(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 June 2017 (22.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/102965 A1

(51) International Patent Classification:
A61K 31/7012 (2006.01) *A61P 25/28* (2006.01)
A61P 3/10 (2006.01) *A61P 43/00* (2006.01)
A61P 9/10 (2006.01)

(21) International Application Number:
PCT/EP2016/081225

(22) International Filing Date:
15 December 2016 (15.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/268,035 16 December 2015 (16.12.2015) US
62/286,728 25 January 2016 (25.01.2016) US

(71) Applicant: **NESTEC S.A.** [CH/CH]; Av. Nestlé 55, 1800 Vevey (CH).

(72) Inventors: **ACTIS GORETTA, Lucas**; Route du Jorat 194, 1000 Lausanne 26 (CH). **PATIN, Amaury**; 13, Route de Marin, 1000 Lausanne 26 (CH). **MICHLIG GONZALEZ, Stéphanie**; Rue du Champ du Bois 18, 1052 Le Mont-sur-lausanne (CH). **CAMACHO, Susana**; Ch. d'Orzens 50, 1095 Lutry (CH). **LEGRAND, Coline**; Route de la Feuillère 15, 1010 Lausanne (CH). **LE COUTRE, Johannes**; Ch. du Fau-Blanc 32, 1009 Pully (CH). **CASTANEDA GUTIERREZ, Euridice**; Route du Port 4, 1009 Pully (CH). **SILVA ZOLEZZI, Irma**; 5, Chemin de la Fontanettaz, 1084 Carrouge (CH).

(74) Agent: **CHAUTARD, Cécile**; Avenue Nestlé 55, 1800 Vevey (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, 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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2017/102965 A1

(54) Title: COMPOSITIONS COMPRISING 3'-O-GLUCURONIDE EPICATECHIN AND METHODS OF MAKING AND USING SUCH COMPOSITIONS

(57) Abstract: Compositions can comprise the flavanol metabolite 3'-O-glucuronide epicatechin (3GEC). In some embodiments, the amount of 3GEC is effective to increase energy expenditure, sympathetic nervous system activity, and/or fat oxidation. Such a composition can be used in a method to support weight management or promote weight loss, a method for preventing obesity or overweight, and a method for treating obesity or overweight. In some embodiments, the composition can improve insulin sensitivity, glucose tolerance, cognitive performance, cognition, mood and/or memory. In some embodiments, the composition can achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body, improvement of blood circulation, e.g. in brain, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof. In some embodiments, the composition can treat or prevent dysphagia, e.g., by provoking the swallowing reflex.

TITLE

COMPOSITIONS COMPRISING 3'-*O*-GLUCURONIDE EPICATECHIN AND METHODS OF MAKING AND USING SUCH COMPOSITIONS

BACKGROUND

[0001] The present disclosure generally relates to compositions comprising a flavanol metabolite. More specifically, the present disclosure relates to compositions comprising the flavanol metabolite 3'-*O*-glucuronide epicatechin and further relates to methods comprising administering such compositions and methods of making such compositions.

[0002] During the past decades, the prevalence of obesity has increased worldwide to epidemic proportion. Approximately 1 billion of people worldwide are overweight or obese, conditions that increase mortality, mobility and economical costs. Obesity develops when energy intake is greater than energy expenditure, the excess energy being stored mainly as fat in adipose tissue. Body weight loss and prevention of weight gain can be achieved by reducing energy intake or bioavailability, increasing energy expenditure, and/or reducing storage as fat.

[0003] Another significant condition afflicting some individuals is dysphagia, a condition typified by a decreased ability to swallow. The normal swallow involves three distinct phases which are interdependent and well coordinated: the oral, the pharyngeal, and the esophageal phases. In the oral phase, which is under voluntary control, food that has been chewed and mixed with saliva is formed into a bolus for delivery by voluntary tongue movements to the back of the mouth, into the pharynx. The pharyngeal phase is involuntary and is triggered by the food/liquid bolus passing through the faucial pillars into the pharynx. Contraction of the three constrictors of the pharynx propels the bolus towards the upper oesophageal sphincter. Simultaneously, the soft palate closes the nasopharynx. The larynx moves upwards to prevent food or liquid passing into the airway, which is aided by the backward tilt of the epiglottis and closure of the vocal folds. The oesophageal phase is also involuntary and starts with the relaxation of the upper oesophageal sphincter followed by peristalsis, which pushes the bolus down to the stomach.

[0004] Esophageal dysphagia affects a large number of individuals of all ages, but is generally treatable with medications and is considered a less serious form of dysphagia. Oral pharyngeal dysphagia, on the other hand, is a very serious condition and is generally not treatable with medication. Oral pharyngeal dysphagia also affects individuals of all ages, but is more prevalent in older individuals. Worldwide, oral pharyngeal dysphagia affects approximately 22 million people over the age of 50.

[0005] The consequences of untreated or poorly managed oral pharyngeal dysphagia can be severe, including dehydration, malnutrition, airway obstruction with solid foods (choking), and airway aspiration of liquids and semi-solid foods, promoting aspiration pneumonia and/or pneumonitis. Severe oral pharyngeal dysphagia may require nutrition to be supplied by tube feeding. Mild to moderate oral pharyngeal dysphagia requires the texture of foods to be modified in order to minimize the likelihood of choking or aspiration.

[0006] Improving an individual's ability and efficiency to swallow improves the individual's safety through reduced risk of pulmonary aspiration. An efficient swallow may permit greater independence from feeding assistance and/or reduced length of time spent in feeding-assistance during meal consumption. Efficient swallow also reduces the viscosity of liquids required for safety (e.g., pudding, honey and nectar thickness products) and may also limit the use of texture-modified foods. All of these previously described factors are aimed at improving an individual's quality of life.

[0007] Research on the molecular mechanisms underlying pungent sensations revealed the existence of two cation channels, TRPV1 (transient receptor potential V1) and TRPA1 (transient receptor potential A1) that are expressed in the somatosensory fibers innervating the oral cavity. TRPV1 is the receptor for heat and burning sensations such as capsaicin, the spicy compound of chili peppers. TRPA1 responds to cold and pungent compounds; at moderate concentrations, TRPA1 agonists exhibit a pleasant tingling sensation.

[0008] The TRPV1 agonist capsaicin is well known as increasing energy expenditure and fat oxidation, but the efficient doses are intermediate to high (20 mg and more). See, e.g., Ludy *et al.*, "The effects of hedonically acceptable red pepper doses on thermogenesis and appetite," Physiol. Behav., Mar. 1, 102(3-4): 251-8 (2011). In addition, oral administration of capsaicin

has been shown to promote a swallow reflex. However, capsaicin is a particularly pungent and toxic compound. Physiological effects associated with oral administration of capsaicin include a burning sensation of heat from the mid-tongue to the throat, shortness of breath, fainting, nausea, and spontaneous vomiting. As a result, only small quantities of capsaicin may be administered without causing discomfort to the individual. Food products containing capsaicin are frequently not accepted by the consumer because such products provide a very unpleasant mouth feeling. In particular, the burning effects are considered to be very unsavory, affecting the consumption of the food product.

[0009] Another condition adversely affecting some individuals is that their body tissues do not respond properly to insulin. Insulin receptors in the tissues cease to function adequately, and gluco-dependent cells fail to recognize the presence of insulin. As a result, the pancreas needs to secrete more insulin to help glucose enter these cells. The pancreas tries to keep up with this increased demand for insulin by producing more. This phenomenon is called insulin resistance (also known as low insulin sensitivity). Many people with insulin resistance have high levels of both glucose and insulin circulating in their blood at the same time. Eventually, the pancreas fails to keep up with the body's need for insulin, leading to Type II diabetes.

[0010] Insulin resistance and Type II diabetes are associated with increased risk of heart attacks, strokes, amputation, diabetic retinopathy, and kidney failure. For extreme cases, circulation of limbs is affected, potentially requiring amputation. Loss of hearing, eyesight, and cognitive ability has also been linked to these conditions. GDM is a pregnancy condition that can increase the risk of a number of maternal-fetal conditions, including macrosomia, birth injury, shoulder dystocia, premature delivery, and caesarian delivery. Mothers suffering from GDM also have an increased risk of developing type II diabetes immediately after pregnancy and later in life. Also, the foetus/infant of mothers suffering from GDM have an increased risk of developing an impaired glucose tolerance and/or suffering from excess weight/adiposity and associated metabolic disorders e.g. type II diabetes and obesity.

[0011] Management of insulin resistance in children and adults, including pregnant women, is essentially based on dietary and lifestyle changes, including healthier dietary habits and increased exercise. These practices can be very efficient in improving insulin sensitivity and

in slowing the progression of the disease, but they are difficult to apply and actually not followed by most patients. Type II diabetes can be treated with drugs promoting insulin sensitivity, but their efficacy in reducing the rate of progression of the disease is quite low. Insulin treatment is required during the most advanced phases of the disease.

[0012] Products containing n-3 polyunsaturated fatty acids, fibers, oligosaccharides and even probiotics have been proposed as nutritional solutions to improve insulin sensitivity and to reduce insulin resistance. However, the efficacy of these nutritional interventions is quite marginal and even controversial, with studies showing no or even deleterious effects.

[0013] The TRPV1 agonist capsaicin can improve insulin sensitivity; however, as noted above, capsaicin is a particularly pungent and toxic compound, and the effective dosage of capsaicin is too intense to be included in a food product, due to spicy taste, or to be ingested, due to gastrointestinal intolerance.

[0014] Yet another condition adversely affecting some individuals is impaired neurotransmission, for example low levels of neurotransmitters such as epinephrine. Impaired neurotransmission is connected to mood disorders such as depression, anxiety disorders, and increased susceptibility to stress, and also connected to cognitive dysfunction and cognitive ageing.

[0015] Carbohydrate-rich foods are known for providing important metabolic fuel for physical performance, but their effects on mood and cognitive performance are not very clear. However, irritability and aggression are influenced by individual differences in insulin release, the frequency that meals are eaten, and the effect of these meals on blood glucose values. Benton, "Carbohydrate ingestion, blood glucose and mood," Neuroscience and Biobehavioral Reviews, 26:293-308 (2002). Furthermore, the ability to control the levels of blood glucose is related to both mood and cognition. For example, in a study in which participants were given an oral glucose tolerance test and cognitive tests, the older age group showed that those with poorer glucose tolerance forgot more words and had slower decision times; and, in those participants with poor glucose tolerance, a tendency for blood glucose to fall below baseline values was associated with better mood and faster working memory. Young and Benton,

"The nature of the control of blood glucose in those with poorer glucose tolerance influences mood and cognition," Metab. Brain Dis. (Mar. 26, 2014).

[0016] Yet another condition adversely affecting some individuals is high blood pressure. Blood pressure is the force of blood pushing against the walls of the arteries as the heart pumps out blood. High blood pressure is a serious condition that is associated with a higher risk of cardiovascular diseases and can lead to, for example, coronary heart disease, heart failure, stroke, kidney failure, and other health problems.

[0017] Hypertension is a condition caused by a sustained high blood pressure. Hypertension is a cardiac chronic medical condition in which the systemic arterial blood pressure is outside a normal range. Hypertension generally refers to a condition where a systolic blood pressure is 140 mmHg or higher or a diastolic blood pressure is 90 mmHg or higher. Hypertension is classified as either primary or secondary. About 90-95% of hypertension cases are primary hypertension, which refers to high blood pressure for which no medical cause has been found. The remaining 5-10% of cases are secondary hypertension, which refers to high blood pressure caused by other conditions that affect the kidneys, arteries, heart, or endocrine system.

[0018] The incidence of hypertension is increasing all over the world. In addition, hypertension may cause fatal complications such as cerebral stroke, heart failure, and coronary artery diseases, even among minor or mild patients exhibiting no external symptoms. High blood pressure and hypertension can also be problems experienced during pregnancy.

[0019] Yet another condition adversely affecting some individuals is endothelium dysfunction. This disorder is an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) the endothelium.

[0020] Each of the above-noted conditions is commonly addressed with interventions that are not fully effective, and thus each of the above-noted conditions could benefit from improved methods and compositions.

SUMMARY

[0021] The present inventors surprisingly and unexpectedly identified 3'-*O*-glucuronide epicatechin (chemical structure shown in **FIG. 1**) as an agonist of the cation channel of

TRPA1, while e.g. 3'-*O*-sulfate epicatechin and 3'-*O*-methyl epicatechin, which are also epicatechin metabolites, were not TRPA1 agonists. Epicatechin is absorbed and metabolized into several different compounds, and to the best knowledge of the inventors, this is the first time that bioactivity of a specific metabolite of a flavanol (e.g., epicatechin, catechin and procyanidins) has been shown.

[0022] Furthermore, without wishing to be bound by theory, the present inventors believe that activation of TRPA1 by 3'-*O*-glucuronide epicatechin is effective to module nitric oxide levels to treat or prevent high blood pressure, treat or prevent a cardiovascular disease, prevent cognitive decline, and/or preeclampsia, and/or intrauterine growth restriction (IUGR), and/or achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body, improvement of blood circulation, improvement of blood circulation in the brain, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof. Still further, the present inventors believe that activation of TRPA1 by 3'-*O*-glucuronide epicatechin is effective to improve one or more of insulin sensitivity, glucose tolerance, mood, memory or cognition by stimulating the sympathetic nervous system and, as a result, catecholamine secretion. Moreover, the present inventors believe that 3'-*O*-glucuronide epicatechin helps to provoke the swallowing reflex of dysphagic patients; this effect might be mediated by TRPA1 but may be mediated alternatively or additionally by another pathway.

[0023] Accordingly, in a general embodiment, the present disclosure provides a method for treating or preventing high blood pressure comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. It can be ingested in a special form to prevent degradation in the stomach. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized. The composition may be administered pre-pregnancy, and in the case of a pregnant individual the composition can be administered for any period of pregnancy.

[0024] In another embodiment, the present disclosure provides a method for treating or preventing a cardiovascular disease and/or preeclampsia and/or IUGR. The method comprises administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized.With respect to preeclampsia and/or IUGR, the composition can be administered for any period of pregnancy, or pre-pregnancy when a woman is trying to get pregnant.

[0025] In another embodiment, the present disclosure provides a method for achieving a therapeutic effect in an individual, the therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body, improvement of blood circulation, improvement of blood brain circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof. The method comprises administering to the individual a composition comprising 3'-*O*-glucuronide epicatechin. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized. In the case of a pregnant individual the composition can be administered for any period of pregnancy. The composition may also be administered pre-pregnancy when a woman is trying to get pregnant.

[0026] In another embodiment, the present disclosure provides a method for making a food product. The method comprises adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof. The 3'-*O*-glucuronide epicatechin is present in the composition in an amount effective to achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body, improvement of blood

circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof.

[0027] In another embodiment, the present disclosure provides a method for weight maintenance or weight loss. The method comprises administering to an individual in need thereof a composition comprising 3'-*O*-glucuronide epicatechin. The composition can be administered to provide an amount of the 3'-*O*-glucuronide epicatechin that increases at least one characteristic selected from the group consisting of energy expenditure, sympathetic nervous system activity, and fat oxidation. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized.

[0028] In another embodiment, the present disclosure provides a method for treating or preventing obesity or overweight. The method comprises administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin. The composition can be administered to provide an amount of the 3'-*O*-glucuronide epicatechin that increases at least one characteristic selected from the group consisting of energy expenditure, sympathetic nervous system activity, and fat oxidation. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized. The composition can further comprise an additional ingredient in an amount effective to promote weight maintenance or weight loss. In an embodiment, the individual is participating in a weight loss program selected from the group consisting of a low-fat diet, a low-carbohydrate diet, a low-calorie diet, a very low-calorie diet, endurance training, strength training, and combinations thereof.

[0029] In another embodiment, the present disclosure provides a method for making a food product for weight maintenance or weight loss. The method comprises adding

3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof.

[0030] In another embodiment, the present disclosure provides a method for improving a characteristic selected from the group consisting of insulin resistance, glucose tolerance and a combination thereof. The method comprises administering to an individual in need thereof a composition comprising 3'-*O*-glucuronide epicatechin. In an embodiment, the individual is selected from the group consisting of an infant born preterm, an infant experiencing intrauterine growth restriction, a pregnant woman suffering from or at risk of suffering from gestational diabetes mellitus, a human suffering from insulin resistance, a human suffering from impaired glucose tolerance, and a human suffering from type II diabetes. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized. With respect to GDM the composition can be administered for any period of pregnancy, or pre pregnancy when a woman is trying to get pregnant.

[0031] In another embodiment, the present disclosure provides a method for improving one or more of cognitive performance, cognition, mood, or memory. The method comprises administering to an individual in need thereof a composition comprising a therapeutically effective amount of 3'-*O*-glucuronide epicatechin. In an embodiment, the individual has a condition selected from the group consisting of cognitive decline, mild cognitive impairment, dementia, a mood disorder, memory loss, and combinations thereof. In a preferred embodiment, the individual is an elderly human having cognitive aging. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized.

[0032] In another embodiment, the present disclosure provides a method for making a food product, the method comprising adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof. The 3'-*O*-glucuronide epicatechin is present in the composition in an amount effective to improve at least one characteristic selected from the group consisting of insulin sensitivity, glucose tolerance, cognitive performance, cognition, mood, and memory in an individual that consumes the food product.

[0033] In another embodiment, the present disclosure provides a method of treating or preventing dysphagia comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin. In an embodiment, the dysphagia is oral pharyngeal dysphagia. The composition can be a thickened beverage. In an embodiment, the composition is administered to provide an amount of the 3'-*O*-glucuronide epicatechin that provokes a swallowing reflex. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin can be present in a concentration of at least 0.01 mg/g of the food product. The composition can be injected into the individual. The composition can be administered to the individual at least once a day for at least one week. The 3'-*O*-glucuronide epicatechin can be chemically synthesized.

[0034] In another embodiment, the present disclosure provides a method for making a food product, the method comprising adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof. The 3'-*O*-glucuronide epicatechin is present in the composition in an amount effective to treat or prevent dysphagia.

[0035] In another embodiment, the present disclosure provides a method for treating or preventing endothelium dysfunction comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin. The composition can be orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product. The composition can be administered to the individual at least once a day for at least one week

[0036] An advantage of the present disclosure is to use a TRPA1 agonist that is easily consumed.

[0037] An additional advantage of the present disclosure is to increase energy expenditure.

[0038] Another advantage of the present disclosure is to increase sympathetic nervous system activity.

[0039] Still another advantage of the present disclosure is to increase fat oxidation.

[0040] Yet another advantage of the present disclosure is to increase energy expenditure, sympathetic nervous system activity, and fat oxidation with a compound that can be easily and safely used in food products.

[0041] Another advantage of the present disclosure is to increase energy expenditure, sympathetic nervous system activity, and fat oxidation with tolerable side effects or no side effects.

[0042] Yet another advantage of the present disclosure is to support weight management, promote weight loss, and/or treat or prevent obesity or overweight.

[0043] Still another advantage of the present disclosure is to increase energy expenditure, sympathetic nervous system activity, and fat oxidation with a compound that has increased acceptability, reduced pungency, and improved tolerance in the gastrointestinal tract relative to capsaicin.

[0044] Yet another advantage of the present disclosure is to improve insulin sensitivity and/or glucose tolerance.

[0045] Still another advantage of the present disclosure is to improve insulin sensitivity and/or glucose tolerance with a compound that can be easily and safely used in food products.

[0046] Another advantage of the present disclosure is to improve insulin sensitivity and/or glucose tolerance with tolerable side effects or no side effects.

[0047] Yet another advantage of the present disclosure is to improve insulin sensitivity and/or glucose tolerance with a compound that has increased acceptability, reduced pungency, and improved tolerance in the gastrointestinal tract relative to capsaicin.

[0048] Still another advantage of the present disclosure is to improve at least one of mood, memory or cognition.

[0049] Still another advantage of the present disclosure is to improve at least one of mood, memory or cognition with a compound that can be easily and safely used in food products.

[0050] Another advantage of the present disclosure is to improve at least one of mood, memory or cognition with tolerable side effects or no side effects.

[0051] Yet another advantage of the present disclosure is to improve at least one of mood, memory or cognition with a compound that has increased acceptability, reduced pungency, and improved tolerance in the gastrointestinal tract relative to capsaicin.

[0052] Yet another advantage of the present disclosure is to achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body (e.g., treatment or prevention of erectile dysfunction), improvement of blood circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof.

[0053] Still another advantage of the present disclosure is to use a compound that can be easily and safely used in food products to achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body (e.g., treatment or prevention of erectile dysfunction), improvement of blood circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof.

[0054] Another advantage of the present disclosure is to provide tolerable side effects or no side effects while achieving a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body (e.g., treatment or prevention of erectile dysfunction), improvement of blood circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof.

[0055] Yet another advantage of the present disclosure is to use a compound that has increased acceptability, reduced pungency, and improved tolerance in the gastrointestinal tract relative to capsaicin to achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body (e.g., treatment or prevention of erectile dysfunction), improvement of blood circulation, stimulation

of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof.

[0056] Still another advantage of the present disclosure is to treat or prevent high blood pressure.

[0057] An additional advantage of the present disclosure is to treat or prevent cardiovascular diseases.

[0058] Another advantage of the present disclosure is to use a compound that can be easily and safely used in food products to prevent aspiration pneumonia in dysphagic patients and/or trigger the swallowing reflex of a dysphagic patient.

[0059] Yet another advantage of the present disclosure is to treat dysphagia with tolerable side effects or no side effects.

[0060] Still another advantage of the present disclosure is to promote safe swallowing of a food bolus.

[0061] Additional features and advantages are described herein, and will be apparent from, the following Detailed Description and the Figures.

BRIEF DESCRIPTION OF THE FIGURES

[0062] **FIG. 1** shows the chemical structure of 3'-*O*-glucuronide epicatechin.

[0063] **FIG. 2** shows the chemical structure of a first compound for the production of 3'-*O*-glucuronide epicatechin.

[0064] **FIG. 3** shows the chemical structure of a second compound which can be coupled to the first compound shown in **FIG. 2** for the production of 3'-*O*-glucuronide epicatechin.

[0065] **FIG. 4** shows experimental data for 3'-*O*-glucuronide epicatechin regarding activation of CHO cells expressing h-TRPA1.

[0066] **FIG. 5** shows the chemical structure of 3'-methyl- epicatechin.

[0067] **FIG. 6** shows experimental data for 3'-methyl- epicatechin regarding activation of CHO cells expressing h-TRPA1.

[0068] **FIG. 7** shows experimental data for 3'-*O*-sulfate epicatechin regarding activation of CHO cells expressing h-TRPA1.

[0069] **FIG. 8** shows the chemical structure of HC030031, a selective antagonist of hTRPA1.

[0070] FIG. 9 shows experimental data for 3'-*O*-glucuronide epicatechin regarding activation of CHO cells expressing h-TRPA1 and blockage thereof by HC030031.

[0071] FIG. 10 shows experimental data for different concentrations of 3'-*O*-glucuronide epicatechin regarding activation of CHO cells expressing h-TRPA1.

[0072] FIG. 11 shows the dose-response curve for 3'-*O*-glucuronide epicatechin regarding activation of CHO cells expressing h-TRPA1.

[0073] FIG. 12 shows comparative experimental data for 3'-O-glucuronide epicatechin versus other metabolites on expression of p-eNOS and eNOS total in isolated aortic rat rings.

DETAILED DESCRIPTION

[0074] All percentages expressed herein are by weight of the total weight of the composition unless expressed otherwise. When reference is made to the pH, values correspond to pH measured at 25 °C with standard equipment. As used in this disclosure and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. As used herein, "about" is understood to refer to numbers in a range of numerals, for example the range of -10% to +10% of the referenced number, preferably -5% to +5% of the referenced number, more preferably -1% to +1% of the referenced number, most preferably -0.1% to +0.1% of the referenced number. Moreover, all numerical ranges herein should be understood to include all integers, whole or fractions, within the range. The compositions disclosed herein may lack any element that is not specifically disclosed herein. Thus, a disclosure of an embodiment using the term "comprising" includes a disclosure of embodiments "consisting essentially of" and "consisting of" the components identified.

[0075] "Prevention" includes reduction of risk and/or severity of a condition or disorder. The terms "treatment," "treat" and "to alleviate" include both prophylactic or preventive treatment (that prevent and/or slow the development of a targeted pathologic condition or disorder) and curative, therapeutic or disease-modifying treatment, including therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder; and treatment of patients at risk of contracting a disease or suspected to have contracted a disease, as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition. The term does not necessarily imply that a subject is treated

until total recovery. The terms "treatment" and "treat" also refer to the maintenance and/or promotion of health in an individual not suffering from a disease but who may be susceptible to the development of an unhealthy condition. The terms "treatment," "treat" and "to alleviate" are also intended to include the potentiation or otherwise enhancement of one or more primary prophylactic or therapeutic measure. The terms "treatment," "treat" and "to alleviate" are further intended to include the dietary management of a disease or condition or the dietary management for prophylaxis or prevention a disease or condition. A treatment can be patient- or doctor-related.

[0076] For adults, "high blood pressure" is a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher. High blood pressure includes both primary and secondary hypertension. Non-limiting examples of individuals "at risk" of high blood pressure include humans of age 60 or older, overweight or obese individuals, individuals who smoke at least once a day, humans who consume at least 2.4 g of sodium each day, humans who consume less than 4.7 g of potassium each day, individuals who perform aerobic exercise less than 3 days per week, men who consume more than 3 units of alcohol per day, women who consume more than 2 units of alcohol per day, individuals who have a mother or father with high blood pressure, and individuals having either (i) a systolic blood pressure from 120 to 139 mmHg and a diastolic blood pressure from 40 to 80 mmHg or (ii) a systolic blood pressure from 70 to 140 mmHg and a diastolic blood pressure from 80 to 89 mmHg.

[0077] Cardiovascular diseases are diseases associated with high blood pressure. Non-limiting examples of cardiovascular diseases include coronary heart disease, heart failure, peripheral arterial disease, hypertensive retinopathy, hypertensive encephalopathy, stroke, kidney failure, and combinations thereof. Non-limiting examples of individuals "at risk" of a cardiovascular disease include individuals with high blood pressure, individuals at risk of high blood pressure, and individuals with high blood cholesterol (e.g., total cholesterol of 240 mg/dL or greater and/or LDL (low-density lipoprotein) of 160 mg/dL or greater), diabetes, and overweight or obesity. On a population basis, a reduction of 2 mm Hg in diastolic blood pressure is estimated to result in a 15% reduction in risk of stroke and a 6% reduction in risk of coronary heart disease.

[0078] As used herein, an "effective amount" is an amount that prevents a deficiency, treats a disease or medical condition in an individual or, more generally, reduces symptoms, manages progression of the diseases or provides a nutritional, physiological, or medical benefit to the individual. The relative terms "improved," "increased," "enhanced" and the like refer to the effects of the composition comprising 3'-*O*-glucuronide epicatechin (disclosed herein) relative to a composition lacking 3'-*O*-glucuronide epicatechin but otherwise identical.

[0079] "Animal" includes, but is not limited to, mammals, which includes but is not limited to, rodents, aquatic mammals, domestic animals such as dogs and cats, farm animals such as sheep, pigs, cows and horses, and humans. Where "animal," "mammal" or a plural thereof is used, these terms also apply to any animal that is capable of the effect exhibited or intended to be exhibited by the context of the passage. As used herein, the term "patient" is understood to include an animal, especially a mammal, and more especially a human that is receiving or intended to receive treatment, as treatment is herein defined. While the terms "individual" and "patient" are often used herein to refer to a human, the present disclosure is not so limited. Accordingly, the terms "individual" and "patient" refer to any animal, mammal or human that can benefit from the treatment. The animal, mammal or human may be a pregnant animal, mammal or human.

[0080] "Overweight" is defined for a human as a BMI between 25 and 30. "Obese" is defined for a human as a BMI greater than 30. "Weight loss" is a reduction of the total body weight. Weight loss may, for example, refer to the loss of total body mass in an effort to improve fitness, health, and/or appearance. "Weight management" or "weight maintenance" relates to maintaining a total body weight. For example, weight management may relate to maintaining a BMI in the area of 18.5-25 which is considered to be normal.The term "GDM" as used herein refers to any degree of impaired glucose tolerance that onsets or is first recognized during pregnancy. The term "preeclampsia" as used herein refers to a pregnancy condition diagnosed by high blood pressure and one or more of the following complications after the 20^{th} week of pregnancy: protein in urine, a low platelet count, impaired liver function, signs of kidney trouble other than protein in urine, fluid in the lungs (pulmonary edema), visual disturbances, new (onset) headaches. The term IUGR is a condition wherein the growth of an individual's foetus/baby is

compromised and restricted in-utero so that said foetus/baby is smaller for gestational age. IUGR may result in said foetus/baby being a low birth weight baby.

[0081] As set forth above, the present inventors surprisingly and unexpectedly found that 3'-*O*-glucuronide epicatechin is an agonist of the cation channel of TRPA1, while 3'-*O*-sulfate epicatechin and 3'-methyl epicatechin, which are also epicatechin metabolites, are not TRPA1 agonists. Consequently, 3'-*O*-glucuronide epicatechin can impact energy expenditure, sympathetic nervous system activity, and fat oxidation. Without being bound by theory, the inventors believe that 3'-*O*-glucuronide epicatechin stimulates the sympathetic nervous system and, as a result, catecholamine secretion. The increased catecholamine secretion enhances thermogenesis and substrate oxidation by β-adrenergic stimulation.

[0082] Accordingly, the composition provided by the present disclosure can comprise an amount of the 3'-*O*-glucuronide epicatechin that is effective to increase at least one of energy expenditure, sympathetic nervous system activity, or fat oxidation, relative to an otherwise identical composition lacking 3'-*O*-glucuronide epicatechin. The composition can be administered to an individual at least once a day for at least one week, preferably for at least one month. The method can comprise identifying the individual as being in need of an increase in energy expenditure, sympathetic nervous system activity, or fat oxidation, e.g., before initial administration of the composition.

[0083] In an embodiment, the composition can comprise an extract enriched with 3'-*O*-glucuronide epicatechin. In an embodiment, the 3'-*O*-glucuronide epicatechin can be synthesized. For example, the 3'-*O*-glucuronide epicatechin can be synthesized as disclosed in WO2013/020979. As set forth therein, a first compound (**FIG. 2**) can be coupled to a second compound (**FIG. 3**) and then subjected to a stereo-selective intra-molecular *trans*-cyclization reaction to form 3'-*O*-glucuronide epicatechin. In these two compounds, R5 and R6 are protecting groups.

[0084] The process can further comprise a Sharpless dihydroxylation reaction step after the coupling reaction and before the stereo-selective intra-molecular *trans*-cyclization reaction. This reaction allows introduction of chirality at C3 in the flavan-3-ol framework with high optical purity. The dihydroxylation can be performed according to Sharpless *et al.* (J. Org.

Chem., 57(10): 2768-2771 (1992) and Chem. Rev. (Washington, D.C.), 94(8): 2483-2547 (1994)) with commercially available stereoselective catalysts AD-mix-α or AD-mix-β.

[0085] In an embodiment, the process further comprises an inversion of the configuration at position C3 of the cyclized product from the stereo-selective intra-molecular *trans*-cyclization reaction. This inversion can be based on a two-step oxidation/reduction sequence (Wan *et al.*, Bioorg. Med. Chem., 12(13): 3521-27 (2004) and Viton *et al.*, Eur. J. Org. Chem., 36:6069-78 (2008)). A Dess-Martin oxidation of (R,S)-catechin derivatives leads to the corresponding ketone compounds with 2R absolute stereochemistry without deterioration of optical purity. Subsequent diastereoselective hydride reduction with L-Selectride® affords the corresponding (2R,3R)- epicatechin derivatives while preserving the optical purity. Hence, the inversion can provide epicatechin conjugate molecules with high optical purity.

[0086] Preferably, the *trans*-cyclization reaction is performed in two sequential steps, first in the presence of triethyl orthoacetate and then followed by a deacetylation reaction at position C3 under reductive conditions. Cyclization using triethyl orthoformate under catalytic pyridinium p-toluenesulfonate conditions proceeds with high stereoselectivity and advantageously allows isolation of the target cyclized product in high purity in the form of protected acetate ester. The resulting 3-acyl protected (R,S)-catechin derivative can then be de-acetylated under mild reductive conditions employing, e.g., DIBAL-H, to afford the desired enantiomer in high yields.

[0087] The protecting group of the first and second compounds can be selected from the group consisting of allyl ether, benzyl ether, tert-butyl ether, tetrahydropyranyl ether, methoxymethyl ether, trimethylsilyl ether tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl ether, trimethylsilyl ether, and tert-butyldimethylsilyl. Preferably, the protecting group is benzyl ether and/or TBDMS.

[0088] The process can further comprise a conjugation of the cyclized product from the stereo-selective intra-molecular *trans*-cyclization reaction after the inversion of the configuration, with a glucuronic acid donor. This reaction step allows generating the desired 3'-*O*-glucuronide epicatechin. For the above process step, the glucuronic acid donor is preferably selected from

2,3,4-tri-*O*-acetyl-α-D-methylglucuronopyranosyl-l-(N-phenyl)-2,2,2-trifluoroacetimidate; 2,3,4-tri-*O*-acetyl-α-D-methylglucopyranosyl-1-(N-4-methoxyphenyl)-2,2,2-trifluoroacetimidate; 2,3,4-tri-*O*-acetyl-α-D-methylglucuronopyranosyl-1-*O*-(2,2,2-trichloroacetimidate); or acetobromo-α-D-glucuronic acid methyl ester; and the glucose donor is preferably selected from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-l-(N-phenyl)-2,2,2-trifluoroacetimidate; 2,3,4,6-tetra-*O*-acetyl-α-D-glucuropyranosyl-1-0-(2,2,2-trichloroacetimidate) or α-acetobromoglucose.

[0089] The 3'-*O*-glucuronide epicatechin can be co-administered with a polyphenol to increase the bioavailability of the 3'-*O*-glucuronide epicatechin, as disclosed in WO2014/083172. For example, the composition can comprise 3'-*O*-glucuronide epicatechin and at least one polyphenolic compound selected from the group consisting of flavonols, flavones, isoflavones, flavanones, and combinations thereof. In a preferred embodiment, a flavone and/or flavanone is selected from the group consisting of isorhamnetin, kaempfernol, diosmetin, nevadensin, chrysin, hesperitin, and combinations thereof.

[0090] In an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be used in a method to support weight management or promote weight loss. For example, the composition can be administered to an individual, such as a mammal, that is managing their weight or undergoing a weight loss program. The weight loss program may include, for example, a weight loss diet (e.g., one or more of a low-fat diet, for example a diet with less than 20% of the calories from fat, preferably less than 15% from fat; a low-carbohydrate diet, for example a diet with less than 20% of the calories from carbohydrates; a low-calorie diet, for example a diet with less calories per day relative to the individual's previous intake before the diet, or a diet with less calories per day relative to an average person of similar body type; or a very low-calorie diet, for example a diet with 800 kcal (3,300 kJ) per day or less). Additionally or alternatively, the weight loss program may include a weight loss training regimen (e.g. endurance and/or strength training).

[0091] In another embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be used in a method for preventing obesity or overweight by administering the composition to an individual at risk thereof. In yet another embodiment, the composition comprising

3'-*O*-glucuronide epicatechin can be used in a method for treating obesity or overweight by administering the composition to an individual in need thereof. In an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin is administered to a mammal, such as a human. The composition can also comprise an additional weight loss ingredient. The method can comprise identifying the individual as being in need of weight management or weight loss and/or identifying the individual as obese or overweight, e.g., before initial administration of the composition.

[0092] The composition comprising 3'-*O*-glucuronide epicatechin can also improve insulin sensitivity and/or glucose tolerance. The composition can thereby reduce glycemia.

[0093] In an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be administered in a method for improving insulin sensitivity and/or glucose tolerance in an individual in need thereof. The composition can be administered to an infant (a child under the age of 12 months) born preterm and/or experiencing intrauterine growth restriction (IUGR), a women desiring to get pregnant, a pregnant woman, a pregnant woman at risk of or suffering from gestational diabetes mellitus (GDM), or a lactating woman; or a child (up to twelve years of age), an adolescent (twelve to eighteen years of age), or an adult (over eighteen years of age) suffering from insulin resistance and/or type II diabetes, such as an animal such as a human. The composition can reduce glycemia by improving insulin sensitivity and/or glucose tolerance in the subject. The composition can be administered at least once a day for at least one week, preferably at least one month, and more preferably at least one year. With respect to GDM the composition can be administered for any period of pregnancy, or pre pregnancy when a woman is trying to get pregnant. Since GDM is most likely to occur in the 2nd and 3rd trimesters it may be beneficial if the composition is administered in the 2nd and/or 3rd trimester of pregnancy. In an embodiment, the method can comprise identifying the individual as in need of an improvement in insulin sensitivity and/or glucose tolerance.

[0094] As noted above, there is a direct link between glucose tolerance and mood, memory and cognition. For example, in a study in which participants were given an oral glucose tolerance test and cognitive tests, the older age group showed that those with poorer glucose tolerance

forgot more words and had slower decision times; and, in those participants with poor glucose tolerance, a tendency for blood glucose to fall below baseline values was associated with better mood and faster working memory. Therefore, without being bound by theory, the inventors believe that 3'-*O*-glucuronide epicatechin enhances insulin sensitivity and/or glucose tolerance and can thereby improve one or more of mood, memory or cognition.

[0095] Accordingly, in an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be administered in a method of improving one or more of cognitive performance, cognition, mood or memory in an individual in need thereof. The composition can treat or prevent one or more of cognitive decline, mild cognitive impairment, dementia, a mood disorder, or memory loss in an individual having or at risk of having one or more of these conditions. The composition can be administered at least once a day for at least one week, preferably at least one month, and more preferably at least one year. The method can comprise identifying the individual as having one or more of cognitive decline, mild cognitive impairment, dementia, a mood disorder, or memory loss, e.g., before initial administration of the composition. The method can comprise identifying the individual as being in need of an improvement in one or more of cognitive performance, cognition, mood or memory, e.g., before initial administration of the composition.

[0096] The composition can be administered to an infant (a child under the age of twelve months), a child (up to twelve years of age), an adolescent (twelve to eighteen years of age), an adult (over eighteen years of age), or an elderly individual (past the first two thirds of the average expected lifespan in its country of origin, preferably past the first three quarters of the average expected lifespan in its country of origin; an elderly human is a person with a chronological age of 65 years or older). The composition may be particularly effective against cognitive aging, and thus a preferred embodiment of the method comprises administration to an elderly human.

[0097] Cognitive performance may be expressed as ability and speed of learning, ability and speed of solving intellectual problems, ability to form and recall memories, reaction time, and the like. Cognition is understood as mental processes such as comprehension, inference, decision-making, planning, learning, memory, association, concept formation, language,

attention, perception, action, problem solving and mental images. Cognitive decline may manifest as reduced memory; forgetfulness; word or name-finding problems; and/or decline in memory, concentration, ability to plan or organize, ability to perform complex tasks, and/or cognitive performance; and may result from age, stress, disease, or other grounds. Cognitive impairment may manifest in one or more of short-term memory loss, diminished capacity to learn, diminished rate of learning, or diminished attention.

[0098] The term "mood" refers to a state or quality of feeling (an emotional state) at a particular time. Moods differ from simple emotions in that they are less specific, less intense, and less likely to be triggered by a particular stimulus or event. Moods generally have either a positive or negative valence. An improved mood may comprise one or more of a decreased anxiety level, a decreased stress level, an increased perceived energy level, or a more positive emotional state.

[0099] In an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be used in methods that modulate nitric oxide (NO) levels. In this regard, TRPA1 may have an effect on NO levels (see, e.g., Sinha *et al.*, PLoS ONE 10(4): e0122189 (Apr. 1, 2015)); and as discussed above, the inventors surprisingly and unexpectedly identified 3'-*O*-glucuronide epicatechin as an agonist of TRPA1. NO is important for relaxation of blood vessels and delivery of blood flow to tissues in the body. With improved blood flow, nutrients and other compounds in the blood can be delivered more efficiently to the skeletal muscle tissues. Furthermore, NO is an anabolic signal as well as a facilitator for stimulation of protein synthesis and release of growth factors such as polyamines. NO also leads to release of insulin and IGF-1, leading to increased uptake of anabolic substrates and also bio-utilization of the substrates. NO is also involved in immune function via T-cell stimulation. It has been suggested that aberrant NO synthesis and/or blood flow in the uterus and/or placenta may contribute to the pathophysiologic changes seen in preeclampsia and IUGR. Preeclampsia is a leading cause of maternal death throughout the world and is responsible for significant baby morbidity and mortality. Furthermore, preeclampsia has healthcare implications for the women later in life with an increased risk of hypertension, coronary artery disease, stroke and type 2 diabetes. IUGR is a major cause of perinatal and neonatal mortality and morbidity and is

associated with an increased risk of several health problems in later life for the foetus/baby e.g. an increased risk of cardio vascular disease and type II diabetes.

[00100] Accordingly, in an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be administered to an individual, such as a human, to modulate nitric oxide (NO) levels in the individual, for example by mitigating diminished release of nitric oxide into the arterial wall because of impaired synthesis and/or excessive oxidative degradation. For example, the composition comprising 3'-*O*-glucuronide epicatechin can be administered to an individual, such as a mammal, that has or is at risk of a cardiovascular disease to treat or prevent the cardiovascular disease. As another example, the composition comprising 3'-*O*-glucuronide epicatechin can be administered to an individual, such as a mammal, that has or is at risk of high blood pressure to treat or prevent the high blood pressure. As yet another example, the composition comprising 3'-*O*-glucuronide epicatechin can be administered to an individual for a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body (e.g., treatment or prevention of erectile dysfunction), improvement of blood circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof. As another example, the composition comprising 3'-*O*-glucuronide epicatechin can be administered to an individual, such as a mammal, that has or is at risk of preeclampsia and/or IUGR to treat or prevent said condition. The composition can be administered to the individual at least once a day for at least one week, preferably for at least one month. With respect to preeclampsia and/or IUGR, the composition can be administered for any period of pregnancy, or pre pregnancy when a woman is trying to get pregnant. Since preeclampsia is most likely to occur in the 3rd trimester, with respect to preeclampsia, it may be beneficial if the composition is administered in the 3rd trimester of pregnancy.

[00101] The method can comprise identifying the individual as having high blood pressure and/or a cardiovascular disease, and/or preeclampsia and/or IUGR e.g., before initial administration of the composition. The method can comprise identifying the individual as being at risk for high blood pressure and/or a cardiovascular disease, and/or preeclampsia and/or IUGR e.g., before initial administration of the composition. The method can comprise

identifying the individual as being in need of one or more of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body (e.g., treatment or prevention of erectile dysfunction), stimulation of protein synthesis, increased release of growth factors, or enhanced immune function, e.g., before initial administration of the composition.

[00102] Due to the unexpected discovery that 3'-*O*-glucuronide epicatechin is an agonist of the cation channel TRPA1, the present inventors believe that 3'-*O*-glucuronide epicatechin can activate TRPA1 to help to provoke the swallowing reflex of dysphagic patients. Accordingly, the present disclosure provides a composition comprising a therapeutically effective amount of 3'-*O*-glucuronide epicatechin for provoking the swallowing reflex of a dysphagic patient. In an embodiment, dysphagia is treated by administering to an individual having the dysphagia the composition comprising a therapeutically effective amount of 3'-*O*-glucuronide epicatechin. The dysphagia can be oral pharyngeal dysphagia and can be a consequence of at least one of surgery for oral cancer, surgery for throat cancer, a stroke, a brain injury, or a progressive neuromuscular disease, such as Parkinson's disease.

[00103] The method can comprise identifying the individual as having dysphagia, e.g., before initial administration of the composition. The method can comprise identifying the individual as being at risk of dysphagia, e.g., before initial administration of the composition.

[00104] In an embodiment, the composition comprising 3'-*O*-glucuronide epicatechin can be used in methods for treating or preventing endothelium dysfunction. For example, the composition comprising 3'-*O*-glucuronide epicatechin can be administered to an individual, such as a mammal, that has or is at risk of endothelium dysfunction to treat or prevent the endothelium dysfunction. The composition can be administered to the individual at least once a day for at least one week, preferably for at least one month.

[00105] The method can comprise identifying the individual as having endothelium dysfunction, e.g., before initial administration of the composition. The method can comprise identifying the individual as being at risk of endothelium dysfunction, e.g., before initial administration of the composition.

[00106] The composition comprising 3'-*O*-glucuronide epicatechin may be a medicament, a food product, a medical food, an oral nutritional supplement, a nutritional composition, an oral cosmetic, or a supplement to a food product and is preferably orally administered. A medical food product is specially formulated and intended for the dietary management of diseases or medical conditions (e.g., prevent or treat diseases or undesirable medical conditions). A medical food product can provide clinical nutrition, for example fulfilling special nutritional needs of patients with a medical condition or other persons with specific nutritional needs. A medical food product can be in the form of a complete meal, part of a meal, as a food additive, or a powder for dissolution. In an embodiment, the composition is administered orally as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product, preferably at least 0.1 mg/g of the food product, more preferably at least 1 mg/g of the food product, even more preferably 10 mg/g of the food product, or more.

[00107] A food product, medical food or nutritional composition includes any number of optional additional ingredients, including conventional food additives, for example one or more proteins, carbohydrates, fats, acidulants, thickeners, buffers or agents for pH adjustment, chelating agents, colorants, emulsifiers, excipients, flavor agents, minerals, osmotic agents, a pharmaceutically acceptable carrier, preservatives, stabilizers, sugars, sweeteners, texturizers and/or vitamins. The optional ingredients can be added in any suitable amount.

[00108] A food product, medical food or nutritional composition can be in any oral nutritional form, e.g. as a health drink, as a ready-made drink, optionally as a soft drink, including juices, milk-shake, yogurt drink, smoothie or soy-based drink, in a bar, or dispersed in foods of any sort, such as baked products, cereal bars, dairy bars, snack-foods, soups, breakfast cereals, muesli, candies, tabs, cookies, biscuits, crackers (such as a rice crackers), and dairy products.

[00109] A supplement may be in the form of tablets, capsules, pastilles or a liquid, for example. The supplement may further contain protective hydrocolloids (such as gums, proteins, modified starches), binders, film forming agents, encapsulating agents/materials, wall/shell materials, matrix compounds, coatings, emulsifiers, surface active agents, solubilizing agents (oils, fats, waxes, lecithins or the like), adsorbents, carriers, fillers,

co-compounds, dispersing agents, wetting agents, processing aids (solvents), flowing agents, taste masking agents, weighting agents, jellifying agents and gel forming agents. The supplement may also contain conventional pharmaceutical additives and adjuvants, excipients and diluents, including, but not limited to, water, gelatin of any origin, vegetable gums, ligninsulfonate, talc, sugars, starch, gum arabic, vegetable oils, polyalkylene glycols, flavoring agents, preservatives, stabilizers, emulsifying agents, buffers, lubricants, colorants, wetting agents, fillers, and the like. The supplement may for example be a maternal supplement for administration to an individual pre pregnancy when individual is trying to get pregnant, and/or during pregnancy and/or during lactation.

[00110] The supplement can be added in a product acceptable to the consumer as an ingestible carrier or support. Non-limiting examples of such carriers or supports are a pharmaceutical, a food composition, and a pet food composition. Non-limiting examples for food and pet food compositions are milks, yogurts, curds, cheeses, fermented milks, milk-based fermented products, fermented cereal based products, milk-based powders, human milks, preterm formulas, infant formulas, oral supplements, and tube feedings.

[00111] In some embodiments, the composition comprising 3'-*O*-glucuronide epicatechin is in an injectable form, and the methods disclosed herein can comprise injecting the individual with the composition.

[00112] EXAMPLE

[00113] The following non-limiting example presents scientific data developing and supporting the concept of 3'-*O*-glucuronide epicatechin acting as an agonist of TRPA1.

[00114] Several epicatechin metabolites were tested *in vitro* to determine if any of these compounds are an agonist of the cation channel of TRPA1. Specifically, the activation of CHO cells expressing h-TRPA1 was tested according to the calcium imaging method described in Riera *et al.* (Riera,C.E., Vogel,H., Simon,S.A., Damak,S., & le Coutre,J. Sensory attributes of complex tasting divalent salts are mediated by TRPM5 and TRPV1 channels. J. Neurosci. 29, 2654-2662 (2009)).

[00115] As shown by the results depicted in **FIG. 4**, 3'-*O*-glucuronide epicatechin is a TRPA1 agonist. In contrast, the epicatechin metabolite 3'-*O*-methyl epicatechin (chemical structure shown in **FIG. 5**) is not a TRPA1 agonist, as shown by the results depicted in **FIG. 6**. Similarly, the epicatechin metabolite 3'-*O*-sulfate epicatechin is not a TRPA1 agonist, as shown by the results depicted in **FIG. 7**.

[00116] Further epicatechin metabolites were tested and results are summarized in Table 1 below.

Compounds	Concentration (Max) tested	Activity vs hTRPA1	EC50
3'-sulfate-EC	100mM	Inactive	
4'-sulfate-EC	100mM	Inactive	
3'-methyl-EC*	100mM	Inactive	
4'-methyl-EC	100mM	Inactive	
3'-methyl-7-sulfate-EC	100mM	Inactive	
3'-O-Glucuronide EC	133mM	Active	~80mM
Hesperetin-3-O- Glucuronide	3mM	Inactive	
Hesperetin-4-O-Glucuronide	3mM	Inactive	
Hesperetin-7-3-O-Glucuronide	3mM	Inactive	

[00117] Table 1

[00118] To confirm that 3'-*O*-glucuronide epicatechin is a TRPA1 agonist, a selective antagonist of hTRPA1 (HC030031, chemical structure shown in **FIG. 8**) was used. This selective antagonist of hTRPA1 blocked the activation of hTRPA1 by 3'-*O*-glucuronide epicatechin, as shown by the results depicted in **FIG. 9**.

[00119] The results depicted in **FIGS. 10** and **11** demonstrate the pharmacology of 3'-*O*-glucuronide epicatechin activating CHO cells expressing h-TRPA1 and show that activation occurs in a concentration-dependent manner.

[00120] Furthermore, comparative experiments were conducted on the expression of endothelial nitric oxide synthase in isolated aortic rat rings.

[00121] Thoracic aortas were obtained from male adults Wistar rats after euthanasia. Each aorta was carefully dissected and harvested cleaned of excess tissue and cut into three equal segments, approximately 7 mm long. All aortic rings were pre-incubated for 30 min in Krebs solution (20 mM Hepes buffer, pH 7.4, containing 119 mM NaCl, 4.7 mM KCl, 1 mM $MgSO_4$, 0.4 mM NaH_2PO_4, 0.15 mM Na_2HPO_4, 5 mM $NaHCO_3$, 1.25 mM $CaCl_2$, 5.5 mM glucose) aerated with 95% O_2 and 5% CO_2 at 37°C and then incubated with vehicle (DMSO 1%) or the different metabolites for 1 h. Metabolites were first dissolved in DMSO 1% and tested in a final concentration of 10 mM. At the end of the incubation period aortic rings were frozen at -70 °C until the homogenate preparation. Homogenates for western blot and western blot determinations were carried out by the regular procedures and phosphorylation level of endothelial nitric oxide synthase was evaluated.
The results depicted in FIG.12 demonstrate that 4'-*O*-glucuronide and 3'-*O*-glucuronide epicatechins increased eNOS phosphorylation relative to control and chemically similar epicatechins.

[00122] It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

The invention is claimed as follows:

1. A method for treating or preventing high blood pressure comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

2. The method of Claim 1 wherein the composition is orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

3. The method of Claim 1 wherein the composition is injected into the individual.

4. The method of Claim 1 wherein the composition is administered to the individual at least once a day for at least one week.

5. The method of Claim 1 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

6. A method for treating or preventing a cardiovascular disease comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

7. The method of Claim 6 wherein the composition is orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

8. The method of Claim 6 wherein the composition is injected into the individual.

9. The method of Claim 6 wherein the composition is administered to the individual at least once a day for at least one week.

10. The method of Claim 6 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

11. A method for achieving a therapeutic effect in an individual, the therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body, improvement of blood circulation, improvement of blood brain circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof, the method comprising administering to the individual a composition comprising 3'-*O*-glucuronide epicatechin.

12. The method of Claim 11 wherein the composition is orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

13. The method of Claim 11 wherein the composition is injected into the individual.

14. The method of Claim 11 wherein the composition is administered to the individual at least once a day for at least one week.

15. The method of Claim 11 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

16. A method for making a food product, the method comprising adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof, the 3'-*O*-glucuronide epicatechin is present in the composition in an amount effective to achieve a therapeutic effect selected from the group consisting of blood vessel dilation, reduced blood pressure, increased delivery of blood flow to tissues in the body, improvement of blood circulation, improvement of brain blood

circulation, stimulation of protein synthesis, increased release of growth factors, enhanced immune function, and combinations thereof.

17. A method for weight maintenance or weight loss comprising administering to an individual in need thereof a composition comprising 3'-*O*-glucuronide epicatechin.

18. The method of Claim 17 wherein the composition is administered to provide an amount of the 3'-*O*-glucuronide epicatechin that increases at least one characteristic selected from the group consisting of energy expenditure, sympathetic nervous system activity, and fat oxidation.

19. The method of Claim 17 wherein the composition is orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

20. The method of Claim 17 wherein the composition is injected into the individual.

21. The method of Claim 17 wherein the composition is administered to the individual at least once a day for at least one week.

22. The method of Claim 17 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

23. A method for treating or preventing obesity or overweight comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

24. The method of Claim 23 wherein the composition is administered to provide an amount of the 3'-*O*-glucuronide epicatechin that increases at least one characteristic selected from the group consisting of energy expenditure, sympathetic nervous system activity, and fat oxidation.

25. The method of Claim 23 wherein the composition is a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

26. The method of Claim 23 wherein the composition further comprises an additional ingredient in an amount effective to promote weight maintenance or weight loss.

27. The method of Claim 23 wherein the individual is participating in a weight loss program selected from the group consisting of a low-fat diet, a low-carbohydrate diet, a low-calorie diet, a very low-calorie diet, endurance training, strength training, and combinations thereof.

28. A method for making a food product for weight maintenance or weight loss, the method comprising adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof.

29. A method for improving a characteristic selected from the group consisting of insulin resistance, glucose tolerance and a combination thereof comprising administering to an individual in need thereof a composition comprising 3'-*O*-glucuronide epicatechin.

30. The method of Claim 29 wherein the individual is selected from the group consisting of an infant born preterm, an infant experiencing intrauterine growth restriction, a pregnant woman suffering from gestational diabetes, a human suffering from insulin resistance, a human suffering from impaired glucose tolerance, and a human suffering from type II diabetes.

31. The method of Claim 29 wherein the composition is administered as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

32. The method of Claim 29 wherein the composition is injected into the individual.

33. The method of Claim 29 wherein the composition is administered to the individual at least once a day for at least one week.

34. The method of Claim 29 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

35. A method for improving one or more of cognitive performance, cognition, mood, or memory comprising administering to an individual in need thereof a composition comprising a therapeutically effective amount of 3'-*O*-glucuronide epicatechin.

36. The method of Claim 35 wherein the individual has a condition selected from the group consisting of cognitive decline, mild cognitive impairment, dementia, a mood disorder, memory loss, and combinations thereof.

37. The method of Claim 35 wherein the individual is an elderly human having cognitive aging.

38. The method of Claim 35 wherein the composition is administered as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

39. The method of Claim 35 wherein the composition is injected into the individual.

40. The method of Claim 35 wherein the composition is administered to the individual at least once a day for at least one week.

41. The method of Claim 35 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

42. A method for making a food product, the method comprising adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof, the 3'-*O*-glucuronide epicatechin is present in the composition in an amount effective to improve at least one characteristic selected from the group consisting of insulin sensitivity, glucose tolerance, cognitive performance, cognition, mood, and memory in an individual that consumes the food product.

43. A method of treating or preventing dysphagia comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

44. The method of Claim 43, wherein the dysphagia is oral pharyngeal dysphagia.

45. The method of Claim 43, wherein the composition is a thickened beverage.

46. The method of Claim 43, wherein the composition is administered to provide an amount of the 3'-*O*-glucuronide epicatechin that provokes a swallowing reflex.

47. The method of Claim 43 wherein the composition is administered as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

48. The method of Claim 43 wherein the composition is injected into the individual.

49. The method of Claim 43 wherein the composition is administered to the individual at least once a day for at least one week.

50. The method of Claim 43 wherein the 3'-*O*-glucuronide epicatechin is chemically synthesized.

51. A method for making a food product, the method comprising adding 3'-*O*-glucuronide epicatechin to a component selected from the group consisting of protein, carbohydrate, fat and combinations thereof, the 3'-*O*-glucuronide epicatechin is present in the composition in an amount effective to treat or prevent dysphagia.

52. A method for treating or preventing endothelium dysfunction comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

53. The method of Claim 52 wherein the composition is orally administered to the individual as a food product in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the food product.

54. The method of Claim 52 wherein the composition is administered to the individual at least once a day for at least one week.

55. A method for treating or preventing preeclampsia and/or IUGR comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

56. The method of Claim 55 wherein the composition is orally administered to the individual as a maternal supplement in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the composition.

57. The method of Claim 55 or Claim 56 wherein the composition is administered to the individual pre-pregnancy when said individual is trying to get pregnant, and/or during pregnancy.

58. A method for treating or preventing preeclampsia gestational diabetes mellitus comprising administering to an individual in need thereof or at risk thereof a composition comprising 3'-*O*-glucuronide epicatechin.

59. The method of Claim 58 wherein the composition is orally administered to the individual as a maternal supplement in which the 3'-*O*-glucuronide epicatechin is present in a concentration of at least 0.01 mg/g of the composition.

60. The method of Claim 58 or Claim 59 wherein the composition is administered to the individual pre-pregnancy when said individual is trying to get pregnant and/or, during pregnancy, and or during lactation.

61. The method according to any of preceding claims wherein the composition is in the form of an extract enriched with 3'-*O*-glucuronide epicatechin.

62. The method according to any of preceding claims wherein the composition is a medical food, a nutritional composition, a pharmaceutical, a food composition or a pet food composition.

FIG. 1

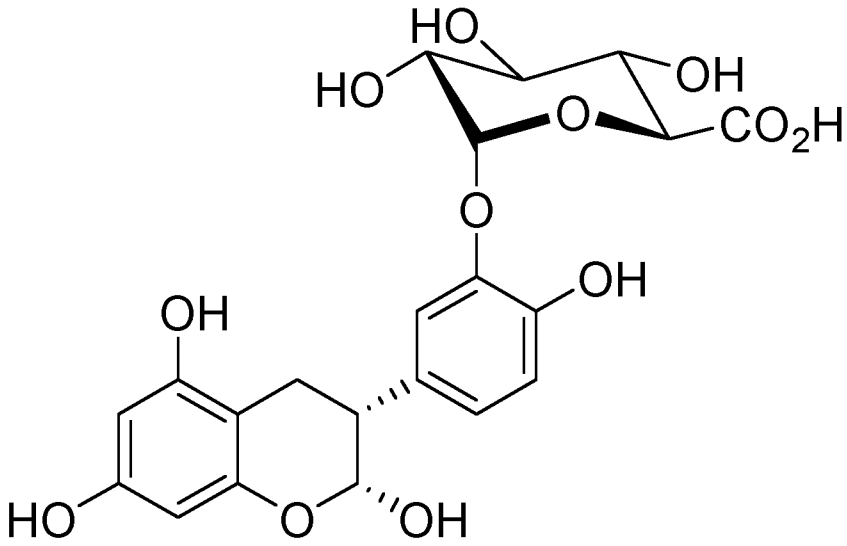


FIG. 2

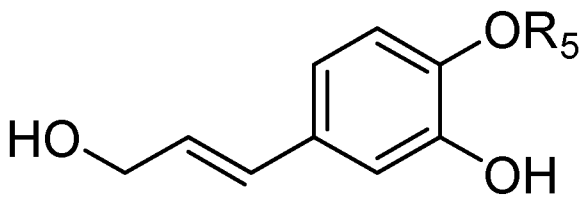


FIG. 3

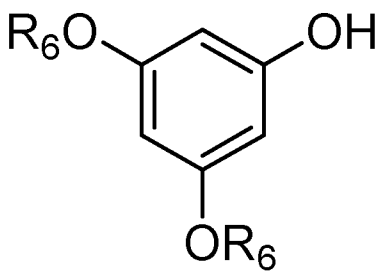


FIG. 4

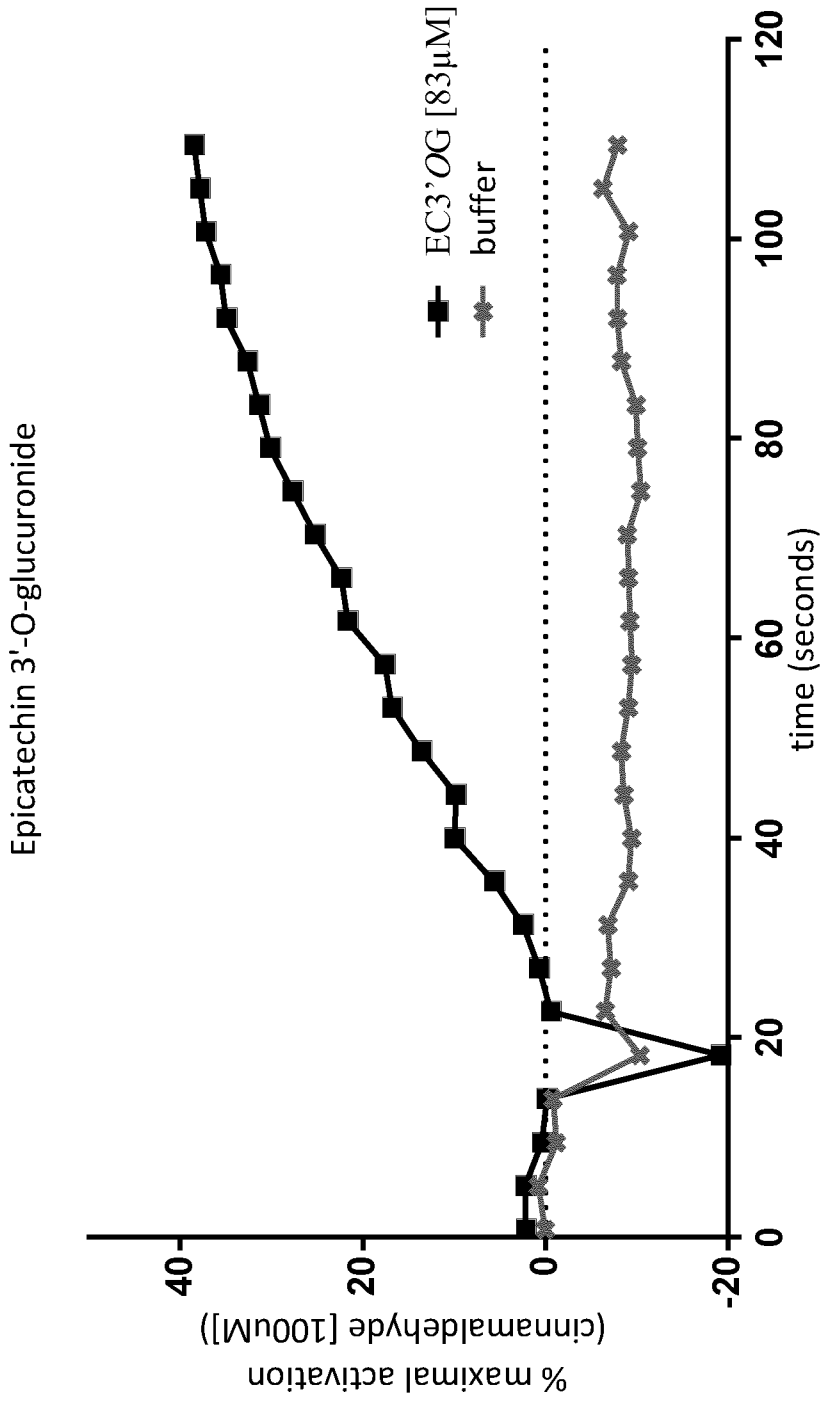

Epicatechin 3'-O-glucuronide
% maximal activation
(cinnamaldehyde [100uM])
40
20
0
-20
0
20
40
60
80
100
120
time (seconds)
EC3'OG [83µM]
buffer

FIG. 5

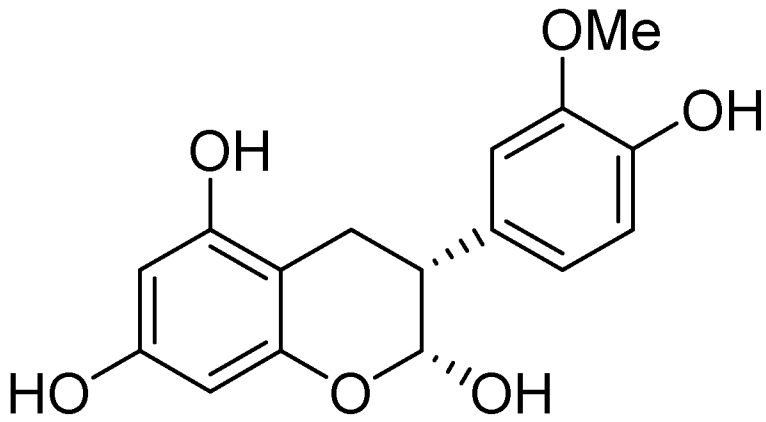


FIG. 6

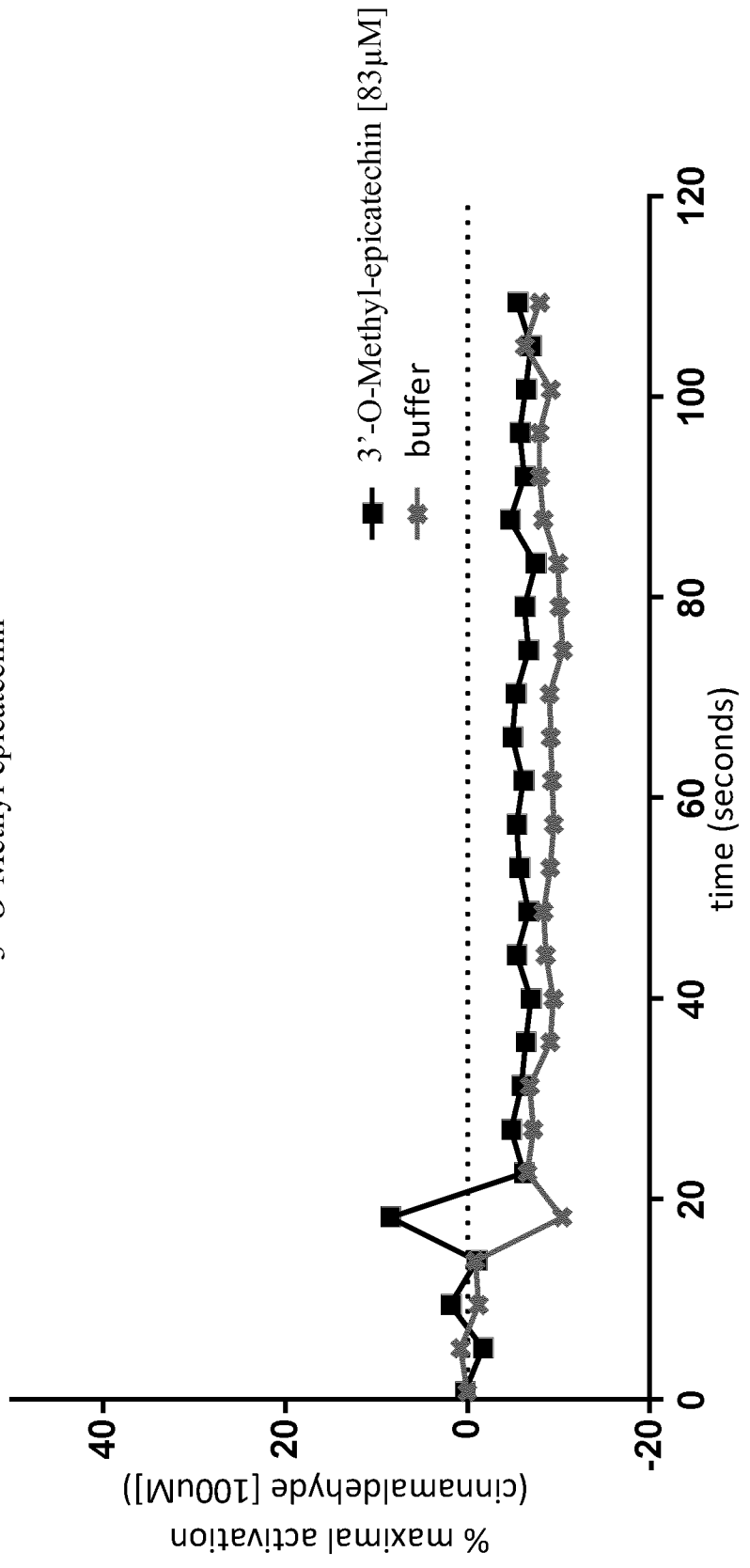

3'-O-Methyl-epicatechin
3'-O-Methyl-epicatechin [83µM]
buffer
% maximal activation
(cinnamaldehyde [100uM])
time (seconds)
40
20
0
-20
0
20
40
60
80
100
120

FIG. 7

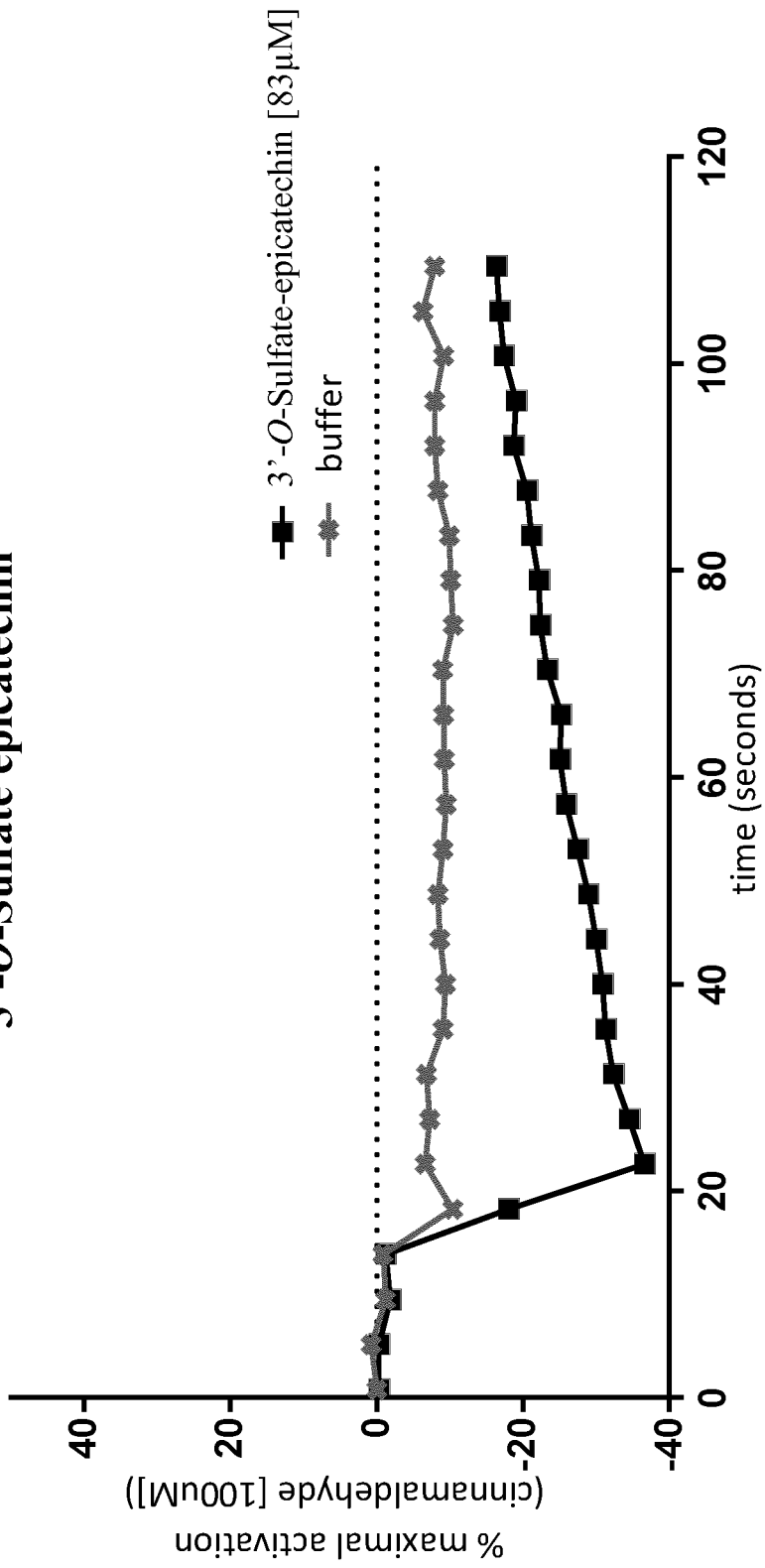

3'-O-Sulfate epicatechin
3'-O-Sulfate-epicatechin [83µM]
buffer
% maximal activation
(cinnamaldehyde [100uM])
time (seconds)
40
20
0
-20
-40
0
20
40
60
80
100
120

FIG. 8

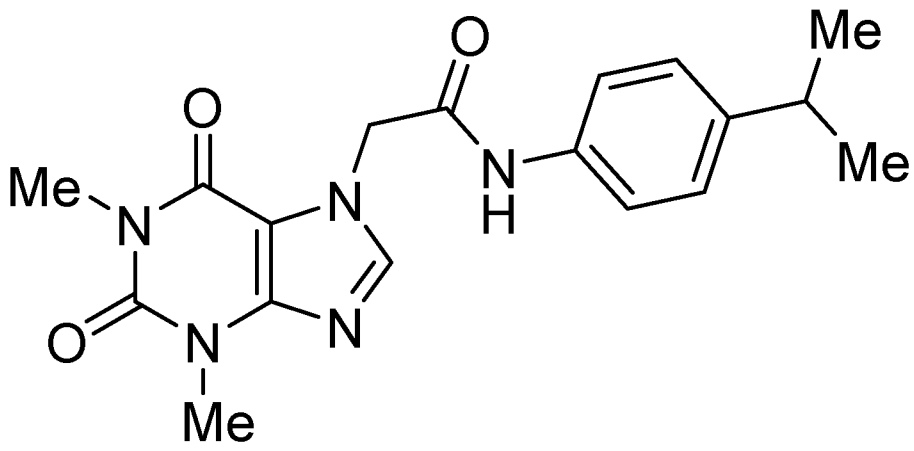


FIG. 9

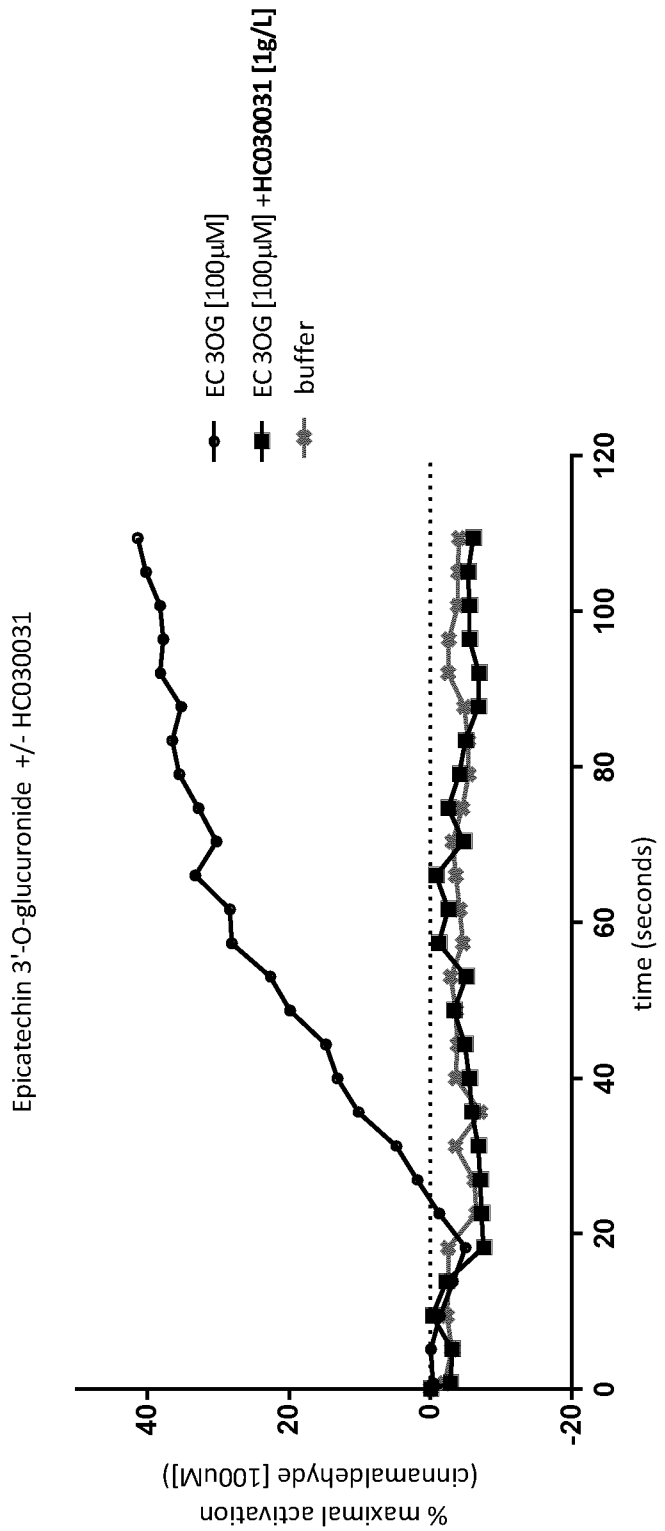

Epicatechin 3'-O-glucuronide +/- HC030031
EC 3OG [100µM]
EC 3OG [100µM] +HC030031 [1g/L]
buffer
% maximal activation
(cinnamaldehyde [100uM])
time (seconds)
40
20
0
-20
0
20
40
60
80
100
120

FIG. 10

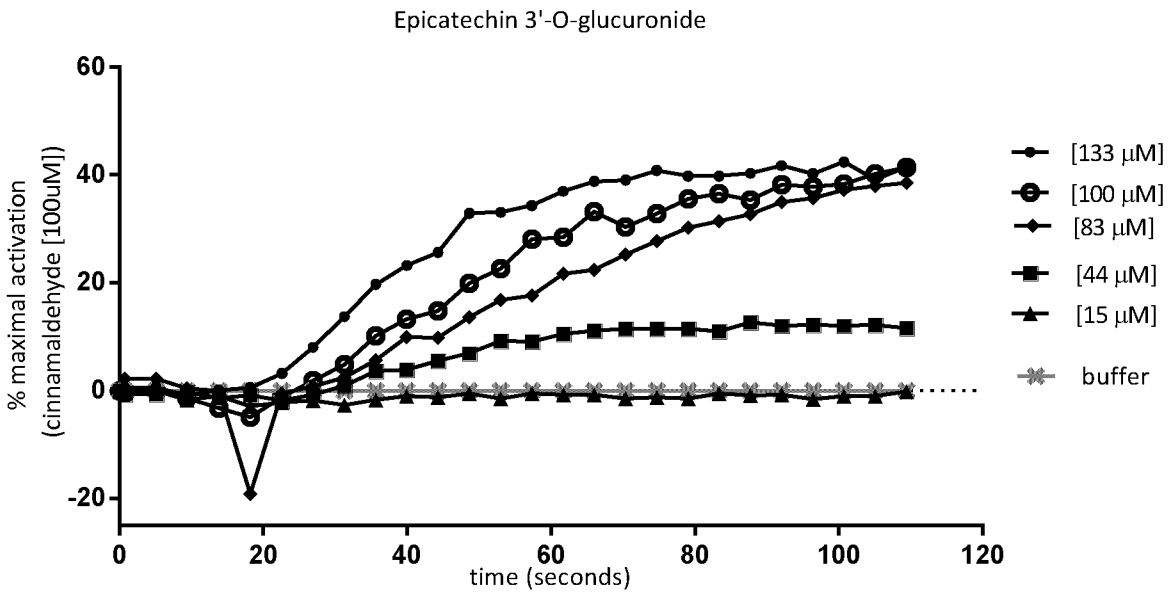

Epicatechin 3'-O-glucuronide
% maximal activation (cinnamaldehyde [100uM])
60
40
20
0
-20
0
20
40
60
80
100
120
time (seconds)
[133 µM]
[100 µM]
[83 µM]
[44 µM]
[15 µM]
buffer

FIG. 11

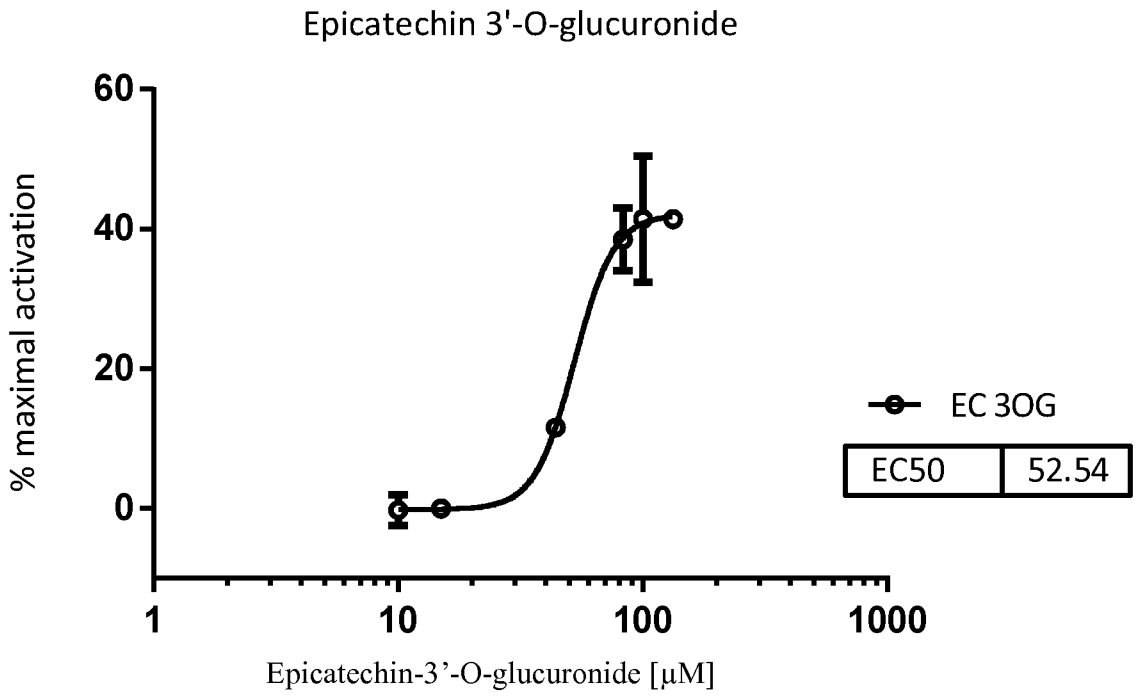
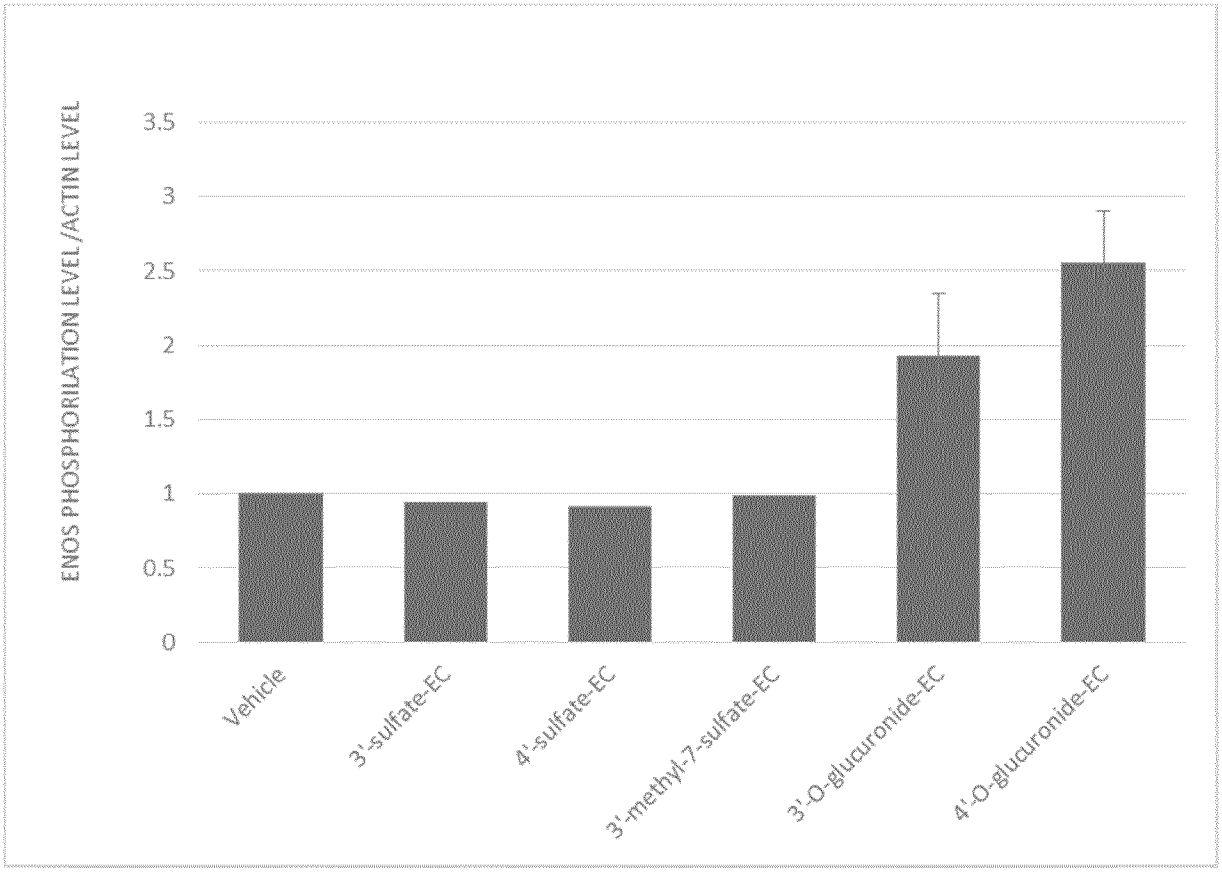

Epicatechin 3'-O-glucuronide
% maximal activation
60
40
20
0
1
10
100
1000
Epicatechin-3'-O-glucuronide [µM]
EC 3OG
EC50
52.54

FIG. 12


ENOS PHOSPHORIATION LEVEL/ACTIN LEVEL
3.5
3
2.5
2
1.5
1
0.5
0
Vehicle
3'-sulfate-EC
4'-sulfate-EC
3'-methyl-7-sulfate-EC
3'-O-glucuronide-EC
4'-O-glucuronide-EC

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081225

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7012 A61P3/10 A61P9/10 A61P25/28 A61P43/00
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

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FEDOR ROMANOV-MICHAILIDIS ET AL: "Epicatechin B-Ring Conjugates: First Enantioselective Synthesis and Evidence for Their Occurrence in Human Biological Fluids", ORGANIC LETTERS , 14(23), 6012-6015 CODEN: ORLEF7; ISSN: 1523-7052, vol. 14, no. 15, 3 August 2012 (2012-08-03), pages 3902-3905, XP55265193, ISSN: 1523-7060, DOI: 10.1021/ol3016463 cited in the application the whole document page 3903, left-hand column, paragraph 1 ----- -/--	1-62

[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
24 February 2017	08/03/2017

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	Economou, Dimitrios

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/020979 A1 (NESTEC SA [CH]; ACTIS GORETTA LUCAS [CH]; VITON FLORIAN [CH]; BARRON D) 14 February 2013 (2013-02-14) cited in the application the whole document page 4, line 5 - line 7 page 10, line 17 - line 32 figure 17; example 7b claims 9,13 -----	1-62
X	YANG KAIYUAN ET AL: "Hydrolysis enhances bioavailability of proanthocyanidin-derived metabolites and improves [beta]-cell function in glucose intolerant", THE JOURNAL OF NUTRITIONAL BIOCHEMISTRY, vol. 26, no. 8, 14 April 2015 (2015-04-14) , pages 850-859, XP029163583, ISSN: 0955-2863, DOI: 10.1016/J.JNUTBIO.2015.03.002 the whole document abstract table 2 figure 1 page 854, left-hand column, last paragraph - page 857, right-hand column, last paragraph -----	1-62
A	LUCAS ACTIS-GORETTA ET AL: "Elucidation of (-)-epicatechin metabolites after ingestion of chocolate by healthy humans", FREE RADICAL BIOLOGY AND MEDICINE, vol. 53, no. 4, 1 June 2012 (2012-06-01), pages 787-795, XP55345871, US ISSN: 0891-5849, DOI: 10.1016/j.freeradbiomed.2012.05.023 the whole document table 2 figure 5 -----	1-62

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/081225

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013020979 A1	14-02-2013	CN 103857665 A	11-06-2014
		EP 2557079 A1	13-02-2013
		EP 2742034 A1	18-06-2014
		JP 2014522870 A	08-09-2014
		US 2014171631 A1	19-06-2014
		WO 2013020979 A1	14-02-2013