Immunological Effects of Metabolites

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] The present patent application claims benefit of priority to U.S. Provisional Patent Application No. 63/081,205, filed September 21, 2020, which is incorporated by reference for all purposes.

BACKGROUND OF THE DISCLOSURE

[0002] Prolonged Fasting has consistently been shown to induce a broad range of functional biochemical benefits in both model organisms and human trials including anti-cancer, anti-inflammatory, cardioprotective, anti-oxidant, stem and immune cell regeneration, and longevity enhancing effects. Despite the wealth of documented benefits of prolonged fasting, the full scope of the biochemical effects of fasting as well as the precise mediators and mechanisms behind these effects remain largely unstudied in humans.

SUMMARY OF THE DISCLOSURE

[0002a] In an aspect of the present disclosure, there is provided a composition comprising all four of or one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject.

[0002b] In another aspect, there is provided a composition comprising one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to induce an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject.

[0002c] In another aspect, there is provided a composition comprising one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in an amount sufficient to induce an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject.

[0002d] In another aspect, there is provided a composition comprising one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in an amount sufficient to elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject.

[0002e] In another aspect, there is provided a use of one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in the manufacture of a medicament for inducing an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject.

[0002f] In another aspect, there is provided a use of the composition as defined above in the manufacture of a medicament for extending lifespan, healthspan, healthy aging, altering biochemical pathways associated with the aging process or the treatment or prevention of age related diseases including but not limited to frailty, sarcopenia, dementia, Alzheimers disease, arthritis, and cancer in a subject.

[0002g] In another aspect, there is provided a use of the composition as defined above in the manufacture of a medicament for increasing plasma cholesterol efflux ability in a subject in need thereof.

[0003] In one ~~aspect~~example, the disclosure provides a composition comprising one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to induce an anti-inflammatory, anti-oxidant, and/or immuno-modulatory effect in a subject. In one ~~aspect~~example, the disclosure provides a composition comprising one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject. In some ~~embodiments~~examples, the composition comprises two of the metabolites (e.g., spermidine and 1-MNA, spermidine and PEA, spermidine and OEA, 1-MNA and PEA, 1-MNA and OEA, or PEA and OEA). In some ~~embodiments~~examples, the composition comprises three of the metabolites (e.g., 1) sperimidine, 1-MNA, and PEA, 2) spermidine, 1-MNA, and OEA, 3) spermidine, PEA, and OEA, or 4) 1-MNA, PEA, and OEA). In some ~~embodiments~~examples, the composition comprises all four of the metabolites.

[0004] In one ~~aspect~~example, the disclosure provides a composition comprising one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in an amount sufficient to induce an anti-inflammatory, anti-oxidant, and/or immuno-modulatory effect in a subject. In one ~~aspect~~example, the disclosure provides a composition comprising one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in an amount sufficient to elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject. In some examples~~embodiments~~, the composition comprises two of the metabolites (e.g., spermidine or a precursor thereofa nd 1-MNA or a precursor thereof, spermidine or a precursor thereof and PEA or a precursor thereof, spermidine or a precursor thereof and OEA or a precursor thereof, 1-MNA or a precursor thereof and PEA or a precursor thereof, 1-MNA or a precursor thereof and OEA or a precursor thereof, or PEA or a precursor thereof and OEA or a precursor thereof). In some examples~~embodiments~~, the composition comprises three of the metabolites (e.g., 1) sperimidine or a precursor thereof, 1-MNA or a precursor thereof, and PEA or a precursor thereof, 2) spermidine or a precursor thereof, 1-MNA or a precursor thereof, and OEA or a precursor thereof, 3) spermidine or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof, or 4) 1-MNA or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof). In some examples~~embodiments~~, the composition comprises all four of the metabolites.

[0005] In some ~~embodiments~~examples, the composition comprises a precurser of 1-MNA selected from the group consisting of nictotinamide, niacinamide, and nicotinamide riboside. In some examples~~embodiments~~, the composition comprises a precurser of PEA is palmitic acid. In some examples~~embodiments~~, the composition comprises a precurser of OEA is oleic acid.

[0006] In some ~~embodiments of this aspect~~examples, the ratio of two, three, or four of the metabolites is about 10000:1000:1:1000 of spermidine:1 MNA:PEA:OEA (w:w:w:w). In some examples~~embodiments~~, the composition comprises 5-15 mg spermidine, 400-1200 mg PEA, 300-600 mg OEA, and 500-1000 mg nicotinamide.

[0007] In some examples~~embodiments,~~ the composition is formulated as a dietary supplement. In certain examples~~embodiments~~, the composition is formulated for oral administration. For example, the composition can be formulated as a pill, a tablet, a powder, a solid food coating gummy, sublingual, spray, candy, nutrition bar, energy shot, beverage, or a syrup. In some examples~~embodiments~~, the composition is formulated for intravenous administration, transdermal administration, sublingual administration, or topical administration.

[0008] In another ~~aspect~~example, the disclosure features a method for inducing an anti-inflammatory, anti-oxidant, and/or immuno-modulatory effect in a subject, comprising administering to the subject one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to induce the anti-inflammatory, anti-oxidant, and/or immuno-modulatory effect in the subject. In another ~~aspect~~example, the disclosure features a method for elevating the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject, comprising administering to the subject one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to induce elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject.

[0009] In some ~~embodiments~~examples, the method decreases the amount of tumor necrosis factor alpha (TNF-α) secreted by macrophages in the subject relative to the amount of TNF-α secreted by macrophages in the subject prior to the subject receiving the metabolite. In certain examples~~embodiments~~, the amount of TNF-α secreted by macrophages after the subject receiving the metabolite is less than 90% (*e.g.*, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 10%, or less than 5%) of the amount of TNF-α secreted by macrophages prior to the subject receiving the metabolite.

[0010] In some ~~embodiments of this aspect~~examples, the method increases total antioxidant capacity of the subject's plasma relative to the total antioxidant capacity of the subject's plasma prior to the subject receiving the metabolite. In some examples~~embodiments~~, the method increases cholesterol

efflux of the subject relative to the cholesterol efflux of the subject prior to the subject receiving the metabolite.

[0011] In some examples~~embodiments~~, the method decreases the amount of reactive oxygen species (ROS) produced by macrophages in the subject relative to the amount of ROS produced by macrophages in the subject prior to the subject receiving the metabolite. In some examples~~embodiments~~, the method decreases cyclooxygenase (COX) activity in macrophages of the subject relative to the COX activity in macrophages of the subject prior to the subject receiving the metabolite. In some examples~~embodiments~~, the method modulates the phenotype of macrophages away from a pro-inflammatory and toward a pro-resolving phenotype (measured as decreased nitric oxide synthase (NOS) activity in macrophages of the subject relative to the NOS activity in macrophages of the subject prior to the subject receiving the metabolite).

[0012] In some examples~~embodiments~~, the method decreases macrophage M1 polarization and/or increases M2 polarization (measured as decreased nitric oxide synthase (NOS) activity in macrophages of the subject relative to the NOS activity in macrophages of the subject prior to the subject receiving the metabolite and/or measured as increased arginase activity in the macrophages of the subject relative to the arginase activity in the macrophages of the subject prior to the subject receiving the metabolite) in the subject relative to the macrophage polarization in the subject prior to the subject receiving the metabolite.

[0013] In some examples~~embodiments~~, the method increases arginase activity in the subject relative to the arginase activity in the subject prior to the subject receiving the metabolite.

[0014] In some examples~~embodiments~~, the method increases macrophage M2 polarization in the subject relative to the macrophage M2 polarization in the subject prior to the subject receiving the metabolite.

[0015] In other examples~~embodiments~~, the method extends longevity and/or improves cognitive and/or physical performance of the subject.

[0016] In some examples~~embodiments~~, the subject is on a fasting diet. In certain examples~~embodiments~~, when the subject is on a fasting diet (e.g., fasting for more than 12 hours (e.g., between 12 and 15 hours, between 15 and 20 hours, between 20 and 25 hours, between 25 and 30 hours, between 30 and 36 hours, or more than 36 hours)), one or more of metabolies selected from the group consisting of pentose acid, indolepropionate, gentisate, piperine, and hydrocinnamate is substantially depleted in the subject.

[0017] In some examples~~embodiments~~, the subject has an inflammatory disorder. In some examples~~embodiments~~, the inflammatory disorder is sected from the group consisting of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ANCA-associated vasculitis, antiphospholipid antibody syndrome, autoimmune hemolytic anemia, chronic inflammatory demyelinating neuropathy, graft-vs-host disease (GVHD), dermatomyositis, Goodpasture's Syndrome, organ system-targeted type II hypersensitivity syndromes, Guillain Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), dermatomyositis, Felty's syndrome, autoimmune thyroid disease, ulcerative colitis, autoimmune liver disease, idiopathic thrombocytopenia purpura, Myasthenia Gravis, neuromyelitis optica, pemphigus, Sjogren's Syndrome, autoimmune cytopenias, synovitis, dermatomyositis, systemic vasculitis, glomerulitis, irritable bowel syndrome (IBS), and vasculitis. In some examples~~embodiments~~, the subject has a metabolic disorder. In some examples~~embodiments~~ the metabolic disorder is selected from the group consisting of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetes, and metabolic syndrome. In certain examples~~embodiments~~, the subject is overweight.

[0018] In certain examples~~embodiments~~, the metabolite is administered to the subject one or more times daily. In certain examples~~embodiments~~, the metabolite is administered to the subject during food intake. In certain examples~~embodiments~~, the metabolite is administered to the subject after at least 5 hours (e.g., between 5 and 10 hours, between 10 and 15 hours, between 15 and 20 hours, between 20 and 25 hours, between 25 and 30 hours, between 30 and 36 hours, or more than 36 hours) of fasting.

[0019] In some examples~~embodiments~~, the method comprises administering two of the metabolites (e.g., spermidine or a precursor thereof and 1-MNA or a precursor thereof, spermidine or a precursor thereof and PEA or a precursor thereof, spermidine or a precursor thereof and OEA or a precursor thereof, 1-MNA or a precursor thereof and PEA or a precursor thereof, 1-MNA or a precursor thereof and OEA or a precursor thereof, or PEA or a precursor thereof and OEA or a precursor thereof). In some examples~~embodiments~~, the method comprises administering three of the metabolites (e.g., 1) sperimidine or a precursor thereof, 1-MNA or a precursor thereof, and PEA or a precursor thereof, 2) spermidine or a precursor thereof, 1-MNA or a precursor thereof, and OEA or a precursor thereof, 3) spermidine or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof, or 4) 1-MNA or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof). In certain examples~~embodiments~~, the method comprises administering all four of the metabolites or a precursor thereof. In particular examples~~embodiments~~ of the method, the subject is a human.

[0020] Also provided is a method extending lifespan, healthspan, healthy aging, altering biochemical pathways associated with the aging process or the treatment or prevention of age related diseases (including but not limited to frailty, sarcopenia, dementia, Alzheimers disease, cognitive decline, cancer, or arthritis) in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition as described above or elsewhere herein. In some examples~~embodiments~~, the subject is a human.

[0021] Also provided is a method of increasing plasma cholesterol efflux ability in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition as described above or elsewhere herein. In some examples~~embodiments~~, the subject is at risk for or has heart disease, stroke, arteral plaque formation or other cardiovascular disease risk factors. In some examples~~embodiments~~, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1: Timeline of 3-day Human Fasting Trial: 20 Participants underwent a 3-day clinical trial consisting of 4 study visits in 4 distinct nutritional states to allow for the sensitive assessment of the effects of 36hrs of fasting versus an overnight fasted state and the carryover effects of fasting onto the next eating day. On Day 1, participants provided an overnight fasting Baseline blood sample (A) then went about their normal routine and habitual diet while tracking their food intake until 6PM where participants ate their last meal. A 2hr postprandial Fed blood sample was taken at 8PM on Day 1 (B) after which, participants began their 36hr fast while being monitored for compliance via glucose monitors. At 8AM on Day 3, participants provided a 36hr Fasted blood draw (C) and then were given a copy of their diet record from Day 1 and instructed to eat the identical diet as they recorded on Day 1. At 6PM on Day 3, participants ate their last meal and received a final 2hr postprandial Refed blood draw (D) concluding the study.

[0023] FIG. 2: CONSORT Diagram Indicating the Structure of the 36 hr Fasting Trial: 72 interested individuals were screened for eligibility and 52 were excluded based on inclusion and exclusion criteria (Supplemental Information). A final 20 participants (10 men and 10 women) were enrolled in the study and underwent the 3-day trial consisting of the intervention of 36hrs of fasting. There were no adverse events, dropouts, or participants lost to follow-up. All 20 participants completed the trial successfully with no protocol violations and were all included in experimental analysis.

WHAT IS CLAIMED IS:

1. A composition comprising all four of or one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject.

2. A composition comprising one or more of metabolites selected from the group consisting of spermidine, 1-methylnicotinamide (1-MNA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) in an amount sufficient to induce an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject.

3. The composition of claim 1 or 2, comprising two of the metabolites.

4. The composition of claim 3, wherein the two metabolites are spermidine and 1-MNA, spermidine and PEA, spermidine and OEA, 1-MNA and PEA, 1-MNA and OEA, or PEA and OEA.

5. The composition of claim 1 or 2, wherein the compostion comprises three of the metabolites.

6. The composition of claim 5, wherein the three metabolites are 1) sperimidine, 1-MNA, and PEA, 2) spermidine, 1-MNA, and OEA, 3) spermidine, PEA, and OEA, or 4) 1-MNA, PEA, and OEA.

7. The composition of claim 1 or 2, wherein the compostion comprises all four of the metabolites.

8. A composition comprising one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in an amount sufficient to induce an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject.

9. A composition comprising one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in an amount sufficient to elevate the circulating levels of the metabolites to a same level or higher than the circulating levels of the metabolites that are achieved through prolonged (e.g., at least 20 hours, e.g., 20-72 hours) fasting in a subject.

10. The composition of claim 8 or 9, comprising two of the metabolites or a precursor thereof.

11. The composition of claim 10, wherein the two metabolites are spermidine or a precursor thereof and 1-MNA or a precursor thereof, spermidine or a precursor thereof and PEA or a precursor thereof, spermidine or a precursor thereof and OEA or a precursor thereof, 1-MNA or a precursor thereof and PEA or a precursor thereof, 1-MNA or a precursor thereof and OEA or a precursor thereof, or PEA or a precursor thereof and OEA or a precursor thereof.

12. The composition of claim 8 or 9, wherein the compostion comprises three of the metabolites or a precursor thereof.

13. The composition of claim 12, wherein the three metabolites are 1) sperimidine or a precursor thereof, 1-MNA or a precursor thereof, and PEA or a precursor thereof, 2) spermidine or a precursor thereof or a precursor thereof, 1-MNA or a precursor thereof, and OEA or a precursor thereof, 3) spermidine or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof, or 4) 1-MNA or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof.

14. The composition of claim 8 or 9, wherein the compostion comprises all four of the metabolites or a precursor thereof.

15. The composition of any one of claims 1-14, wherein the composition comprises a precurser of 1-MNA selected from the group consisting of nictotinamide, niacinamide, and nicotinamide riboside.

16. The composition of any one of claims 1-14, wherein the precurser of PEA is palmitic acid.

17. The composition of any one of claims 1-14, wherein the precurser of OEA is oleic acid.

18. The composition of any one of claims 1 to 14, wherein the ratio of two, three, or four of the metabolites is about 10000:1000:1:1000 of spermidine:1-MNA:PEA:OEA (w:w:w:w).

19. The composition of any one of claims 1 to 14, wherein the composition comprises 5-15 mg spermidine, 400-1200 mg PEA, 300-600 mg OEA, and 500-1000 mg nicotinamide.

20. The composition of any one of claims 1 to 18, wherein the composition is formulated as a dietary supplement.

21. The composition of any one of claims 1 to 20, wherein the composition is formulated for oral administration.

22. The composition of claim 21, wherein the composition is formulated as a pill, a tablet, gummy, sublingual, spray, candy, nutrition bar, energy shot, beverage, or a syrup.

23. The composition of any one of claims 1 to 20, wherein the composition is formulated for intravenous administration, transdermal administration or topical administration.

24. ~~A method for inducing an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject, comprising administering to the subject~~ A use of one or more of metabolites selected from the group consisting of spermidine or a precursor thereof, 1-methylnicotinamide (1-MNA) or a precursor thereof, palmitoylethanolamide (PEA) or a precursor thereof, and oleoylethanolamide (OEA) or a precursor thereof in the manufacture of a medicament for inducing an anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in a subject~~an amount sufficient to induce the anti-inflammatory, anti-oxidant, and/or anti-apoptotic effect in the subject~~.

25. The ~~method~~ use of claim 24, wherein the use~~method~~ decreases the amount of tumor necrosis factor alpha (TNF-α) secreted by macrophages in the subject relative to the amount of TNF-α secreted by macrophages in the subject prior to the subject receiving the metabolite.

26. The ~~method~~ use of claim 25, wherein the amount of TNF-α secreted by macrophages after the subject receiving the metabolite is less than 90% of the amount of TNF-α secreted by macrophages prior to the subject receiving the metabolite.

27. The use~~method~~ of any one of claims 24 to 26, wherein the use~~method~~ increases total antioxidant capacity of the subject's plasma relative to the total antioxidant capacity of the subject's plasma prior to the subject receiving the metabolite.

28. The use~~method~~ of any one of claims 24 to 27, wherein the use~~method~~ increases cholesterol efflux of the subject relative to the cholesterol efflux of the subject prior to the subject receiving the metabolite.

29. The use~~method~~ of any one of claims 24 to 28, wherein the use~~method~~ decreases the amount of reactive oxygen species (ROS) produced by macrophages in the subject relative to the amount of ROS produced by macrophages in the subject prior to the subject receiving the metabolite.

30. The use~~method~~ of any one of claims 24 to 29, wherein the use~~method~~ decreases cyclooxygenase (COX) activity in the subject relative to the COX activity in the subject prior to the subject receiving the metabolite.

31. The use~~method~~ of any one of claims 24 to 30, wherein the use~~method~~ decreases nitric oxide synthases (NOS) activity in the subject relative to the NOS activity in the subject prior to the subject receiving the metabolite.

32. The use~~method~~ of any one of claims 24 to 31, wherein the use~~method~~ decreases macrophage M1 polarization in the subject relative to the macrophage M1 polarization in the subject prior to the subject receiving the metabolite.

33. The use~~method~~ of any one of claims 24 to 32, wherein the use~~method~~ increases arginase activity in the subject relative to the arginase activity in the subject prior to the subject receiving the metabolite.

34. The use~~method~~ of any one of claims 24 to 33, wherein the use~~method~~ increases macrophage M2 polarization in the subject relative to the macrophage M2 polarization in the subject prior to the subject receiving the metabolite.

35. The use~~method~~ of any one of claims 24 to 34, wherein the use~~method~~ extends longevity and/or improves cognitive and/or physical performance of the subject.

36. The use~~method~~ of any one of claims 24 to 35, wherein the subject is on a fasting diet.

37. The use~~method~~ of claim 36, wherein one or more of metabolies selected from the group consisting of pentose acid, indolepropionate, gentisate, piperine, and hydrocinnamate are substantially depleted in the subject.

38. The use~~method~~ of any one of claims 24 to 37, wherein the subject has an inflammatory disorder.

39. The use~~metod~~ of claim 38, wherein the inflammatory disorder is sected from the group consisting of , rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ANCA-associated vasculitis, antiphospholipid antibody syndrome, autoimmune hemolytic anemia, chronic inflammatory demyelinating neuropathy, graft-vs-host disease (GVHD), dermatomyositis, Goodpasture's Syndrome, organ system-targeted type II hypersensitivity syndromes, Guillain Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), dermatomyositis, Felty's syndrome, autoimmune thyroid disease, ulcerative colitis, autoimmune liver disease, idiopathic thrombocytopenia purpura, Myasthenia Gravis, neuromyelitis optica, pemphigus, Sjogren's Syndrome, autoimmune cytopenias, synovitis, dermatomyositis, systemic vasculitis, glomerulitis, and vasculitis.

40. The use~~method~~ of any one of claims 24 to 38, wherein the subject has a metabolic disorder.

41. The use~~method~~ of claim 40, wherein the metabolic disorder is selected from the group consisting of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetes, and metabolic syndrome.

42. The use~~method~~ of any one of claims 24 to 40, wherein the subject is overweight.

43. The use~~method~~ of any one of claims 24 to 42, wherein the metabolite is to be administered to the subject one or more times daily.

44. The use~~method~~ of any one of claims 24 to 43, wherein the metabolite is to be administered to the subject during food intake.

45. The use~~method~~ of any one of claims 24 to 44, wherein the metabolite is to be administered to the subject after at least 5 hours of fasting.

46. The use~~method~~ of any one of claims 24 to 45, wherein the ~~method~~ use comprises ~~administering~~ two of the metabolites to be administered.

47. The use~~method~~ of claim 46, wherein the two metabolites are spermidine or a precursor thereof and 1-MNA or a precursor thereof, spermidine or a precursor thereof and PEA or a precursor thereof, spermidine or a precursor thereof and OEA or a precursor thereof, 1-MNA or a precursor thereof and PEA or a precursor thereof, 1-MNA or a precursor thereof and OEA or a precursor thereof, or PEA or a precursor thereof and OEA or a precursor thereof.

48. The use~~method~~ of any one of claims 24 to 45, wherein the use~~method~~ comprises ~~administering~~ three of the metabolites to be administered.

49. The use~~method~~ of claim 48, wherein the three metabolites are 1) sperimidine or a precursor thereof, 1-MNA or a precursor thereof, and PEA or a precursor thereof, 2) spermidine or a precursor thereof, 1-MNA or a precursor thereof, and OEA or a precursor thereof, 3) spermidine or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof, or 4) 1-MNA or a precursor thereof, PEA or a precursor thereof, and OEA or a precursor thereof.

50. The use~~method~~ of claims 24 to 45, wherein the use~~method~~ comprises ~~administering~~ all four of the metabolites to be administered.

51. The use~~method~~ of any one of claims 24 to 50, wherein the subject is a human.

52. ~~A method extending lifespan, healthspan, healthy aging, altering biochemical pathways associated with the aging process or the treatment or prevention of age related diseases including but not limited to frailty, sarcopenia, dementia, Alzheimers disease, arthritis, and cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of~~ A use of the composition of any one of claims 1-23 in the manufacture of a medicament for extending lifespan, healthspan, healthy aging, altering biochemical pathways associated with the aging process or the treatment or prevention of age related diseases including but not limited to frailty, sarcopenia, dementia, Alzheimers disease, arthritis, and cancer in a subject.

53. The ~~method~~ use of claim 52, wherein the subject is a human.

54. ~~A method of increasing plasma cholesterol efflux ability in a subject in need thereof comprising administering to the subject a therapeutically effective amount of~~ A use of the composition of any one of claims 1-23 in the manufacture of a medicament for increasing plasma cholesterol efflux ability in a subject in need thereof.

55. The ~~method~~ use of claim 54, wherein the subject is at risk for or has heart disease, stroke, arteral plaque formation or other cardiovascular disease risk factors.

56. The ~~method~~ use of claim 54 or 55, wherein the subject is a human.