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[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR REDUCING BODY FAT AND ADIPOCYTES

(57) Abstract: Provided are methods and compositions for reducing body fat, and/or adipocytes in a subject, comprising administering a compound and/or natural product extract that is an activator of adenosine monophosphate-activated kinase (AMPK).

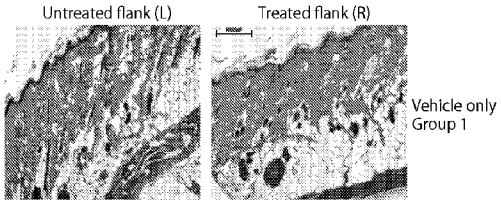


Fig. 1A

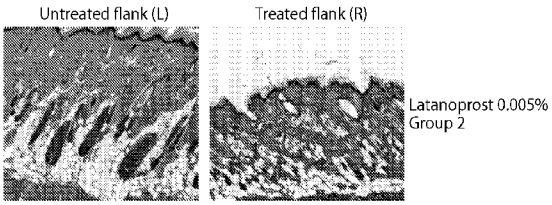


Fig. 1B

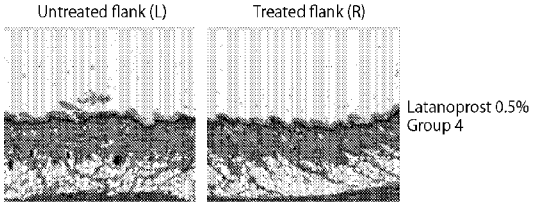


Fig. 1C

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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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METHODS AND COMPOSITIONS FOR REDUCING BODY FAT AND ADIPOCYTES

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 61/773,942 filed March 7, 2013, which is incorporated herein by reference.

Field of the Invention

[0002] The present invention relates to methods and compositions for reducing fat and/or adipocytes in the body of a subject. More specifically, body fat and/or adipocytes, by administering to a subject compounds and/or compositions as described herein.

Background of the Invention

[0003] Excess body fat is an important cause of human disease, disability, and cosmetic disturbance.

[0004] As one form of excess body fat, obesity is responsible for much of the morbidity and health care costs. It is a risk factor for a wide array of diseases, for example, type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, stroke, breast and colon cancer, sleep apnea, gall bladder disease, gastroesophogeal reflux disease, fatty liver, gout, and thromboembolism. Blood pressure, blood sugar, serum cholesterol, and serum uric acid are usually higher in obese people than in those of normal weight. Despite increased awareness of these health risks, the prevalence of obesity has risen steadily for decades in many industrialized nations. As a result, there has been considerable interest in methods to reduce obesity.

[0005] Another problem, which may exist with or without obesity, is excess body fat concentrated on particular portion(s) of the body. This may involve, for example, prominent and undesired deposits of fat on the abdomen, buttocks, thighs, breast, arms, neck, and/or chin. Such local accumulations of body fat (alternatively known as fat maldistribution) may result from disease, hormonal status, or as side effects of medication or other substances. In some cases, there is a desire to remove fat that is displaced, *e.g.,* age-related descent of facial fat pads, descent of submental fat, and orbital fat prolapse (*e.g.,* fat bulging from behind the eyelids).

[0006] Excess body fat is typically deposited in adipose tissue. This tissue and its

principal cell type, the adipocyte, have been implicated in a wide array of diseases, for example, metabolic syndrome, type 2 diabetes, atherosclerosis, fatty liver, hepatic fibrosis, breast cancer, inflammation, depression, and dementia. The causative role of adipose tissue in these diseases appears to involve mediators such as adiponectin, resistin, tumor necrosis factor alpha (TNF–α), interleukin–6 (IL–6), *C*–reactive protein (CRP), fibrinogen, plasminogen activator inhibitor–1 (PAI–1), and/or C–terminal binding protein (CtBP). As a result, the adipocyte *per se*, rather than being a mere storehouse for calories, plays a pathogenic role in many diseases and represents a target for therapeutic intervention.

[0007] A number of medical conditions are considered to be causes of excess body fat. Examples include drug-induced obesity, hypothyroidism, pseudohypoparathyroidism, hypothalamic obesity, polycystic ovarian disease, depression, binge eating, Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, Down syndrome, Turner syndrome, growth hormone deficiency, growth hormone resistance, and leptin deficiency or resistance.

[0008] Disfiguring excess regional fat deposits, for example excess dorsocervical fat, may be found in conditions such as HIV-associated lipodystrophy syndrome, Cushing syndrome and pseudo-Cushing syndrome (*i.e.,* characteristic syndrome of excess body fat and other findings due to excessive endogenous or exogenous corticosteroid levels), other acquired lipodystrophies, familial lipodystrophies, lipoma, lipomatosis, and Madelung disease. For some of these conditions, concentration of fat on particular parts of the body, *e.g.,* dorsocervical fat ("buffalo hump"), facial fat ("moon facies"), visceral fat, and/or lipoma, can make local therapy a preferred option.

[0009] Some tumors, for example lipomas, are characterized by local collections of fat cells that may be amenable to methods used to reduce body fat. Lipomatosis is any condition characterized by the formation of multiple lipomas on the body, *e.g.,* familial multiple lipomatosis, adiposis dolorosis (Dercum's disease), pelvic lipomatosis, etc.

[0010] Medications known to cause obesity or local excesses of body fat include cortisol and analogs, other corticosteroids, megace, sulfonylureas, antiretrovirals, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, oral contraceptives, insulin, risperidone, clozapine, and thiazolidinediones.

[0011] Changes in hormonal status, including physiologic changes such as pregnancy or menopause, may result in excess body fat in a subject. Smoking cessation commonly leads to weight gain and excess body fat. Trauma may favor the accumulation of excess body fat by virtue of immobility or disuse of an extremity. Similar problems may affect an immobile

subject, such as a bedridden subject who is immobilized for an extended period of time.

[0012] Even in the absence of underlying pathology, a subject may have cosmetic or other concerns about body fat. These can usually be attributed to constitutional or hereditary factors, developmental history, age, gender, diet, alcohol use, or other aspects of lifestyle.

[0013] A number of methods have been developed to reduce or remove excess body fat. It is helpful to classify these methods as extractive, metabolic, or adipolytic. Extractive methods, such as lipoplasty (*e.g.*, liposuction) or local excision, are methods whereby fat is physically removed from areas of interest. Such methods are costly and may involve scars, postsurgical deformity or regression, discomfort, infection, and other adverse reactions.

[0014] In contrast to extractive methods, metabolic methods, which include medications, nutritional supplements, devices, and exercise or other body treatment, seek to modify the subject's metabolism (*e.g.*, whether caloric consumption, expenditure, or both) such that the subject incurs a net loss of fat. A disadvantage is potential concomitant loss of water, carbohydrates, protein, vitamins, minerals, and other nutrients. Furthermore, traditional diet medications may have undesired side effects, for example palpitations, tremor, insomnia, and/or irritability in a subject who uses stimulants as appetite suppressants. Despite salubrious value, the traditional metabolic methods of diet and exercise are not practical for everybody.

[0015] Adipolytic methods aim to cause breakdown of adipocytes and/or their lipid contents. For example, fat deposits can be reduced by exposure to cold temperature or to deoxycholate, a solubilizer which lyses cell membranes and results in local necrosis. Drawbacks of these methods can include poor discrimination between adipose and other nearby tissues, barriers to delivery that require hypodermic needles or special equipment, and adverse effects such as necrosis, inflammation, and pain.

[0016] Therefore, there is a need for new methods and compositions for reducing fat and/or adipocytes in a body of a subject. In some circumstances, there is a particular need for new methods and compositions for local administration, whereby therapy can be directed to a particular part of the body for the purpose of minimizing or avoiding systemic drug exposure and/or adverse effects.

[0017] AMP-activated protein kinase (AMPK or AMP kinase) is a heterotrimeric intracellular enzyme that serves as a master regulator of cellular metabolic homeostasis. When AMPK is activated, *e.g.* by phosphorylation of threonine 172, it phosphorylates downstream substrates to exert myriad effects, *e.g.*, regulation of energy homeostasis, autophagy, cell polarity, cell growth and differentiation, and mitochondrial biogenesis and

disposal. See, *e.g.,* Hardie, *Genes Dev.* 2011, 25, 1895-1908. Endogenous physiological activators of AMPK include adenosine monophosphate (AMP), adenosine diphosphate (ADP), and some cytokines and hormones.

[0018] A primary function of AMPK is energy sensing and homeostasis. See, *e.g.,* Hardie, *supra.* AMPK can be activated by an increase in the AMP:ATP or ADP:ATP ratio, reflects metabolic stress. Generally, metabolic stressors can be classified as those that interfere with ATP generation (*e.g.,* glucose deprivation, hypoxia, ischemia, or metabolic poisons) and those that increase ATP consumption (*e.g.*, muscle contraction). In such cases AMPK activation can restore energy homeostasis by phosphorylating certain substrates, for example, acetyl-CoA carboxylase 1 and 2 (ACC1 and ACC2), SREBP 1c, HMG-CoA reductase, and hormone-sensitive lipase. See, *e.g.,* Hardie, *supra.* Phosphorylation of these substrates in skeletal muscle, liver, and adipose tissue down-regulates anabolic pathways, *e.g.* by inhibiting fatty acid synthesis, protein synthesis, lipogenic gene expression, and gluconeogenic gene expression. See, *e.g.,* Hardie, *supra.*

[0019] AMPK can also be activated by Thr 172 phosphorylation by the Ca2+/calmodulin-dependent protein kinase CaMKKβ, providing a Ca2+-activated pathway to switch on AMPK. See, *e.g.,* Hardie, *supra.* The phenomenon can occur without an increase in the AMP:ATP or ADP:ATP ratio.

[0020] AMPK regulates cell division, as well as normal growth and development. See, *e.g.,* Lee *et al. Nature* (2007) 447:1017-1020; Baena-Gonzalez *et al. Nature* (2007) 448:938-942.

Summary of the Invention

[0021] The present invention arises from the observation that local administration of certain AMPK activators to the skin or subcutaneous fat of a subject causes local reduction of body fat and adipocytes in the subject.

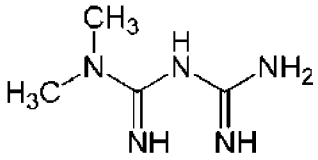
[0022] U.S. Patent 7,666,912, contemplates that local administration (*e.g.,* topical, subcutaneous, intralesional) of certain prostaglandins, *e.g.*, latanoprost and travoprost, would locally reduce fat in a subject at the site of administration. The present inventor(s) have verified this experimentally. Furthermore, the inventor(s) have discovered that this effect, *i.e.,* local reduction of subcutaneous fat and adipocytes, is mediated by local activation of AMPK. Based on this observation, the inventors now contemplate that other AMPK activators can be administered locally (*e.g.,* topically to the skin) to reduce fat or adipocytes

in the body of a subject. For certain uses as described herein, local administration has particular advantages over systemic administration (*e.g.*, the ability to treat particular part(s) of the body without systemic exposure or systemic side effects).

[0023] In one aspect, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject a direct or indirect activator of AMPK.

[0024] In another aspect, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject one or more compounds of the Formulae (**I**), (**II**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX**), (**X**), (**XI**), (**XII**), (**XIII**), (**XIV**), (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XIX**), (**XX**), (**XXI**), (**XXII**), (**XXIII**), (**XXIV**), (**XXV**), (**XXVI**), (**XXVII**), (**XXVIII**), (**XXIX**), and (**XXX**), as described herein, pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

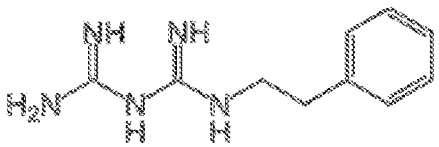
[0025] In certain embodiments, the compound for use in the present invention is of the Formula (**I**):



(**I**)

also described herein as metformin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

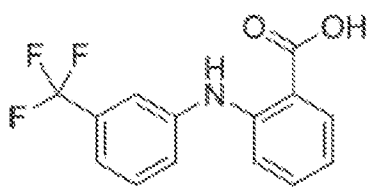
[0026] In certain embodiments, the compound for use in the present invention is of the Formula (**II**):



(**II**)

also described herein as phenformin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

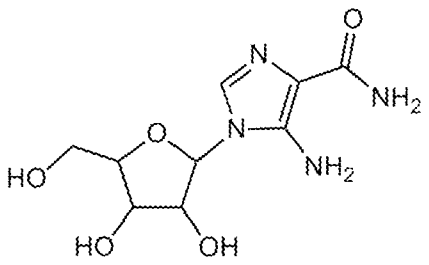
[0027] In certain embodiments, the compound for use in the present invention is of the Formula (**III**):



(**III**)

also described herein as flufenamic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

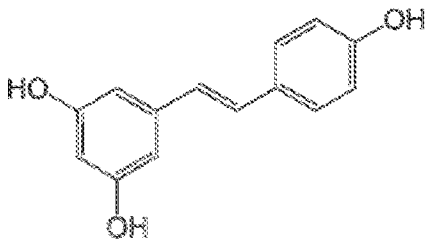
[0028] In certain embodiments, the compound for use in the present invention is of the Formula (**IV**):



(**IV**)

also described herein as AICAR, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

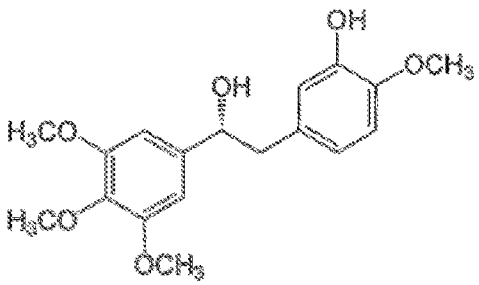
[0029] In certain embodiments, the compound for use in the present invention is of the Formula (**V**):



(**V**)

also described herein as resveratrol, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

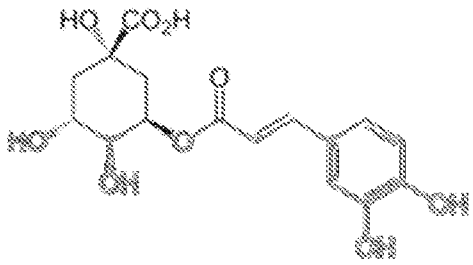
[0030] In certain embodiments, the compound for use in the present invention is of the Formula (**VI**):



(**VI**)

also described herein as combretastatin A4, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

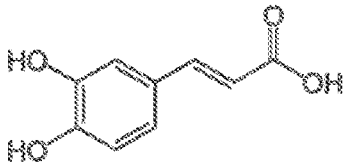
[0031] In certain embodiments, the compound for use in the present invention is of the Formula (**VII**):



(**VII**)

also described herein as chlorogenic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

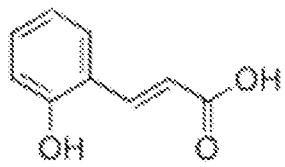
[0032] In certain embodiments, the compound for use in the present invention is of the Formula (**VIII**):



(**VIII**)

also described herein as caffeic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

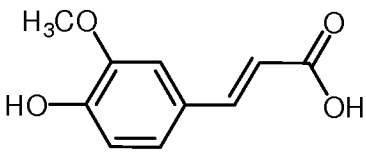
[0033] In certain embodiments, the compound for use in the present invention is of the Formula (**IX**):



(**IX**)

also described herein as *ortho*-coumaric acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

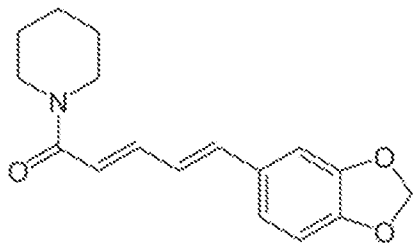
[0034] In certain embodiments, the compound for use in the present invention is of the Formula (**X**):



(**X**)

also described herein as ferulic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

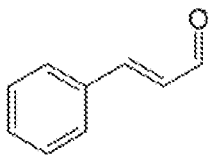
[0035] In certain embodiments, the compound for use in the present invention is of the Formula (**XI**):



(**XI**)

also described herein as piperine, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

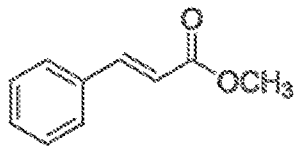
[0036] In certain embodiments, the compound for use in the present invention is of the Formula (**XII**):



(**XII**)

also described herein as cinnamaldehyde, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

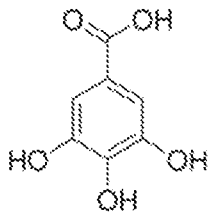
[0037] In certain embodiments, the compound for use in the present invention is of the Formula (**XIII**):



(**XIII**)

also described herein as methyl cinnamate, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

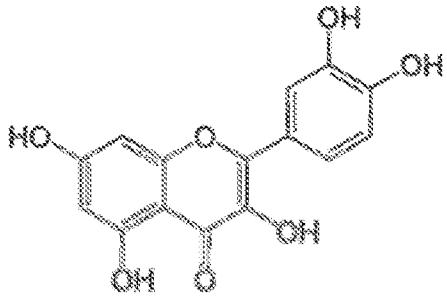
[0038] In certain embodiments, the compound for use in the present invention is of the Formula (**XIV**):



(**XIV**)

also described herein as gallic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

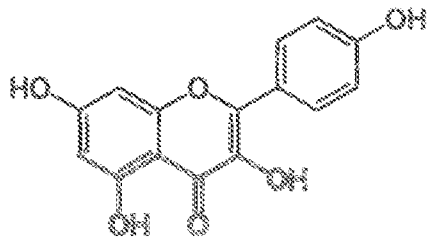
[0039] In certain embodiments, the compound for use in the present invention is of the Formula (**XV**):



(**XV**)

also described herein as quercetin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

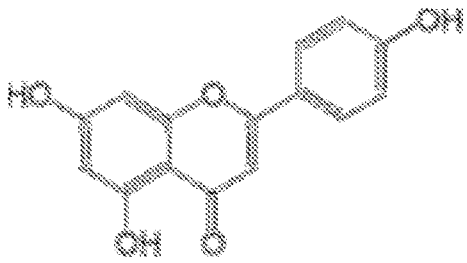
[0040] In certain embodiments, the compound for use in the present invention is of the Formula (**XVI**):



(**XVI**)

also described herein as kaempferol, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

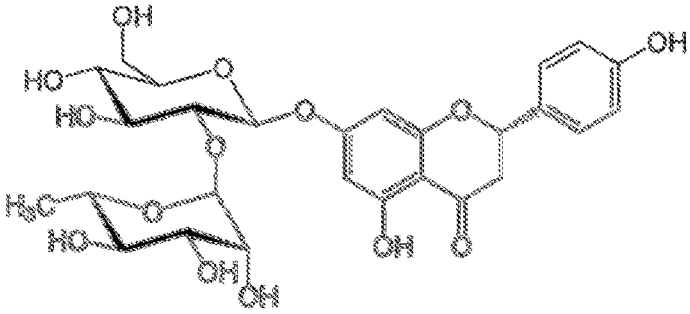
[0041] In certain embodiments, the compound for use in the present invention is of the Formula (**XVII**):



(**XVII**)

also described herein as apigenin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

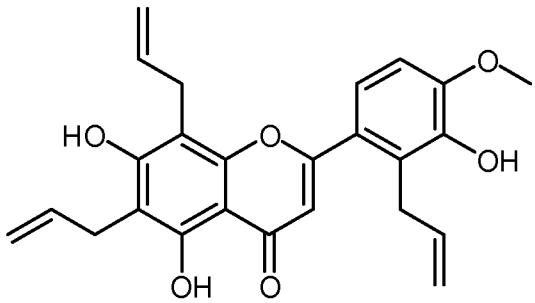
[0042] In certain embodiments, the compound for use in the present invention is of the Formula (**XVIII**):



(**XVIII**)

also described herein as naringin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

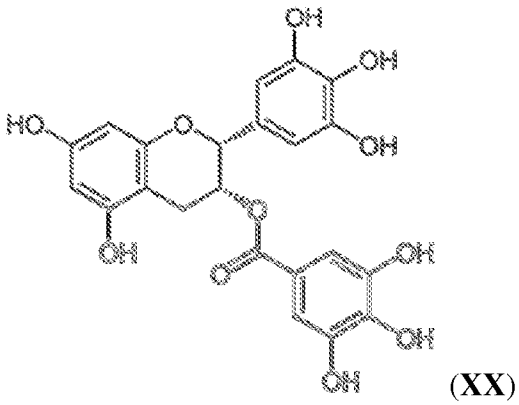
[0043] In certain embodiments, the compound for use in the present invention is of the Formula (**XIX**):



(**XIX**)

also described herein as S17384, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

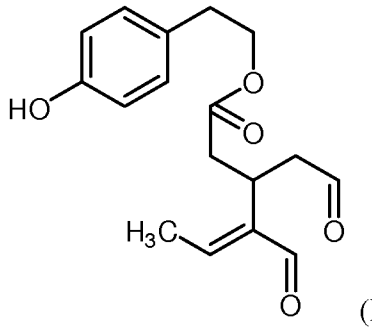
[0044] In certain embodiments, the compound for use in the present invention is of the Formula (**XX**):



(**XX**)

also described herein as epigallocatechin-3-gallate, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

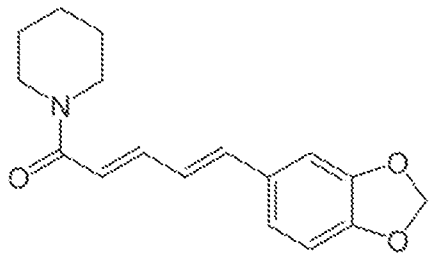
[0045] In certain embodiments, the compound for use in the present invention is of the Formula (**XXI**):



(**XXI**)

also described herein as *para*-HPEA-EDA, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

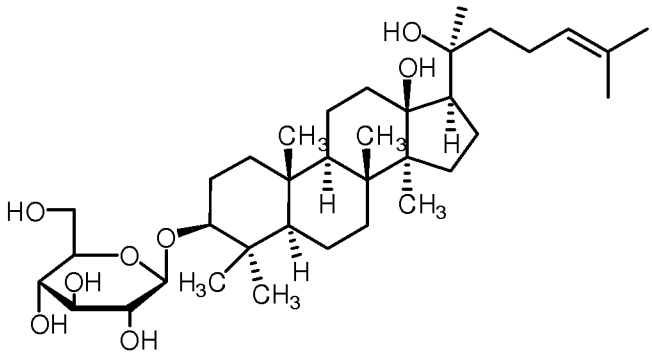
[0046] In certain embodiments, the compound for use in the present invention is of the Formula (**XXII**):



(**XXII**)

also described herein as curcumin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

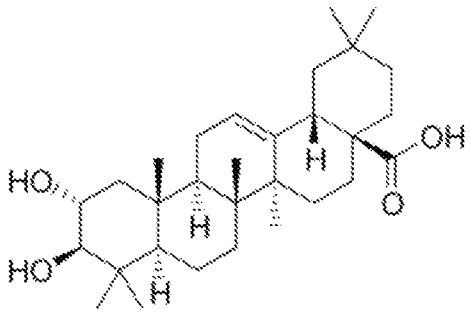
[0047] In certain embodiments, the compound for use in the present invention is of the Formula (**XXIII**):



(**XXIII**)

also described herein as ginsenoside Rh2, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

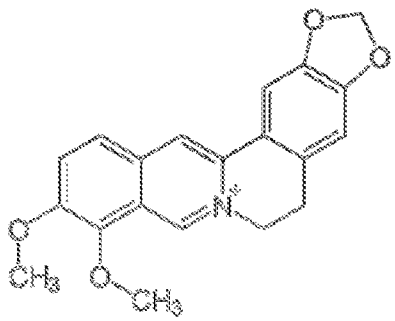
[0048] In certain embodiments, the compound for use in the present invention is of the Formula (**XXIV**):



(**XXIV**)

also described herein as maslinic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

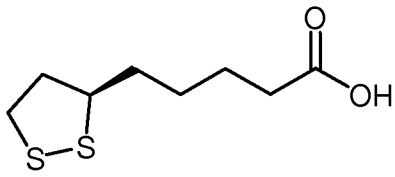
[0049] In certain embodiments, the compound for use in the present invention is of the Formula (**XXV**):



(**XXV**)

also described herein as berberine, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

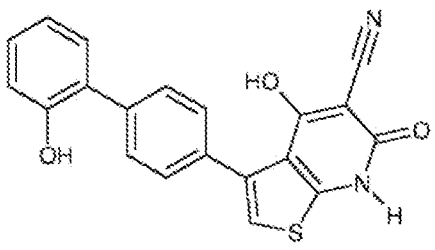
[0050] In certain embodiments, the compound for use in the present invention is of the Formula (**XXVI**):



(**XXVI**)

also described herein as α-lipoic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

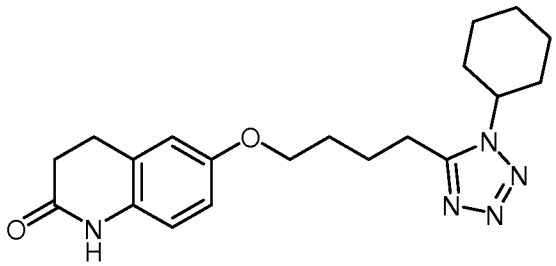
[0051] In certain embodiments, the compound for use in the present invention is of the Formula (**XXVII**):



(**XXVII**)

also described herein as A769662, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

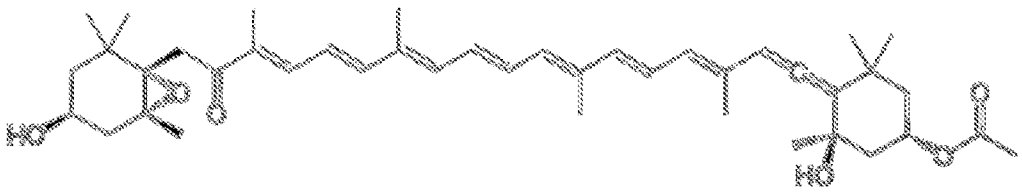
[0052] In certain embodiments, the compound for use in the present invention is of the Formula (**XXVIII**):



(**XXVIII**)

also described herein as cilostazole, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

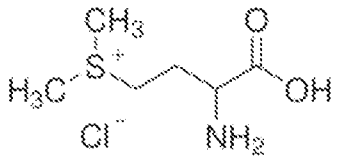
[0053] In certain embodiments, the compound for use in the present invention is of the Formula (**XXIX**):



(**XXIX**)

also described herein as fucoxanthin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

[0054] In certain embodiments, the compound for use in the present invention is of the Formula (**XXX**):



(**XXX**)

also described herein as methyl-methionine sulphonium chloride, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

[0055] In yet another aspect, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject a composition comprising one of more natural product extracts, as described herein.

[0056] In certain embodiments, the natural product extract for use in the present

invention is obtained from a mushroom of the genus *Ganoderma, e.g., Ganoderma lucidum* or *Ganoderma tsugae*.

[0057] In certain embodiments, the natural product extract for use in the present invention is obtained from *Coix lacryma-jobi*, *e.g.,* from the grains thereof.

[0058] In certain embodiments, the natural product extract for use in the present invention is obtained from *Boesenbergia pandurata*, *e.g.,* from the roots thereof.

[0059] In certain embodiments, the natural product extract for use in the present invention is obtained from a tree of the genus *Mangifera, e.g., Mangifera indica*, *e.g.,* from the leaves, fruit, stems, and/or twigs thereof.

[0060] In certain embodiments, the natural product extract for use in the present invention is obtained from a tree of the genus *Combretum*, *e.g.*, *Combretum caffrum* or *Combretum molle*, *e.g.,* from the leaves, fruit, stems, and/or twigs thereof.

[0061] In certain embodiments, the natural product extract for use in the present invention is obtained from *Flor sophorae*, *e.g.,* from the flowers or stems thereof.

[0062] In certain embodiments, the natural product extract for use in the present invention is obtained from *Lysimachia foenum-graecum*, *e.g.,* from the flowers, stems, and/or leaves thereof.

[0063] In any of the above embodiments, administering locally can comprise administering to the skin, administering percutaneously, administering topically, administering subcutaneously, administering by injection (*e.g.,* to a visceral fat deposit), and administering intralesionally (*e.g.,* within a lipoma).

[0064] In certain embodiments, the compound or composition is administered to the skin in a dosage form of a cream, gel, ointment, or lotion. In certain embodiments, the compound or composition is administered to the skin as a percutaneous patch. In certain embodiments, the compound or composition is administered to an adipose depot or lesion as an aqueous injection. In certain embodiments, the compound or composition is administered as a sustained-release injectable form comprising, *e.g.,* biodegradable microspheres.

[0065] In any of the above embodiments, the compound or composition can be administered in a sustained-release formulation.

[0066] In certain embodiments, the method of reducing fat comprises reducing adipocytes.

[0067] In certain embodiments, the subject suffers from a disease or condition characterized in part by a local excess of body fat. In certain embodiments, the disease or condition is selected from the group consisting of HIV-associated lipodystrophy syndrome,

Cushing syndrome, pseudo-Cushing syndrome, a familial lipodystrophy (*e.g.*, familial partial lipodystrophy), lipoma, lipomatosis, Madelung disease, and excess visceral fat.

[0068] In certain embodiments, the subject also suffers from or is likely to suffer from an adipocyte-related disease. In certain embodiments, the adipocyte-related disease is selected from the group consisting of metabolic syndrome, excess body fat (*e.g.*, being overweight, obesity), dyslipidemia, hypercholesterolemia, hypertriglyceridemia, diabetes (*e.g.*, type 2 diabetes), atherosclerosis, vascular disease, coronary artery disease, stroke, cerebrovascular disease, peripheral vascular disease, fatty liver, hepatic fibrosis, pancreatitis, cancer (*e.g.*, breast cancer, uterine cancer, colon cancer, colorectal cancer, kidney cancer, esophageal cancer), inflammation or inflammatory disease, depression, and dementia.

[0069] The foregoing aspects and embodiments of the invention may be more fully understood by reference to the following Detailed Description, Examples, and the Claims.

Definitions

[0070] As used herein, the terms "salt", "acceptable salt", or "pharmaceutically acceptable salt" refer to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate,

sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0071] As used herein, the term "prodrug" means a biologically active derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the pharmacologically active compound. In this instance, the "prodrug" is a compound administered to a subject, and the pharmacologically active compound is the "active metabolite thereof." In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The advantage of a prodrug can lie in its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from across the skin, or it may enhance drug stability for long–term storage.

[0072] As used herein, "polymorph" refers to a compound having more than one crystal structure, *e.g.,* resulting from differences in molecular packing and/or molecular conformation of the compound in the solid state.

[0073] As used herein, the term "hydrate" refers to a compound non–covalently associated with one or more molecules of water. Likewise, "solvate" refers to a compound non–covalently associated with one or more molecules of an organic solvent.

[0074] The term "stereoisomer" as used herein includes geometric isomers, enantiomers, diastereomers, mixtures thereof. A stereoisomer which is provided in excess of one or more other stereoisomers is referred to as "optically enriched." In certain embodiments the compound of the present invention is made up of at least about 90% by weight of a stereoisomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a stereoisomer. Preferred stereisomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.,*

Tetrahedron 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0075] The term "tautomer" as used herein includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.,* a single bond to a double bond, a triple bond to a single bond, or *vice versa*). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.,* the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto–to–enol; amide–to–imide; lactam–to–lactim; enamine–to–imine; and enamine–to–(a different) enamine tautomerizations.

[0076] As used herein, "isotopically labeled derivatives" of a compound refer to derivatives of the compound wherein at least one atom of the compound is enriched for an isotope that is higher or lower in molecular weight than the most abundant isotope of the atom found in nature.

[0077] As used herein, an "individual" or "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)), other primates (*e.g.,* cynomolgus monkeys, rhesus monkeys) and commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs.

[0078] As used herein, and unless otherwise specified, a "therapeutically effective amount" "an amount sufficient" or "sufficient amount" of a compound means the level, amount or concentration of the compound needed to treat a disease, disorder or condition, or to reduce or lower a particular parameter (*e.g.*, adipocytes and/or body fat) in the body of a subject, without causing significant negative or adverse side effects to body or the treated tissue. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease, disorder, or condition, or enhances the therapeutic efficacy of another therapeutically active agent.

[0079] As used herein, the terms "reduce", "reduction", "reducing", "lower", or "lowering" means to diminish or lessen the volume, size, mass, bulk, density, amount, and/or quantity of a substance (*e.g.*, body fat, adipocytes, adipose tissue, lipid concentration) in the body of a subject.

[0080] As used herein, the term "eliminate" means to completely remove any unwanted or undesired volume, size, mass, bulk, density, amount, and/or quantity of a substance (*e.g.*, excess body fat, excess adipocytes, excess adipose tissue) in the body of a subject.

[0081] As used herein, "suffer", "suffers" or "suffering from" refers to a subject having a particular disease, disorder, or condition. As used herein, "likely to suffer" refers to a subject who has not been diagnosed with a particular disease, disorder, or condition by a medical practitioner, but has a predisposition (*e.g.*, genetic and/or physiologic predisposition), or exhibits signs or symptoms of the disease, disorder, or condition.

[0082] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder, or condition, which reduces the severity of the disease, disorder, or condition, or retards or slows the progression of the disease, disorder, or condition.

[0083] As used herein, unless otherwise specified, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a subject begins to suffer from the specified disease, disorder, or condition, which inhibits or reduces the severity of the disease, disorder, or condition.

[0084] As used herein, "local administration" or "administering locally" or "local effect" means administration/application of the active ingredient or active metabolite thereof directly, or in proximity to, a part of the body, tissue, or lesion where said active substance is intended to exert its action. This may include, for example, topical administration to a part of the skin or injection directly into a tissue or lesion where treatment is needed.

[0085] As used herein, "natural product" or "natural product extract" means any substance or chemical compound obtained from a living organism.

Description of Drawings

[0086] *Figures 1A-1C* depict a series of photomicrographs of hematoxylin- and eosin-stained skin and subcutaneous fat from untreated and treated flanks of rats that were treated either with vehicle alone or with latanoprost 0.005% or 0.5%. The images are more fully explained in Example 1. All photos were taken at same scale. Scale bar = 500 microns

[0087] *Figures 2A-2D* depicts photomicrographs of immunostained rat skin and subcutaneous adipocytes, as more fully explained in Example 2. The immunohistochemistry used an antibody specific for activated (phosphorylated) AMPK. Figure 2A: untreated side of a control (vehicle-treated) animal. Figure 2B: treated side of same animal. Figure 2C: untreated side of an animal treated with topical latanoprost. Figure 2D: treated side same

animal (treated with topical latanoprost). All photos were taken at same scale. Scale bar = 100 microns.

Detailed Description of Certain Embodiments of the Invention

[0088] The present invention arises from the observation that local administration of certain AMPK activators to the skin or a fat deposit of a subject causes local reduction of body fat and adipocytes in the subject.

[0089] Systemically administering AMPK activators has been shown to have broad, systemic, endocrine and neuro-endocrine effects which are not expected to occur with local therapy. See, *e.g.,* Gaidhu *et al. J. Lipid Res* (2011) 52:1702-1711. Such effects are not expected to occur with local therapy.

[0090] Because the present invention contemplates therapy in mature adipose tissue in the body of a subject, it is to be distinguished from the effects of some AMPK activators on the differentiation of pre-adipocyte fibroblasts in cell culture. See, *e.g.,* Habinowski and Witters, *Biochem Biophys Res Comm* (2001) 286:852-856; Ha *et al.*, *Bioorg Med Chem Lett* (2010) 20:6076-6081; Ha *et al.; J Med Food* (2010) 13:1331-1339; Huang *et al.; J Agric Food Chem* (2011) 59: 3666-3673; Zhang *et al., J Agric Food Chem* (2011) 59:11526-11533; Lee *et al., Int J Mol Med* (2011) 28:65-71; Chen *et al., J Agric Food Chem* (2012) 60:955-963; Lai *et al., J Agric Food Chem* (2012) 60:1094-1101; Seo *et al., Biochem Biophys Res Comm* (2012) 417:800-806.

[0091] U.S. Patent 7,666,912, contemplates that local administration (*e.g.,* topical, subcutaneous, intralesional) of certain prostaglandins, *e.g.*, latanoprost and travoprost, would locally reduce fat in a subject at the site of administration. The present inventors have verified this experimentally. Furthermore, the inventor(s) have discovered that this effect, *i.e.,* local reduction of subcutaneous fat and adipocytes, is mediated by local activation of AMPK. Based on this observation, the inventors now contemplate that other AMPK activators can be administered locally to reduce fat or adipocytes in the body of a subject. For certain uses as described herein, local administration has particular advantages over systemic administration.

[0092] As disclosed herein, it has also been demonstrated that administration of certain AMPK activators, *e.g.,* latanoprost and travoprost, results not only in reduction of fat in the subject's body on the macroscopic level, but also in the reduction of adipocytes in the subject on the microscopic level. The inventors contemplate that any of a wide array of AMPK activators, if properly formulated for local delivery, can be used to reduce adipocyte

in this manner. When appropriate, treatment can be directed to particular affected areas of the body of the subject. *Local* administration to visceral fat, *e.g.,* central abdominal fat, could nevertheless have benefits for a systemic condition, *e.g.,* metabolic syndrome, hyperlipidemia, insulin resistance, hypertension, etc.

[0093] Thus, in one aspect, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject a direct or indirect activator of AMPK.

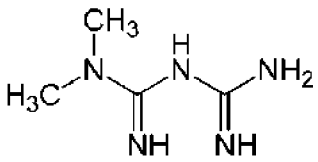
[0094] Without being bound by theory, reduction in fat as a function of administration of the compounds disclosed herein may include reducing the number of fat cells, reducing the volume of one or more fat cells, reducing maturation of one or more fat cells, and/or dedifferentiating one or more fat cells.

Compounds for Use in the Present Invention

[0095] In some embodiments, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject one or more compounds of the Formulae (**I**), (**II**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX**), (**X**), (**XI**), (**XII**), (**XIII**), (**XIV**), (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XIX**), (**XX**), (**XXI**), (**XXII**), (**XXIII**), (**XXIV**), (**XXV**), (**XXVI**), (**XXVII**), (**XXVIII**), (**XXIX**), and (**XXX**), as described herein, pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

[0096] Each of these compounds is a direct or indirect activator of AMPK.

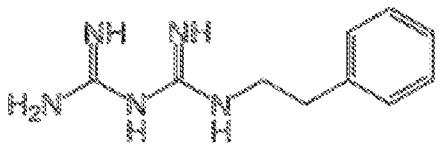
[0097] In certain embodiments, the compound for use in the present invention is of the Formula (**I**):



(**I**)

also described herein as metformin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

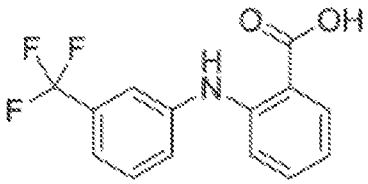
[0098] In certain embodiments, the compound for use in the present invention is of the Formula (**II**):



(**II**)

also described herein as phenformin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

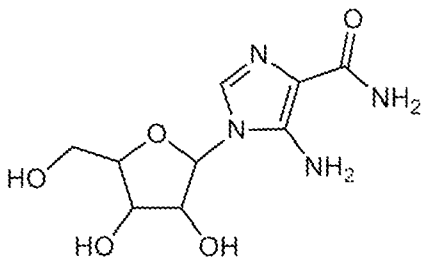
[0099] In certain embodiments, the compound for use in the present invention is of the Formula (**III**):



(**III**)

also described herein as flufenamic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

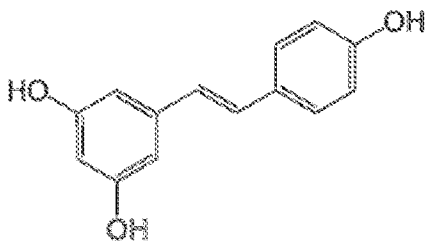
[00100] In certain embodiments, the compound for use in the present invention is of the Formula (**IV**):



(**IV**)

also described herein as AICAR, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

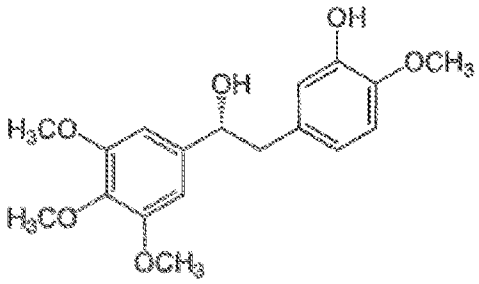
[00101] In certain embodiments, the compound for use in the present invention is of the Formula (**V**):



(**V**)

also described herein as resveratrol, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

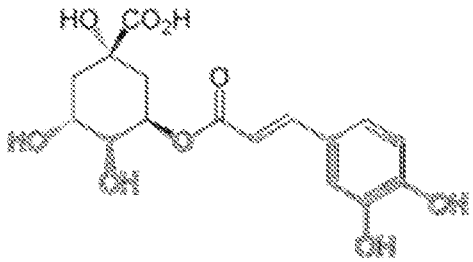
[00102] In certain embodiments, the compound for use in the present invention is of the Formula (**VI**):



(**VI**)

also described herein as combretastatin A4, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

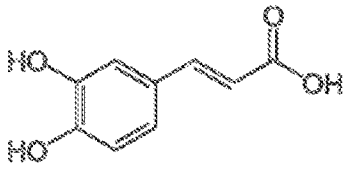
[00103] In certain embodiments, the compound for use in the present invention is of the Formula (**VII**):



(**VII**)

also described herein as chlorogenic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

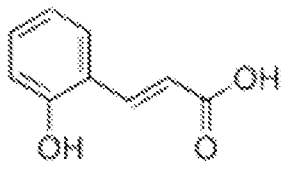
[00104] In certain embodiments, the compound for use in the present invention is of the Formula (**VIII**):



(**VIII**)

also described herein as caffeic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

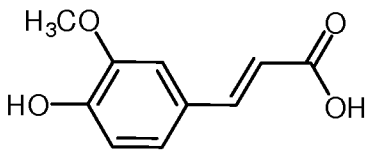
[00105] In certain embodiments, the compound for use in the present invention is of the Formula (**IX**):



(**IX**)

also described herein as *ortho*-coumaric acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

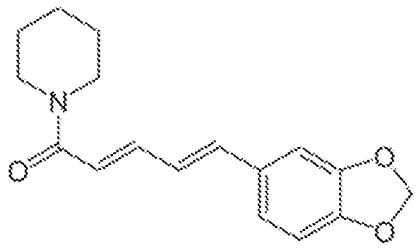
[00106] In certain embodiments, the compound for use in the present invention is of the Formula (**X**):



(**X**)

also described herein as ferulic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

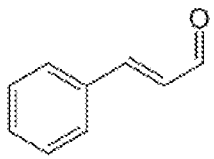
[00107] In certain embodiments, the compound for use in the present invention is of the Formula (**XI**):



(**XI**)

also described herein as piperine, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

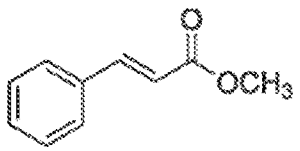
[00108] In certain embodiments, the compound for use in the present invention is of the Formula (**XII**):



(**XII**)

also described herein as cinnamaldehyde, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

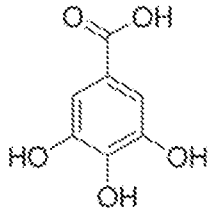
[00109] In certain embodiments, the compound for use in the present invention is of the Formula (**XIII**):



(**XIII**)

also described herein as methyl cinnamate, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

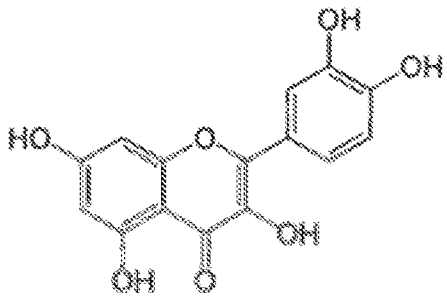
[00110] In certain embodiments, the compound for use in the present invention is of the Formula (**XIV**):



(**XIV**)

also described herein as gallic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

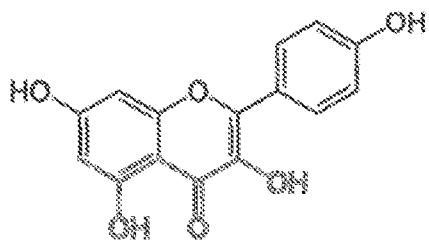
[00111] In certain embodiments, the compound for use in the present invention is of the Formula (**XV**):



(**XV**)

also described herein as quercetin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

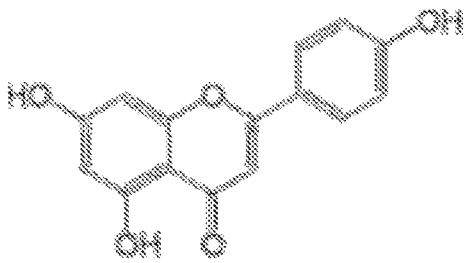
[00112] In certain embodiments, the compound for use in the present invention is of the Formula (**XVI**):



(**XVI**)

also described herein as kaempferol, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

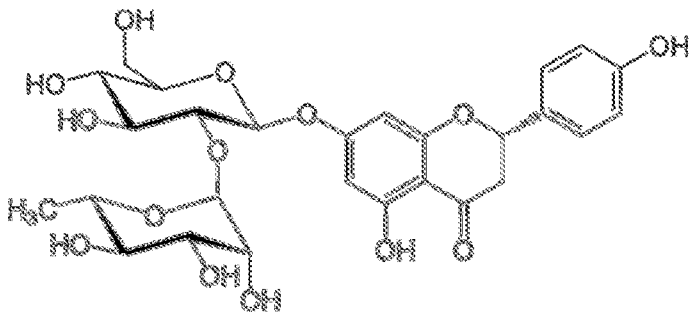
[00113] In certain embodiments, the compound for use in the present invention is of the Formula (**XVII**):



(**XVII**)

also described herein as apigenin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

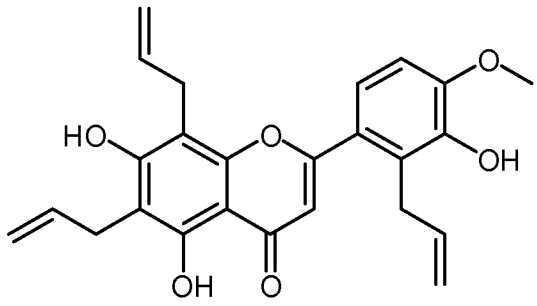
[00114] In certain embodiments, the compound for use in the present invention is of the Formula (**XVIII**):



(**XVIII**)

also described herein as naringin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

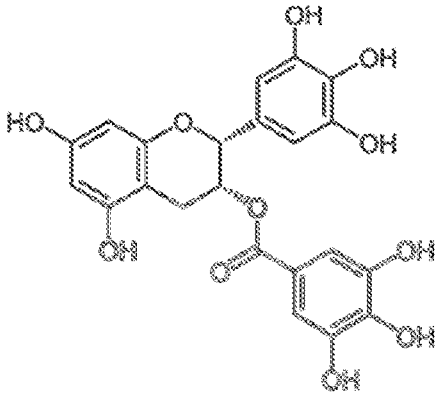
[00115] In certain embodiments, the compound for use in the present invention is of the Formula (**XIX**):



(**XIX**)

also described herein as S17384, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

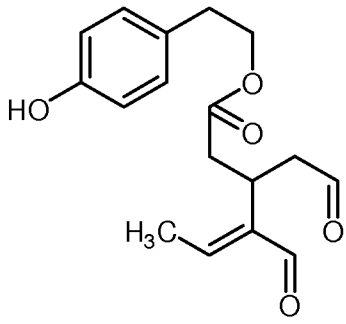
[00116] In certain embodiments, the compound for use in the present invention is of the Formula (**XX**):



(**XX**)

also described herein as epigallocatechin-3-gallate, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

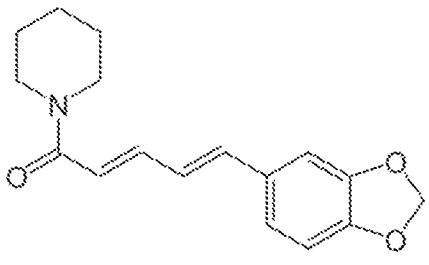
[00117] In certain embodiments, the compound for use in the present invention is of the Formula (**XXI**):



(**XXI**)

also described herein as *para*-HPEA-EDA, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

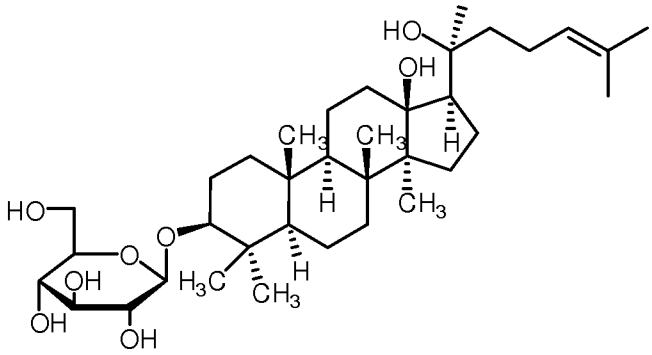
[00118] In certain embodiments, the compound for use in the present invention is of the Formula (**XXII**):



(**XXII**)

also described herein as curcumin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

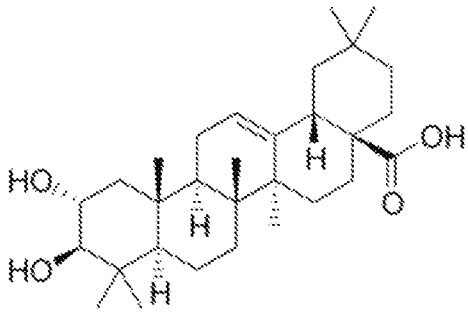
[00119] In certain embodiments, the compound for use in the present invention is of the Formula (**XXIII**):



(**XXIII**)

also described herein as ginsenoside Rh2, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

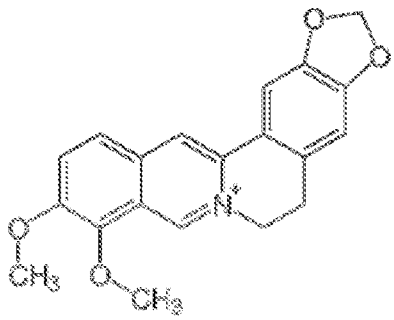
[00120] In certain embodiments, the compound for use in the present invention is of the Formula (**XXIV**):



(**XXIV**)

also described herein as maslinic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

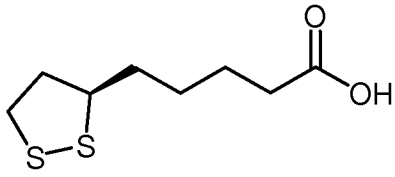
[00121] In certain embodiments, the compound for use in the present invention is of the Formula (**XXV**):



(**XXV**)

also described herein as berberine, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

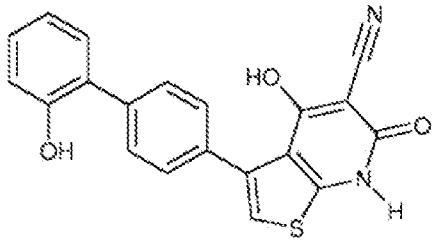
[00122] In certain embodiments, the compound for use in the present invention is of the Formula (**XXVI**):



(**XXVI**)

also described herein as α-lipoic acid, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

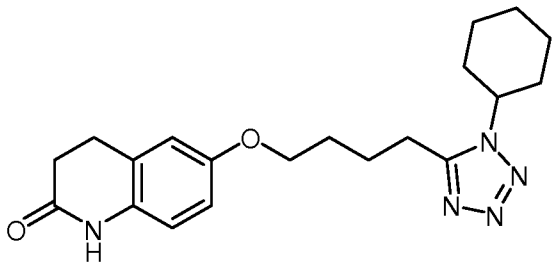
[00123] In certain embodiments, the compound for use in the present invention is of the Formula (**XXVII**):



(**XXVII**)

also described herein as A769662, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

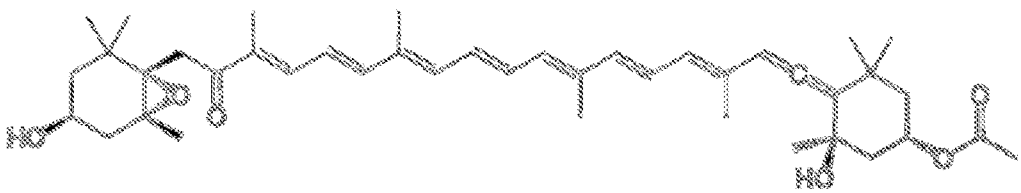
[00124] In certain embodiments, the compound for use in the present invention is of the Formula (**XXVIII**):



(**XXVIII**)

also described herein as cilostazol, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

[00125] In certain embodiments, the compound for use in the present invention is of the Formula (**XXIX**):

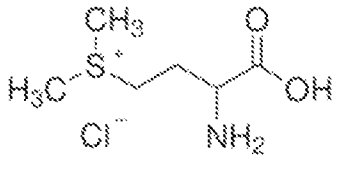


(**XXIX**)

also described herein as fucoxanthin, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

[00126] In certain embodiments, the compound for use in the present invention is of

the Formula (**XXX**):



(**XXX**)

also described herein as methyl-methionine sulphonium chloride, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

Natural Product Extracts for Use in the Present Invention

[00127] In some embodiments, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject a composition comprising one of more natural product extracts, as described herein.

[00128] Methods for preparing natural product extracts from plants and/or fungi are generally known in the art. See, *e.g.,* Hoffmann, *Herbalism: the science and practice of herbal medicine,* Healing Arts Press, 2003.

[00129] In certain embodiments, the natural product extract for use in the present invention is obtained from a mushroom of the genus *Ganoderma, e.g., Ganoderma lucidum* or *Ganoderma tsugae*.

[00130] In certain embodiments, the natural product extract for use in the present invention is obtained from *Coix lacryma-jobi*, *e.g.,* from the grains thereof.

[00131] In certain embodiments, the natural product extract for use in the present invention is obtained from *Boesenbergia pandurata*, *e.g.,* from the roots thereof.

[00132] In certain embodiments, the natural product extract for use in the present invention is obtained from a tree of the genus *Mangifera, e.g., Mangifera indica*, *e.g.,* from the leaves, fruit, stems, and/or twigs thereof.

[00133] In certain embodiments, the natural product extract for use in the present invention is obtained from a tree of the genus *Combretum*, *e.g.*, *Combretum caffrum* or *Combretum molle*, *e.g.,* from the leaves, fruit, stems, and/or twigs thereof.

[00134] In certain embodiments, the natural product extract for use in the present invention is obtained from *Flor sophorae*, *e.g.,* from the flowers thereof.

[00135] In certain embodiments, the natural product extract for use in the present invention is obtained from *Lysimachia foenum-graecum*, *e.g.,* from the flowers, stems, and/or

leaves thereof.

Pharmaceutical Compositions and Formulations

[00136] In certain embodiments, the present invention provides pharmaceutical compositions and formulations for use in any of the inventive methods, described herein, *e.g.*, comprising a direct or indirect activator of AMPK. In certain embodiments, the pharmaceutical composition comprises a natural product extract as described herein and/or one or more compounds of the Formulae (**I**), (**II**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX**), (**X**), (**XI**), (**XII**), (**XIII**), (**XIV**), (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XIX**), (**XX**), (**XXI**), (**XXII**), (**XXIII**), (**XXIV**), (**XXV**), (**XXVI**), (**XXVII**), (**XXVIII**), (**XXIX**), and (**XXX**) (collectively referred to herein as the "active ingredient") and, optionally, a pharmaceutically acceptable excipient.

[00137] Pharmaceutically acceptable excipients include any and all solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in the formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00138] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the active ingredient into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

[00139] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

[00140] Relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and

further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00141] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00142] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and combinations thereof.

[00143] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and combinations thereof.

[00144] Exemplary surface active agents and/or emulsifiers include lipids/natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate

[Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* Cremophor), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether [Brij 30]), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, *etc.* and/or combinations thereof.

[00145] Exemplary binding agents include starch (*e.g.* cornstarch and starch paste), gelatin, sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, *etc.*, and/or combinations thereof.

[00146] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00147] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00148] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol,

ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00149] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00150] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00151] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00152] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00153] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and combinations thereof.

[00154] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, *etc.*, and combinations thereof.

[00155] Exemplary oils include almond, apricot kernel, avocado, babassu, bergamot,

black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[00156] Liquid dosage forms for parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents (*e.g.*, ethyl carbonate, ethyl acetate, benzyl benzoate, dimethylformamide), fatty acid esters of sorbitan, polysorbates, solubilizing agents such as alcohols (*e.g.*, ethyl alcohol, isopropyl alcohol, tetrahydrofurfuryl alcohol, benzyl alcohol, glycerol and glycols (*e.g.*, 1,3–butylene glycol, propylene glycol, polyethylene glycols)), oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), Cremophor, cyclodextrins, polymers) and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments, for parenteral administration, the active ingredient is mixed with solubilizing agents such as Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

[00157] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the

preparation of injectables.

[00158] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00159] Time release formulations, including but not limited to, sustained-release (SR), sustained-action (SA), extended-release (ER, XR, or XL), timed-release (TR), controlled-release (CR), modified release (MR), and continuous-release (CR) formulations, refer to solid dosage forms useful in releasing an active ingredient at a predetermined rate by maintaining a constant level of the active ingredient or active metabolite thereof in the bloodstream for a specific period of time with minimum side effect. Time-release formulations may comprise imbedding the active ingredient in a matrix of insoluble particles, micro-encapsulation, use of liposomes and/or use of hydrogels.

[00160] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the active ingredient with a suitable non–irritating excipient or carrier such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00161] Dosage forms for topical and/or transdermal administration of an active ingredient may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00162] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which

deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00163] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00164] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically–administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[00165] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the formulation and/or manufacture of

pharmaceutical compositions can be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005.

[00166] Still further encompassed by the invention are pharmaceutical packs and/or kits. Pharmaceutical packs and/or kits provided may comprise a provided composition and a container (*e.g.*, a vial, ampoule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a suitable aqueous carrier for dilution or suspension of the provided composition for preparation of administration to a subject. In some embodiments, contents of provided formulation container and solvent container combine to form at least one unit dosage form.

[00167] The active ingredient can be administered using any amount and any route of administration effective for treatment. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular composition, its mode of administration, its mode of activity, and the like.

[00168] The active ingredient is typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the condition being treated and the severity of the condition; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00169] The exact amount of the active ingredient required to achieve a therapeutically effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more

administrations). As demonstrated in the accompanying Examples, daily administration to the subject can be adequate (but not necessarily preferable) to achieve the desired effect. A daily administration schedule is considered convenient for human use. The active ingredient may be administered by the subject to himself or herself repeatedly and without special equipment or training, although a medical professional also can also administer the active ingredient to the subject.

[00170] In certain embodiments, a therapeutically effective amount of the active ingredient for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of the active ingredient per unit dosage form. A therapeutically effective concentration may comprise between about 0.0001% to about 5.0% (w/v) in liquid or semisolid formulations. It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00171] It will be also appreciated that the active ingredient can be administered in combination with one or more additional therapeutically active agents ("agents" or "active agents"). The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional agents. In general, the active ingredient and each additional active agent will be administered at a dose and/or on a time schedule determined for the ingredient and agent. In will further be appreciated that the active ingredient and active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of the active ingredient with the active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00172] The active ingredient can be administered in combination with active agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that

therapy employed may achieve a desired effect for the same disorder (for example, an active ingredient can be administered in combination with an anti–inflammatory and/or anti–depressive agent, *etc.*), and/or it may achieve different effects (*e.g.*, control of adverse side–effects).

[00173] Exemplary active agents include, but are not limited to, antibiotics, anti-obesity agents, anesthetics, anti–coagulants, steroidal agents, steroidal anti–inflammatory agent, non–steroidal anti–inflammatory agents, antihistamines, immunosuppressant agents, antigens, vaccines, antibodies, opioids, pain–relieving agents, analgesics, hormones, prostaglandins, progestational agents, anti–glaucoma agents, ophthalmic agents, anti–cholinergics, anti–depressants, anti–psychotics, hypnotics, tranquilizers, anti–convulsants/anti-epileptics (*e.g.*, Neurontin, Lyrica, valproates (*e.g.*, Depacon), and other neurostabilizing agents), muscle relaxants, anti–spasmodics, muscle contractants, channel blockers, miotic agents, anti–secretory agents, anti–thrombotic agents, anticoagulants, anti–cholinergics, β–adrenergic blocking agents, diuretics, cardiovascular active agents, vasoactive agents, vasodilating agents, anti–hypertensive agents, angiogenic agents, modulators of cell–extracellular matrix interactions (*e.g.* cell growth inhibitors and anti–adhesion molecules), or inhibitors/intercalators of DNA, RNA, protein–protein interactions, protein–receptor interactions, *etc.* Active agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the Food and Drugs Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

Methods for Reducing Body Fat and Adipocytes

[00174] In one aspect, the invention provides a method for reducing body fat and/or adipocytes in a subject in need thereof, the method comprising administering locally to the subject a direct or indirect activator of AMPK. In certain embodiments, the method comprising administering locally to the subject one or more natural product extracts and/or one or more compounds of the Formulae (**I**), (**II**), (**III**), (**IV**), (**V**), (**VI**), (**VII**), (**VIII**), (**IX**), (**X**), (**XI**), (**XII**), (**XIII**), (**XIV**), (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XIX**), (**XX**), (**XXI**), (**XXII**), (**XXIII**), (**XXIV**), (**XXV**), (**XXVI**), (**XXVII**), (**XXVIII**), (**XXIX**), and (**XXX**), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer,

isotopically enriched derivative, or prodrug thereof.

[00175] In certain embodiments, the natural product extract for use in the present invention is obtained from a mushroom of the genus *Ganoderma, e.g., Ganoderma lucidum* or *Ganoderma tsugae*.

[00176] In certain embodiments, the natural product extract for use in the present invention is obtained from *Coix lacryma-jobi*, *e.g.,* from the grains thereof.

[00177] In certain embodiments, the natural product extract for use in the present invention is obtained from *Boesenbergia pandurata*, *e.g.,* from the roots thereof.

[00178] In certain embodiments, the natural product extract for use in the present invention is obtained from a tree of the genus *Mangifera, e.g., Mangifera indica*, *e.g.,* from the leaves, fruit, stems, and/or twigs thereof.

[00179] In certain embodiments, the natural product extract for use in the present invention is obtained from a tree of the genus *Combretum*, *e.g.*, *Combretum caffrum* or *Combretum molle*, *e.g.,* from the leaves, fruit, stems, and/or twigs thereof.

[00180] In certain embodiments, the natural product extract for use in the present invention is obtained from *Flor sophorae*, *e.g.,* from the flowers thereof.

[00181] In certain embodiments, the natural product extract for use in the present invention is obtained from *Lysimachia foenum-graecum*, *e.g.,* from the flowers, stems, and/or leaves thereof.

[00182] Fat reduction can include reducing fat as measured by at least one of volume, size, mass, bulk, density, amount, and/or quantity. The present invention is expected to reduce fat by greater than or equal to 75%, greater than or equal to 70%, greater than or equal to 60%, greater than or equal to 50%, greater than or equal to 40%, greater than or equal to 30%, greater than or equal to 25%, greater than or equal to 20%, greater than or equal to 15%, greater than or equal to 10%, or greater than or equal to 5%. For example, fat reduction can also include reducing fat cell amount (for example, fat cell number), reducing fat cell volume, reducing fat cell maturation, and/or dedifferentiating a fat cell.

[00183] The present method encompasses administering one or more inventive compounds and/or natural product extracts to a subject by any suitable local route (*e.g.*, topically, dermally, subcutaneously, intralesionally), in an amount sufficient to reduce body fat in a subject.

[00184] In certain embodiments, the subject has excess body fat. As used herein, "excess body fat" refers to any unwanted fatty tissue on the subject's body, and encompasses a subject who is not overweight but has excess body fat, or a subject who is overweight.

[00185] In certain embodiments, the subject is overweight. "Overweight" is a medical condition, and is defined by the subject's body mass index (BMI). Any subject with a BMI of greater than or equal to 25 is considered overweight. An overweight subject encompasses pre-obese subjects (*e.g.*, having a BMI of between 25 and 30) and obese subjects (*e.g.*, having a BMI of greater than or equal to 30).

[00186] In certain embodiments, the overweight subject is obese and suffers from obesity. Any subject with a BMI of between 35 and 40, inclusive, is considered "severely obese" and suffers from "super obesity". Any subject with a BMI between 40 and 45 is considered "morbidly obese" and suffers from "morbid obesity". Any subject with a BMI greater than or equal to 45 is considered "super obese" and suffers from "super obesity".

[00187] In certain embodiments, the subject has excess body fat as a side effect of medication (*e.g.*, for example, cortisol and analogs, corticosteroids, megace, sulfonylureas, anti-retrovirals, antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, oral contraceptives, insulin or a form of insulin, risperidone, clozapine, and thiazolidinediones).

[00188] In certain embodiments, the subject has excess body fat due to changes in hormonal status (*e.g.*, as a result of physiologic changes such as pregnancy or menopause).

[00189] In certain embodiments, the subject with excess body fat is undergoing or has recently undergone smoking cessation.

[00190] In certain embodiments, the subject has excess body fat due to immobility or disuse of an extremity.

[00191] In certain embodiments, the subject suffers from obesity, drug-induced obesity, HIV-associated lipodystrophy syndrome, hypothyroidism, pseudohypoparathyroidism, hypothalamic obesity, polycystic ovarian disease, depression, binge eating, postpartum obesity, obesity associated with smoking cessation, Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, Down syndrome, Turner syndrome, growth hormone deficiency, growth hormone resistance, leptin deficiency or resistance, Cushing syndrome, pseudo-Cushing syndrome, dorsocervical fat hypertrophy ("buffalo hump"), moon facies, HIV lipodystrophy, other acquired lipodystrophy, familial lipodystrophy, lipoma, lipomatosis, or Madelung disease

[00192] In certain embodiments, the subject is not overweight. For example, the method of reducing body fat in a subject is useful for not only treating obesity in a subject, but also useful in treating subjects who are not overweight, but still desire to increase the proportion of lean body mass to total body mass.

[00193] In certain embodiments, the methods of the present invention are useful in increasing the proportion of lean body mass to total body mass in a subject.

[00194] This aspect of invention may also be useful as an adjunct to any of various kinds of surgery, whether used in the pre-operative, peri-operative, or post-operative period. The invention further contemplates uses preceding abdominal, thoracic, oncologic, endocrine, neurologic, transplant, and dermatologic surgery, whereby surgical exposure may be improved; and preceding or following orthopedic procedures, whereby surgical exposure as well as post-operative recovery may be improved.

[00195] In certain embodiments, methods and compositions of the present invention are useful for local reduction of orbital fat in Graves disease (thyroid-related orbitopathy), whereby the orbital contents can be decompressed and exophthalmos treated by reduction in the overall volume of orbital contents.

[00196] Reducing adipocytes in a subject includes, but is not limited to, reducing fat cell amount (*e.g.*, for example, fat cell number), reducing fat cell volume, reducing fat cell formation, reducing fat cell maturation, dedifferentiating a fat cell, and/or inducing the death of a fat cell (*e.g.,* for example, by apoptosis) as measured by at least one of volume, size, mass, bulk, density, amount, and/or quantity. In certain embodiments, the method of reducing adipocytes comprises reducing the fat cell amount, reducing fat cell volume, reducing fat cell formation, or reducing fat cell maturation, in a subject by greater than or equal to 75%, greater than or equal to 70%, greater than or equal to 60%, greater than or equal to 50%, greater than or equal to 40%, greater than or equal to 30%, greater than or equal to 25%, greater than or equal to 20%, greater than or equal to 15%, greater than or equal to 10%, or greater than or equal to 5%.

[00197] The active ingredient can be administered by any suitable local route, parenteral (*e.g.*, subcutaneous, intradermal, intralesional, *e.g.,* as in a lipoma), and topical administration (*e.g.*, transdermal, transmucosal, ophthalmic). In general the most appropriate route of administration will depend upon a variety of factors including the nature of the active ingredient (*e.g.*, its stability in the part of body where it is administered), the condition of the subject (*e.g.*, whether the subject is able to tolerate subcutaneous administration), *etc.*

[00198] It should be understood that, in certain embodiments, treatment of an adipocyte-related disease can be accomplished by reduction of adipocytes that is microscopic rather than macroscopic, or diffuse rather than focal.

[00199] Thus, in certain embodiments, the present invention also contemplates a method of treating an adipocyte-related disease, comprising administering locally to a subject

in need thereof one or more of the compounds and/or natural product extracts described herein within the scope of the invention.

[00200] As used herein, "adipocyte-related disease" means a disease: (i) wherein reduction of adipocytes treats the disease, disorder, or condition from which the subject is suffering; or (ii) whose mechanism comprises an adipocyte and/or its molecular products, *e.g.*, secreted proteins, *e.g.*, adiponectin, resistin, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and/or C-terminal binding protein (CtBP).

[00201] Exemplary adipocyte-related diseases include, but are not limited to, metabolic syndrome, excess body fat (*e.g.*, being overweight, obesity), dyslipidemia, hypercholesterolemia, hypertriglyceridemia, diabetes (*e.g.*, type 2 diabetes), atherosclerosis, vascular disease, coronary artery disease, stroke, cerebrovascular disease, peripheral vascular disease, fatty liver, hepatic fibrosis, pancreatitis, cancer (*e.g.*, breast cancer, uterine cancer, colon cancer, colorectal cancer, kidney cancer, esophageal cancer), inflammation or inflammatory disease, depression, and dementia. In certain embodiments, the adipocyte-related disease is selected from the group consisting of metabolic syndrome, diabetes (*e.g.*, type 2 diabetes), liver disease, atherosclerosis, fatty liver, hepatic fibrosis, breast cancer, colon cancer, inflammation or inflammatory disease, depression, and dementia.

Examples

[00202] In light of the foregoing description, the specific non-limiting examples presented below are for illustrative purposes and not intended to limit the scope of the invention in any way.

Example 1

[00203] A randomized controlled trial was conducted on Zucker Diabetic Fatty Rats, which are defective for the leptin receptor (Charles River Laboratories). These rats are hyperphagic and consequently obese, hyperglycemic, and hyperlipidemic. Rats approximately eight weeks old were prospectively randomized into groups and assigned to the following treatment conditions (n = 3 animals per group):

Table I.

Group	Compound	Formulation (w/v)	Dose

1	Untreated	not applicable	
2	Latanoprost	0.005% topical cream	0.3 cc subcutaneously, daily
3	Latanoprost	0.5% topical cream	0.3 cc subcutaneously, daily

[00204] Animals were fed *ad libitum* and weighed daily for 28 days. On Day 28 necropsy was performed, and samples of skin and subcutaneous fat were collected for immunohistochemistry.

[00205] *Figures 1A-1C* show hematoxylin and eosin-stained histologic sections from the aforementioned samples. Latanoprost 0.005% (Group 2) was associated with local reduction of the subcutaneous adipose layer and adipocyte size at the treatment site but not on the contralateral, untreated flank. Latanoprost 0.5% (Group 3) was associated with similar reductions in adipose thickness and adipocyte size, but on both treated and untreated flanks, indicative of a systemic effect. All photos are at same scale; scale bar = 500 microns.

[00206] *Figures 2A-2D* show histologic sections from the aforementioned samples stained with a monoclonal antibody specific for activated AMPK (phosphorylated threonine 172): untreated flank of control animal (treated with vehicle only) (A); treated flank of same control animal (B); untreated flank of animal treated with latanoprost 0.5% with faint immunoreactivity for phosphorylated AMPK in subcutaneous tissues, indicative of a mild systemic effect (C); and treated flank of same animal shows cutaneous and subcutaneous immunoreactivity for phosphorylated AMPK, indicative of a strong local effect (D). A-D are depicted at same scale (scale bar = 100 microns).

[00207] The results show that local administration of latanoprost, a prodrug of a potent and selective Prostaglandin FP receptor agonist (latanoprost free acid), leads to local reductions of subcutaneous fat and adipocytes, and preferential local activation of AMPK, in the body of a mammal.

Example 2

[00208] A randomized controlled trial is conducted on (*db-/db-*) mice. Mice approximately six weeks old are prospectively randomized into groups and assigned to the following treatment conditions (n = 5 animals per group):

Table III.			
Group	Compound	Formulation*	Dose
1	Vehicle (negative control)	Lipoderm®	0.1 cc to flank, daily

Table III.			
Group	Compound	Formulation*	Dose
2	Latanoprost (positive control)	5 mM Lipoderm®	0.1 cc to flank, daily
3	AICAR	5 mM Lipoderm®	0.1 cc to flank, daily
4	Flufenamic acid	5 mM Lipoderm®	0.1 cc to flank, daily
5	Piperine	5 mM Lipoderm®	0.1 cc to flank, daily
6	S17384	5 mM Lipoderm®	0.1 cc to flank, daily
7	Curcumin	5 mM Lipoderm®	0.1 cc to flank, daily
8	Ginsenoside Rh2	5 mM Lipoderm®	0.1 cc to flank, daily
9	Maslinic acid	5 mM Lipoderm®	0.1 cc to flank, daily
10	Berberine	5 mM Lipoderm®	0.1 cc to flank, daily
11	α-lipoic acid	5 mM Lipoderm®	0.1 cc to flank, daily
12	A769662	5 mM Lipoderm®	0.1 cc to flank, daily
13	Cilostazol	5 mM Lipoderm®	0.1 cc to flank, daily
14	Fucoxanthin	5 mM Lipoderm®	0.1 cc to flank, daily

*final concentration shown; mM=millimolar

[00209] Animals are housed under identical conditions and fed *ab libitum*. Animals are weight daily. Following 28 consecutive days of treatment, mice are sacrificed and samples of skin and adjacent fat from the treated flanks are taken for histologic examination.

[00210] On histologic examination, it is predicted that animals in Group 2 (Latanoprost, positive control) will show significantly lower mean cross-sectional area for subcutaneous fat and adipocytes on the treated flanks, as compared to Group 1 (Vehicle, negative control). It is further predicted that animals in Groups 3 through 14 will show significantly lower mean cross-sectional area for subcutaneous fat and adipocytes on the treated flanks, as compared to Group 1 (Vehicle, negative control).

[00211] Thus, the foregoing experiment is predicted to show that local administration of certain AMPK activators reduces subcutaneous fat and adipocytes in a mouse.

Example 3

[00212] The following experiment describes a randomized, double-blind study in human subjects to test whether locally administered AMPK activators reduce fat in the dorsocervical fat pad of HIV-seropositive patients on antiretroviral therapy who are suffering from HIV lipodystrophy.

[00213] Eligible subjects (for example, n = 60) with HIV lipodystrophy and abnormal accumulation of fat on the dorsal neck are entered into a randomized double-blind study. Subjects are randomized to 6 groups of 10 subject each to receive vehicle alone, or one of five AMPK activators, *e.g.,* AICAR, flufenamic acid, piperine, berberine, and A769662. The vehicle is, for example, Lipoderm® (PCCA, Houston, Texas). The final concentration of each active ingredient is, for example, 5 millimolar. Unit-dose syringes (for example, 0.5 ml per syringe) are furnished to subjects by a study pharmacist; syringes are unlabeled as to the presence of an active ingredient or vehicle.

[00214] Subjects are instructed to apply, once a day, the contents of one syringe to the affected area on the back of the neck.

[00215] Serial ultrasound (US) and/or computed tomography (CT) scans are conducted at the beginning of the study and then at monthly intervals. Treatment continues for 6 months.

[00216] It is contemplated that over time, for example after 3 months of treatment, patients assigned to an AMPK activator, *e.g.,* AICAR, flufenamic acid, piperine, berberine, or A769662, will show more reduction in the depth and/or cross-sectional area of dorsocervical fat, as measured by serial US or CT, as compared to patients assigned to vehicle alone.

Example 4

[00217] The following description exemplifies a clinical application of local administration of Tafluprost to reduce local fat deposits of functional and/or cosmetic significance.

[00218] A 56-year-old female flight attendant is troubled by prominent fat deposits on her hips and thighs, which interfere with her work and lower her self-esteem. Her physician recommends diet and exercise. The woman loses 7 pounds, but there is no noticeable reduction in the fat deposits. She is referred to a plastic surgeon but declines lipoplasty due to potential adverse effects.

[00219] The plastic surgeon prescribes a daily application of an AMPK activator solution, *e.g.,* caffeic acid 0.3% in a dimethyl sulfoxide vehicle, to the hips and thighs as treatment for the fat deposits. After a period of time, for example from a few days to several months, the fatty deposits on the woman's hips and/or thighs are reduced.

Equivalents and Scope

[00220] Throughout the description, where compositions are described as having,

including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present invention may also consist essentially of, or consist of, the recited components, and that the processes of the present invention may also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

[00221] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00222] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim.

[00223] Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00224] In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00225] Each of the foregoing patents, patent applications, and references is hereby incorporated by reference, particularly for the teaching referenced herein.

[00226] The foregoing has been a description of certain non-limiting embodiments of the invention. Those of ordinary skill in the art will appreciate that various changes and

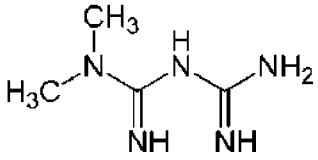
modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

Claims

What is claimed is:

1. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a direct or indirect activator of AMPK.

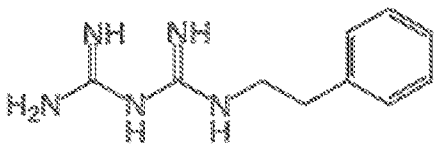
2. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

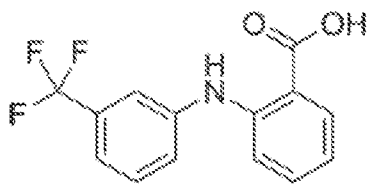
3. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**II**):



(**II**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

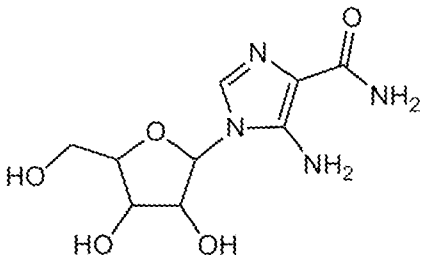
4. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**III**):



(**III**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

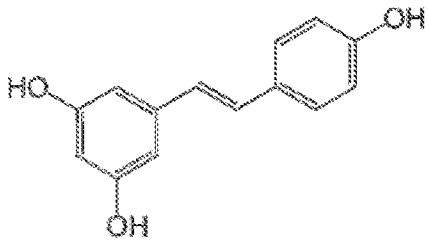
5. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**IV**):



(**IV**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

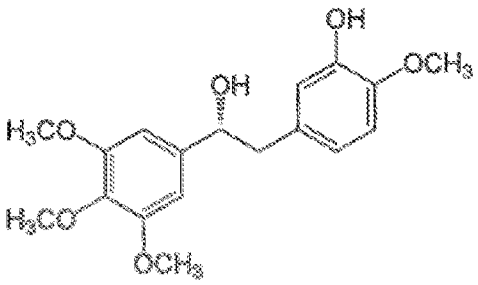
6. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**V**):



(**V**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

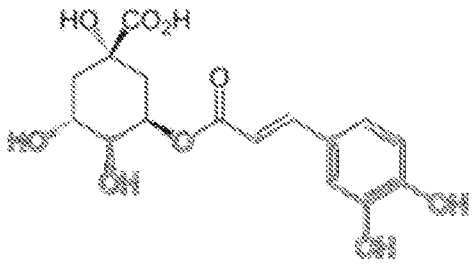
7. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**VI**):



(**VI**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

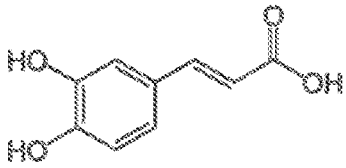
8. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**VII**):



(**VII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

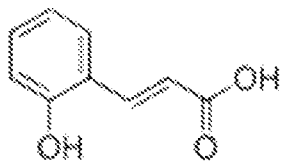
9. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**VIII**):



(**VIII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

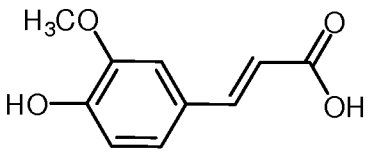
10. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**IX**):



(**IX**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

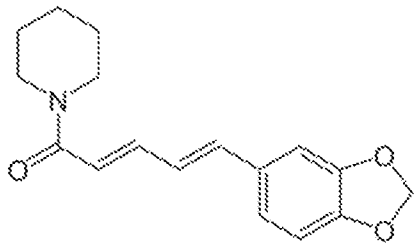
11. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**X**):



(**X**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

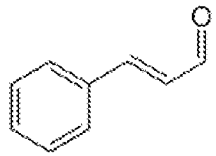
12. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XI**):



(**XI**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

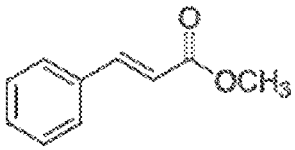
13. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XII**):



(**XII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

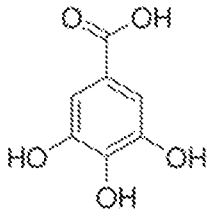
14. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XIII**):



(**XIII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

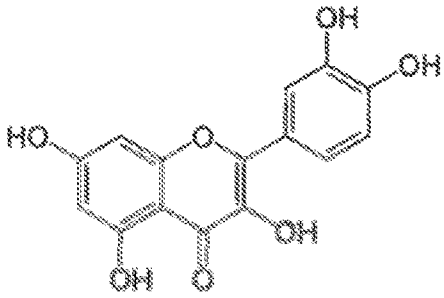
15. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XIV**):



(**XIV**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

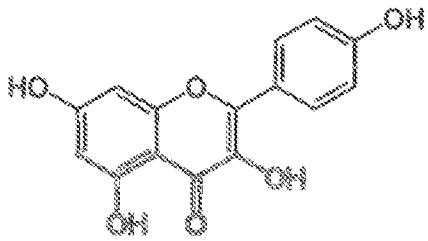
16. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XV**):



(**XV**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

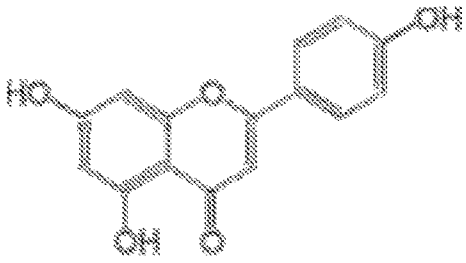
17. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XVI**):



(**XVI**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

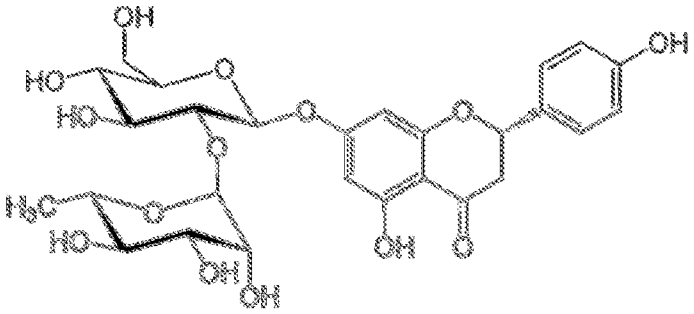
18. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XVII**):



(**XVII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

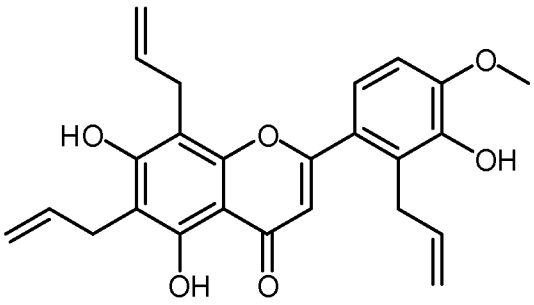
19. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XVIII**):



(**XVIII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

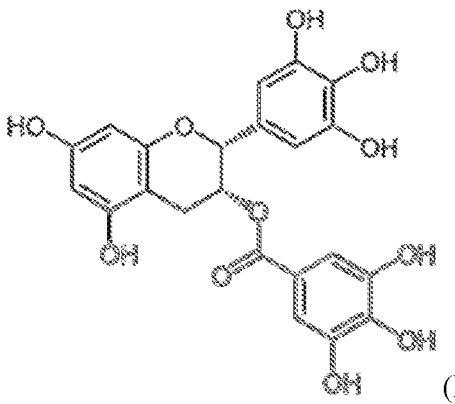
20. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XIX**):



(**XIX**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

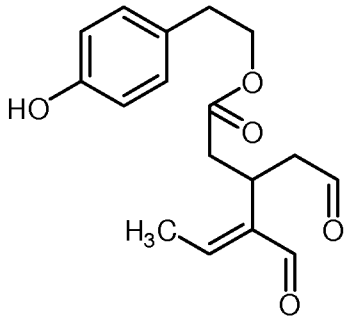
21. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XX**):



(**XX**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

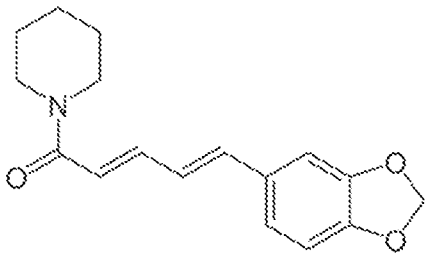
22. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXI**):



(**XXI**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

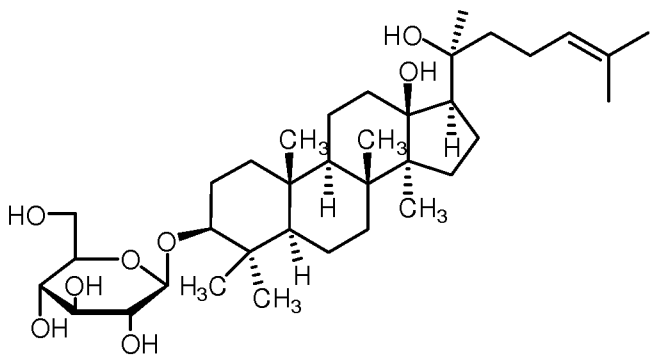
23. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXII**):



(**XXII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

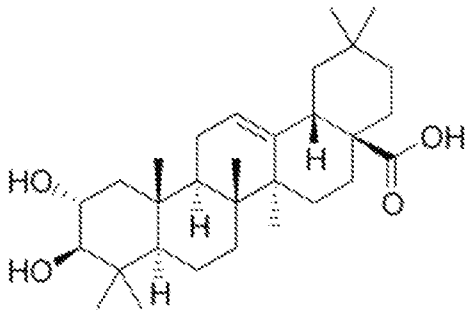
24. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXIII**):



(**XXIII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

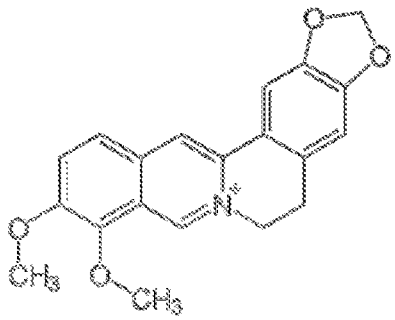
25. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXIV**):



(**XXIV**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

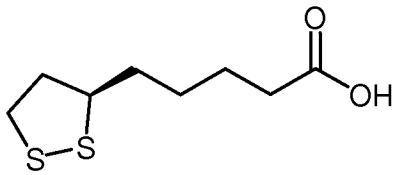
26. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXV**):



(**XXV**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

27. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXVI**):

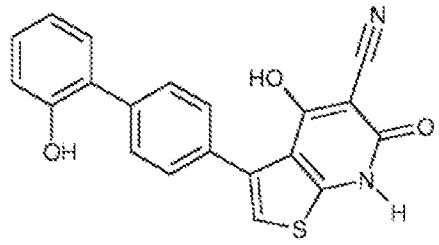


(**XXVI**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

28. A method for reducing fat in a body of a subject in need thereof, the method

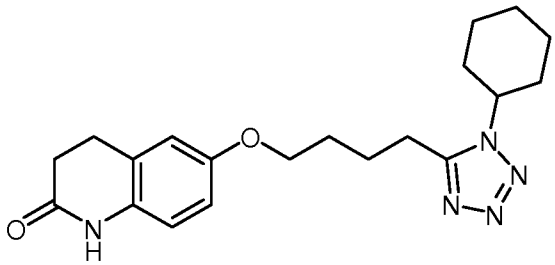
comprising administering locally to the subject a compound of the Formula (**XXVII**):



(**XXVII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

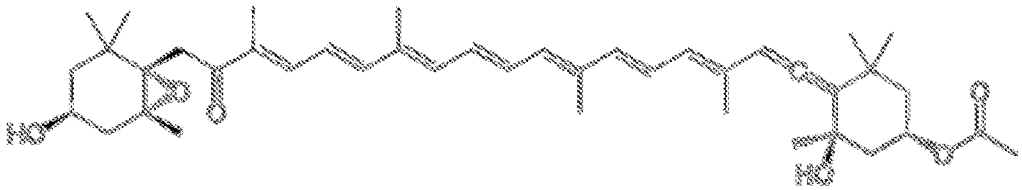
29. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXVIII**):



(**XXVIII**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

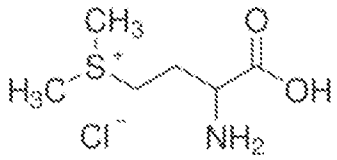
30. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXIX**):



(**XXIX**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

31. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a compound of the Formula (**XXX**):



(**XXX**)

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof.

32. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from a mushroom of the genus *Ganoderma*.

33. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from *Coix lacryma-jobi*.

34. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from *Boesenbergia pandurata*.

35. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from a tree of the genus *Mangifera*.

36. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from a tree of the genus *Combretum*.

37. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from *Flor sophorae*.

38. A method for reducing fat in a body of a subject in need thereof, the method comprising administering locally to the subject a composition comprising an extract from *Lysimachia foenum-graecum*.

39. The method of any one of claims 1 to 38, wherein reducing fat comprises reducing adipocytes.

40. The method of any one of claims 1 to 38, wherein the subject suffers from obesity.

41. The method of any one of claims 1 to 38, wherein the subject suffers from excessive fat on the breast.

42. The method of any one of claims 1 to 37, wherein the subject suffers from gynecomastia.

43. The method of any one of claims 1 to 38, wherein the subject suffers from HIV lipodystrophy.

44. The method of any one of claims 1 to 38, wherein the subject suffers from Cushing syndrome or pseudo-Cushing syndrome.

45. The method of any one of claims 1 to 38, wherein the subject suffers from hypertrophy of dorsocervical fat.

46. The method of any one of claims 1 to 38, wherein the subject suffers from moon facies.

47. The method of any one of claims 1 to 38, wherein the subject suffers from a familial lipodystrophy.

48. The method of any one of claims 1 to 38, wherein the subject suffers from Madelung disease.

49. The method of any one of claims 1 to 38, wherein the subject suffers from lipoma.

50. The method of claim 49, wherein the subject suffers from lipomatosis.

51. The method of any one of claims 1 to 38, wherein the subject suffers from orbital fat prolapse.

52. The method of any one of claims 1 to 38, wherein the subject suffers from age-related descent of fat.

53. The method of any one of claims 1 to 38, wherein the route of said administering is topical.

54. The method of claim 53, wherein the site of said administering is selected from the group consisting of the skin, the eye, or a mucosal membrane.

55. The method of any one of claims 1 to 38, wherein the route of said administering is selected from the group consisting of subcutaneous, intradermal, and intralesional.

56. The method of any one of claims 1 to 38, wherein the compound is administered to visceral fat.

57. The method of any one of claims 1 to 38, wherein the composition is administered to visceral fat.

58. The method of any one of claims 1 to 38, wherein the administering is to a body part selected from the group consisting of the abdomen, chest, breast, buttocks, hips, thighs, legs, knees, arms, chin, neck, face, and eyelids.

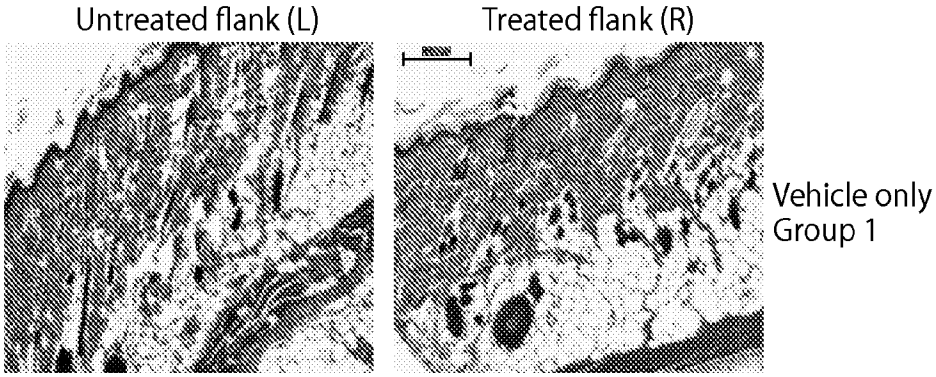


Fig. 1A

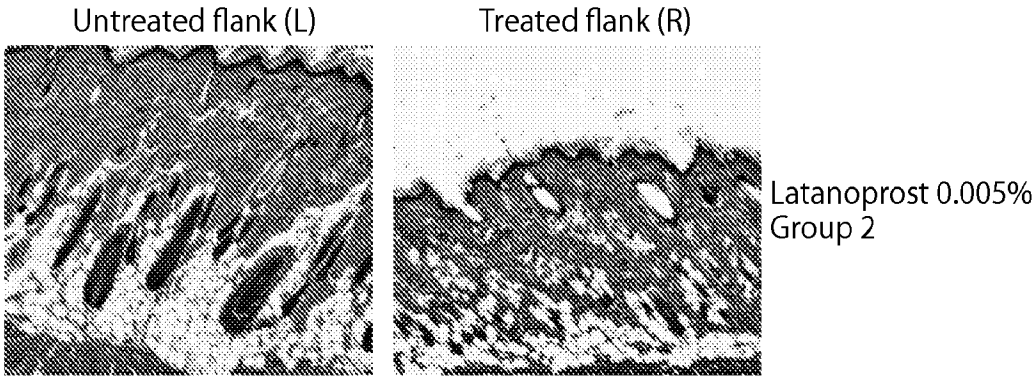


Fig. 1B

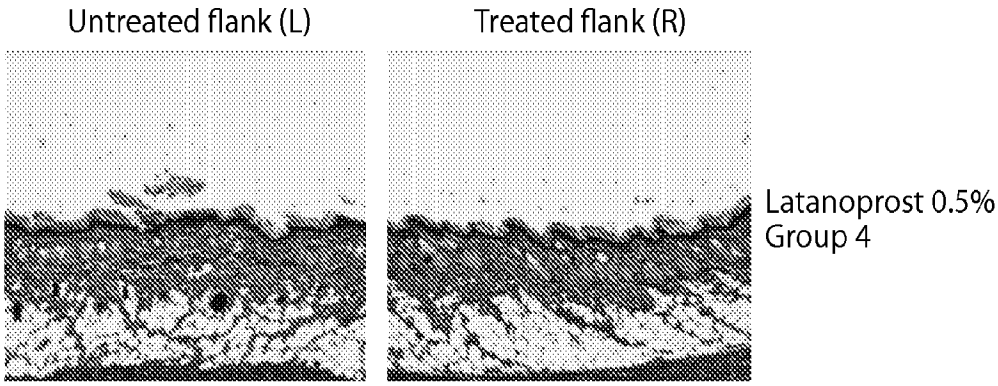


Fig. 1C

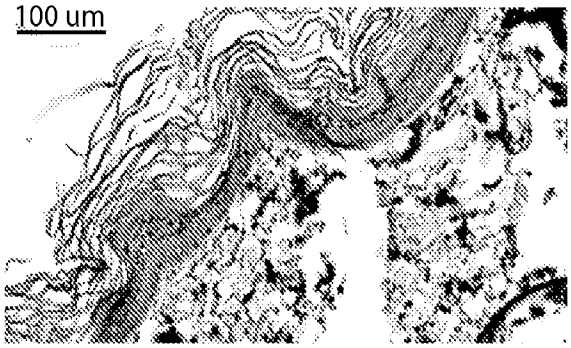


Fig. 2A



Fig. 2B

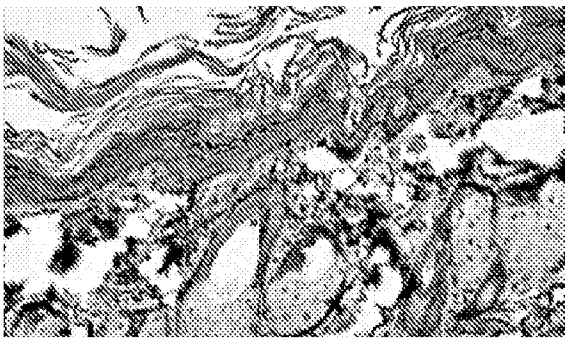


Fig. 2C

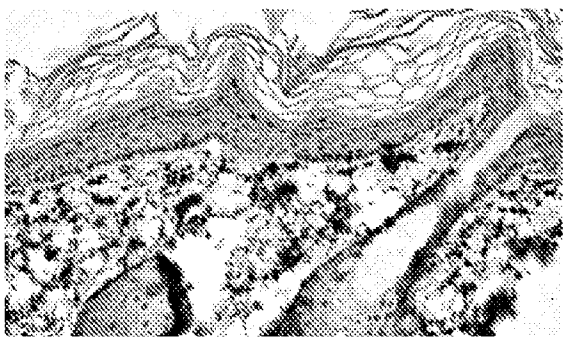


Fig. 2D