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(54) **Title**: PELTATIN FOR USE IN THE TREATMENT OF CARDIOVASCULAR DISORDERS

(57) **Abstract**: The present invention relates to the field of cardiovascular disorders and aims to identify natural compounds that can be used effectively in this field. In particular, the present invention provides a composition comprising at least one peltatin for use in the treatment or prevention of cardiovascular disorders or risk factors thereof.

PELTATIN FOR USE IN THE TREATMENT OF CARDIOVASCULAR DISORDERS

The present invention relates to the field of cardiovascular disorders and aims to identify natural compounds that can be used effectively in this field. In particular, the present invention provides a composition comprising at least one peltatin for use in the treatment or prevention of cardiovascular disorders or risk factors thereof.

Cardiovascular Diseases (CVDs) are the leading cause of death and disability globally. More people are severely affected annually by CVDs than from any other cause. From a WHO report, an estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke. By 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death.

The pathophysiology of the development of cardiovascular diseases may be complex and multifactorial.

However, there are measures that can be taken to reduce the risk of cardiovascular disorders.

It is generally accepted that keeping blood pressure under control, exercising regularly, refrain from smoking, maintaining a healthy weight, having a diet rich in fruit and vegetables, and/or keeping cholesterol and triglyceride levels under control helps to reduce the risk.

Hence, healthy eating habits and a physically active lifestyle are good measures prevent cardiovascular disorders.

However, there remains to be a need in the art for natural compositions that can be used to assist in the prevention, alleviation or treatment of cardiovascular disorders.

The present inventors have addressed this need.

Consequently, it was the object of the present invention to provide the art with a natural composition that can be used in the prevention, alleviation or treatment of cardiovascular disorders.

The present inventors were surprised to see that they could achieve this objective by the subject matter of the independent claim. The subject matter of the dependant claims further develops the idea of the present invention.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA and immunology, which are within the capabilities of a person of ordinary skill in the art. Such techniques are explained in the literature. See, for example, J. Sambrook, E. F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Books 1-3, Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al. (1995 and periodic supplements; *Current Protocols in Molecular Biology*, ch. 9, 13, and 16, John Wiley & Sons, New York, N.Y.); B. Roe, J. Crabtree, and A. Kahn, 1996, *DNA Isolation and Sequencing: Essential Techniques*, John Wiley & Sons; J. M. Polak and James O'D. McGee, 1990, *In Situ Hybridization: Principles and Practice*; Oxford University Press; M. J. Gait (Editor), 1984, *Oligonucleotide Synthesis: A Practical Approach*, Irl Press; D. M. J. Lilley and J. E. Dahlberg, 1992, *Methods of Enzymology: DNA Structure Part A: Synthesis and Physical Analysis of DNA* Methods in Enzymology, Academic Press; and E. M. Shevach and

W. Strober, 1992 and periodic supplements, *Current Protocols in Immunology*, John Wiley & Sons, New York, NY. Each of these general texts is herein incorporated by reference.

The present inventors have found in screening assays that peltatins can effectively activate hPPARs, which makes them interesting candidates for, e.g., nutritional applications.

The peroxisome proliferators-activated receptors (PPARα, γ and β/δ) are nuclear receptors that act as a transcription factor upon activation. These nuclear factors are expressed with distinct patterns in many cell types. They regulate the transcription and expression of key target genes with a wide range of effects on the immune response. There are a variety of potential endogenous or synthetic ligands that bind PPARs with varying affinities and specificities, resulting in transcriptional activation or repression of target genes.

The PPARγ nutrient sensing pathway is of high importance for cell metabolism and diabetes, for example, both risk factors for the development of cardiovascular disorders. The peroxisome proliferators-activated receptors (PPARα, γ and β/δ) are nuclear receptors that act as a transcription factor upon activation. These nuclear factors are expressed with distinct patterns in many cell types. They regulate the transcription and expression of key target genes with a wide range of effects on metabolism. There are a variety of potential endogenous or synthetic ligands that bind PPARs with varying affinities and specificities, resulting in transcriptional activation or repression of target genes.

PPARγ ligands are involved in the carbohydrate and lipid metabolism, leading to the improvement of insulin sensitivity in muscle, liver and adipose tissue.

As indicated above, peltatins were found to bind to PPARs, for example to PPARα. Agonists of PPARα (fibrate) are used in the art to treat dyslipidemia (Moutzouri et al., Vascular Health and Risk Management 2010:6 525-539). Peltatins may hence be used to treat, ameliorate of prevent dyslipidemia, hypertriglycerinemia and cardiovasczular diseases in general.

Consequently, the present invention relates in part to a composition comprising at least one peltatin for use in the treatment or prevention of cardiovascular disorders.

There is also provided herein a method of treating or preventing a cardiovascular disorder in a subject comprising administering a composition comprising at least one peltatin to said subject.

The cardiovascular disorder may be one which is treatable or preventable by activation of a hPPAR, e.g., PPARγ and/or PPARα. In one embodiment the disease is one which is treatable or preventable by activation of both PPARγ and PPARα.

There is also provided herein the use of at least one peltatin as an agonist of a hPPAR e.g., PPARγ and/or PPARα.

There is also provided herein a method of activating a hPPAR in a subject comprising administering at least one peltatin to said subject.

The invention also relates to the use of at least one peltatin for the preparation of a composition to treat or prevent cardiovascular disorders.

Peltatins are well known in the art. They belong to lignans and may be found in some plants in the rhizome and in roots, for example. Peltatins and their derivatives (e.g.,

glycosides, esters) may be converted by the gut flora and the inventors speculate that they might be bioavailable as enterolactones and/or enterodiols.

The inventors currently believe that the general effectiveness against cardiovascular disorders is due to the mechanism of action via activation of hPPARs and PPARγ in particular.

Consequently, it seems to be in particularly preferred if the cardiovascular disorder is a disorder associated with hyperlipidemia and/or hypercholesterolemia, for example, dyslipidemia, and/or hypertriglycerinemia.

Disorders associated with hyperlipidemia and/or hypercholesterolemia are well known to those of skill in the art (see for example Bhatnagar D. et al., BMJ 2008;337:a993, herewith incorporated by reference). For example, hypercholesterolaemia is one of the major causes of atherosclerosis or coronary heart diseases.

Hyperlipidemia is characterized by abnormally elevated levels of any or all lipids and/or lipoproteins in the blood.

Cardiovascular disorders are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, deep vein thrombosis and pulmonary embolism, etc. "Cardiovascular disorders" generally refers to any disease that affects the cardiovascular system, and in particular refers to those disorders related to atherosclerosis (arterial disease). These conditions usually have similar causes, mechanisms, and treatments.

Atherosclerosis is the buildup of fatty deposits (such as cholesterol) called plaque on the inside walls of arteries. By

the time that heart problems are detected, atherosclerosis is usually quite advanced, having progressed for decades. Most commonly, the plaque suddenly ruptures which causing the formation of a thrombus that will rapidly block the blood flow, leading to death of the surrounding tissues only in 5 minutes. This catastrophic event is called an infarction. One of the most common recognized scenarios is called coronary thrombosis of a coronary artery, causing myocardial infarction (a heart attack). The same process in an artery to the brain is commonly called stroke. Another common scenario in a very advanced disease state is claudication from insufficient blood supply to the legs, typically caused by a combination of both stenosis and aneurysmal segments narrowed with clots.

The main cause of atherosclerosis is yet unknown, it is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, caused largely by the accumulation of macrophages and promoted by low-density lipoproteins (LDL, plasma lipoproteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries. This is caused by the formation of multiple plaques within the arteries.

Hyperlipidemia is the most important risk factor for atherosclerosis, which is the major cause of cardiovascular disease. Hyperlipidemias may also be classified directly into which types of lipids are elevated, that is hypercholesterolemia, hypertriglyceridemia or both in combined hyperlipidemia. Elevated levels of Lipoprotein(a) may also be classified as a form of hyperlipidemia.

The composition of the present invention may be to be administered to humans or animals, for example pet animals, such as dogs, cats, birds, rabbits, or guinea pigs.

The composition of the present invention may in particular be to be administered orally, enterally, or parenterally. The compositions may be provided in any galenical form normally available for the selected mode of administration.

The composition of the present invention may be administered to any age group. For example, the composition of the present invention may be to be administered to teenagers, adults, or the elderly.

For example, the composition of the present invention may be to be administered together with foods with high sugar content, such as sweet dishes, deserts or confectionary, for example.

The composition may, e.g., be selected from the group consisting of food compositions, food products, drinks, pet food products, dairy products, nutritional formulas, powdered nutritional formulations to be reconstituted in milk or water, food additives, nutritional supplements, nutraceuticals, pharmaceutical compositions, and/or food ingredients.

The composition may be provided in the form of a shelf stable powder. To obtain shelf stability and to ensure viability of the probiotics the composition may be provided with a water activity smaller than 0.2, for example in the range of 0.19-0.05, preferably smaller than 0.15. Water activity or aw is a measurement of the energy status of the water in a system. It is defined as the vapor pressure of water deriving from the powder/product divided by that of pure water at the same

temperature; therefore, pure distilled water has a water activity of exactly one.

In one embodiment, the composition of the present invention is a drinkable composition.

The composition of the invention may contain a spring and/or mineral water, in particular chosen from Vittel water, waters from the Vichy basin, and la Roche Posay water.

In the case of oral use in accordance with the invention for oral administration, the use of an ingestible support or carrier is preferred. The ingestible support or carrier may be of diverse nature depending on the type of composition under consideration.

Milk, yogurt, cheese, fermented milks, milk-based fermented products, ice creams, cereal-based products or fermented cereal-based products, milk-based powders, infant and baby formulas, food products of confectionary, chocolate or cereal type, animal feed, in particular for domestic animals, tablets, gel capsules or lozenges, liquid bacterial suspensions, oral supplements in dry form and oral supplements in liquid form are especially suitable for use as ingestible support or carrier.

The composition according to the invention to be administered orally may be formulated for example in the form of coated tablets, gel capsules, gels, emulsions, tablets, capsules, hydrogels, food bars, compact or loose powders, liquid suspensions or solutions, confectionery products, fermented milks, fermented cheeses, chewing gum, toothpaste or spray solutions or food carriers.

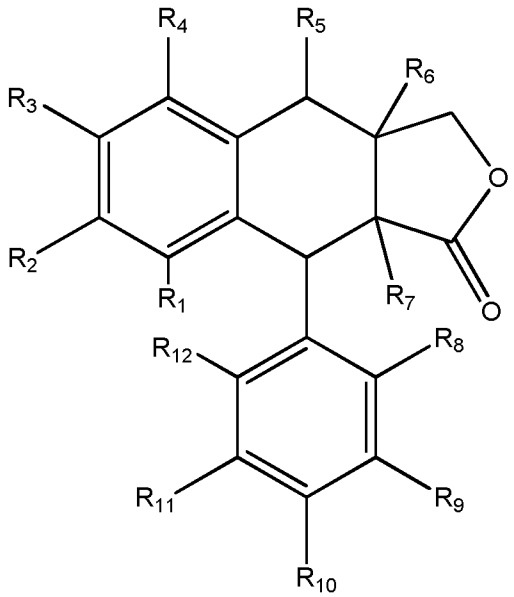
Tablets or lozenges, oral supplements in dry form and oral supplements in liquid form are suitable for use as dietetic or pharmaceutical supports or food carriers.

The composition may be, for example, a food supplement, which may be formulated via the usual processes for in particular producing sugar-coated tablets, gel capsules, gels, emulsions, tablets, capsules and hydrogels allowing controlled release.

The formulating agents and excipients for oral compositions, and in particular for food supplements, are known in this field and will not be the subject of a detailed description herein.

Any peltatin may be used for the purpose of the present invention. The peltatin used in the present invention is an agonist of a peroxisome proliferator-activated receptor PPAR.

The at least one peltatin may have the following core structure



wherein R_1, R_2, R_3, R_4, R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from H, OH, OMe and O-sugar, or wherein adjacent R

groups (e.g., R_1 and R_2, R_2 and R_3, R_3 and R_4, R_8 and R_9, R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12}, preferably R_2 and R_3) together are -O-CH2-O- forming a cyclic 5-membered ring,

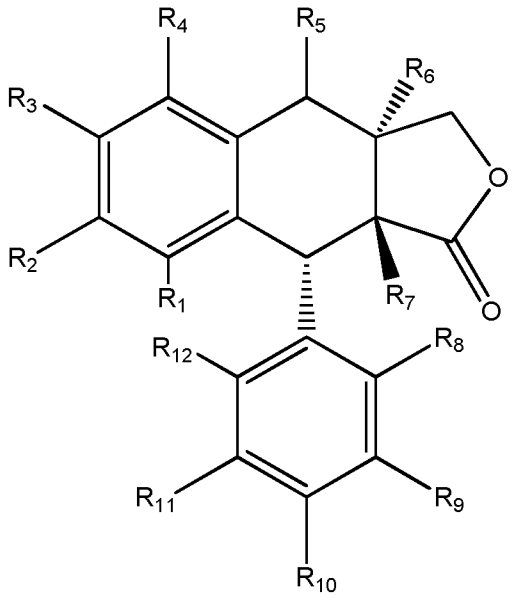
R_5 is selected from H, OH, OCO-alkyl wherein the alkyl is preferably C1 to C4 alkyl, O-alkyl wherein the alkyl is preferably C1-C4 alkyl, =O, and O-sugar,

R_6 and R_7 are independently selected from H and OH.

The peltatin according to the present invention preferably has a structure such that R4 is selected from OH, OMe and O-sugar, preferably OH. Preferably R5 is H.

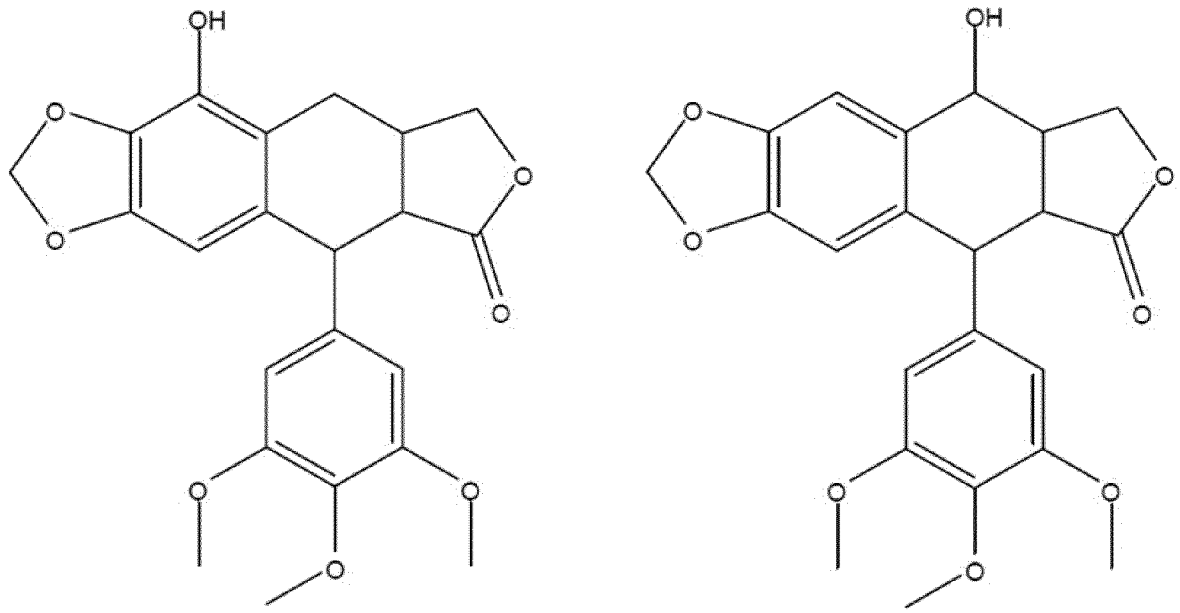
In one embodiment, the peltatin contains no more than 2 hydroxy groups. In one embodiment, the peltatin contains one hydroxyl group.

The at least one peltatin preferably has the following stereochemistry:

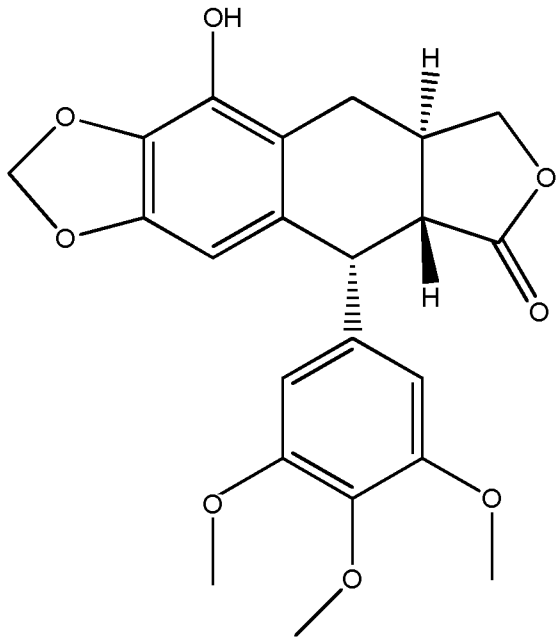


The at least one peltatin may be selected from the group consisting of α-peltatin or a derivative thereof or β-peltatin or a derivative thereof. The at least one pelatin may be a combination of α-peltatin or a derivative thereof and β-peltatin or a derivative thereof. For example, the at least one peltatin may be β-peltatin.

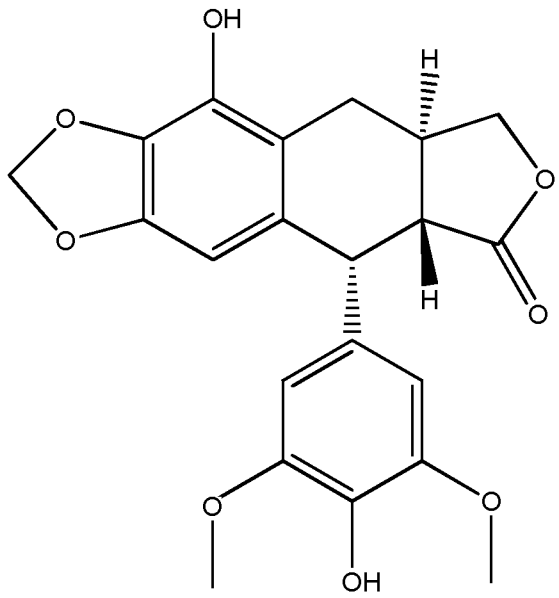
Typical peltatins that may be used in the framework of the present invention are depicted below:



In a particularly preferred embodiment, peltatins that may be used in the framework of the present invention are depicted below:



β-peltatin



α-peltatin

The at least one peltatin may be provided as chemically pure compound. It may be synthesized chemically. It may also be provided as a plant extract, for example. A typical known plant sources of peltatins that may be used as source for the plant extract are may apple (*Podophyllum peltatum*), or cow parsley (*Anthriscus sylvestris*, for example.

Preferably the peltatin used in the present invention is a natural compound.

Other possible plant sources for peltatins might be thymus, chestnuts, hazelnuts, chicory roots, flax seeds, sesame seeds, buckwheat seeds, or combinations thereof. These plant sources have the example, that they are generally approved for human or animal consumption, and hence food-grade.

Any extract may be used. For example, the extract may be a water extract, an alcoholic extract, and/or an extract with an organic solvent.

In one embodiment the extract is an alcoholic extract.

In a further embodiment the extract is a water extract.

The synthesis of peltatins is well known in the art. By way of example, the synthesis of peltatins is described in Masunari et al., Synthetic Communications 2001, 31(14), 2127-2136); and Yamaguchi et al., Chemical and Pharmaceutical Bulletin (Tokyo) 1984, 32, 1754-60.

Further synthetic methods are described in: Pelter et al., Tetrahedron Letters, 1985, 26(51), 6377-80 ; Takano et al., Heterocycles, 1987, 25(1), 69-73; Pelter et al., Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry, 1988, 1972-1999, (6), 1615-23; Ogiku et al, Bulletin of the Chemical Society of Japan, 1992, 65(12), 3495-7; Pelter et al., Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry, 1993, (21), 2621-9.

Assays for determining the hPPAR agonist activity of the peltatins described herein are well known in the art (see, for example, Forman et al., Cell. 1995 Dec 1;83(5):803-12; Han et al., Biol Pharm Bull. 2006 Jan;29(1):110-3; Han et al., Diabetes. 2008 Mar;57(3):737-45. Epub 2007 Dec 7).

One such method involves utilizing a reporter gene construct wherein PPAR binding is assayed by measuring luciferase activity (see e.g., Forman et al., Cell. 1995 Dec 1;83(5):803-12; Han et al., Biol Pharm Bull. 2006 Jan;29(1):110-3; Han et al., Diabetes. 2008 Mar;57(3):737-45. Epub 2007 Dec 7; US 2007244094).

In more detail, when PPARs fix their ligands they are able to shuttle from cytoplasm to the nucleus of HeLa cells. Then, PPARs heterodimerize with co-receptors called Retinoid-X-Receptors (RXR). Heterodimeric transcription factors PPAR/RXR are responsible for PPARs-mediated transcriptional program. In this system, hPPARs are fused to Gal4. Gal4 is a yeast transcription activator which specifically binds a Gal4 responsive element so-called Upstream Activation Sequence (UAS) - this short section in a promoter region strongly activates gene transcription. Therefore, cotransfection of Gal4-hPPARs with UAS-luciferase constructs allows identification hPPARs agonists. Agonists will stimulate luciferase transcription resulting in the formation of a functional enzyme that converts substrate to detectable signal by a chemiluminescent reaction.

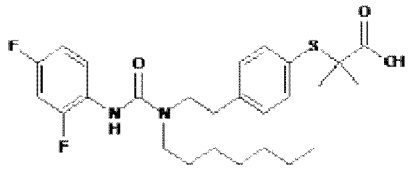
An example of such a transfection assay method is described in US 2007244094 and comprises the following steps: HEK293 cells were grown in DMEM/F12 medium supplemented with 10% FBS and glutamine (Invitrogen) and incubated in a 5% CO_2 incubator at 37° C. The cells were co-transfected using DMRIE-C reagent (Invitrogen) in serum free medium (Opti-MEM, Invitrogen) with two mammalian expression plasmids, one containing the DNA sequence coding for the ligand binding domains of a PPAR fused to the yeast GAL4 DNA binding domain and the other containing the promoter sequence of the yeast GAL4 (UAS) fused to the firefly luciferase cDNA reporter. The next day, the medium was changed to DMEM/F12 medium supplemented with 5% charcoal

treated serum (Hyclone) and glutamine. After 6 hrs the cells were trypsinized and seeded at a density of 50,000 cells/well into 96 well plates and incubated overnight as above. The cells were then treated with test compounds or vehicle and incubated for 18-24 hrs as above. Luciferase reporter activity was measured using the Steady-Glo Luciferase Assay Kit from Promega.

Preferably, the at least one peltatin used in the present invention has a maximum PPARγ activation activity of at least 70%, more preferably at least 100%, more preferably at least 120%, still more preferably at least 140% relative to the known PPARγ agonist Rosiglitazone. Preferably, the at least one peltatin has an AC50 with respect to PPARγ activation of less than 150nM, more preferably less 100nM, more preferably less than 80nM. The agonist activity of the peltatin may be ascertained using the above described luciferase reporter gene assay.

Preferably, the at least one peltatin used in the present invention has a maximum PPARα activation activity of at least 70%, more preferably at least 100%, still more preferably at least 110% relative to the known PPARα agonist GW 9578. Preferably, the art least one peltatin has an AC50 with respect to PPARα activation of less than 100nM, more preferably less 80nM, still more preferably less 50nM. The agonist activity of the peltatin may be ascertained using the above described luciferase reporter gene assay.

The GW 9578 referred to above is



GW 9578 is well known in the art and described, for example, in Brown et al., Journal of Medicinal Chemistry (1999), 42(19), 3785-3788.

Derivatives of α-peltatin and β-peltatin according to the present invention preferably have PPARγ and PPARα agonist activity that is substantially similar to, or greater than, that of α-peltatin and β-peltatin, respectively.

Preferably, the β-peltatin derivatives have a maximum PPARγ activity of at least 70%, more preferably at least 100%, still more preferably at least 120%, still more preferably at least 140% relative to the known PPARγ agonist Rosiglitazone. Preferably, the β-peltatin derivatives used in the present invention have a maximum PPARα activation activity of at least 70%, more preferably at least 100%, still more preferably at least 110% relative to the known PPARα agonist GW 9578.

The effectiveness of the composition of the present invention follows a dose-response curve.

Any amount above a certain minimum level will achieve the object of the present invention, while larger amounts will produce more pronounced effects up to a saturation level.

In therapeutic applications, compositions are administered in an amount sufficient to at least partially cure or arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "a therapeutically

effective dose". Amounts effective for this purpose will depend on a number of factors known to those of skill in the art such as the severity of the disease and the weight and general state of the patient.

In prophylactic applications, compositions according to the invention are administered to a patient susceptible to or otherwise at risk of a particular disease in an amount that is sufficient to at least partially reduce the risk of developing a disease. Such an amount is defined to be "a prophylactically effective dose". Again, the precise amounts depend on a number of patient specific factors such as the patient's state of health and weight.

The compositions of the present invention may be administered in a therapeutically effective dose or a prophylactically effective dose.

For example the composition of the present invention may be to be administered in an amount corresponding to about 0.01 to 100 mg dry weight peltatins/kg body weight, e.g., about 0.05 to 50 mg dry weight peltatins/kg body weight, or about 1 to 20 mg dry weight peltatins/kg body weight.

To ensure regular intake of peltatins, the composition may be to be administered immediately before or during a meal. For example, peltatins may be an integral part of the meal, so that the composition of the present invention is administered with each meal.

To ensure a certain effectiveness of the composition of the present invention, the composition may contain a therapeutically effective dose or a prophylactically effective dose of the present invention per serving.

For example, the composition may comprise an amount of about 1 - 1000 mg peltatins per kg dry weight of the composition, e.g., an amount of about 5 - 200 mg peltatins per kg dry weight of the composition, or an amount of about 10 - 100 mg peltatins per kg dry weight of the composition.

Those skilled in the art will understand that they can freely combine all features of the present invention described herein, without departing from the scope of the invention as disclosed. In particular, features described for the composition of the present invention may be applied to the use of the present invention and vice versa.

Further advantages and features of the present invention are apparent from the following Examples and Figures.

Figure 1 shows the principle of hPPAR bioassay used for screening. The assays detect binding of a ligand to the hPPAR of interest by directly measuring luciferase activity. When PPARs fixe their ligands they are able to shuttle from cytoplasm to the nucleus of HeLa cells. Then, PPARs heterodimerize with co-receptors called Retinoid-X-Receptors (RXR). Heterodimeric transcription factors PPAR/RXR are responsible for PPARs-mediated transcriptional program. In this system, hPPARs are fused to Gal4. Gal4 is a yeast transcription activator which specifically binds a Gal4 responsive element so-called Upstream Activation Sequence (UAS), this short section in a promoter region strongly activates gene transcription. Therefore, cotransfection of Gal4-hPPARs with UAS-luciferase constructs allows identification hPPARs agonists. Agonists will stimulate luciferase transcription resulting in the formation of a functional enzyme that converts substrate to detectable signal by a chemiluminescent reaction.

Figure 2 shows dose-responses effects of beta-Peltatin used at different concentration (nM) for PPARa activation (black curve). The AC50 (upper part of the insert) and the maximum % activation (lower part of the insert) are given. Cellular toxicity was also assessed with standard method compared to untreated cells and shown in % of toxicity. As shown in the below grey curve no toxicyty was observed even at highest dose of beta-Peltatin used.

Figure 3 shows dose-responses effects of beta-Peltatin used at different concentration (nM) for PPARg activation (black curve). The AC50 (upper part of the insert) and the maximum % activation (lower part of the insert) are given. Cellular toxicity was also assessed with standard method compared to untreated cells and shown in % of toxicity. As shown in the below grey curve no toxicyty was observed even at highest dose of beta-Peltatin used.

Figure 4 shows dose-responses effects of beta-Peltatin used at different concentration (nM) for PPARd activation (black curve). The AC50 (upper part of the insert) and the maximum % activation (lower part of the insert) are given. Cellular toxicity was also assessed with standard method compared to untreated cells and shown in % of toxicity. As shown in the below grey curve no toxicyty was observed even at highest dose of beta-Peltatin used.

Examples:

An edible plant fraction library was tested for PPARs agonist activity and toxicity. Then relevant plant fractions were further analyzed and bioactive(s) characterized and validated with the same hPPARa, hPPARg or hPPARd reporter bioassays. The reporter bioassay we used in order to identify anti-inflammatory plant properties targeted activation of human

PPARs in human HeLa cells (as described in the figure 1). All isolated bioactives were tested in a dose response manner in duplicate. Assays were repeated 3-4 times. Shown are mean values obtained. Therefore specificity (for all the three known human PPAR receptors namely PPARa, PPARd and PPARg) and efficacy (full agonist i.e. % maximal activity >100% or partial agonist i.e. % maximal activity <100%) were tested (figure 2-4).

It was found that β-peltatin displayed dual agonistic activity on PPARα and PPARγ. It was further found that podophyllotoxin also displayed dual agonistic activity on PPARα and PPARγ.

PPARg nutrient sensing pathway is of high importance for cell metabolism, diabetes and inflammation and is supported by many published reports. Hence, pharma industries are already tackling PPARs pathways for many purposes. Peltatins or plant extracts containing peltatins might represent a novel and valuable nutritional approach for treatment, alleviation or prevention of cardiovascular disorders.

Claims

1. Composition comprising at least one peltatin for use in the treatment or prevention of cardiovascular disorders.

2. Composition for use according to claim 1 wherein the cardiovascular disorder is one which is treatable or preventable by activation of a peroxisome proliferator-activated receptor (PPAR).

3. Composition in accordance with claim 1 or 2, wherein the cardiovascular disorder is selected from the group consisting of artherosclerosis, myocardinal infarction, stroke, peripheral vascular diseases, hyperlipidemia, hypercholesterolemia, dyslipidemia, hypertriglycerinemia or combinations thereof.

4. Composition for use in accordance with any one of the preceding claims, wherein the peltatin is (i) α-peltatin or a derivative thereof, (ii) β-peltatin or a derivative thereof, or a combination of (i) and (ii).

5. Composition for use in accordance with any one of the preceding claims, wherein the peltatin is β-peltatin or a derivative thereof.

6. Composition for use in accordance with any one of the preceding claims, wherein the peltatin is provided as a plant extract, for example from *Podophyllum peltatum* or *Anthriscus sylvestris*.

7. Composition for use in accordance with any one of the preceding claims to be administered in an amount

corresponding to about 0.01 to 100 mg dry weight peltatins/kg body weight.

8. Composition for use in accordance with any one of the preceding claims wherein the composition is selected from the group consisting of food products, drinks, pet food products, food additives, nutritional supplements, and powdered nutritional formulations to be reconstituted in milk or water.

9. Composition for use in accordance with any one of the preceding claims to be administered to infants, teenagers, adults, or the elderly.

10. Composition for use in accordance with any one of the preceding claims to be administered immediately before or during a meal.

11. Composition for use in accordance with any one of the preceding claims to be administered with each meal.

12. Composition for use in accordance with any one of the preceding claims comprising and amount of about 1 - 1000 mg peltatin per kg dry weight of the composition.

Figure 1:

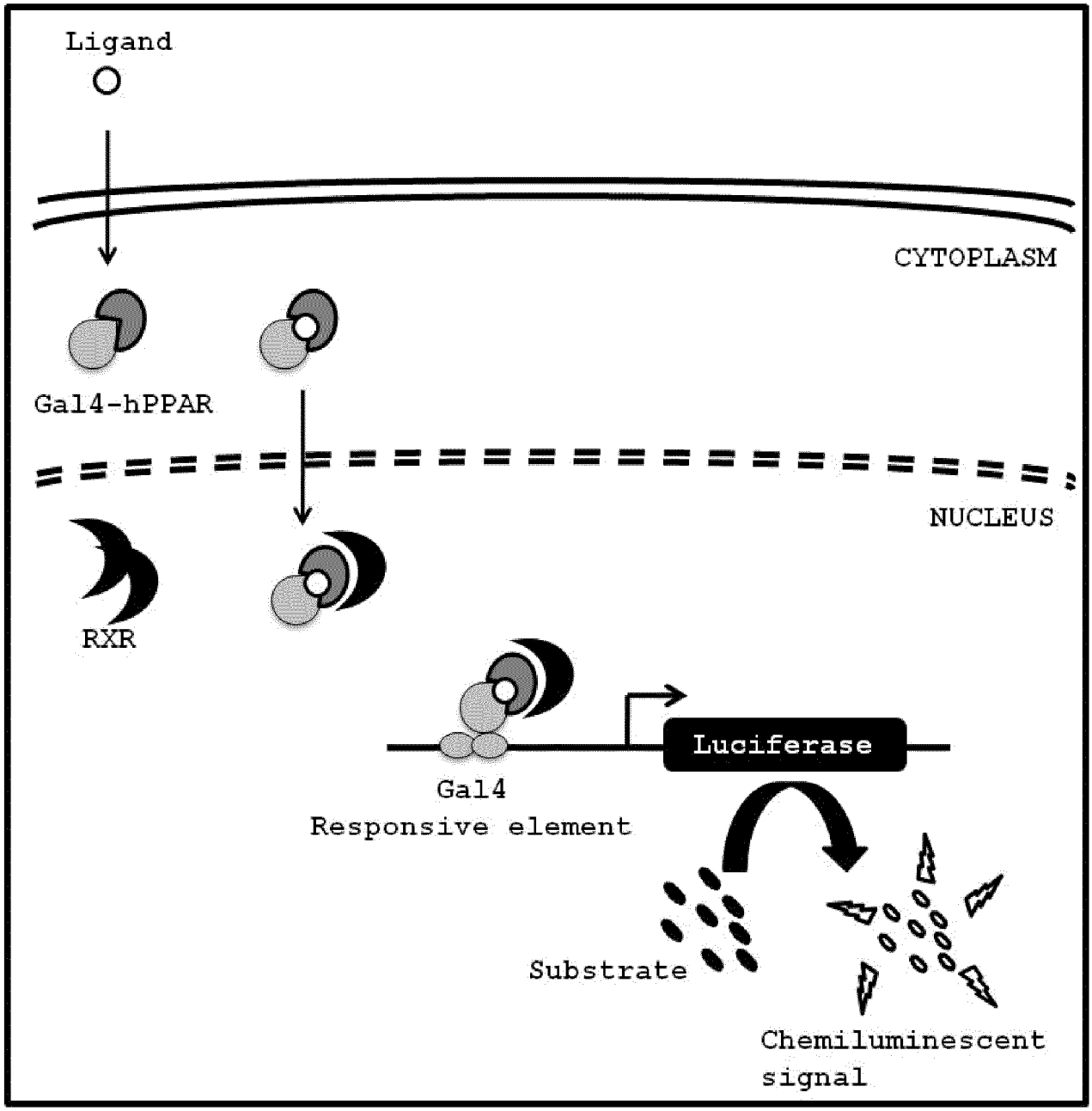

Ligand
CYTOPLASM
Gal4-hPPAR
NUCLEUS
RXR
Luciferase
Gal4
Responsive element
Substrate
Chemiluminescent
signal

Figure 2:

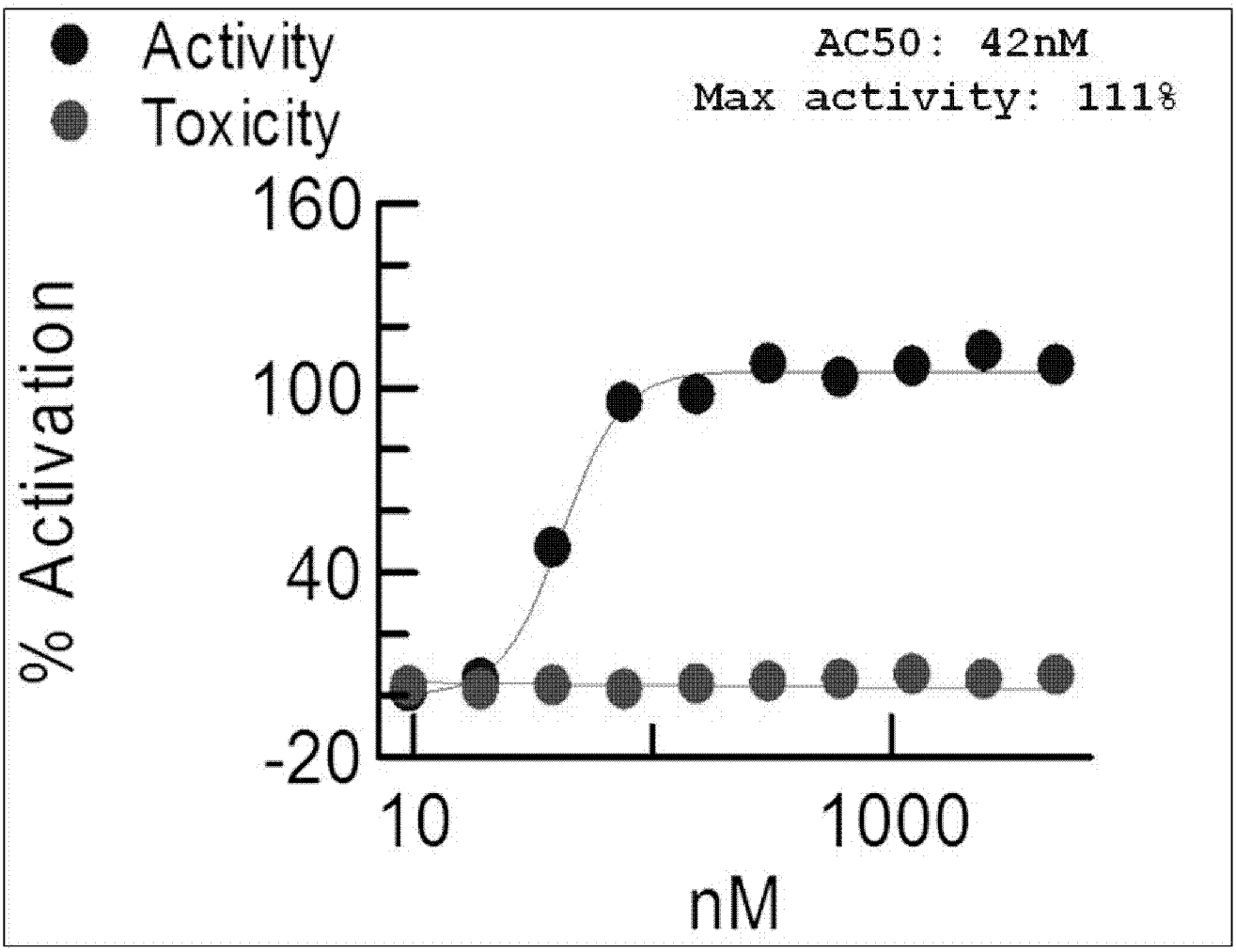
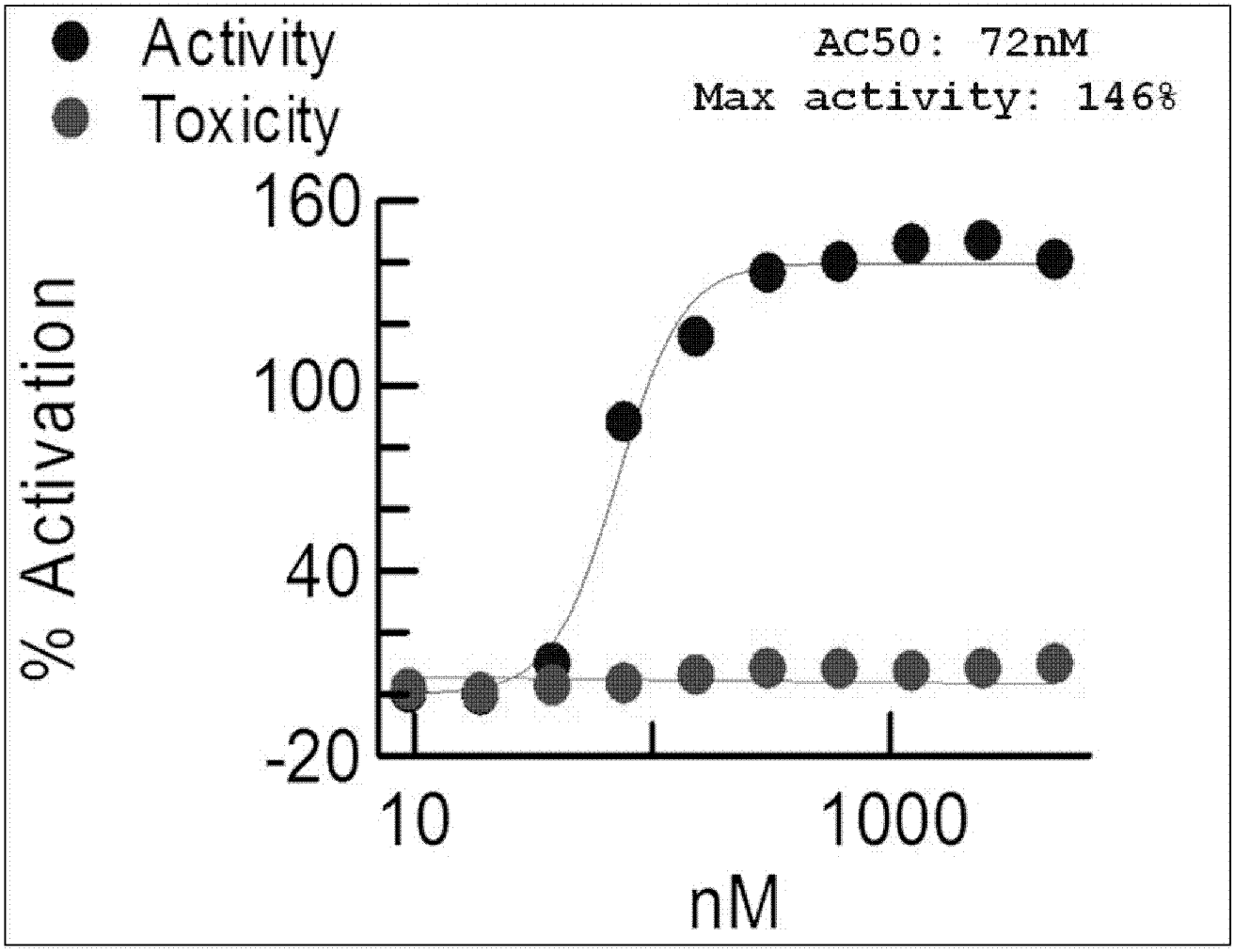

Activity
Toxicity
AC50: 42nM
Max activity: 111%
% Activation
160
100
40
-20
10
1000
nM

Figure 3:


Activity
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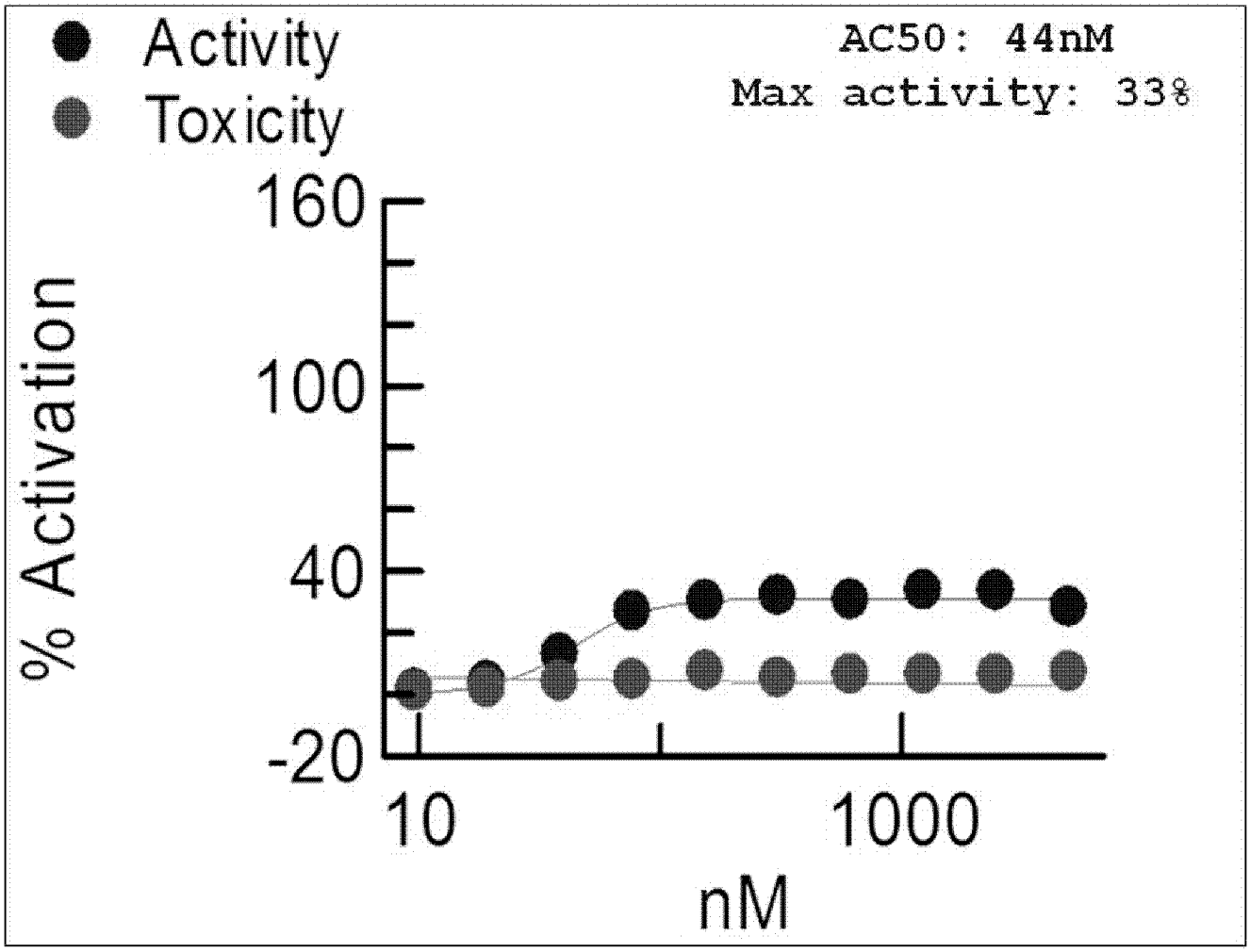
AC50: 72nM
Max activity: 146%
160
100
40
-20
% Activation
10
1000
nM

Figure 4:


Activity
Toxicity
AC50: 44nM
Max activity: 33%
% Activation
160
100
40
-20
10
1000
nM

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/053496

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P9/00 A61K31/365 A61K36/23 A61K36/29
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MACRAE W ET AL: "Biological activities of lignans", PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 23, no. 6, 14 May 1984 (1984-05-14), pages 1207-1220, XP026609373, ISSN: 0031-9422, DOI: 10.1016/S0031-9422(00)80428-8 [retrieved on 1984-05-14] abstract table 2 page 1211	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2013	10/05/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/053496

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No
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International application No
PCT/EP2013/053496

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