virus (HIV); (5) subjects who have clinically significant abnormal lab results at screening (*e.g.* AST, ALT or ALP > 2 x ULN, and/or bilirubin > 1 x ULN); (6) subjects who had planned surgery during the course of the trial; (7) subjects who have history of or current diagnosis of any cancer (except for successfully treated basal cell carcinoma) diagnosed less than 5 years prior to screening. Subjects with cancer in full remission more than 5 years after diagnosis were acceptable; (8) subjects who have history of blood/bleeding disorders; (9) subjects who have donated blood in the past 2 months; (10) subjects who have alcohol abuse (>2 standard alcoholic drinks per day) or drug abuse within the past 6 months; (11) subjects who have participated in a clinical research trial within 30 days prior to randomization; (12) subjects who have allergy or sensitivity to study supplement ingredients provided during the study; (13) Individuals who are cognitively impaired and/or who were unable to give informed consent; and (14) any other condition which in the Investigator's opinion may adversely affect the subject's ability to complete the study or its measures or which may pose significant risk to the subject.

[0399] Each subject is evaluated clinically before receiving the first oral dose of the anti-HHcy composition and NR and at the end of the study to determine changes in the health of the patient over the course of the study. Clinical data and samples collected include: (1) height, weight, temperature, BP, heart rate, demographics; (2) physical examination; (3) medical history, concomitant dietary supplements (if any) and concomitant medications (if any); (4) collection of blood/urine samples for homocysteine level assessments and routine laboratory tests of levels of biomarkers and analyte, including methionine, cysteine, serine, glutathione, quercetin, quercetin metabolites, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, creatinine, HDL, LDL and triglycerides; and (5) adverse events.

Example 3 – A case study of anti-HHcy treatment

[0400] This example described a case study of effects of nicotinamide riboside (NR), nicotinic acid (NA) and anti-HHcy treatments on a healthy subject. A 62-year old healthy

Asian male subject without significant medical problems developed elevated homocysteine levels while taking nicotinamide riboside, 500 mg QD. He took no prescription medications and was on low-carbohydrate, low animal-protein diet. His main source of protein was from legumes and nuts. His weight was stable at 180 – 183 lb and his height was 6 ft 0 in (BMI 24.4 – 24.8 kg/m^2). FIG. 1 summarizes the treatments received by the subject and his homocysteine levels during the course of the study.

[0401] From March 23 to June 5, the subject received NR at 300 mg and NA at 1000 mg daily. On May 30, the homocysteine level of the subject was elevated at 16 μmole/L. On June 5, the subject started to receive betaine (*i.e.*, trimethylglycine) at 5 grams per day. The homocysteine levels of the subject on June 5, June 8 and June 11 were 16 μmole/L, 14 μmole/L and 12 μmole/L, respectively. FIG. 1 shows the effect of betaine on decreasing the homocysteine level of the subject, which became elevated due to NR and NA treatment. FIG. 2

[0402] On July 6 (Day 1) of the study, the subject's baseline serum homocysteine level was normal at 12 μmole/L (Upper Limit of Normal [ULN] 12 μmole/L) and the subject was started on nicotinamide riboside (NIASUN®) 250 mg, two capsules daily by mouth (500 mg per day). The subject tolerated nicotinamide riboside very well without any subjective adverse events. On July 16 (Day 11), repeat serum homocysteine testing revealed that his serum homocysteine level was elevated at 16 μmole/L.

[0403] The subject continued taking the same daily dose of nicotinamide riboside (500 mg PO qd) and on July 18, the homocysteine level was elevated at 17 μmole/L. On July 19 (Day 14), the subject started taking daily doses of vitamin B_6 (pyridoxine HCl) 75 mg and L-serine, 2 grams in addition to NR at 500 mg/day. On July 24 (Day 19), i.e., within 6 days, his serum homocysteine level decreased by 23.5% to 13 μmole/L. Repeat serum homocysteine testing on July 30 (Day 25) revealed that his serum homocysteine level was again 13 μmole/L. On July 30 (Day 25), the dose of vitamin B_6 was increased to 150 mg/day, and the doses for L-serine and NR remained the same. On August 6, the serum homocysteine level of the subject remained at 13 μmole/L.

[0404] On August 7 (Day 33), the subject started taking vitamin B_{12} (cyanocobalamin) 0.5 mg and folic acid 0.8 mg daily, in addition to vitamin B_6 (pyridoxine HCl) 100 mg, L-serine 2 grams, and nicotinamide riboside 500 mg daily. On August 14 (Day 40), his serum homocysteine level decreased to 12 μmole/L and on August 23 (Day 49), his homocysteine further decreased to 11 μmole/L (ULN 12 μmole/L). On August 24 (Day 50), the subject stopped NR but continued with same doses of other vitamins and serine. On September 12

(Day 69), his serum homocysteine level was unchanged at 11 μmole/L. On September 13 (Day 70), all the vitamins and serine were continued as previously, except vitamin B_{12} was increased to 3 mg per day. On September 18 (Day 75), his homocysteine level decreased to 9 μmole/L. FIG. 3 shows the effect of serine and vitamin B_6 treatment on the homocysteine levels of the subject during concurrent NR treatment.

[0405] On September 27 (Day 84), the homocysteine level of the subject became 11 μmole/L. On September 28 (Day 85), the subject started taking nicotinic acid (NA) 500 mg daily, in addition to vitamin B_{12} (cyanocobalamin) 3 mg, vitamin B_9 (folic acid) 0.8 mg daily, vitamin B_6 (pyridoxine HCl) 100 mg, and L-serine 2 grams daily. On October 10 (Day 97), the homocysteine level of the subject remained at 11 μmole/L. On October 12 (Day 99), the doses were adjusted as follows: vitamin B_{12} (cyanocobalamin) 0.5 mg, folic acid 0.8 mg daily, vitamin B_6 (pyridoxine HCl) 100 mg, L-serine 4 grams, glycine 4 grams, and NA 500 mg daily. ON October 17 (Day 104), the homocysteine level of the subject remained at 11 μmole/L. On October 22 (Day 109), his homocysteine level was 8.8 μmole/L as determined using Quest Diagnostics test. All the other homocysteine level determinations until this point used Any Labs, Inc.'s test. On October 22, 1018 (Day 109), the subject started to receive NR against at 500 mg/day, in addition to vitamin B_{12} (cyanocobalamin) 0.5 mg, folic acid 0.8 mg daily, vitamin B_6 (pyridoxine HCl) 100 mg, L-serine 4 grams, glycine 4 grams, and NA 500 mg daily. On November 9 (Day 127), the homocysteine level of the subject increased to 13 μmole/L according to Any Labs' test. On November 11 (Day 129), the subject's homocysteine level was 9.9 μmole/L according to Quest Diagnostics' test. On November 28 (Day 146), the subject's homocysteine level decreased to 11 μmole/L according to Any Labs' test. FIG. 4 shows the effect of the anti-HHcy treatment including serine, vitamin B_6, vitamin B_{12} and vitamin B_9 on the subject during concurrent NR, or NR and NA treatment.

[0406] On November 28 (Day 146), the subject started receiving NR 1000 mg, and NA 2000mg, in addition to vitamin B_{12} (cyanocobalamin) 0.5 mg, vitamin B_9 (folic acid) 0.8 mg daily, vitamin B_6 (pyridoxine HCl) 100 mg, L-serine 4 grams, and glycine 4 grams daily. On November 29 (Day 147), the subject's fasting glucose level rose to 130 mg/dL. On December 7 (Day 155), the subject's fasting glucose level was 122 mg/dL. The subject then stopped taking all medication. On December 13 (Day 161), the subject's fasting glucose was 102 mg/dL.

Example 4 – Nicotinamide riboside causes elevated serum homocysteine levels

[0407] A 74-year old healthy Caucasian female subject (subject #110) had normal baseline serum homocysteine level at 10.6 µmole/L (Upper Limit of Normal [ULN] 12 µmole/L) on Day 1, and the subject was started on nicotinamide riboside 250 mg, two capsules daily by mouth (500 mg per day). The subject tolerated nicotinamide riboside very well without any subjective adverse events. On Day 21, her serum homocysteine level was elevated at 12.6 µmole/L. The subject continued taking the same daily doses of nicotinamide riboside and on Day 29, her serum homocysteine level was 17.9 µmole/L. Repeat measurement on Day 35 showed that her serum homocysteine level was12.8 µmole/L. On Day 37, her serum homocysteine level was 13.5. FIG. 5 shows her serum homocysteine levels over the course of the study.

[0408] A 61-year old healthy Caucasian male had baseline serum homocysteine level at 11.6 µmole/L (Upper Limit of Normal [ULN] 12 µmole/L) on Day 1 and the subject was started on nicotinamide riboside 250 mg, two capsules daily by mouth (500 mg per day). The subject tolerated nicotinamide riboside very well without any subjective adverse events. On Day 20, his serum homocysteine level was elevated at 12.3 µmole/L. On Day 26, his serum homocysteine level was 11.6 µmole/L.

[0409] FIGs. 6 and 7 show elevated homocysteine levels in two of the subjects caused by NR treatment.

Example 5 – Preparation of anti-hyperhomocysteinemia compositions

[0410] Two anti-hyperhomocysteinemia ("anti-HHcy") compositions were prepared containing the ingredients set out in Table 2 below:

Table 2. Anti-HHcy formulations.

Ingredient	*Formulations— Quantity/dose (mg)*	
	1	*2*
Vitamin B_1 (thiamine)	1.2	1.2
Vitamin B_2 (riboflavin)	1.3	1.3
Vitamin B_3 (Nicotinic Acid)	50	16
Vitamin B_6 (pyridoxine)	25	50
Vitamin B_9 (folate)	0.8	1
Vitamin B_{12} (cobalamin)	0.5	0.5
Quercetin	100	0
N-acetyl cysteine	0	1500
Magnesium bisglycinate (14.1% Mg)	0	300
Serine	1700	1200

Blueberry extract (organic)	5	5
Ginger extract (organic)	5	5
Cranberry extract (organic)	5	5
Turmeric extract with black pepper extract (organic)	5	5
Strawberry whole fruit powder (organic)	5	5
Pomegranate juice powder (organic)	5	5
Grape—Concord juice powder (organic)	5	5

[0411] The compositions were made according to the following method. A batch of a composition set out in Table 2 was produced by weighing out and mixing together one hundred times the quantities from Table 2. The ingredients were combined and mixed until homogeneous.

[0412] Size 0 or Size 1 capsules were then loaded into an encapsulation tray by separating the two halves of a capsule, placing the bottom half into the tray and placing the top half in the detachable tray. The mixture of active ingredients was poured over the capsules and smoothed flat with a scraper. The powder was compressed and the step of pouring, smoothing and compressing was repeated until no further compression was possible. Once the capsules were full, the top halves of the capsules were attached to the bottom haves by pressing the detachable tray into place. The capsules were removed from the tray and transferred into an airtight bottle.

[0413] The safety, pharmacokinetics and pharmacodynamics and efficacy of the anti-HHcy formulations as dietary supplements are evaluated in patients.

CLAIMS

What is claimed is:

1. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}.
2. The composition of claim 1, wherein the composition comprises about 90 wt% to about 99 wt% serine, based on the total weight of active agents (a)-(d) in the composition.
3. The composition of claim 1 or 2, wherein the composition comprises about 1 wt% to about 7.5 wt% vitamin B_6, based on the total weight of active agents (a)-(d) in the composition.
4. The composition of any one of claims 1-3, wherein the composition comprises about 0.01 wt% to about 0.10 wt% vitamin B_9, based on the total weight of active agents (a)-(d) in the composition.
5. The composition of any one of claims 1-4, wherein the composition comprises about 0.01 wt% to about 0.05 wt% vitamin B_{12}, based on the total weight of active agents (a)-(d) in the composition.
6. The composition of any one of claims 1-5, further comprising vitamin B_1, a magnesium-containing compound, and *N*-acetyl cysteine.
7. The composition of any one of claims 1-5, further comprising vitamin B_1 and quercetin.
8. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}; (e) quercetin; and (f) fisetin.
9. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2.
10. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) *S*-adenosylmethionine (SAM).
11. The composition of any one of claims 1-10, further comprising: (j) trimethylglycine.
12. A composition comprising the active agents: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; (f) *N*-acetylcysteine; and (g) trimethylglycine.
13. The composition of any one of claims 1-12, further comprising: (k) a nicotinamide adenine dinucleotide pathway agent (NPA) selected from the group consisting of nicotinamide riboside (NR), nicotinic acid (NA), nicotinic acid riboside (NAR), nicotinamide mononucleotide (NMN), nicotinic acid adenine dinucleotide (NAAD), nicotinamide adenine dinucleotide (NAD+), and mixtures thereof.

14. The composition of claim 13, wherein the NPA is NR, NA, or NR and NA.
15. The composition of any one of claims 1-14, wherein vitamin B_6 comprises pyridoxal 5'-phosphate.
16. The composition of any one of claims 1-15, wherein vitamin B_9 comprises folic acid or tetrahydrofolate.
17. The composition of any one of claims 1-16, further comprising vitamin D_3, fruit extracts, plant extracts, vegetable extracts, dimethylglycine, monomethylglycine, glycine, choline, and/or phosphatidylcholine.
18. A pharmaceutical composition comprising a therapeutically effective amount of the composition of any one of claims 1-17, and a pharmaceutically acceptable carrier, excipient, binder, or diluent.
19. The pharmaceutical composition of claim 18, formulated for oral, topical, intramuscular, intravenous, intrabuccal or sublingual administration to a subject.
20. The pharmaceutical composition of claim 18 or 19, in the form of a tablet, a capsule, an extended-release tablet, a liquid, a powder, granules, a dragee or a lozenge.
21. The pharmaceutical composition of claim 18 or 19, in unit dosage form, comprising:

1) (a) about 2000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12};

2) (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 0.075 mg vitamin B_{12}; (e) about 75 mg quercetin; and (f) about 300 mg fisetin;

3) (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 0.075 mg vitamin B_{12}; (e) about 75 mg quercetin; (f) about 300 mg fisetin; and (g) about 75 mg vitamin B_2;

4) (a) about 2000 mg serine; (b) about 75 mg vitamin B_6; (c) about 0.4 mg vitamin B_9; (d) about 0.075 mg vitamin B_{12}; (e) about 75 mg quercetin; (f) about 300 mg fisetin; (g) about 75 mg vitamin B_2; (h) about 2000 mg *N*-acetylcysteine; and (i) about 2000 mg SAM;

5) (a) about 1700 mg serine; (b) about 25 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; (e) about 100 mg quercetin; (g) about 1.3 mg vitamin B_2; (k) about 50 mg NA; and about 1.2 mg vitamin B_1;

6) (a) about 1200 mg serine; (b) about 50 mg vitamin B_6; (c) about 1 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; (g) about 1.3 mg vitamin B_2; (h) about 1500 mg *N*-acetylcysteine; (k) about 16 mg NA; about 1.2 mg vitamin B_1, and about 300 mg magnesium bisglycinate;

7) (a) about 2000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 3 mg vitamin B_{12}; or

8) (a) about 4000 mg serine; (b) about 100 mg vitamin B_6; (c) about 0.8 mg vitamin B_9; (d) about 0.5 mg vitamin B_{12}; and about 4000 mg glycine.

22. A food product or dietary supplement comprising the composition of any one of claims 1-17.

23. A method of reducing the level of total plasma homocysteine in a subject or treating or preventing a disease or condition characterized by high levels of total plasma homocysteine in a subject, comprising administering to the subject a therapeutically effective amount of the composition of any one of claims 1-17, the pharmaceutical composition of any one of claims 18-21 or the food product or dietary supplement of claim 22.

24. The method of claim 23, wherein the subject has a high initial level of total plasma homocysteine caused by administration of an NPA to the subject.

25. The method of claim 23 or 24, wherein the initial level of total plasma homocysteine in the subject is at least 12 μmol/L.

26. The method of any one of claims 23-25, wherein the disease or condition is selected from the group consisting of hyperhomocysteinemia, homocystinuria, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, thrombosis, stroke, atherothrombotic coronary artery disease (CAD), myocardial infarction (MI), Alzheimer's disease, cognitive impairment, dementia, diabetic retinopathy, intraocular lens dislocation, schizophrenia and osteoporosis.

27. A method of treating or preventing hyperhomocysteinemia in a subject, comprising administering to the subject a therapeutically effective amount of the composition of any one of claims 1-17, the pharmaceutical composition of any one of claims 18-21 or the food product or dietary supplement of claim 22.

28. A kit comprising two or more components, wherein:

1) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12}; provided that each of active agents (a)-(d) are contained within the kit;

2) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin, provided that each of active agents (a)-(f) are contained within the kit;

3) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2, provided that each of active agents (a)-(g) are contained within the kit;

4) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2, provided that each of active agents (a)-(d) and (g) are contained within the kit;

5) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM, provided that each of active agents (a)-(i) are contained within the kit;

6) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) vitamin B_2; (f) *N*-acetylcysteine; and (g) trimethylglycine, provided that each of active agents (a)-(g) are contained within the kit;

7) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA; and vitamin B_1;

8) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA; vitamin B_1, and a magnesium-containing compound; or

9) each component comprises one or more active agents independently selected from: (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and glycine.

29. A method of reducing the level of total plasma homocysteine in a subject, comprising co-administering to the subject a therapeutically effective amount of the active agents:

1) (a) serine; and (b) vitamin B_6;

2) (a) serine; (b) vitamin B_6; (c) vitamin B_9; and (d) vitamin B_{12};

3) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; and (f) fisetin;

4) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; and (g) vitamin B_2;

5) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and (g) vitamin B_2;

6) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (f) fisetin; (g) vitamin B_2; (h) *N*-acetylcysteine; and (i) SAM;

7) (a) serine; (b) vitamin B_6; (c) vitamin B9; (d) vitamin B12; (e) vitamin B2; and (f) *N*-acetylcysteine;

8) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (e) quercetin; (g) vitamin B_2; (k) an NPA; and vitamin B_1;

9) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; (g) vitamin B_2; (h) *N*-acetylcysteine; (k) an NPA; vitamin B_1, and a magnesium-containing compound; or

10) (a) serine; (b) vitamin B_6; (c) vitamin B_9; (d) vitamin B_{12}; and glycine.

30. A capsule comprising the composition of any one of claims 1-17.

Date	Days	NR (mg)	NA (mg)	Hcy (µM AnyLabs)	Hcy (µM Quest)	Betain (g)	Serine (g)	B6 (mg)	B12 (µg)	Folic acid (mg)	Glycine (g)	Comments
3/23	-74	300	1000									*last dose of NR+NA*
5/5	-31	300	1000									*Continuous daily NR+NA dosing*
5/12	-24	300	1000									*Continuous daily NR+NA dosing*
5/19	-17	300	1000									*Continuous daily NR+NA dosing*
5/26	-10	300	1000									*Continuous daily NR+NA dosing*
5/30	-6	300	1000	16								*Continuous daily NR+NA dosing; first Hcy measurement*
6/5	1	300	1000	16		5						*Continuous daily NR+NA+betaine dosing*
6/8	3	300	1000	14		5						*Continuous daily NR+NA+betaine dosing*
6/11	6	300	1000	12		5						*Last doses NR+NA+betaine*
												washout period
6/20	15			13								
6/26	21			14								*Started low methionine diet (no egg whites)*
7/6	-1			12								*Baseline Hcy, normalized on low methionine diet; next day, started continuous daily NR dosing*
7/7	1	500										*Continuous daily NR dosing + low methionine diet*
7/16	9	500		16								*Continuous daily NR dosing + low methionine diet; rapidly rising Hcy on NR alone*
7/18	11	500		17								*Continuous daily NR dosing + low methionine diet; confirmed rising Hcy on NR*
7/19	12	500					2	75				*Started serine/B6; continuous daily NR dosing + low methionine diet*

FIG. 1

Date	Days	NR (mg)	NA (mg)	Hcy (µM AnyLabs)	Hcy (µM Quest)	Betain (g)	Serine (g)	B6 (mg)	B12 (µg)	Folic acid (mg)	Glycine (g)	Comments
7/24	17	500		13			2	75				Dropping Hcy on daily serine/B6; continuous daily NR dosing + low methionine diet
7/30	23	500		13			2	150				Doubled B6 dose, kept serine dose same; continuous daily NR dosing + low methionine diet
8/6	30	500		13			2	150				Continuous daily NR dosing + low methionine diet
8/7	31	500					2	100	500	0.8		Started antihtcy combo; continuous daily NR dosing + low methionine diet
8/14	38	500		12			2	100	500	0.8		
8/24	48	500		11			2	100	500	0.8		Last dose of NR; continue antihtcy combo
							2	100	500	0.8		Antihtcy combo alone daily
9/12	-16			11			2	100	500	0.8		
9/13							2	100	3000	0.8		Raised B12 to 3000 ug/day
9/18	-10			9			2	100	3000	0.8		Continue B12 at 3000 ug/day
9/27	-1			11			2	100	3000	0.8		Continue B12 at 3000 ug/day
9/28	1	500					2	100	3000	0.8		Continue B12 at 3000 ug/day
10/10	12	500		11			2	100	3000	0.8		Continue B12 at 3000 ug/day
10/12		500					4	100	500	0.8	4	Lower B12 to 500 ug/day; double serine to 4g/d; add glycine 4g/d
10/17	19	500		11			4	100	500	0.8	4	Lower B12 to 500 ug/day; double serine to 4g/d; add glycine 4g/d
10/22	24	500			8.8		4	100	500	0.8	4	
10/22	24	500	500				4	100	500	0.8	4	Evening, start NA; B12 @ 500 ug/day; serine 4g/d; glycine 4g/d
11/8		500	500		9.9		4	100	500	0.8	4	Continue daily NA+NR; B12 @ 500 ug/day; serine 4g/d; glycine 4g/d
11/28	61	500	500	11			4	100	500	0.8	4	Visit off

FIG. 1 (continued)

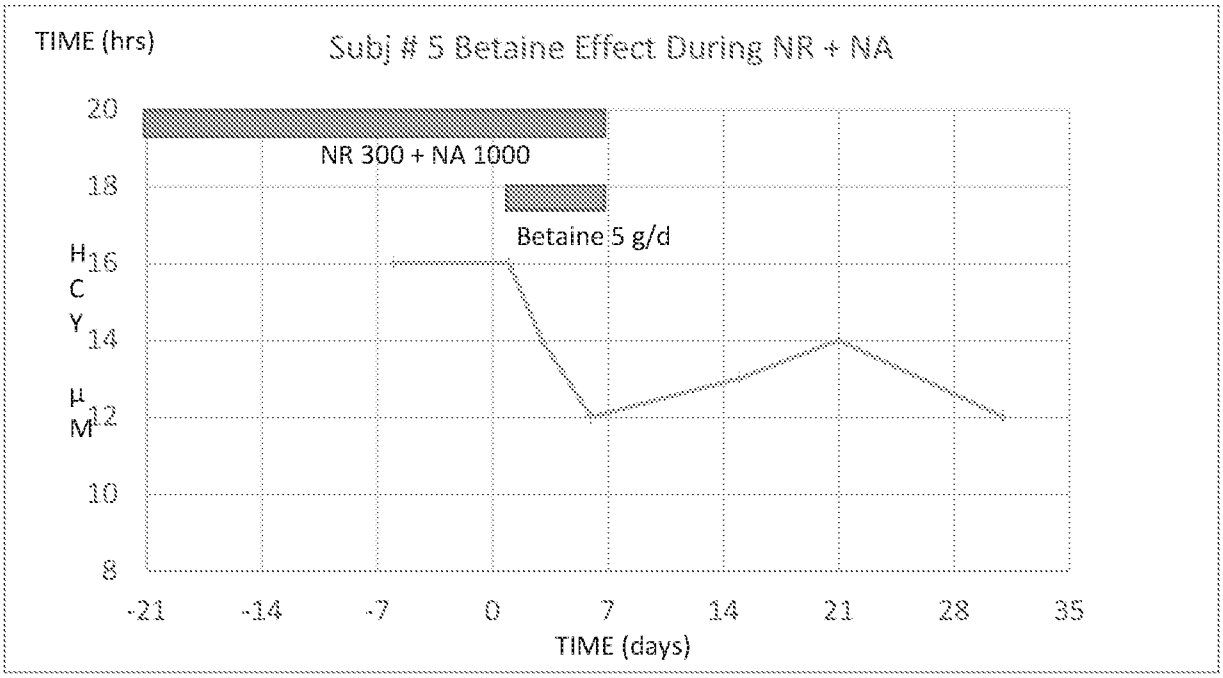

TIME (hrs)
Subj # 5 Betaine Effect During NR + NA
NR 300 + NA 1000
Betaine 5 g/d
HCY µM
20
18
16
14
12
10
8
-21
-14
-7
0
7
14
21
28
35
TIME (days)

FIG. 2

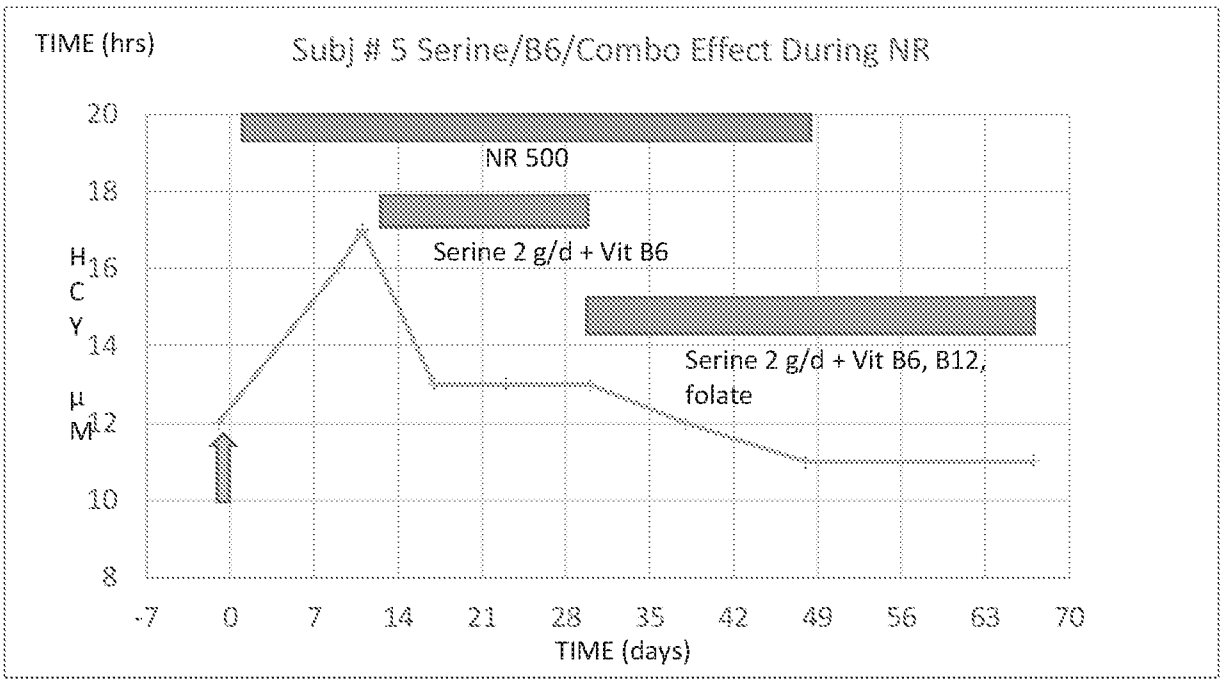

TIME (hrs)
Subj # 5 Serine/B6/Combo Effect During NR
NR 500
Serine 2 g/d + Vit B6
Serine 2 g/d + Vit B6, B12, folate
HCY µM
20
18
16
14
12
10
8
-7
0
7
14
21
28
35
42
49
56
63
70
TIME (days)

FIG. 3

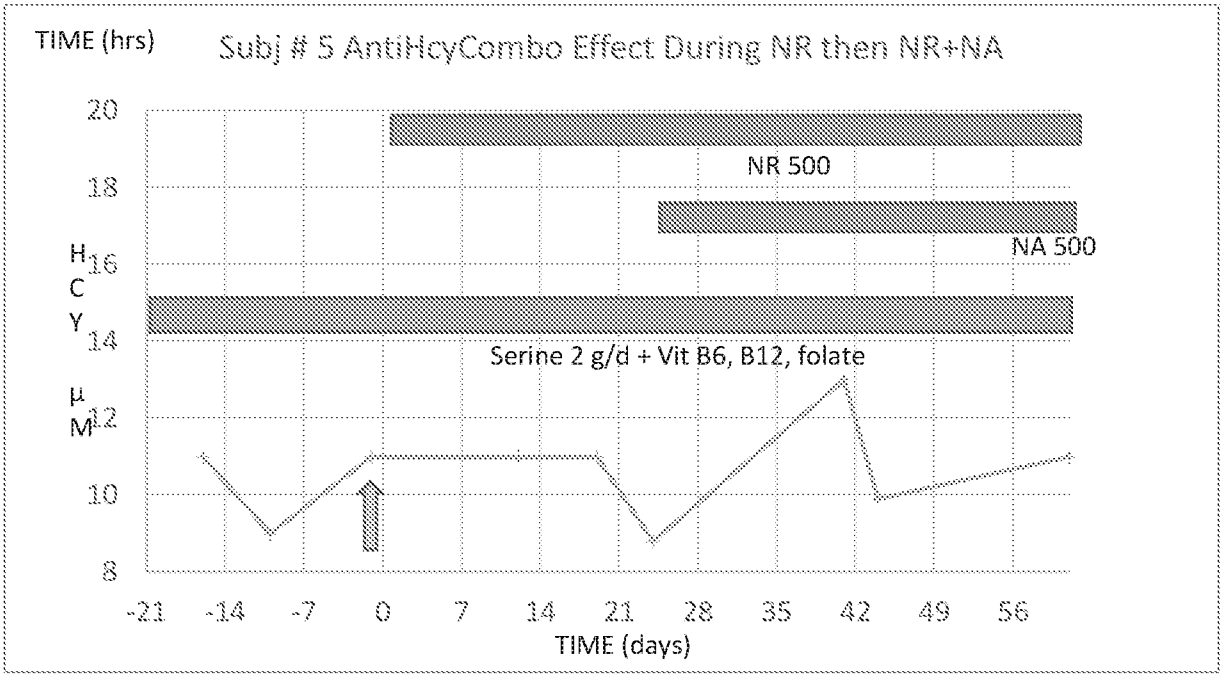

TIME (hrs)
Subj # 5 AntiHcyCombo Effect During NR then NR+NA
NR 500
NA 500
Serine 2 g/d + Vit B6, B12, folate
Hcy µM
20
18
16
14
12
10
8
-21
-14
-7
0
7
14
21
28
35
42
49
56
TIME (days)

FIG. 4

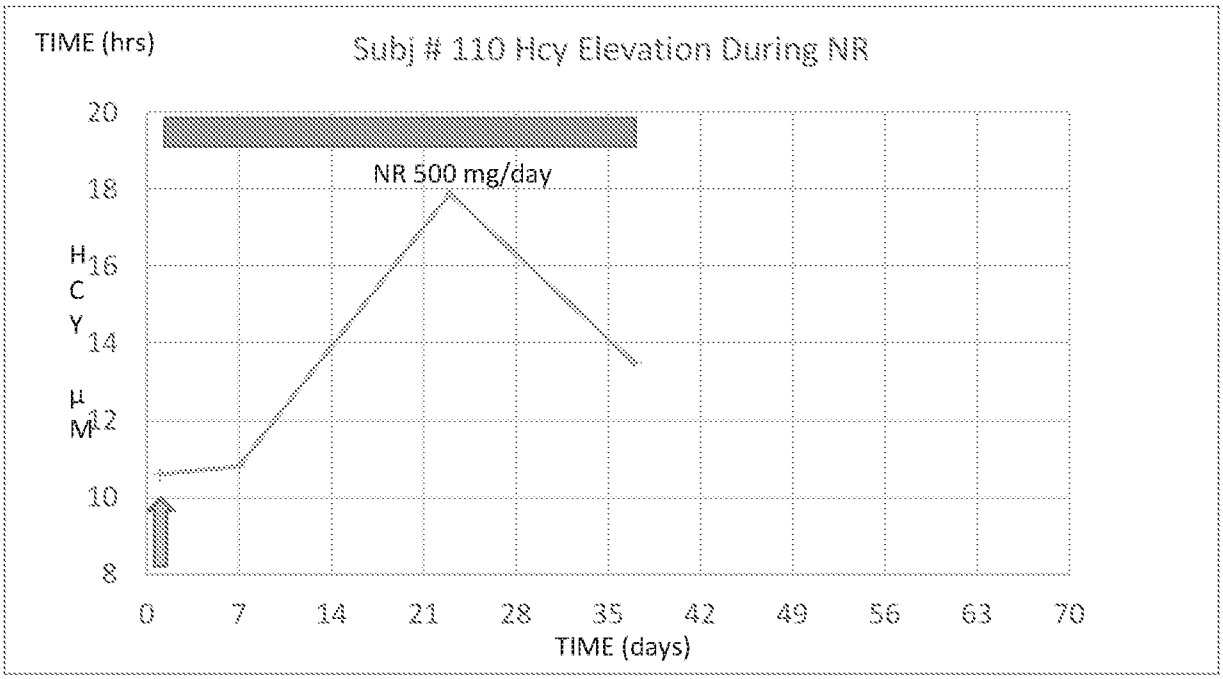

TIME (hrs)
Subj # 110 Hcy Elevation During NR
NR 500 mg/day
Hcy µM
20
18
16
14
12
10
8
0
7
14
21
28
35
42
49
56
63
70
TIME (days)

FIG. 5

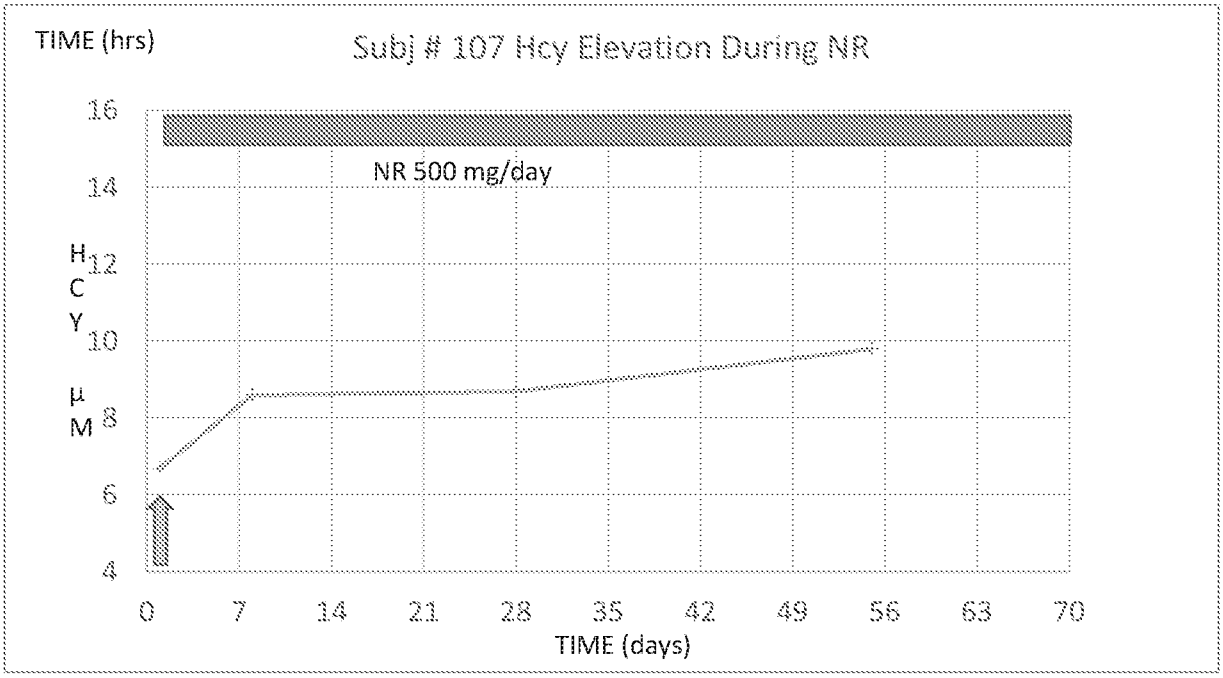

TIME (hrs)
Subj # 107 Hcy Elevation During NR
NR 500 mg/day
Hcy µM
16
14
12
10
8
6
4
0
7
14
21
28
35
42
49
56
63
70
TIME (days)

FIG. 6

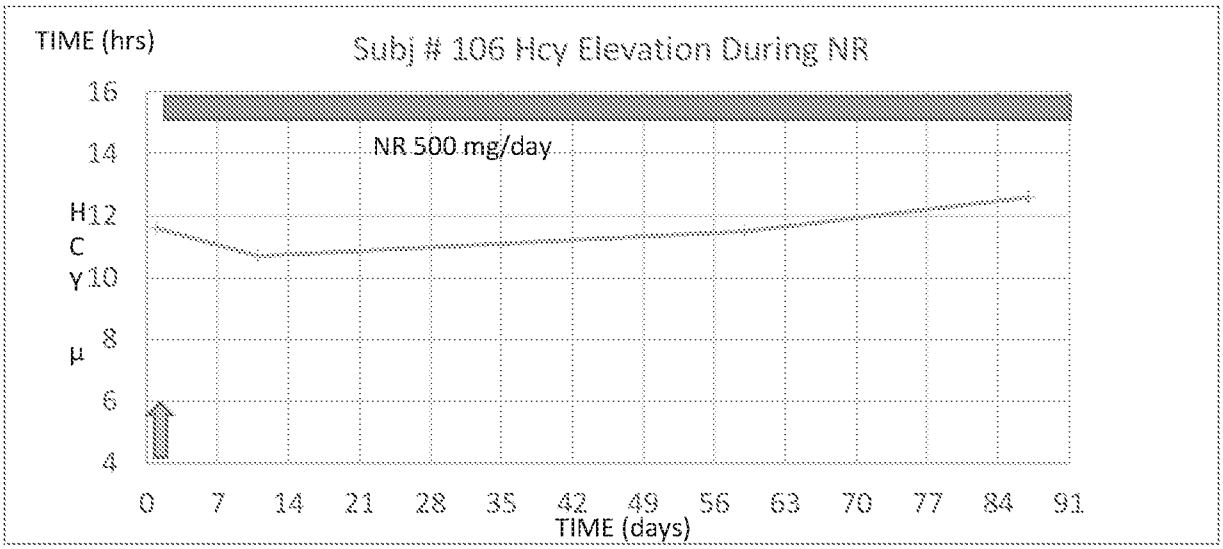

TIME (hrs)
Subj # 106 Hcy Elevation During NR
NR 500 mg/day
Hcy µ
16
14
12
10
8
6
4
0
7
14
21
28
35
42
49
56
63
70
77
84
91
TIME (days)

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/058925

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/198 A61K31/4415 A61K31/455 A61K31/519 A61K31/714
A61P9/00 A61P13/00
ADD.
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)
A61K A61P

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)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2019/118519 A1 (FILTRICINE INC [US]) 20 June 2019 (2019-06-20) example 16 -----	1,13,14, 16, 18-20,22
Y	SUNDER-PLASSMANN G ET AL: "THERAPEUTIC POTENTIAL OF TOTAL HOMOCYSTEINE-LOWERING DRUGS ON CARDIOVASCULAR DISEASE", EXPERT OPINION ON INVESTIGATIONAL DRUGS, INFORMA HEALTHCARE, UK, vol. 9, no. 11, 1 November 2000 (2000-11-01), pages 2637-2651, XP001069655, ISSN: 1354-3784, DOI: 10.1517/13543784.9.11.2637 the whole document abstract ----- -/--	1-30

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2020	13/02/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Economou, Dimitrios

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/058925

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/30352 A1 (CARY PHARMACEUTICALS INC [US]) 3 May 2001 (2001-05-03)	1-30
Y	the whole document page 1, line 3 - line 5 page 3, line 11 - line 15 page 4, line 3 - line 21 page 7, line 17 - page 12, line 21 page 13, line 10 - line 15 page 15, line 1 - line 8 examples 1-7	1-30

Y	TAPAN K. BASU ET AL: "Niacin (nicotinic acid) in non-physiological doses causes hyperhomocysteineaemia in Sprague-Dawley rats", BRITISH JOURNAL OF NUTRITION, vol. 87, no. 2, 1 February 2002 (2002-02-01), pages 115-119, XP55664644, UK ISSN: 0007-1145, DOI: 10.1079/BJN2001486 abstract	1-30

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/058925

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019118519 A1	20-06-2019	NONE	
WO 0130352 A1	03-05-2001	AU 1243101 A	08-05-2001
		WO 0130352 A1	03-05-2001