FORMULATIONS FOR EXTENDING LIFESPAN AND HEALTHSPAN

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/489,884 filed April 25, 2017; and U.S. Provisional Application No. 62/646,734 filed March 22, 2018, which are incorporated by reference herein in their entirety.

BACKGROUND OF THE INVENTION

[0002] Pharmacological treatment and prevention of the natural declines of age and aging-related diseases has presented challenges to the medical community in part because of the stringent characteristics required of pharmacological agents for this purpose. Aging patient populations impose unusually high burdens on pharmacological therapies to be bioavailable, nontoxic, and lacking long-term adverse effects. Prevention requires treatment of patients which may be at risk to aging-related disorders but experiencing no or mild symptoms, requiring agents that do not damage existing health. Treatment of patients with existing age-related disease requires a high requirement for nontoxicity, so as to not exacerbate existing health conditions. Moreover, treatment or prevention of aging-related disorders in general likely requires treatment with pharmacological agents for many years, thus requiring such agents to lack cumulative toxicity or long-term deleterious effects on organ systems.

[0003] Accordingly, there is a need for discovery of pharmacological agents and combinations of pharmacological agents that are nontoxic and suitable for administration to subjects before age related disorders are apparent or acute, or for the longer-term administration.

[0004] The primary and secondary metabolites present in dietary fruits and vegetables are a chemically diverse pharmacopeia which meets the criteria for treatment of aging related diseases. Due to their longstanding presence in the human diet, many of these compounds have very low toxicity and well-understood pharmacokinetic parameters. Screening of compounds from these sources thus provides great potential for the therapy of aging and aging-related conditions.

SUMMARY OF THE DISCLOSURE

[0004a] In one aspect, disclosed herein are uses of a composition comprising α-ketoglutarate (AKG) and a vitamin A compound in the manufacture of a medicament for delaying onset or delaying progression of frailty.

[0005] Disclosed herein, in certain examples, are methods of extending lifespan in a subject in need thereof comprising administering to the subject a therapeutically effective amount of berberine, a vitamin A compound, and α-ketoglutarate (AKG). In some instances, berberine, the vitamin A compound and AKG is administered to the subject as a single composition. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered to the subject separately. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered to the subject within a 24 hour period. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some

instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered once daily. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered twice daily. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered in the morning and evening. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered once a week. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered once a month.

[0006] Disclosed herein, in certain examples, are methods of delaying onset or delaying progression of frailty in a subject in need thereof comprising administering to the subject a therapeutically effective amount of berberine, a vitamin A compound, and α-ketoglutarate (AKG). In some instances, berberine, the vitamin A compound and AKG is administered to the subject as a single composition. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered to the subject separately. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered to the subject within a 24 hour period. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals.In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered once daily. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered twice daily. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered in the morning and evening. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered once a week. In some instances, the berberine, the vitamin A compound, and α-ketoglutarate are administered once a month.

[0007] Disclosed herein, in certain examples, are compositions comprising a therapeutically effective amount of berberine, a therapeutically effective amount of a vitamin A compound, a therapeutically effective amount of AKG, and a pharmaceutically acceptable excipient. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the composition further comprises silymarin. In some instances, the therapeutically effective amount of berberine is at least 1,000 mg and no greater than 5,000 mg. In some instances, the therapeutically effective amount of the vitamin A compound is at least 10,000 IU and no greater than 20,000 IU. In some instances, the therapeutically effective amount of α-ketoglutarate is at least 350 mg and no greater than 750 mg. In some instances, the composition is formulated into an orally administered

form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the orally administered form is a sustained release dosage form. In some instances, the orally administered form is formulated into animal feed. In some instances, the orally administered form is the gel. In some instances, the composition is formulated into an injectable administered form. In some instances, the injectable administered form comprises a liquid, a suspension, or a solution. In some instances, the injectable administered form is a sustained release dosage form. In some instances, the composition is formulated into a topically administered form. In some instances, the topically administered form is a cream, a foam, a gel, a lotion, an ointment, or a serum. In some instances, the composition is formulated into a hair care product. In some instances, the hair care product is a shampoo, a conditioner, hair spray, or a moisturizer. In some instances, the pharmaceutically acceptable excipient comprises an antiadherent, a binder, a coating, a color, disintegrant, a flavor, a glidant, a lubricant, a preservative, a sorbent, or a vehicle.

[0008] Disclosed herein, in certain examples, are methods of delaying onset or delaying progression of frailty in a subject in need thereof comprising administering to the subject a therapeutically effective amount of AKG and a vitamin A compound. In some instances, AKG and the vitamin A compound is administered to the subject as a single composition. In some instances, AKG and the vitamin A compound are administered to the subject separately. In some instances, AKG and the vitamin A compound are administered to the subject within a 24 hour period. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the AKG and the vitamin A compound are administered once daily. In some instances, AKG and the vitamin A compound are administered twice daily. In some instances, AKG and the vitamin A compound are administered in the morning and evening. In some instances, AKG and the vitamin A compound are administered once a week. In some instances, AKG and the vitamin A compound are administered once a month. In some instances, the subject is female.

[0009] Disclosed herein, in certain examples, are methods of treating or preventing alopecia in a subject in need thereof comprising administering to the subject a therapeutically effective amount of AKG and a vitamin A compound. In some instances, AKG and the vitamin A compound is administered to the subject as a single composition. In some instances, AKG and the vitamin A compound are administered to the subject separately. In some instances, AKG and the vitamin A compound are administered to the subject within a 24 hour period. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl

palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the AKG and the vitamin A compound are administered once daily. In some instances, AKG and the vitamin A compound are administered twice daily. In some instances, AKG and the vitamin A compound are administered in the morning and evening. In some instances, AKG and the vitamin A compound are administered once a week. In some instances, AKG and the vitamin A compound are administered once a month.

[0010] Disclosed herein, in certain examples, are methods of extending lifespan in a subject in need thereof comprising administering to the subject a therapeutically effective amount of AKG and vitamin D. In some instances, AKG and vitamin D is administered to the subject as a single composition. In some instances, AKG and vitamin D are administered to the subject separately. In some instances, AKG and vitamin D are administered to the subject within a 24 hour period. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, AKG and vitamin D are administered once daily. In some instances, AKG and vitamin D are administered twice daily. In some instances, AKG and vitamin D are administered in the morning and evening. In some instances, AKG and vitamin D are administered once a week. In some instances, AKG and vitamin D are administered once a month. In some instances, the subject is female.

[0011] Disclosed herein, in certain examples, are methods of delaying onset or delaying progression of frailty in a subject in need thereof comprising administering to the subject a therapeutically effective amount of AKG and vitamin D. In some instances, AKG and vitamin D is administered to the subject as a single composition. In some instances, AKG and vitamin D are administered to the subject separately. In some instances, AKG and vitamin D are administered to the subject within a 24 hour period. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, AKG and vitamin D are administered once daily. In some instances, AKG and vitamin D are administered twice daily. In some instances, AKG and vitamin D are administered in the morning and evening. In some instances, AKG and vitamin D are administered once a week. In some instances, AKG and vitamin D are administered once a month. In some instances, the subject is female.

[0012] Disclosed herein, in certain examples, are methods of extending lifespan in a subject in need thereof comprising administering to the subject a composition comprising a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, the composition consists

essentially of a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the composition is administered once daily. In some instances, the composition is administered twice daily. In some instances, the composition is administered in the morning and evening. In some instances, the composition is administered once a week. In some instances, the composition is administered once a month. In some instances, the subject is female.

[0013] Disclosed herein, in certain examples, are methods of delaying onset or delaying progression of frailty in a subject in need thereof comprising administering to the subject a composition comprising a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, the delaying onset or delaying progression of frailty comprises delaying onset or delaying progression of a frailty phenotype. In some instances, the frailty phenotype is selected from the group consisting of dermatitis, kyphosis, tremor, and alopecia. In some instances, the frailty phenotype is dermatitis. In some instances, the frailty phenotype is kyphosis. In some instances, the frailty phenotype is tremor. In some instances, the frailty phenotype is alopecia. In some instances, the composition consists essentially of a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the composition is administered once daily. In some instances, the composition is administered twice daily. In some instances, the composition is administered in the morning and evening. In some instances, the composition is administered once a week. In some instances, the composition is administered once a month. In some instances, the subject is female. In some instances, the composition is formulated into an orally administered form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the orally administered form is a sustained release dosage form. In some instances, the orally administered form is formulated into animal feed. In some instances, the orally administered form is the gel. In some instances, the composition is formulated into an injectable administered form. In some instances, the injectable administered form comprises a liquid, a suspension, or a solution. In some instances, the injectable administered form is a sustained release dosage form. In some instances, the composition is formulated into a topically administered form. In some instances, the topically administered form is a cream, a foam, a gel, a lotion, an ointment, or a serum. In some instances, the composition is formulated into a hair care product. In some instances, the hair care product is a shampoo, a conditioner, hair spray, or a moisturizer. In some instances, the composition further comprises a pharmaceutically acceptable excipient selected from the group consisting of an antiadherent, a binder, a coating, a color, disintegrant, a flavor, a glidant, a lubricant, a

preservative, a sorbent, or a vehicle. In some instances, the composition is administered to the subject for at least 4 months. In some instances, the composition is administered to the subject for at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 14 months, at least 16 months, or at least 18 months.

[0014] Disclosed herein, in certain examples, are methods of extending healthspan in a subject in need thereof comprising administering to the subject a composition comprising a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, extending healthspan comprises a delay in onset or progression of an age-related phenotype. In some instances, the age-related phenotype is selected from the group consisting of graying hair, hair loss, and increased cell senescence. In some instances, the age-related phenotype is graying hair. In some instances, the age-related phenotype is hair loss. In some instances, the age-related phenotype is increased cell senescence. In some instances, the composition consists essentially of a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the composition is administered once daily. In some instances, the composition is administered twice daily. In some instances, the composition is administered in the morning and evening. In some instances, the composition is administered once a week. In some instances, the composition is administered once a month. In some instances, the subject is female. In some instances, the composition is formulated into an orally administered form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the orally administered form is a sustained release dosage form. In some instances, the orally administered form is formulated into animal feed. In some instances, the orally administered form is the gel. In some instances, the composition is formulated into an injectable administered form. In some instances, the injectable administered form comprises a liquid, a suspension, or a solution. In some instances, the injectable administered form is a sustained release dosage form. In some instances, the composition is formulated into a topically administered form. In some instances, the topically administered form is a cream, a foam, a gel, a lotion, an ointment, or a serum. In some instances, the composition is formulated into a hair care product. In some instances, the hair care product is a shampoo, a conditioner, hair spray, or a moisturizer. In some instances, the composition further comprises a pharmaceutically acceptable excipient selected from the group consisting of an antiadherent, a binder, a coating, a color, disintegrant, a flavor, a glidant, a lubricant, a preservative, a sorbent, or a vehicle. In some instances, the composition is administered to the subject for at least 4 months. In some instances, the composition is administered to the subject for at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 14 months, at least 16 months, or at least 18 months.

[0015] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition comprising a therapeutically effective amount of

berberine, a vitamin A compound, and α-ketoglutarate (AKG). In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the helping to maintain health comprises helping to maintain a healthy musculoskeletal system. In some instances, the composition is formulated into an orally administered form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the subject is a human. In some instances, the composition is administered to the subject once daily. In some instances, the composition is administered to the subject twice daily.

[0016] Disclosed herein, in certain examples, are methods for helping to maintain health in need thereof comprising administering to the subject a composition comprising a therapeutically effective amount of a vitamin A compound, and α-ketoglutarate (AKG). In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the helping to maintain health comprises helping to maintain a healthy musculoskeletal system. In some instances, the composition is formulated into an orally administered form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the subject is a human. In some instances, the composition is administered to the subject once daily. In some instances, the composition is administered to the subject twice daily.

[0017] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition comprising a therapeutically effective amount of a vitamin D, and α-ketoglutarate (AKG). In some instances, AKG is formulated as a calcium salt. In some instances, the helping to maintain health comprises helping to maintain a healthy musculoskeletal system. In some instances, the composition is formulated into an orally administered form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the subject is a human. In some instances, the composition is administered to the subject once daily. In some instances, the composition is administered to the subject twice daily.

[0018] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition comprising a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG). In some instances, the helping to maintain health comprises helping to maintain a healthy musculoskeletal system. In some instances, the composition is formulated into an orally administered form. In some instances, the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup. In some instances, the subject is a human. In some instances, the composition is administered to

the subject once daily. In some instances, the composition is administered to the subject twice daily. In some instances, the helping to maintain health comprises helping to maintain hair density. In some instances, the helping to maintain health comprises helping to maintain hair pigmentation. In some instances, the helping to maintain health comprises helping to maintain skin health. In some instances, the helping to maintain health comprises helping to maintain normal spine curvature.

[0019] Disclosed herein, in certain examples, are methods of treating or preventing alopecia in a subject in need thereof comprising administering to the subject a therapeutically effective amount of AKG and vitamin D. In some instances, AKG and vitamin D are administered to the subject as a single composition. In some instances, AKG and vitamin D are administered to the subject separately. In some instances, AKG and vitamin D are administered to the subject within a 24 hour period. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the AKG and vitamin D are administered once daily. In some instances, AKG and vitamin D are administered twice daily. In some instances, AKG and vitamin D are administered in the morning and evening. In some instances, AKG and vitamin D are administered once a week. In some instances, AKG and vitamin D are administered once a month.

[0020] Disclosed herein, in certain examples, are methods of extending lifespan in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a vitamin A compound and α-ketoglutarate (AKG). In some instances, the vitamin A compound and AKG is administered to the subject as a single composition. In some instances, the vitamin A compound and α-ketoglutarate are administered to the subject separately. In some instances, the vitamin A compound and α-ketoglutarate are administered to the subject within a 24 hour period. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, the subject is a mammal. In some instances, the mammal is a human. In some instances, the mammal is a dog. In some instances, the mammal is a cat. In some instances, the mammal is livestock. In some instances, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, and equine animals. In some instances, the vitamin A compound and α-ketoglutarate are administered once daily. In some instances, the vitamin A compound and α-ketoglutarate are administered twice daily. In some instances, the vitamin A compound and α-ketoglutarate are administered in the morning and evening. In some instances, the vitamin A compound and α-ketoglutarate are administered once a week. In some instances, the vitamin A compound and α-ketoglutarate are administered once a month.

[0021] Disclosed herein, in certain examples, are methods of extending healthspan in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a vitamin A compound and α-ketoglutarate (AKG). In some instances, the vitamin A compound and AKG is

administered to the subject as a single composition. In some instances, the vitamin A compound and α-ketoglutarate are administered to the subject separately. In some instances, the vitamin A compound and α-ketoglutarate are administered to the subject within a 24 hour period. In some instances, the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene. In some instances, the vitamin A compound is retinoic acid or retinyl palmitate. In some instances, AKG is formulated as a calcium salt. In some instances, extending healthspan comprises a delay in onset or progression of an age-related phenotype. In some instances, the age-related phenotype is selected from the group consisting of graying hair, hair loss, and increased cell senescence. In some instances, the age-related phenotype is graying hair. In some instances, the age-related phenotype is hair loss. In some instances, the age-related phenotype is increased cell senescence. In some instances, the subject is a mammal. In some instances, the mammal is a human.

[0022] Disclosed herein, in certain examples, are methods of extending healthspan in a subject in need thereof comprising administering to the subject a therapeutically effective amount of vitamin D and α-ketoglutarate (AKG). In some instances, vitamin D and AKG is administered to the subject as a single composition. In some instances, vitamin D and AKG are administered to the subject separately. In some instances, vitamin D and α-ketoglutarate are administered to the subject within a 24 hour period. In some instances, AKG is formulated as a calcium salt. In some instances, extending healthspan comprises a delay in onset or progression of an age-related phenotype. In some instances, the age-related phenotype is selected from the group consisting of graying hair, hair loss, and increased cell senescence. In some instances, the age-related phenotype is graying hair. In some instances, the age-related phenotype is hair loss. In some instances, the age-related phenotype is increased cell senescence. In some instances, the subject is a mammal. In some instances, the mammal is a human.

[0023] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition that modulates pathways associated with normal aging process wherein the composition comprises a therapeutically effective amount of berberine, a vitamin A compound, and α-ketoglutarate (AKG).

[0024] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition that modulates pathways associated with normal aging process wherein the composition comprises a therapeutically effective amount of a vitamin A compound and α-ketoglutarate (AKG).

[0025] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition that modulates pathways associated with normal aging process wherein the composition comprises a therapeutically effective amount of vitamin D and α-ketoglutarate (AKG).

[0026] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition that modulates pathways associated with normal

aging process wherein the composition comprises a therapeutically effective amount of a calcium salt of alpha-ketoglutarate (Ca-AKG).

[0027] Disclosed herein, in certain examples, are methods for helping to maintain health in a subject comprising administering to the subject a composition that modulates pathways associated with normal aging process wherein the composition comprises a therapeutically effective amount of nicotinamide mononucleotide (NMN) and α-ketoglutarate (AKG).

INCORPORATION BY REFERENCE

[0028] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0030] **Fig. 1** shows the lifespan effects of indicated compounds on *C. elegans* aging. Compound 1 is Ca-AKG. Compound 2 is retinoic acid (RA), a metabolite of vitamin A that mediates its functions. Compound 3 is berberine. Both Ca-AKG + RA and the combination of all three compounds have robust effects on longevity.

[0031] **Fig. 2** shows the effect of the combination of berberine, Ca-AKG, and retinoic acid (RA) has on survival in female mice compared to control female mice. (Cohort 1)

[0032] **Fig. 3** shows the effect of the combination of berberine, Ca-AKG, and vitamin A has on frailty scores in female mice (bottom line) compared to control female mice (top line). (Cohort 1)

[0033] **Fig. 4** shows the effect of berberine, control, or retinoic acid (RA) on female mice lifespan. (Cohort 1)

[0034] **Fig. 5** shows the effect of the combination of berberine, Ca-AKG, and retinoic acid (RA) (triple) and the combination of Ca-AKG and berberine (double) on female mice lifespan. (Cohort 1)

[0035] **Fig. 6** shows the effect of Ca-AKG + RP, Ca-AKG + Vitamin D, Vitamin D, retinyl palmitate (RP), Ca-AKG, and control on female mice lifespan (left), and the effect Ca-AKG + RP, Vitamin D, RP, Ca-AKG, and control on male mice lifespan (right). (Cohort 2)

[0036] **Fig. 7** shows the effect of Ca-AKG, Vitamin D, RP, and the combination of Ca-AKG + RP, has on frailty scores in combined female and male mice compared to control. (Cohort 2)

[0037] **Fig. 8** shows the effect of Ca-AKG, Vitamin D, RP, Ca-AKG + RP, Ca-AKG + Vitamin D and control on female mice frailty scores after 2 months of treatment (left), and the effect Ca-AKG, Vitamin D, RP, Ca-AKG + RP, and control on male mice frailty scores after 2 months of treatment (right). (Cohort 2)

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a composition comprising α-ketoglutarate (AKG) and a vitamin A compound in the manufacture of a medicament for delaying onset or delaying progression of frailty.

2. The use of claim 1, wherein the delaying onset or delaying progression of frailty comprises delaying onset or delaying progression of a frailty phenotype.

3. The use of claim 2, wherein the frailty phenotype is selected from the group consisting of hair loss, dermatitis, kyphosis, grip strength, a gait disorder, hearing loss, cataracts, corneal opacity, eye discharge, vision loss, nasal discharge, age-related fat loss and tremors.

4. The use of claim 2, wherein the frailty phenotype is dermatitis.

5. The use of claim 2, wherein the frailty phenotype is kyphosis.

6. The use of claim 2, wherein the frailty phenotype is grip strength.

7. The use of claim 2, wherein the frailty phenotype is the gait disorder.

8. The use of claim 2, wherein the frailty phenotype is hair loss.

9. The use of claim 2, wherein the frailty phenotype is hearing loss.

10. The use of claim 2, wherein the frailty phenotype is tremors.

11. The use of claim 1, wherein the AKG is formulated as a calcium salt of AKG.

12. The use of claim 11, wherein the calcium salt of AKG comprises a mono-hydrate calcium α-ketoglutarate.

13. The use of claim 1, wherein the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene.

14. The use of claim 1, wherein the vitamin A compound is retinoic acid or retinyl palmitate.

15. The use of claim 1, wherein the medicament is to be administered once daily.

16. The use of claim 1, wherein the medicament is to be administered twice daily.

17. The use of claim 1, wherein the medicament is formulated into an orally administered form.

18. The use of claim 17, wherein the orally administered form comprises a tablet, a powder, a suspension, a serum, an emulsion, a capsule, a granule, a pill, a gel, a solution, or a syrup.

19. The use of claim 18, wherein the orally administered form comprises a tablet.

20. The use of claim 17, wherein the orally administered form comprises a sustained release dosage form.

21. The use of claim 1, wherein the composition further comprises a pharmaceutically acceptable excipient.

22. The use of claim 1, wherein the pharmaceutically acceptable excipient comprises an anti-adherent, a binder, a coating, a color, disintegrant, a flavor, a glidant, a lubricant, a preservative, a sorbent, or a vehicle.