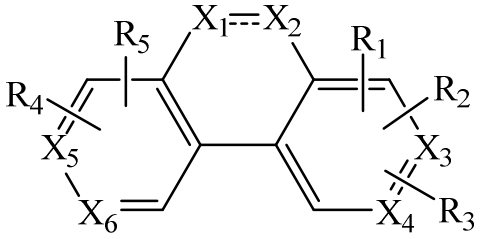
compounds. Some embodiments include methods of using the inventive compound (e.g., in compositions or in pharmaceutical compositions) for administering and treating (e.g., diseases). Further embodiments include methods for making the inventive compounds. Additional embodiments of the invention are also discussed herein.

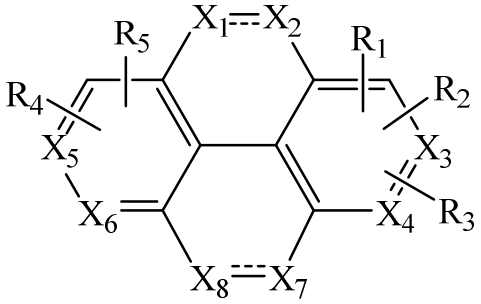
[0005] This invention was made with the Government of India support under BT/PR12490/AAQ/3/716/2015 awarded by Department of Biotechnology

SUMMARY

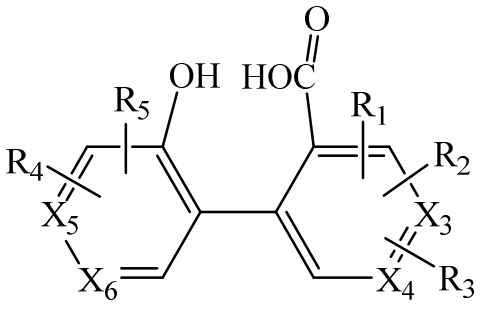
[0005a] In one aspect, the present disclosure refers to a compound selected from



(I),



(II),



(III), salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof,

wherein

- the bond between X_1 and X_2 is a single bond or a double bond;

- the bond between X_7 and X_8 is a single bond or a double bond;

- X_1, X_2, X_7, and X_8 are the same or different and each can be independently selected from CH, CH_2, O, S, C-NH_2, C-N=CH_2, C(H)(NH_2), C=O, C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-S(O)H, C=NC(EtOH)$_3$, C=NCH(EtOH)$_2$, C=NEtOH, C(CH_3)(OH), N, NH, C-halogen, C(H)(halogen), C-(halogen)$_2$, C-cycloalkyl, C-heterocyclyl, C-aryl, C-heteroaryl, C(H)(cycloalkyl), C(H)(heterocyclyl), C(H)(aryl), or C(H)(heteroaryl), which CH, CH_2, C-NH_2, C-N=CH_2, C(H)(NH_2), C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-S(O)H, C=NC(EtOH)$_3$, C=NCH(EtOH)$_2$, C=NEtOH, C(CH_3)(OH), NH, C(H)(halogen), C-cycloalkyl, C-heterocyclyl, C-aryl, C-heteroaryl, C(H)(cycloalkyl), C(H)(heterocyclyl), C(H)(aryl), or C(H)(heteroaryl), are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl;

- X_1 and X_2 are optionally further cyclized to form a 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered

heteroaryl, which 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), $-COCH_3$, carboxy ($-CO_2H$), ethynyl (-CCH), cyano (-CN), sulfo ($-SO_3H$), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl;

- X_7 and X_8 are optionally further cyclized to form a 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl, which 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), $-COCH_3$, carboxy ($-CO_2H$), ethynyl (-CCH), cyano (-CN), sulfo ($-SO_3H$), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl;

- R_1, R_2, R_3, R_4, and R_5 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), $-OCF_3$, $-COCH_3$, carbonyl, carboxy ($-CO_2H$), ethynyl (-CCH), cyano (-CN), amine, $-NO_2$, sulfo ($-SO_3H$), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, cycloalkyl, or heterocyclyl, which H, OH, methanoyl (-COH), $-COCH_3$, carbonyl, carboxy ($-CO_2H$), ethynyl (-CCH), sulfo ($-SO_3H$), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, cycloalkyl, or heterocyclyl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), $-COCH_3$, carboxy ($-CO_2H$), ethynyl (-CCH), cyano (-CN), sulfo ($-SO_3H$), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl; and

- X_3, X_4, X_5, and X_6 are the same or different and each is independently selected from CH or N, which CH is optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl.

[0005b] In another aspect, the present disclosure refers to a urolithin derivative having a chemical group substitution of the urolithin cyclic ester resulting in improved potency of the derivative as compared to urolithin A, or improved stability of the derivative at acidic pH and/or in presence of esterase and/or protease as compared to urolithin A.

[0005c] In yet another aspect, the present disclosure refers to a composition comprising a compound as disclosed herein.

[0005d] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein.

[0005e] In yet another aspect, the present disclosure refers to a method for providing an animal with a compound comprising one or more administrations of one or more compositions comprising the compound as disclosed herein, wherein the compositions may be the same or different if there is more than one administration.

[0005f] In yet another aspect, the present disclosure refers to use of one or more compositions comprising the compound as disclosed herein in the manufacture of a medicament for treating an animal for a disease, wherein the use comprising the one of more compositions to be administered once or more times, wherein the compositions may be the same or different if it is to be administered more than once.

[0005g] In yet another aspect, the present disclosure refers to use of an effective amount of a pharmaceutical composition comprising a urolithin structural analogue in the manufacture of a medicant for inducing the expression of tight junction proteins in a tissue, wherein the pharmaceutical composition is to be administered to a subject in need.

[0005h] In yet another aspect, the present disclosure refers to use of an effective amount of the composition as disclosed herein in the manufacture of a medicament for inducing the expression of tight junction proteins in a tissue, wherein the pharmaceutical composition is to be administered to a subject in need.

[0005i] In yet another aspect, the present disclosure refers to use of an effective amount of a composition as disclosed herein in the manufacture of a medicament for treating systemic inflammation, wherein the composition is to be administered to a subject in need thereof.

[0005j] In yet another aspect, the present disclosure refers to use of an effective amount of a composition as disclosed herein in the manufacture of a medicament for treating neuroinflammatory disorder, wherein the composition is to be administered to a subject in need thereof.

[0005k] In yet another aspect, the present disclosure refers to use of an effective amount of the composition as disclosed herein in the manufacture of a medicament for treating anxiety or depression, wherein the composition is to be administered to a subject in need, in an amount effective to inhibit monoamine oxidase enzymes in the subject.

[0005l] In yet another aspect, the present disclosure refers to use of an effective amount of a composition as disclosed herein in the manufacture of a

medicament for enhancing airway barrier integrity in lungs, wherein the composition is to be administered to a subject in need thereof.

[0005m] In yet another aspect, the present disclosure refers to use of an effective amount of the composition as disclosed herein in the manufacture of a medicament for improving or increasing autophagy in a subject, wherein the composition is to be administered to a subject in need thereof.

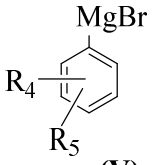
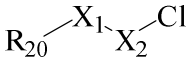
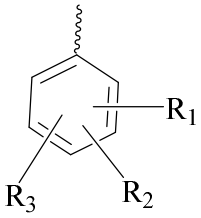
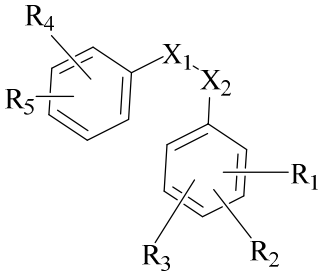
[0005n] In yet another aspect, the present disclosure refers to use of the composition as disclosed herein in the manufacture of a medicament for increasing longevity in a subject, wherein a regimen of the composition as disclosed herein effective to increase longevity in an animal is to be administered to the subject.

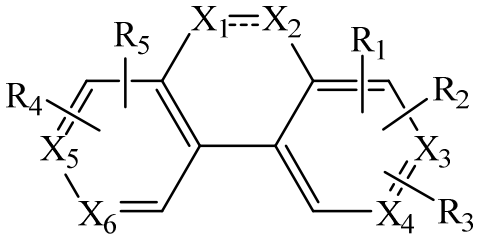
[0005o] In yet another aspect, the present disclosure refers to a method of increasing autophagy in a cell, comprising contacting a cell with an effective amount of a compound as disclosed herein.

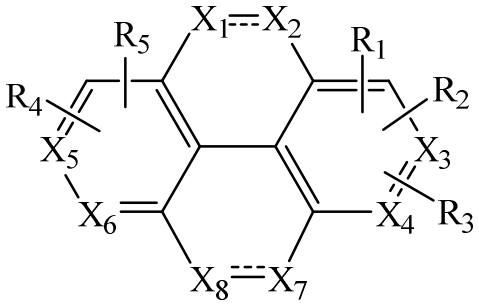
[0005p] In yet another aspect, the present disclosure refers to a method of increasing longevity of eukaryotic cells in vitro, comprising contacting the cells with the compound as disclosed herein effective to increase longevity of the cells.

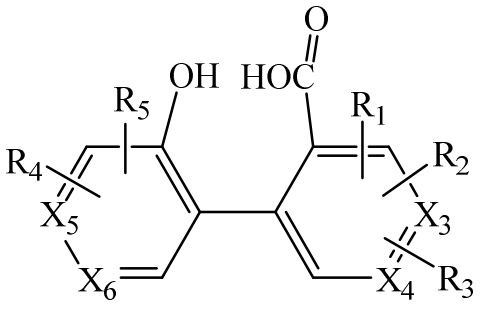
[0005q] In yet another aspect, the present disclosure refers to a method for preparing a compound of Formula (I) as disclosed herein comprising (a) reacting a compound of Formula (V) with a compound of Formula (VI) to result in a mixture comprising a compound of Formula (VII); (b) reacting the compound of Formula (VII) with a suitable compound to result in a mixture comprising a compound of Formula (I); (c) optionally further reacting the compound of Formula (I) to result in a different compound of Formula (I) so that the identity of one or more of R_1, R_2, R_3, R_4, R_5, X_1 or X_2 is changed by the further reacting; and

(d) recovering Formula (I),

[0006] wherein Formula (V) is  **(V)**; Formula (VI) is  **(VI)** where R_{20} is a halogen or ; and Formula (VII) is  **(VII)**. Some examples of the disclosure include a compound selected from

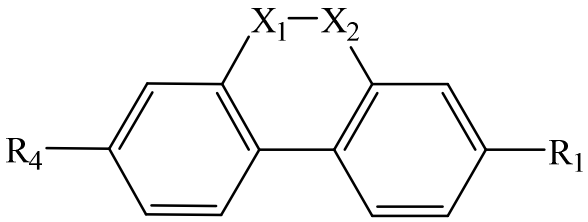
[0007]  (I),

[0008]  (II),

[0009]  (III), salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof. In other examples, the bond between X_1 and X_2 is a single bond or a double bond. In other examples, the bond between X_7 and X_8 is a single bond or a double bond. In still other examples, X_1, X_2, X_7, and X_8 are the same or different and each can be independently selected from CH, CH_2, O, S, C-NH_2, C-N=CH_2, C(H)(NH_2), C=O, C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-S(O)H, C=NC(EtOH)$_3$, C=NCH(EtOH)$_2$, C=NEtOH, C(CH_3)(OH), N, NH, C-halogen, C(H)(halogen), C-(halogen)$_2$, C-cycloalkyl, C-heterocyclyl, C-aryl, C-heteroaryl, C(H)(cycloalkyl), C(H)(heterocyclyl), C(H)(aryl), or C(H)(heteroaryl), which CH, CH_2, C-NH_2, C-N=CH_2, C(H)(NH_2), C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-S(O)H, C=NC(EtOH)$_3$, C=NCH(EtOH)$_2$, C=NEtOH, C(CH_3)(OH), NH, C(H)(halogen), C-cycloalkyl, C-heterocyclyl, C-aryl, C-heteroaryl, C(H)(cycloalkyl), C(H)(heterocyclyl), C(H)(aryl), or C(H)(heteroaryl), are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In some examples, X_1 and X_2 are optionally further cyclized to form a 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl, which 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered

heteroaryl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In still other examples, X_7 and X_8 are optionally further cyclized to form a 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl, which 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In certain examples, R_1, R_2, R_3, R_4, and R_5 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), -OCF_3, -$COCH_3$, carbonyl, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), amine, -NO_2, sulfo (-SO_3H), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, cycloalkyl, or heterocyclyl, which H, OH, methanoyl (-COH), -$COCH_3$, carbonyl, carboxy (-CO_2H), ethynyl (-CCH), sulfo (-SO_3H), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, cycloalkyl, or heterocyclyl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In some examples, X_3, X_4, X_5, and X_6 are the same or different and each is independently selected from CH or N, which CH is optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl.

[0010] In some examples X_1, X_2, X_7, and X_8 are the same or different and each can be independently selected from CH_2, O, $C(H)(NH_2)$, C=O, $C=N\text{-}NH_2$, C=NH, C=N-cycloalkyl, C=N-adamantane, $C=NC(EtOH)_3$, $C=NCH(EtOH)_2$, C=NEtOH, $C(CH_3)(OH)$, or C(H)(cycloalkyl). In other examples, X_1 and X_2 are the same, X_7 and X_8 is the same, X_1 and X_7 is the same, X_2 and X_8 is the same, or a combination thereof. In still other examples, X_3, X_4, X_5, and X_6 are the same or different and each is independently selected from CH or N. In yet other examples, R_1, R_2, R_3, R_4, and R_5 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), $-OCF_3$, $-COCH_3$, carbonyl, carboxy ($-CO_2H$), cyano (-CN), amine, $-NO_2$, methoxy, ethoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, cycloalkyl, bicycloalkyl, heterocyclyl, or imidazolyl. In some examples, the compound is selected from Formula (IA)



(IA), salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof. In certain examples, X_1 and X_2 are the same or different and each is independently selected from CH_2, O, $C(H)(NH_2)$, C=O, $C=N\text{-}NH_2$, C=NH, C=N-cycloalkyl, $C=NC(EtOH)_3$, $C=NCH(EtOH)_2$, C=NEtOH, $C(CH_3)(OH)$, or C(H)(cycloalkyl), which CH_2, $C(H)(NH_2)$, $C=N\text{-}NH_2$, C=NH, C=N-cycloalkyl, $C=NC(EtOH)_3$, $C=NCH(EtOH)_2$, C=NEtOH, $C(CH_3)(OH)$, or C(H)(cycloalkyl), are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), $-COCH_3$, carboxy ($-CO_2H$),

ethynyl (-CCH), cyano (-CN), sulfo ($-SO_3H$), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In other examples, X_1 and X_2 are the same or different and each is independently selected from CH_2, O, C=O, C=NH, C=N-cycloalkyl, $C=NC(EtOH)_3$, $C=NCH(EtOH)_2$, C=NEtOH, $C(CH_3)(OH)$, or C(H)(cycloalkyl). In yet other examples, R_1 and R_2 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), $-OCF_3$, $-COCH_3$, carbonyl, carboxy ($-CO_2H$), ethynyl (-CCH), cyano (-CN), amine, $-NO_2$, sulfo ($-SO_3H$), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, which H, OH, methanoyl (-COH), $-COCH_3$, carbonyl, carboxy ($-CO_2H$), ethynyl (-CCH), sulfo ($-SO_3H$), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, or ethyl, are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), $-COCH_3$, carboxy ($-CO_2H$), ethynyl (-CCH), cyano (-CN), sulfo ($-SO_3H$), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In still other examples, R_1 and R_2 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), $-OCF_3$, $-COCH_3$, carbonyl, carboxy ($-CO_2H$), cyano (-CN), amine, $-NO_2$, methoxy, ethoxy, methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl. In certain examples, the compound (a) is not I-1, I-2, I-3, I-5, I-7, I-20, I-26, I-27, I-28, I-33, I-53, I-54, I-55, I-56, I-57, I-59, I-94, I-98, II-99, II-100, II-101, II-102, II-103, II-118, II-119, II-120, II-121, and II-122, (b) is a compound selected from Table 1, or (c) both. In certain examples, the compound (a) is not I-1, I-3, I-5, I-7, I-20, I-26, I-27, I-28, I-33, I-53, I-54, I-55, I-56, I-57, I-59, I-94, I-98, II-99, II-100, II-101, II-102, II-103, II-118, II-119, II-120, II-121, and II-122, (b) is a compound selected from Table 1, or (c) both.

[0011] Some examples of the disclosure include a urolithin derivative having a chemical group substitution of the urolithin cyclic ester resulting in improved potency of the derivative as compared to urolithin A, or improved stability of the derivative at acidic pH and/or in presence of esterase and/or protease as compared to urolithin A. In other examples, the urolithin cyclic ester is replaced with a cyclic ether. In yet other examples, the urolithin cyclic ether comprises one or more substituents. In still other examples, the cyclic ether substituents are independently selected from halo, amine, substituted amine, hydroxyl, and a C5 or C6 heterocycle having one or two heteroatoms independently selected from O, N, or S. In certain examples, the urolithin cyclic ester is replaced with a carbocycle having adjacent carbonyl groups. In some examples, the urolithin cyclic ester is replaced with a cyclic alkenyl group, which is optionally aromatic, and optionally substituted. In other examples, the cyclic alkenyl group has one or more substituents. In still other examples, the cyclic alkenyl group substituents are independently selected from ketone, optionally substituted imine, optionally substituted amine, halo, and hydroxyl. In yet other examples, the urolithin cyclic ester is replaced with a cyclic amide. In some examples, the urolithin cyclic ester is replaced with a non-cyclic bridge. In some examples, the urolithin aromatic groups have one or more substituents. In other examples, the aromatic groups are phenyl groups which are optionally substituted. In certain examples, the one or more aromatic substituents are independently selected from hydroxyl, alkoxy, halo, amine, a 5 or 6 membered carbocyclic or heterocyclic ring, nitro, nitrile, alkyl, alkyl ether, and haloalkyl. In other examples, one or more urolithin aromatic rings are heterocyclic. In still other examples, the heteroatoms of the heterocyclic ring are independently

selected from N, O, and S. In yet other examples, substituents of each aromatic ring together form a second bridging ring. In certain examples. the second bridging ring is identical in structure to a first bridging ring. In other examples, the second bridging ring is different in structure to the first bridging ring.

[0012] Some examples of the disclosure include a composition comprising a compound of any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, or a urolithin derivative). In other examples, the amount of the compound in the composition is from about 0.0001% (by weight total composition) to about 99%. In still other examples, the composition further comprises a formulary ingredient, an adjuvant, or a carrier. In yet other examples, the composition further comprises 5-florouracil.

[0013] Some examples of the disclosure include a pharmaceutical composition comprising a compound of any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, or a urolithin derivative). In other examples, the amount of the compound in the pharmaceutical composition is from about 0.0001% (by weight total composition) to about 50%. In still other examples, the pharmaceutical composition further comprises a formulary ingredient, an adjuvant, or a carrier. In yet other examples, the pharmaceutical composition further comprises 5-florouracil.

[0014] Some examples of the disclosure include methods for providing an animal with a compound comprising one or more administrations of one or more compositions comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative), wherein the compositions may be the same or different if there is more than one administration. In certain examples, at least

one of the one or more compositions further comprises a formulary ingredient. In other examples, at least one of the one or more compositions comprises any composition as disclosed herein or any pharmaceutical as disclosed herein. In still other examples, at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration. In still other examples, if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration. In yet other examples, the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.01 mg/kg animal body weight to about 50 mg/kg animal body weight. In certain examples, the animal is a human, a rodent, or a primate.

[0015] Some examples of the disclosure include a method for treating an animal for a disease, comprising one or more administrations of one or more compositions comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative), wherein the compositions may be the same or different if there is more than one administration. In other examples, at least one of the one or more compositions further comprises a formulary ingredient. In other examples, at least one of the one or more of any of the compositions disclosed herein or the pharmaceutical composition any of the compositions disclosed herein. In still other examples, at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration,

subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration. In yet other examples, if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration. In certain examples, the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.005 mg/kg animal body weight to about 50 mg/kg animal body weight. In other examples, the animal is a human, a rodent, or a primate. In still other examples, the animal is in need of the treatment. In other examples, the method is for treating alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), intestinal permeability, leaky gut, metal induced gut leakiness, stress induced gut leakiness, radiation induced gut permeability, colitis, local inflammation, inflammation in the brain, inflammation in the mouth, inflammation in the esophagus, inflammation in the stomach, inflammation in the small intestine, systemic inflammation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, infection-induced inflammatory disease, sepsis, sepsis-induced kidney injury, sepsis-induced lung injury, scleroderma, vasculitis, drug-induced vasculitis, neuroinflammatory disorders, Alzheimer's Disease, Parkinson's Disease, anxiety, depression, metabolic stress, cardiovascular disease, sarcopenia, muscle degenerative disease, Duchenne muscular dystrophy, nonalcoholic fatty liver disease, drug-induced liver injury, alpha -antitrypsin deficiency, ischemia/reperfusion injury, obesity, metabolic syndrome, type II diabetes mellitus, hyperlipidemia, osteoarthritis, neurodegenerative disease, amyotrophic lateral sclerosis (ALS), cancer, cancerous tumors, breast cancer, colon cancer, cognitive disorder, stress, mood disorder, or

fibrosis. In still other examples, the method is for treating alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), colitis, intestinal permeability, leaky gut, metal induced gut leakiness, stress induced gut leakiness, radiation induced gut permeability, local inflammation, systemic inflammation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, infection-induced inflammatory disease, sepsis, sepsis-induced kidney injury, sepsis-induced lung injury, scleroderma, vasculitis, drug-induced vasculitis, neuroinflammatory disorders, Alzheimer's Disease, Parkinson's Disease, cancer, cancerous tumors, breast cancer, colon cancer, or fibrosis. In yet other examples, the method is for treating alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), intestinal permeability, leaky gut, metal induced gut leakiness, stress induced gut leakiness, radiation induced gut permeability, local inflammation, systemic inflammation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, sepsis, Alzheimer's Disease, Parkinson's Disease, cancer, cancerous tumors, breast cancer colon cancer, or fibrosis. In still other examples, the method is for treating vasculitis, drug-induced vasculitis, scleroderma, internal vascular bleeding, drug-induced internal bleeding, atopic dermatitis, perfusion-related injury, perfusion related inflammation, diabetic retinopathy, celiac disease, Non-Alcoholic SteatoHepatitis (NASH), Alcoholic SteatoHepatitis (ASH), metabolic stress, cardiovascular disease, sarcopenia, muscle degenerative disease, Duchenne muscular dystrophy, alcoholic liver disease, nonalcoholic fatty liver disease, drug-induced liver injury, chronic kidney disease, alpha-antitrypsin deficiency, ischemia/reperfusion injury, inflammation, inflammatory bowel disease, Crohn's disease, obesity, metabolic syndrome, type II diabetes mellitus, hyperlipidemia, osteoarthritis, neurodegenerative disease,

neuroinflammatory disorder, Alzheimer's disease, Parkinson's disease, multiple sclerosis, myotrophic lateral sclerosis (ALS), pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute lung injury, blood transfusion related acute lung injury, acute respiratory distress syndrome, asthma, cancer, cognitive disorder, stress, or mood disorder. In some examples, the method is for treating cancer and the cancer is pancreatic cancer, pancreatic ductal adenocarcinoma, lung cancer, liver cancer, colorectal cancer, colon cancer, rectal cancer, melanoma, cutaneous malignant melanoma, melanoma tumorigenesis, bladder cancer, prostate cancer, malignant nerve sheath tumors, multiple myeloma, breast cancer, squamous cell carcinoma, head and neck squamous cell carcinoma, lymphoma, leukemia, bone marrow cancer, non-Hodgkin lymphoma, diffuse large B-cell lymphoma, glioblastoma multiforme, endometrial cancer, kidney cancer, basal cell carcinoma, thyroid cancer, neuroblastoma, ovarian cancer, renal cell carcinoma, hepatocellular carcinoma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia, rhabdomyosarcoma, meningioma, gastric cancer, Glioma, oral cancer, nasopharyngeal carcinoma, stomach cancer, uterine cancer, medulloblastoma, cancers that can result in metastasis, cancers resulting from metastasis, or cancerous tumors thereof.

[0016] Some examples of the disclosure include a method of inducing the expression of tight junction proteins in a tissue, comprising administering an effective amount of a pharmaceutical composition comprising a urolithin structural analogue to a subject in need. In other examples, there is a method of inducing the expression of tight junction proteins in a tissue, comprising administering an effective amount of the composition of any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative) to a subject in need. In some examples, the

subject exhibits symptoms of gastrointestinal permeability or inflammation, and the composition is administered to the small and/or large intestine. In other examples, the subject has an inflammatory bowel disease. In still other examples, the inflammatory bowel disease is Crohn's disease or ulcerative colitis. In yet other examples, the subject has celiac disease. In certain examples, the inflammatory bowel disease comprises colonic inflammation. In some examples, the composition is administered systemically in an amount effect to improve endothelial or vascular barrier integrity in organs. In still other examples, the organs are one or more selected from liver, kidneys, pancreas, heart, lungs, skin, muscle, fat, brain, eyes, bone, and intestine. In yet other examples, the subject has a condition selected from vasculitis, drug-induced vasculitis, scleroderma, internal vascular bleeding, drug-induced internal bleeding, atopic dermatitis, perfusion-related injury, perfusion related inflammation, and diabetic retinopathy.

[0017] Some examples of the disclosure include a method of treating systemic inflammation comprising administering to a patient in need thereof an effective amount of a composition comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative). In other examples, the composition is administered enterally or parenterally. In still other examples, the subject has or is at risk of sepsis or an infection-induced inflammatory disease. In yet other examples, the subject has or is at risk of alcoholic liver disease (ALD). In certain examples, the subject has or is at risk of Non-Alcoholic SteatoHepatitis (NASH) or Alcoholic SteatoHepatitis (ASH). In some examples, the subject has inflammation of one or more organs or tissues selected from liver, kidneys, pancreas, heart, lungs, skin, muscle, fat, brain, eyes, bone, marrow, intestine, and cartilage.

[0018] Some examples of the disclosure include a method for treating neuroinflammatory disorder comprising administering to a patient in need thereof an effective amount of a composition comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative). In other examples, the neuroinflammatory disorder is Alzheimer's Disease. In still other examples, the neuroinflammatory disorder is Parkinson's Disease. In yet other examples, the neuroinflammatory disorder is a neurodegenerative disease, which is optionally multiple sclerosis. In certain examples,

[0019] Some examples of the disclosure include a method for treating anxiety or depression, comprising administering an effective amount of the composition comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative) to a subject in need, in an amount effective to inhibit monoamine oxidase enzymes in the subject. In other examples, the composition is administered systemically or locally to the brain. In still other examples, the composition is administered enterally, parenterally, or intranasally.

[0020] Some examples of the disclosure include a method of enhancing airway barrier integrity in lungs comprising administering to a subject in need thereof an effective amount of a composition comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative). In certain examples, the subject has pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute lung injury, blood transfusion related acute lung injury, acute respiratory distress syndrome, or asthma.

[0021] Some examples of the disclosure include a method of improving or increasing autophagy in a subject, comprising administering to a subject in need

thereof an effective amount of the composition comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative). In other examples, autophagy is improved or increased in a tissue or organ of the subject selected from brain, eye, skin, bone, marrow, cartilage, heart, lung, stomach, intestine, liver, pancreas, kidney, muscle, and fat. In certain examples, autophagy is improved or increased in cells of the subject selected from adult stem cells, differentiated cells, blood cells, hematopoietic cells, endothelial cells, epithelial cells, exocrine cells, endocrine cells, connective tissue cells, adipose cells, bone cells, smooth muscle cells, striated muscle cells, nerve cells, sensory cells, cardiac cells, hepatic cells, gastric cells, intestinal cells, pulmonary cells, kidney cells, and germ cells. In still other examples, the subject has a disease or condition selected from metabolic stress, cardiovascular disease, sarcopenia, muscle degenerative disease, Duchenne muscular dystrophy, alcoholic liver disease, nonalcoholic fatty liver disease, drug-induced liver injury, chronic kidney disease, alpha-antitrypsin deficiency, ischemia/reperfusion injury, inflammation, inflammatory bowel disease, Crohn's disease, obesity, metabolic syndrome, type II diabetes mellitus, hyperlipidemia, osteoarthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), cancer, cognitive disorder, stress, and mood disorder, whereby the administering treats or ameliorates the disease or condition.

[0022] Some examples of the disclosure include a method of increasing longevity in a subject, comprising administering to a subject a regimen of the composition comprising any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative) effective to increase longevity in an animal. In

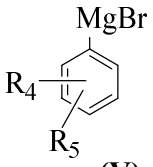
other examples, the subject is a vertebrate animal. In still other examples, the subject is a mammal, which is optionally a primate. In yet other examples, the subject is a human. In certain examples, the subject is a veterinary patient.

[0023] Some examples of the disclosure include a method of increasing autophagy in a cell, comprising contacting a cell with an effective amount of any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative). In other examples, the autophagy is mitophagy. In still other examples, the cell is selected from: embryonic stem cells, induced pluripotent stem cells, adult stem cells, differentiated cells, blood cells, hematopoietic cells, epithelial cells, exocrine cells, endocrine cells, connective tissue cells, adipose cells, bone cells, smooth muscle cells, striated muscle cells, nerve cells, sensory cells, cardiac cells, hepatic cells, gastric cells, intestinal cells, pulmonary cells, kidney cells, and germ cells.

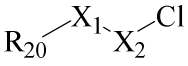
[0024] Some examples of the disclosure include a method of increasing longevity of eukaryotic cells in vitro, comprising contacting the cells with any compound disclosed herein (e.g., Formula (I), (II), (III), (IA), I-1, or I-2, a urolithin derivative) to increase longevity of the cells. In other examples, the eukaryotic cells are eukaryotic cells in primary culture. In yet other examples, the eukaryotic cells are part of a cell line. In certain examples, the eukaryotic cells are cells selected from: embryonic stem cells, induced pluripotent stem cells, adult stem cells, differentiated cells, blood cells, hematopoietic cells, epithelial cells, exocrine cells, endocrine cells, connective tissue cells, adipose cells, bone cells, smooth muscle cells, striated muscle cells, nerve cells, sensory cells, cardiac cells, hepatic cells, gastric cells, intestinal cells, pulmonary cells, kidney cells, and germ cells. In some

examples, the eukaryotic cells are cells selected from: embryonic stem cells, induced pluripotent stem cells, and adult stem cells.

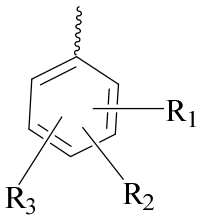
[0025] Some examples of the disclosure include a method for preparing a compound of Formula (I) comprising (a) reacting a compound of Formula (V) with a compound of Formula (VI) to result in a mixture comprising a compound of Formula (VII); (b) reacting the compound of Formula (VII) with a suitable compound to result in a mixture comprising a compound of Formula (I); (c) optionally further reacting the compound of Formula (I) to result in a different compound of Formula (I) so that the identity of one or more of R_1, R_2, R_3, R_4, R_5, X_1 or X_2 is changed by the further reacting; and (d) recovering Formula (I). In other examples, Formula (V) is



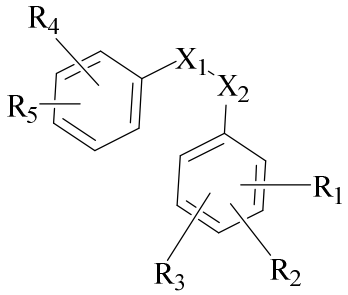
(V) ; Formula (VI) is



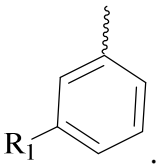
(VI) where R_{20} is a halogen or

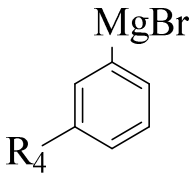


; and Formula (VII) is



(VII) . In certain examples, the suitable compound in step b comprises Ti(IV)chloride, molybdenum(V)chloride, or a combination thereof. In other examples, Formula

(I) is Formula (IA), I-1, or I-2. In yet other examples, R_{20} is Cl or 

. In other examples, Formula (V) is 

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[0026] Other embodiments of the invention are also discussed herein.

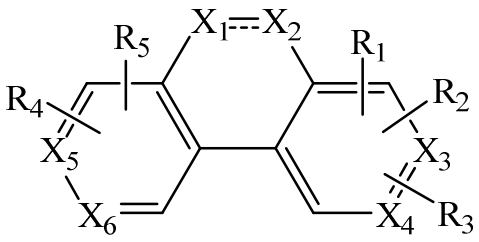
BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the description of specific embodiments presented herein.

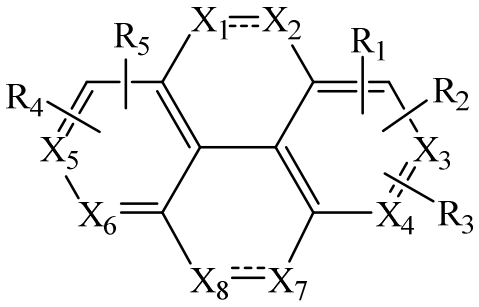
[0028] **FIG. 1**: **UAS03 is a potent anti-inflammatory structural analogue of UroA and induces tight junction proteins.** (**A)** Chemical structures of UroA, UAS03. UroA/UAS03 stability was examined in the presence of gastric pH 2.0 and digestive enzymes. UroA and UAS03 (0.2 mg/ml) were incubated with digestive enzymes (esterases and proteases, 100 U/ml) for 12 h at 37°C and compound levels were quantified. **(B)** BMDMs were stimulated with LPS (50 ng/ml) without or with UroA (blue line) /UAS03 (purple line) (0.1, 1, 10, 25 and 50 µM) for 6 hours. IL-6 and TNF-α levels in supernatants were measured. **(C)** C57BL/6 mice (n=3-4) were pretreated with UroA (20 mg/kg) and UAS03 (20 mg/kg). After 4 hours, LPS (2 mg/kg) was injected intraperitoneally. Post 4 h of LPS administration, serum levels of IL-6 and TNF-α was measured. **(D)** Canonical pathway analysis of RNA-Seq data.

CLAIMS

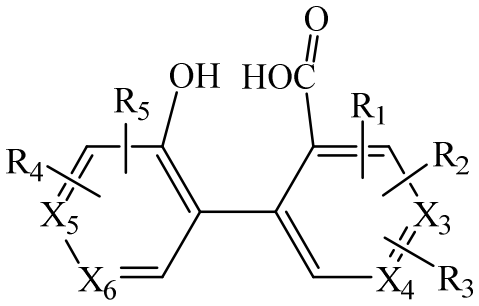
1. A compound selected from



(I),



(II),



(III), salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof,

wherein

- the bond between X_1 and X_2 is a single bond or a double bond;

- the bond between X_7 and X_8 is a single bond or a double bond;

- X_1, X_2, X_7, and X_8 are the same or different and each can be independently selected from CH, CH_2, O, S, C-NH_2, C-N=CH_2, C(H)(NH_2), C=O, C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-S(O)H, C=NC(EtOH)$_3$, C=NCH(EtOH)$_2$, C=NEtOH, C(CH_3)(OH), N, NH, C-halogen, C(H)(halogen), C-(halogen)$_2$, C-

cycloalkyl, C-heterocyclyl, C-aryl, C-heteroaryl, C(H)(cycloalkyl), C(H)(heterocyclyl), C(H)(aryl), or C(H)(heteroaryl), which CH, CH_2, C-NH_2, C-N=CH_2, C(H)(NH_2), C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-S(O)H, C=NC(EtOH)$_3$, C=NCH(EtOH)$_2$, C=NEtOH, C(CH_3)(OH), NH, C(H)(halogen), C-cycloalkyl, C-heterocyclyl, C-aryl, C-heteroaryl, C(H)(cycloalkyl), C(H)(heterocyclyl), C(H)(aryl), or C(H)(heteroaryl), are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl;

- X_1 and X_2 are optionally further cyclized to form a 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl, which 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl;

- X_7 and X_8 are optionally further cyclized to form a 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl, which 5 or 6 membered cycloalkyl, 5 or 6 membered heterocyclyl, 5 or 6 membered aryl, or 5 or 6 membered heteroaryl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl;

- R_1, R_2, R_3, R_4, and R_5 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), -OCF_3, -$COCH_3$, carbonyl, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), amine, -NO_2, sulfo (-SO_3H), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, cycloalkyl, or heterocyclyl, which H, OH, methanoyl (-COH), -$COCH_3$, carbonyl, carboxy (-CO_2H), ethynyl (-CCH), sulfo (-SO_3H), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, cycloalkyl, or heterocyclyl are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl; and

- X_3, X_4, X_5, and X_6 are the same or different and each is independently selected from CH or N, which CH is optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl.

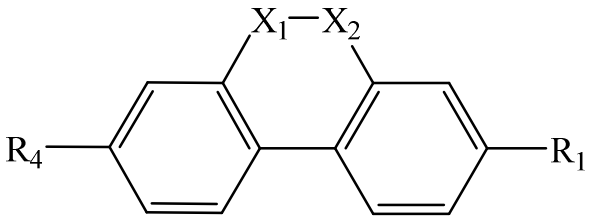
2. The compound of claim 1, wherein X_1, X_2, X_7, and X_8 are the same or different and each can be independently selected from CH_2, O, C(H)(NH_2), C=O, C=N-NH_2, C=NH, C=N-cycloalkyl, C=N-adamantane, C=NC($EtOH)_3$, C=NCH($EtOH)_2$, C=NEtOH, C(CH_3)(OH), or C(H)(cycloalkyl).

3. The compound of claim 1 or claim 2, wherein X_1 and X_2 are the same, X_7 and X_8 is the same, X_1 and X_7 is the same, X_2 and X_8 is the same, or a combination thereof.

4. The compound of any of claims 1-3, wherein X_3, X_4, X_5, and X_6 are the same or different and each is independently selected from CH or N.

5. The compound of any of claims 1-4, wherein R_1, R_2, R_3, R_4, and R_5 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), $-OCF_3$, $-COCH_3$, carbonyl, carboxy ($-CO_2H$), cyano (-CN), amine, $-NO_2$, methoxy, ethoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, cycloalkyl, bicycloalkyl, heterocyclyl, or imidazolyl.

6. The compound of any of claims 1-5, wherein the compound is selected from Formula (IA)



(IA), salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof.

7. The compound of any of claims 1-6, wherein X_1 and X_2 are the same or different and each is independently selected from CH_2, O, $C(H)(NH_2)$, C=O, $C=N-NH_2$, C=NH, C=N-cycloalkyl, $C=NC(EtOH)_3$, $C=NCH(EtOH)_2$, C=NEtOH, $C(CH_3)(OH)$, or C(H)(cycloalkyl), which CH_2, $C(H)(NH_2)$, $C=N-NH_2$, C=NH, C=N-cycloalkyl, $C=NC(EtOH)_3$, $C=NCH(EtOH)_2$, C=NEtOH, $C(CH_3)(OH)$, or C(H)(cycloalkyl), are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-

COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl.

8. The compound of any of claims 1-7, wherein X_1 and X_2 are the same or different and each is independently selected from CH_2, O, C=O, C=NH, C=N-cycloalkyl, C=NC$(EtOH)_3$, C=NCH$(EtOH)_2$, C=NEtOH, C(CH_3)(OH), or C(H)(cycloalkyl).

9. The compound of any of claims 1-8, wherein R_1 and R_2 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), -OCF_3, -$COCH_3$, carbonyl, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), amine, -NO_2, sulfo (-SO_3H), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, ethyl, perfluorinated methyl, perfluorinated ethyl, which H, OH, methanoyl (-COH), -$COCH_3$, carbonyl, carboxy (-CO_2H), ethynyl (-CCH), sulfo (-SO_3H), C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, methyl, or ethyl, are optionally substituted with one or more of halogen, hydroxy (-OH), methanoyl (-COH), -$COCH_3$, carboxy (-CO_2H), ethynyl (-CCH), cyano (-CN), sulfo (-SO_3H), methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl.

10. The compound of any of claims 1-9, wherein R_1 and R_2 are the same or different and each is independently selected from H, OH, halogen, methanoyl (-COH), -OCF_3, -$COCH_3$, carbonyl, carboxy (-CO_2H), cyano (-CN), amine, -NO_2, methoxy, ethoxy, methyl, ethyl, perfluorinated methyl, or perfluorinated ethyl.

11. The compound of any of claims 1-10, the compound (a) is not I-1, I-3, I-5, I-7, I-20, I-26, I-27, I-28, I-33, I-53, I-54, I-55, I-56, I-57, I-59, I-94, I-98, II-99, II-100, II-101, II-102, II-103, II-118, II-119, II-120, II-121, and II-122, (b) is a compound selected from Table 1, or (c) both.

12. A urolithin derivative having a chemical group substitution of the urolithin cyclic ester resulting in improved potency of the derivative as compared to urolithin A, or improved stability of the derivative at acidic pH and/or in presence of esterase and/or protease as compared to urolithin A.

13. The urolithin derivative of claim 12, wherein the urolithin cyclic ester is replaced with a cyclic ether.

14. The urolithin derivative of claim 13, wherein the urolithin cyclic ether comprises one or more substituents.

15. The urolithin derivative of claim 14, wherein the cyclic ether substituents are independently selected from halo, amine, substituted amine, hydroxyl, and a C5 or C6 heterocycle having one or two heteroatoms independently selected from O, N, or S.

16. The urolithin derivative of claim 12, wherein the urolithin cyclic ester is replaced with a carbocycle having adjacent carbonyl groups.

17. The urolithin derivative of claim 12, wherein the urolithin cyclic ester is replaced with a cyclic alkenyl group, which is optionally aromatic, and optionally substituted.

18. The urolithin derivative of claim 17, wherein the cyclic alkenyl group has one or more substituents.

19. The urolithin derivative of claim 18, wherein the cyclic alkenyl group substituents are independently selected from ketone, optionally substituted imine, optionally substituted amine, halo, and hydroxyl.

20. The urolithin derivative of claim 12, wherein the urolithin cyclic ester is replaced with a cyclic amide.

21. The urolithin derivative of claim 12, wherein the urolithin cyclic ester is replaced with a non-cyclic bridge.

22. The urolithin derivative of any one of claims 12 to 21, wherein the urolithin aromatic groups have one or more substituents.

23. The urolithin derivative of claim 22, wherein the aromatic groups are phenyl groups which are optionally substituted.

24. The urolithin derivative of claim 22 or 23, wherein the one or more aromatic substituents are independently selected from hydroxyl, alkoxy, halo, amine, a 5 or 6

membered carbocyclic or heterocyclic ring, nitro, nitrile, alkyl, alkyl ether, and haloalkyl.

25. The urolithin derivative of any one of claims 12 to 24, wherein one or more urolithin aromatic rings are heterocyclic.

26. The urolithin derivative of claim 25, wherein the heteroatoms of the heterocyclic ring are independently selected from N, O, and S.

27. The urolithin derivative of any one of claims 12 to 26, wherein substituents of each aromatic ring together form a second bridging ring.

28. The urolithin derivative of claim 27, wherein the second bridging ring is identical in structure to a first bridging ring.

29. The urolithin derivative of claim 27, wherein the second bridging ring is different in structure to the first bridging ring.

30. A composition comprising a compound of any of claims 1-29.

31. The composition of claim 30, wherein the amount of the compound is from about 0.0001% (by weight total composition) to about 99%.

32. The composition of claim 30 or claim 31, further comprising a formulary ingredient, an adjuvant, or a carrier.

33. The composition of any of claims 30-32, further comprising 5-florouracil.

34. A pharmaceutical composition comprising a compound of any of claims 1-29.

35. The pharmaceutical composition of claim 34, wherein the amount of the compound is from about 0.0001% (by weight total composition) to about 50%.

36. The pharmaceutical composition of claim 34 or claim 35, further comprising a formulary ingredient, an adjuvant, or a carrier.

37. The pharmaceutical composition of any of claims 34-36, further comprising 5-florouracil.

38. A method for providing an animal with a compound comprising one or more administrations of one or more compositions comprising the compound of any of claims 1-29, wherein the compositions may be the same or different if there is more than one administration.

39. The method of claim 38, wherein at least one of the one or more compositions further comprises a formulary ingredient.

40. The method of claim 38 or claim 39, wherein at least one of the one or more compositions comprises the composition of any of claims 30-33 or the pharmaceutical composition of any of claims 34-37.

41. The method of any of claims 38-40, wherein at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration.

42. The method of any of claims 38-41, wherein if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration.

43. The method of any of claims 38-42, wherein the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.01 mg/kg animal body weight to about 50 mg/kg animal body weight.

44. The method of any of claims 38-43, wherein the animal is a human, a rodent, or a primate.

45. Use of one or more compositions comprising the compound of any of claims 1-29 in the manufacture of a medicament for treating an animal for a disease, wherein the use comprising the one of more compositions to be administered once or more times,

wherein the compositions may be the same or different if it is to be administered more than once.

46. The use of claim 45, wherein at least one of the one or more compositions further comprises a formulary ingredient.

47. The use of claim 45 or claim 46, wherein at least one of the one or more compositions comprises the composition of any of claims 30-33 or the pharmaceutical composition of any of claims 34-37.

48. The use of any of claims 45-47, wherein at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration.

49. The use of any of claims 45-48, wherein if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration.

50. The use of any of claims 45-49, wherein the compound of at least one of the one or more compositions is to be administered to the animal in an amount of from about 0.005 mg/kg animal body weight to about 50 mg /kg animal body weight.

51. The use of any of claims 45-50, wherein the animal is a human, a rodent, or a primate.

52. The use of any of claims 45-51, wherein the animal is in need of the treatment.

53. The use of any of claims 45-52, wherein the disease is alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), intestinal permeability, leaky gut, metal induced gut leakiness, stress induced gut leakiness, radiation induced gut permeability, colitis, local inflammation, inflammation in the brain, inflammation in the mouth, inflammation in the esophagus, inflammation in the stomach, inflammation in the small intestine, systemic inflammation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, infection-induced inflammatory disease, sepsis, sepsis-induced kidney injury, sepsis-induced lung injury, scleroderma, vasculitis, drug-induced vasculitis, neuroinflammatory disorders, Alzheimer's Disease, Parkinson's Disease, anxiety, depression, metabolic stress, cardiovascular disease, sarcopenia, muscle degenerative disease, Duchenne muscular dystrophy, nonalcoholic fatty liver disease, drug-induced liver injury, alpha -antitrypsin deficiency, ischemia/reperfusion injury, obesity, metabolic syndrome, type II diabetes mellitus, hyperlipidemia, osteoarthritis, neurodegenerative disease, amyotrophic lateral sclerosis (ALS), cancer, cancerous tumors, breast cancer, colon cancer, cognitive disorder, stress, mood disorder, or fibrosis.

54. The use of any of claims 45-53, wherein the disease is alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), colitis, intestinal permeability, leaky

gut, metal induced gut leakiness, stress induced gut leakiness, radiation induced gut permeability, local inflammation, systemic inflammation, inflammatory bowel disease, ulcerative colitis, Crohn’s disease, infection-induced inflammatory disease, sepsis, sepsis-induced kidney injury, sepsis-induced lung injury, scleroderma, vasculitis, drug-induced vasculitis, neuroinflammatory disorders, Alzheimer’s Disease, Parkinson’s Disease, cancer, cancerous tumors, breast cancer, colon cancer, or fibrosis.

55. The use of any of claims 45-54, wherein the disease is alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), intestinal permeability, leaky gut, metal induced gut leakiness, stress induced gut leakiness, radiation induced gut permeability, local inflammation, systemic inflammation, inflammatory bowel disease, ulcerative colitis, Crohn’s disease, sepsis, Alzheimer’s Disease, Parkinson’s Disease, cancer, cancerous tumors, breast cancer colon cancer, or fibrosis.

56. The use of any of claims 45-55, wherein the disease is vasculitis, drug-induced vasculitis, scleroderma, internal vascular bleeding, drug-induced internal bleeding, atopic dermatitis, perfusion-related injury, perfusion related inflammation, diabetic retinopathy, celiac disease, Non-Alcoholic SteatoHepatitis (NASH), Alcoholic SteatoHepatitis (ASH), metabolic stress, cardiovascular disease, sarcopenia, muscle degenerative disease, Duchenne muscular dystrophy, alcoholic liver disease, nonalcoholic fatty liver disease, drug-induced liver injury, chronic kidney disease, alpha-antitrypsin deficiency, ischemia/reperfusion injury, inflammation, inflammatory bowel disease, Crohn's disease, obesity, metabolic syndrome, type II diabetes

mellitus, hyperlipidemia, osteoarthritis, neurodegenerative disease, neuroinflammatory disorder, Alzheimer's disease, Parkinson's disease, multiple sclerosis, myotrophic lateral sclerosis (ALS), pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute lung injury, blood transfusion related acute lung injury, acute respiratory distress syndrome, asthma, cancer, cognitive disorder, stress, or mood disorder.

57. The use of any of claims 45-56, wherein the disease is cancer and the cancer is pancreatic cancer, pancreatic ductal adenocarcinoma, lung cancer, liver cancer, colorectal cancer, colon cancer, rectal cancer, melanoma, cutaneous malignant melanoma, melanoma tumorigenesis, bladder cancer, prostate cancer, malignant nerve sheath tumors, multiple myeloma, breast cancer, squamous cell carcinoma, head and neck squamous cell carcinoma, lymphoma, leukemia, bone marrow cancer, non-Hodgkin lymphoma, diffuse large B-cell lymphoma, glioblastoma multiforme, endometrial cancer, kidney cancer, basal cell carcinoma, thyroid cancer, neuroblastoma, ovarian cancer, renal cell carcinoma, hepatocellular carcinoma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia, rhabdomyosarcoma, meningioma, gastric cancer, Glioma, oral cancer, nasopharyngeal carcinoma, stomach cancer, uterine cancer, medulloblastoma, cancers that can result in metastasis, cancers resulting from metastasis, or cancerous tumors thereof.

58. Use of an effective amount of a pharmaceutical composition comprising a urolithin structural analogue in the manufacture of a medicant for inducing the

expression of tight junction proteins in a tissue, wherein the pharmaceutical composition is to be administered to a subject in need.

59. Use of an effective amount of the composition of any one of claims 30 to 32 in the manufacture of a medicament for inducing the expression of tight junction proteins in a tissue, wherein the pharmaceutical composition is to be administered to a subject in need.

60. The use of claim 58 or 59, wherein the subject exhibits symptoms of gastrointestinal permeability or inflammation, and the composition is to be administered to the small and/or large intestine.

61. The use of claim 60, wherein the subject has an inflammatory bowel disease.

62. The use of claim 61, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

63. The use of claim 60, wherein the subject has celiac disease.

64. The use of claim 61, wherein the inflammatory bowel disease comprises colonic inflammation.

65. The use of claim 58 or 59, wherein the composition is to be administered systemically in an amount effect to improve endothelial or vascular barrier integrity in organs.

66. The use of claim 65, wherein the organs are one or more selected from liver, kidneys, pancreas, heart, lungs, skin, muscle, fat, brain, eyes, bone, and intestine.

67. The use of claim 66, wherein the subject has a condition selected from vasculitis, drug-induced vasculitis, scleroderma, internal vascular bleeding, drug-induced internal bleeding, atopic dermatitis, perfusion-related injury, perfusion related inflammation, and diabetic retinopathy.

68. Use of an effective amount of a composition of claim 30 in the manufacture of a medicament for treating systemic inflammation, wherein the composition is to be administered to a subject in need thereof.

69. The use of claim 68, wherein the composition is to be administered enterally or parenterally.

70. The use of claim 69, wherein the subject has or is at risk of sepsis or an infection-induced inflammatory disease.

71. The use of claim 69, wherein the subject has or is at risk of alcoholic liver disease (ALD).

72. The use of claim 69, wherein the subject has or is at risk of Non-Alcoholic SteatoHepatitis (NASH) or Alcoholic SteatoHepatitis (ASH).

73. The use of claim 68, wherein the subject has inflammation of one or more organs or tissues selected from liver, kidneys, pancreas, heart, lungs, skin, muscle, fat, brain, eyes, bone, marrow, intestine, and cartilage.

74. Use of an effective amount of a composition of claim 30 in the manufacture of a medicament for treating neuroinflammatory disorder, wherein the composition is to be administered to a subject in need thereof.

75. The use of claim 74, wherein the neuroinflammatory disorder is Alzheimer's Disease.

76. The use of claim 74, wherein the neuroinflammatory disorder is Parkinson's Disease.

77. The use of claim 74, wherein the neuroinflammatory disorder is a neurodegenerative disease, which is optionally multiple sclerosis.

78. Use of an effective amount of the composition of claim 30 in the manufacture of a medicament for treating anxiety or depression, wherein the composition is to be

administered to a subject in need, in an amount effective to inhibit monoamine oxidase enzymes in the subject.

79. The use of claim 78, wherein the composition is to be administered systemically or locally to the brain.

80. The use of claim 79, wherein the composition is to be administered enterally, parenterally, or intranasally.

81. Use of an effective amount of a composition of claim 30 in the manufacture of a medicament for enhancing airway barrier integrity in lungs, wherein the composition is to be administered to a subject in need thereof.

82. The use of claim 81, wherein the subject has pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute lung injury, blood transfusion related acute lung injury, acute respiratory distress syndrome, or asthma.

83. Use of an effective amount of the composition of claim 30 in the manufacture of a medicament for improving or increasing autophagy in a subject, wherein the composition is to be administered to a subject in need thereof.

84. The use of claim 83, wherein autophagy is improved or increased in a tissue or organ of the subject selected from brain, eye, skin, bone, marrow, cartilage, heart, lung, stomach, intestine, liver, pancreas, kidney, muscle, and fat.

85. The use of claim 84, wherein autophagy is improved or increased in cells of the subject selected from adult stem cells, differentiated cells, blood cells, hematopoietic cells, endothelial cells, epithelial cells, exocrine cells, endocrine cells, connective tissue cells, adipose cells, bone cells, smooth muscle cells, striated muscle cells, nerve cells, sensory cells, cardiac cells, hepatic cells, gastric cells, intestinal cells, pulmonary cells, kidney cells, and germ cells.

86. The use of any one of claims 83-84, wherein the subject has a disease or condition selected from metabolic stress, cardiovascular disease, sarcopenia, muscle degenerative disease, Duchenne muscular dystrophy, alcoholic liver disease, nonalcoholic fatty liver disease, drug-induced liver injury, chronic kidney disease, alpha-antitrypsin deficiency, ischemia/reperfusion injury, inflammation, inflammatory bowel disease, Crohn's disease, obesity, metabolic syndrome, type II diabetes mellitus, hyperlipidemia, osteoarthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), cancer, cognitive disorder, stress, and mood disorder, whereby the administering treats or ameliorates the disease or condition.

87. Use of the composition of claim 30 in the manufacture of a medicament for increasing longevity in a subject, wherein a regimen of the composition of claim 30 effective to increase longevity in an animal is to be administered to the subject.

88. The use of any one of claims 58 to 87, wherein the subject is a vertebrate animal.

89. The use of claim 88, wherein the subject is a mammal, which is optionally a primate.

90. The use of claim 89, wherein the subject is a human.

91. The use of claim 88, wherein the subject is a veterinary patient.

92. A method of increasing autophagy in a cell, comprising contacting a cell with an effective amount of a compound of any one of claims 1 to 29.

93. The method of claim 92, wherein the autophagy is mitophagy.

94. The method of claim 92, wherein the cell is selected from: embryonic stem cells, induced pluripotent stem cells, adult stem cells, differentiated cells, blood cells, hematopoietic cells, epithelial cells, exocrine cells, endocrine cells, connective tissue cells, adipose cells, bone cells, smooth muscle cells, striated muscle cells, nerve cells, sensory cells, cardiac cells, hepatic cells, gastric cells, intestinal cells, pulmonary cells, kidney cells, and germ cells.

95. A method of increasing longevity of eukaryotic cells in vitro, comprising contacting the cells with the compound of any one of claims 1 to 29 effective to increase longevity of the cells.

96. The method of claim 95, wherein the eukaryotic cells are eukaryotic cells in primary culture.

97. The method of claim 95 or 96, wherein the eukaryotic cells are part of a cell line.

98. The method of any one of the claims of 95-97, wherein, the eukaryotic cells are cells selected from: embryonic stem cells, induced pluripotent stem cells, adult stem cells, differentiated cells, blood cells, hematopoietic cells, epithelial cells, exocrine cells, endocrine cells, connective tissue cells, adipose cells, bone cells, smooth muscle cells, striated muscle cells, nerve cells, sensory cells, cardiac cells, hepatic cells, gastric cells, intestinal cells, pulmonary cells, kidney cells, and germ cells.

99. The method of claim 98, wherein the eukaryotic cells are cells selected from: embryonic stem cells, induced pluripotent stem cells, and adult stem cells.

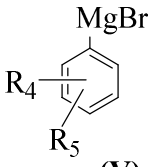
100. A method for preparing a compound of Formula (I) of any of claims 1-11 comprising

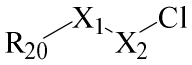
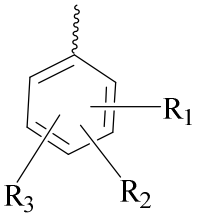
(a) reacting a compound of Formula (V) with a compound of Formula (VI) to result in a mixture comprising a compound of Formula (VII);

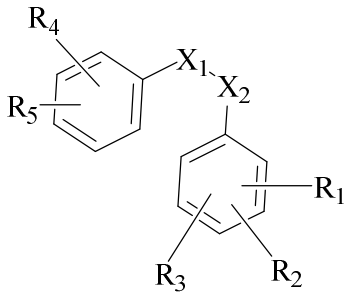
(b) reacting the compound of Formula (VII) with a suitable compound to result in a mixture comprising a compound of Formula (I);

(c) optionally further reacting the compound of Formula (I) to result in a different compound of Formula (I) so that the identity of one or more of R_1, R_2, R_3, R_4, R_5, X_1 or X_2 is changed by the further reacting; and

(d) recovering Formula (I),

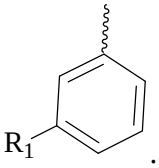
wherein Formula (V) is  **(V)** ;

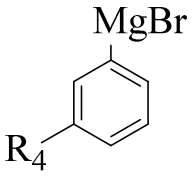
Formula (VI) is  **(VI)** where R_{20} is a halogen or  ;

and Formula (VII) is  **(VII)** .

101. The method of claim 100, wherein the suitable compound in step b comprises Ti(IV)chloride, molybdenum(V)chloride, or a combination thereof.

102. The method of claim 100 or claim 101, wherein Formula (I) is Formula (IA), I-1, or I-2.

103. The method of any of claims 100-102, wherein R_{20} is Cl or  .

104. The method of any of claims 100-103, wherein Formula (V) is 

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