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(54) **PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR LIGAND**

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(57) **ABSTRACT**

An object of the present invention is to provide a peroxisome proliferator-activated receptor γ (PPARγ) ligand derived from a natural product and to provide a composition for prevention or improvement of insulin resistant syndrome, diabetes mellitus, obesity, or visceral fat obesity, characterized by comprising the ligand as an active ingredient. The present invention provides a PPARγ ligand comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof. The present invention also provides a composition for prevention or improvement of insulin resistant syndrome, diabetes mellitus, obesity, or visceral fat obesity comprising the compound as an active ingredient.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR LIGAND

TECHNICAL FIELD

[0001] The present invention relates to a peroxisome proliferator-activated receptor γ ligand and to a composition for prevention or improvement of visceral fat obesity and related conditions and syndromes thereof.

BACKGROUND ART

[0002] Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcriptional regulators belonging to a nuclear receptor family, which were identified as transcriptional regulators to control the expression of a gene cluster that maintains lipid metabolism. Three subtypes, PPARα, PPARδ (PPARβ, NUC-1, FAAR), and PPARγ, are known in mammals. PPARα is expressed mainly in the liver, and PPARδ is expressed universally. PPARγ includes two isoforms, PPARγ1 and PPARγ2. PPARγ1 is expressed in adipose tissues as well as in immune-system organs, adrenal glands, and small intestine. PPARγ2 is expressed specifically in adipose tissues and is a master regulator that regulates the differentiation and maturation of adipocytes (Non-Patent Document 1: T. Kawada, Progress in Medicine (Igaku no Ayumi in Japanese), 184, 519-523, 1998).

[0003] Known PPARγ ligands include: arachidonic acid metabolites such as 15-deoxy-Δ12,14-prostaglandin J2 and Δ12-prostaglandin J2; unsaturated fatty acids such as ω-3 polyunsaturated fatty acid, α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA); and eicosanoids such as 9-hydroxyoctadecadienoic acid and 13-hydroxyoctadecadienoic acid (Non-Patent Document 2: J. Auwerx, Diabetologia, 42, 1033-1049, 1999). Moreover, it has been disclosed that conjugated unsaturated fatty acids having conjugated triene structures or conjugated tetraene structures and having 10 to 26 carbon atoms are also PPARγ ligands (Patent Document 1: Japanese Patent Laid-Open No. 2000-355538). Furthermore, among synthetic compounds, thiazolidine derivatives such as troglitazone, pioglitazone, and rosiglitazone have been known to be PPARγ ligands.

[0004] The thiazolidine derivatives serving as PPARγ ligands were developed as insulin resistance-improving drugs for type II diabetes mellitus (non-insulin-dependent diabetes mellitus: NIDDM), since the link of the thiazolidine derivatives to insulin resistance-improving effects received attention because of the correlation of their agonist activities with hypoglycemic effects. Specifically, the thiazolidine derivatives serving as PPARγ ligands activate PPARγ and thereby improve insulin resistance by causing an increase in the number of normally functioning small adipocytes differentiated from precursor adipocytes as well as an apoptosis-induced decrease in the number of enlarged adipocytes, wherein the production and secretion of TNF-α or free fatty acid has been enhanced (Non-Patent Document 3: A. Okuno, et al., Journal of Clinical Investigation, 101, 1354-1361, 1998). The PPARγ ligands improve insulin resistance, and therefore, are also effective for the prevention or improvement of not only type II diabetes mellitus but also insulin resistant syndrome such as hyperinsulinemia, lipid metabolism abnormality, obesity, hypertension, and arteriosclerotic diseases (Non-Patent Document 4: R. A. Degronze, et al., Diabetes Care, 14, 173-194, 1991). It has been reported about their effects on obesity that the administration of troglitazone to patients with type II diabetes mellitus reduces visceral fat (Non-Patent Document 5: I. E. Kelly, et al., Diabetes Care, 22, 288-293, 1999; and Non-Patent Document 6: Y. Mori, et al., Diabetes Care, 22, 908-912, 1999). Therefore, the PPARγ ligands are also effective for the prevention or improvement of visceral fat obesity.

[0005] Coumaperine and derivatives thereof are components contained in natural plants such as spices typified by *Piper nigrum* L. Coumaperine has shown to have physiological functions such as antioxidative effects (Non-Patent Document 7: Environmental Health Perspectives 67, 135-142, 1986) and inhibitory effects on carcinogenesis (Patent Document 2: Japanese Patent Laid-Open No. 11-12174).

Patent Document 1: Japanese Patent Laid-Open No. 2000-355538

Patent Document 2: Japanese Patent Laid-Open No. 11-12174

Non-Patent Document 1: T. Kawada, Progress in Medicine (Igaku no Ayumi in Japanese), 184, 519-523, 1998

Non-Patent Document 2: J. Auwerx, Diabetologia 42, 1033-1049, 1999

Non-Patent Document 3: A. Okuno, et al., Journal of Clinical Investigation, 101, 1354-1361, 1998

Non-Patent Document 4: R. A. Degronze, et al., Diabetes Care, 14, 173-194, 1991

Non-Patent Document 5: I. E. Kelly, et al., Diabetes Care, 22, 288-293, 1999

Non-Patent Document 6: Y. Mori, et al., Diabetes Care, 22, 908-912, 1999

Non-Patent Document 7: Environmental Health Perspectives 67, 135-142, 1986

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

[0006] In view of the foregoing, an object of the present invention is to provide a PPARγ ligand and to provide a composition capable of treating or preventing visceral fat obesity or type II diabetes mellitus and further capable of treating or preventing insulin resistant syndrome, metabolic syndrome, or visceral fat syndrome.

Means for Solving the Problems

[0007] The present inventors have found for the first time that coumaperine and derivatives thereof have PPARγ ligand activities and have consequently completed the present invention. Specifically, the present invention provides the following inventions:

(1) A peroxisome proliferator-activated receptor γ ligand comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

[0008] (2) The peroxisome proliferator-activated receptorγ ligand according to (1), wherein the compound is at least one compound selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine,

and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

(3) A composition for prevention or treatment of visceral fat obesity comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

(4) A composition for prevention or treatment of type II diabetes mellitus comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

(5) A composition for prevention or treatment of insulin resistant syndrome comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

(6) A composition for prevention or treatment of metabolic syndrome comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

(7) A composition for prevention or treatment of visceral fat syndrome comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

[0009] (8) The composition according to any of (3) to (7), wherein the compound is one or more compound(s) selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

(9) The composition according to any of (3) to (7), wherein the composition comprises 0.1% by weight to 99% by weight in total of the compound(s) selected from the group consisting of coumaperine and derivatives thereof.

ADVANTAGES OF THE INVENTION

[0010] The present invention provides a peroxisome proliferator-activated receptor γ (PPARγ) ligand. A composition of the present invention is capable of treating or preventing visceral fat obesity or type II diabetes mellitus and further capable of treating or preventing insulin resistant syndrome, metabolic syndrome, or visceral fat syndrome.

BEST MODE FOR CARRYING OUT THE INVENTION

[0011] Hereinafter, the embodiments of the present invention will be described in detail.

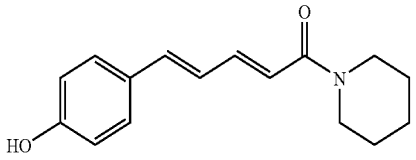
[0012] Peroxisome proliferator-activated receptors (PPARs) used herein are ligand-dependent transcriptional regulators belonging to a nuclear receptor family, which were identified as transcriptional regulators to control the expression of a gene cluster that maintains lipid metabolism. PPARγ, one of subtypes thereof, is encoded by chromosome 3p25 in the human genome (PPARα and PPARδ are encoded by chromosomes 22q12-q13.1 and 6p21.2-p21.1, respectively) (Folia Pharmacol. Jpn., 117, 319-327, 2001).

[0013] A PPARγ ligand of the present invention comprises as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof. The ligand used herein is an agonist or antagonist. The ligand of the present invention is preferably an agonist from the viewpoint of treating or preventing visceral fat obesity and so on. Whether a compound has PPARγ ligand activities can be confirmed by, for example, an assay described in Example 2 below.

[0014] The coumaperine used herein is N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine (I), which is a *Piper nigrum* L. spice-derived compound represented by the formula (I) below.

[Chemical Formula 1]

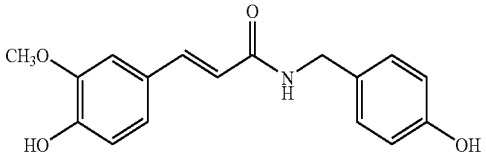
(I)



[0015] Examples of the coumaperine derivatives of the present invention include, but not particularly limited to, phenolic amide compounds such as N-trans-feruloyl tyramine (II), N-trans-feruloyl piperidine (III), N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine (IV), and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine (V) represented by the formulas (II) to (V) below. Further examples thereof include salts, oxidized forms, reduced forms, glycosides, esterified forms, acetylated forms, and methylated forms of these compounds. Those compounds may be plant-derived or chemically synthesized.

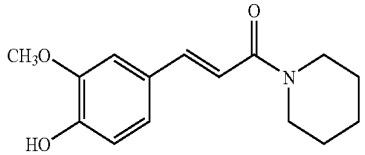
[Chemical Formula 2]

(II)



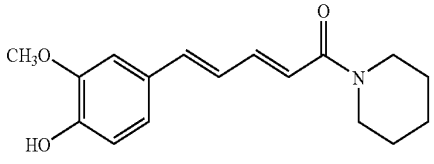
[Chemical Formula 3]

(III)



[Chemical Formula 4]

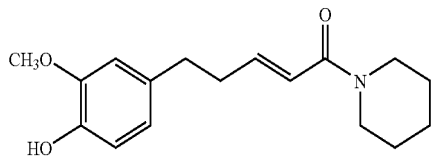
(IV)



-continued

[Chemical Formula 5]

(V)



[0016] In the present invention, the coumaperine or derivatives thereof are preferably N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine (I) (coumaperine), N-trans-feruloyl tyramine (II), N-trans-feruloyl piperidine (III), N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine (IV), N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine (V), or salts or esterified forms thereof, more preferably N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine (I) (coumaperine), N-trans-feruloyl tyramine (II), N-trans-feruloyl piperidine (III), N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine (IV), or N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine (V). Of course, they may be used alone or in combination of two or more of them.

[0017] The coumaperine and derivatives thereof used herein are found in natural products and, particularly preferably, can be separated and collected from *Piper nigrum* L. Alternatively, they can be separated and collected from *Piper nigrum* L. oleoresin extracted from powdered dry fruits of *Piper nigrum* L. with an organic solvent or the like.

[0018] In the present invention, a method for obtaining the coumaperine and derivatives thereof from *Piper nigrum* L. or *Piper nigrum* L. oleoresin is not particularly limited. For example, powdered dry fruits of *Piper nigrum* L. or *Piper nigrum* L. oleoresin are treated with an organic solvent, and insoluble components are separated to obtain an organic solvent layer. Examples of the organic solvent utilized in this treatment include n-hexane, methylene chloride, and ethylene dichloride.

[0019] Subsequently, this organic solvent layer is treated with, for example, an aqueous bicarbonate solution. The obtained organic solvent layer is further treated with an aqueous alkali solution. This aqueous alkali solution layer is adjusted from neutral to acidic pH. Examples of the bicarbonate utilized in the treatment include potassium hydrogen carbonate, sodium hydrogen carbonate, potassium carbonate, sodium carbonate, and combinations thereof. Examples of a pH adjuster include hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, lactic acid, citric acid, and combinations thereof.

[0020] Subsequently, the prepared solution can be extracted with an organic solvent to thereby obtain a separated product containing several species of phenolic amid compounds. The obtained phenolic amide compounds can be eluted, for example, with a mixed solvent of methylene chloride and methanol through a silica gel column to isolate the coumaperine and derivatives thereof (I) to (V).

[0021] In addition, the coumaperine and derivatives thereof (I) to (V) can also be obtained by a method described in Environmental Health Perspectives, 67, 135-142, 1986.

[0022] Furthermore, the coumaperine and derivatives thereof of the present invention can also be obtained by synthesis. The coumaperine and derivatives thereof (I) to (V) can be synthesized by, but not limited to, the methods described in, for example, Agricultural and Biological Chemistry, 44, 2831, 1980, Tetrahedron, 59, 5337, 2003, and Japanese Patent Publication No. 1-21951.

[0023] Specifically, for example, bromocrotonic acid dissolved in dry benzene at 0° C. is added to thionyl bromide in dry benzene. The solvent is distilled off. The obtained bromide of 4-bromocrotonic acid is dissolved in dry benzene and reacted with piperidine at approximately 0° C. The reaction solution is heated to room temperature, then poured to chilled water for additional 1 hour, and extracted with benzene. The organic solvent layer is washed with an aqueous saturated $NaHCO_3$ solution and water. After drying and concentration, syrup is obtained. This syrup is purified by silica gel column chromatography to obtain an amide.

[0024] The purified amide is added to triethylphosphite, for example, at 100 to 110° C. The reaction temperature is raised and kept for an appropriate time. Excessive triethylphosphite is distilled off under reduced pressure. The residue is dissolved in dry DMF and mixed with a dry DMF solution of p-benzyloxybenzaldehyde. This mixed solution is treated with an NaOEt solution and stirred at room temperature. The mixed solution is diluted with water and extracted with methylene chloride. The dried extract is recrystallized from benzene to obtain white needles.

[0025] Concentrated hydrochloric acid is added to the acetic acid solution of benzylamide thus obtained. The mixed solution is treated at approximately 100° C. and left at room temperature for an appropriate time. The mixed solution is concentrated under vacuum, then supplemented with water, and extracted with methylene chloride. The organic layer is washed with an aqueous saturated $NaHCO_3$ solution to remove acetic acid. After extraction with a sodium hydroxide solution, the alkali extract thereof is made acidified with dilute hydrochloric acid. The aqueous solution is extracted with methylene chloride. The concentrated product can be recrystallized from acetone to obtain coumaperine needles.

[0026] The salts of the coumaperine and derivatives thereof (I) to (V) are intended to include the forms of non-toxic acid or base addition salts that can be formed from the compounds. For example, the compounds can be treated with an appropriate acid and thereby converted to pharmaceutically acceptable acid addition salts thereof. In this case, exemplary acids include: inorganic acids such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, and phosphoric acid; and organic acids such as acetic acid, propionic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, p-aminosalicylic acid, pamoic acid, benzoic acid, and ascorbic acid. Examples of bases for the base addition salt forms include: sodium, potassium, and calcium; pharmaceutically acceptable amines such as ammonia, alkylamine, and benzathine; and amino acids such as arginine and lysine. The term "addition salts" used herein also includes solvates that can be formed from the compounds and salts thereof, for example, hydrates and alcoholates.

[0027] The oxidized forms, reduced forms, glycosides, esterified forms, acetylated forms, and methylated forms of the coumaperine and derivatives thereof (I) to (V) can respectively be obtained by treating the compounds with methods known in the art or can be obtained by extraction from plants containing them.

[0028] In the present invention, at least one compound selected from the coumaperine and derivatives thereof that can be used is, but not limited to, a pure compound. Semi-purified or crude products can also be used as long as they do not contain impurities inappropriate as drugs or foods.

[0029] A "composition for treatment or prevention of visceral fat obesity or type II diabetes mellitus" and a "composition for treatment or prevention of insulin resistant syndrome, metabolic syndrome, or visceral fat syndrome" used herein are characterized by comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

[0030] The insulin resistant syndrome used herein means a disease group that is characterized by the presence of two conditions, insulin resistance and hyperinsulinemia, and complicates one or more related lesion(s) of obesity, type II diabetes mellitus, hypertension, arteriosclerotic diseases, or lipid metabolism abnormality (Netherlands Journal of Medicine, 50, 191-197, 1997).

[0031] The metabolic syndrome used herein is a syndrome corresponding to a case that has abdominal obesity (particularly, visceral fat obesity) as a basic condition and additionally has multiple risk factors such as fasting hyperglycemia, hypertriglyceridemia, hypo-HDL-cholesterolemia, and hypertension (Circulation Journal, 68, 975-981, 2004).

[0032] Diagnostic criteria of metabolic syndrome differ from nation to nation and, in Japan, are as follows (Internal Medicine, 94, 188-202, 2005):

[0033] Abdominal obesity: abdominal circumference for male≧85 cm, for female≧90 cm Besides, two or more items of the followings:

[0034] Hypertriglyceridemia≧150 mg/dl and/or Hypo-HDL-cholesterolemia<40 mg/dL

[0035] Fasting hyperglycemia≧110 mg/dL

[0036] Systolic blood pressure≧130 mmHg and/or Diastolic blood pressure≧85 mmHg

[0037] The visceral fat syndrome used herein is a disease group that complicates five conditions, visceral fat accumulation, abnormal glucose tolerance, hyperlipidemia, hypertension, and hypo-HDL-cholesterolemia (Internal Medicine, 81, 1831-1835, 1992).

[0038] Visceral fat obesity is common in men and is different from subcutaneous fat obesity common in women. In studies on the development and progression of risk factors causing arteriosclerosis, insulin resistance is placed in a rank higher than risk factors such as hyperlipidemia, diabetes mellitus, and hypertension, and visceral fat obesity is placed in the highest rank. Diagnostic criteria of obesity also place importance particularly on visceral fat as bad fat causing the onset of the syndrome, and the accumulation of visceral fat is said to increase the risk (Circulation Journal, 66, 987-992, 2002).

[0039] PPARγ agonists are characterized by specifically reducing visceral fat. Therefore, the composition of the present invention can particularly treat or prevent visceral fat obesity and thereby treats or prevents insulin resistance, further, diabetes mellitus, hyperlipidemia, hypertension, and so on.

[0040] The content (in terms of the total weight) of the at least one compound selected from the coumaperine and derivatives thereof in the composition is not limited as long as it is suitable to the treatment or prevention of the diseases described above. The content can be, for example, 0.1 to 100% by weight. The composition comprises 0.1 to 99% by weight, more preferably 1% to 99% by weight of the compound(s), from the viewpoint of sufficient effects. More preferably, the content can be 10 to 90% by weight.

[0041] The composition is not limited by form and can be used as, for example, food and drink such as food with health claims (food for specified health use and food with nutrient function claims) and health food, a drug, and a quasi drug.

[0042] The composition, when used as food and drink, can be ingested directly or can be ingested after being prepared into a easily taken form such as a capsule, tablet, or granule by use of a carrier, auxiliary agent, or the like known in the art.

[0043] Furthermore, the composition can be mixed with materials for food and drink and thereby used in all foods and drinks including: confectionery such as chewing gums, chocolates, candies, jellies, biscuits, and crackers; frozen desserts such as ice creams and ice cubes; drinks such as tea, soft drinks, nutritional supplement drinks, and beauty supplement drinks; noodles such as udon noodle, Chinese noodle, spaghetti, and instant noodle; fish paste products such as boiled fish paste (kamaboko), tube-shaped fish paste cake (chikuwa), and pounded fish cake (hanpen); seasonings such as dressing, mayonnaise, and sauce; oils and fats such as margarine, butter, and salad oil; and bread, ham, soup, pouch-packed foods, and frozen foods. These compositions for food and drink may be ingested by one adult at a dose of usually 0.1 to 3000 mg/kg of body weight, preferably 1 to 300 mg/kg of body weight, per day in terms of the amount of the coumaperine or a derivative thereof. The composition of the present invention can also be used as feed or pet food for livestock and pets and may be ingested at a dose of preferably 0.1 to 3000 mg/kg of body weight per day in terms of the amount of the coumaperine or a derivative thereof.

[0044] The composition, when used as a drug, is not limited by dosage form. Examples thereof include preparations such as capsules, tablets, granules, injections, suppositories, and patches. To make the composition into such preparations, other pharmaceutically acceptable formulation materials, for example, excipients, disintegrants, lubricants, binders, antioxidants, coloring agents, anti-aggregation agents, absorption promoters, solubilizers, and stabilizers can be added appropriately thereto. These preparations are administered to one adult at a dose of usually 0.1 to 3000 mg/kg of body weight, preferably 1 to 300 mg/kg of body weight, in a single or divided dose per day in terms of the amount of the coumaperine or a derivative thereof. The composition can also be used as a drug for livestock and pets and is administered at a dose of preferably 0.1 to 3000 mg/kg of body weight per day in terms of the amount of the coumaperine or a derivative thereof.

EXAMPLES

[0045] Hereinafter, the present invention will be described more specifically with reference to Examples. However, the present invention is not intended to be limited to these Examples.

Example 1

Synthesis of Coumaperine

[0046] Coumaperine was prepared by a synthesis method described below.

[0047] Bromocrotonic acid (74.3 g, 0.03 M) dissolved in dry benzene (180 ml) at 0° C. was added to thionyl bromide (34.8 ml, 0.01 M) in dry benzene (45 ml). The solvent was

distilled off. The obtained bromide of 4-bromocrotonic acid was dissolved in dry benzene (75 ml) and reacted with piperidine (89 ml, 0.08 M) at 0° C. The reaction solution was heated to room temperature, then poured to chilled water for additional 1 hour, and extracted with benzene. The organic solvent layer was washed with an aqueous saturated $NaHCO_3$ solution and water. After drying and concentration, 32.4 g of syrup was obtained. This syrup was purified by silica gel column chromatography to obtain an amide.

[0048] The purified amide was added to triethylphosphite (9.6 g) at 105° C. The reaction temperature was raised to 150° C. and kept for 1 hour. Excessive triethylphosphite was distilled off under reduced pressure. The residue was dissolved in dry DMF (30 ml) and mixed with a dry DMF solution (45 ml) containing 12.2 g of p-benzyloxybenzaldehyde. This mixed solution was treated with an NaOEt solution and stirred at room temperature. The mixed solution was diluted with water and extracted with methylene chloride. The dried extract (19.2 g) was recrystallized from benzene to obtain white needles.

[0049] Concentrated hydrochloric acid (150 ml) was added to the acetic acid solution (300 ml) of benzylamide (6 g) thus obtained. The mixed solution was treated at 100° C. for 2 hours and left overnight at room temperature. The mixed solution was concentrated under vacuum, then mixed with water, and extracted with methylene chloride. The organic layer was washed with an aqueous saturated $NaHCO_3$ solution to remove acetic acid. After extraction with 1N sodium hydroxide solution, the alkali extract thereof was made acidic with dilute hydrochloric acid. The aqueous solution was extracted with methylene chloride. The concentrated product (3 g) could be recrystallized from acetone to obtain coumaperine needles (2.1 g).

Example 2

PPARγ Ligand Activity

[0050] CV-1 cells (cultured cells derived from male African green monkey kidney) were seeded at 6×10^3 cells/well into a 96-well culture plate and cultured at 37° C. for 24 hours under 5% CO_2 conditions. The medium used was DMEM (Dulbecco's Modified Eagle Medium; GIBCO) containing 10% FBS (fetal bovine serum), 10 ml/L penicillin/streptomycin solution (5000 IU/ml and 5000 μg/ml, respectively; GIBCO), and 37 mg/L ascorbic acid (Wako Pure Chemical Industries, Ltd.). The cells were washed with OPTI-MEM (GIBCO) and then transfected with pM-mPPARγ and 4×UASg-luc by use of Lipofectamine plus (GIBCO). The pM-mPPARγ is a chimeric protein expression plasmid in which a yeast-derived transcription factor GAL4 gene (amino acid sequence at 1 to 147 positions) is ligated with a mouse PPARγ ligand-binding site gene (amino acid sequence at 174 to 475 positions). The 4×UASg-luc is a reporter plasmid in which four copies of the upstream activating sequence of GAL4 (UASg) are incorporated upstream of a luciferase gene. Approximately 24 hours after transfection, the medium was replaced with a sample-containing medium (n=4), followed by culture for additional 24 hours. The sample dissolved in dimethyl sulfoxide (DMSO) or DMSO used as an untreated control was added at 1/1000 of the volume to the medium. The cells were washed with Ca- and Mg-containing phosphate-buffered saline (PBS+). Then, Luclite (Packard) was added thereto, and the luminescence intensity of luciferase was measured with a TopCount microplate scintillation/luminescence counter (Packard).

[0051] pM (plasmid from which PPARγ ligand-binding site gene was removed) was used as a control group instead of the pM-mPPARγ and subjected to measurement in the same way as for the measurement group. The ratio (measurement group/control group) of the average luminescence intensity values (n=4) between the measurement and control groups was calculated for each sample. Specific activity relative to the untreated control was used as the PPARγ ligand activity of the sample. The results are shown in Table 1.

TABLE 1

	Concentration added	PPARγ ligand activity
Untreated control (DMSO)	(0.1%)	1.00
Troglitazone	0.5 μM	2.20
	2 μM	4.05
	10 μM	7.52
Coumaperine	0.5 μg/ml	1.05
	1 μg/ml	1.07
	2 μg/ml	1.24
	5 μg/ml	1.78
	10 μg/ml	2.07
	20 μg/ml	2.53
	30 μg/ml	2.38
	50 μg/ml	2.44

[0052] Troglitazone (Sankyo Co., Ltd.) was used as a positive control to compare the PPARγ ligand activity among the compounds. As seen from Table 1, the coumaperine was observed to have a concentration-dependent PPARγ ligand activity.

Example 3

Toxicity Test on Coumaperine

[0053] A toxicity test was conducted on the coumaperine of the present invention.

Coumaperine was orally administered at 2000 mg/kg of body weight to rats. As a result, no death case was observed, and toxic conditions were not particularly observed therein. Thus, the coumaperine was confirmed to have no or exceedingly low toxicity.

Example 4

Preparation of Tablet Containing Coumaperine

[0054]

Coumaperine	45 parts by weight
Lactose	35 parts by weight
Crystalline cellulose	15 parts by weight
Sucrose fatty acid ester	5 parts by weight

A tablet for food and drink containing coumaperine was prepared by a standard method from the composition.

Example 5

Preparation of Soft Capsule Containing Coumaperine

[0055]

Coumaperine	40 parts by weight
Sesame oil	55 parts by weight
Glycerin fatty acid ester	5 parts by weight

A soft capsule for food and drink containing coumaperine was prepared by a standard method from the composition.

Example 6

Preparation of Cracker Containing Coumaperine

[0056]

Coumaperine	1 part by weight
Soft flour	120 parts by weight
Common salt	1 part by weight
Baking powder	2 parts by weight
Butter	30 parts by weight
Water	40 parts by weight

A cracker containing coumaperine was prepared by a standard method from the composition.

Example 7

Preparation of Udon Noodle Containing Coumaperine

[0057]

Coumaperine	1 part by weight
Hard flour	100 parts by weight
Soft flour	100 parts by weight
Common salt	10 parts by weight
Water	100 parts by weight

An udon noodle containing coumaperine was prepared by a standard method from the composition.

Example 8

Preparation of Dressing Containing Coumaperine

[0058]

Coumaperine	10 parts by weight
Olive oil	80 parts by weight
Vinegar	60 parts by weight
Common salt	3 parts by weight
Pepper	1 part by weight
Lemon juice	5 parts by weight

A dressing containing coumaperine was prepared by a standard method from the composition.

1. A peroxisome proliferator-activated receptor γ ligand comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

2. The peroxisome proliferator-activated receptor γ ligand according to claim **1**, wherein the compound is at least one compound selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

3. A composition for prevention or treatment of visceral fat obesity comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

4. A composition for prevention or treatment of type II diabetes mellitus comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

5. A composition for prevention or treatment of insulin resistant syndrome comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

6. A composition for prevention or treatment of metabolic syndrome comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

7. A composition for prevention or treatment of visceral fat syndrome comprising as an active ingredient, at least one compound selected from the group consisting of coumaperine and derivatives thereof.

8. The composition according to claim **3**, wherein the compound is one or more compound(s) selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

9. The composition according to claim **3**, wherein the composition comprises 0.1% by weight to 99% by weight in total of the compound(s) selected from the group consisting of coumaperine and derivatives thereof.

10. The composition according to claim **4**, wherein the compound is one or more compound(s) selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

11. The composition according to claim **5**, wherein the compound is one or more compound(s) selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

12. The composition according to claim **6**, wherein the compound is one or more compound(s) selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

13. The composition according to claim **7**, wherein the compound is one or more compound(s) selected from the group consisting of N-5-(4-hydroxyphenyl)-2E,4E-pentadienoyl piperidine, N-trans-feruloyl tyramine, N-trans-feruloyl piperidine, N-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pen-

tadienoyl piperidine, and N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, salts thereof, and esterified forms thereof.

14. The composition according to claim **4**, wherein the composition comprises 0.1% by weight to 99% by weight in total of the compound(s) selected from the group consisting of coumaperine and derivatives thereof.

15. The composition according to claim **5**, wherein the composition comprises 0.1% by weight to 99% by weight in total of the compound(s) selected from the group consisting of coumaperine and derivatives thereof.

16. The composition according to claim **6**, wherein the composition comprises 0.1% by weight to 99% by weight in total of the compound(s) selected from the group consisting of coumaperine and derivatives thereof.

17. The composition according to claim **7**, wherein the composition comprises 0.1% by weight to 99% by weight in total of the compound(s) selected from the group consisting of coumaperine and derivatives thereof.

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