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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 November 2008 (06.11.2008)

PCT

(10) International Publication Number
WO 2008/131910 A1

(51) International Patent Classification:
A61K 36/185 (2006.01) *A61P 3/04* (2006.01)

(21) International Application Number:
PCT/EP2008/003322

(22) International Filing Date: 24 April 2008 (24.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/926,328 26 April 2007 (26.04.2007) US
0719542.3 8 October 2007 (08.10.2007) GB

(71) Applicant *(for all designated States except US)*: **BARRY CALLEBAUT AG** [CH/CH]; P.O. Box 8021, CH-Zurich (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BERNAERT, Herwig** [BE/BE]; Barry Callebaut Belgium N.V., Aalsterse-straat 122, B-9280 Lebbeke-Wieze (BE). **ALLEGAERT, Leen** [BE/BE]; Barry Callebaut Belgium N.V., Aalsterse-straat 122, B-9280 Lebbeke-Wieze (BE).

(74) Agent: **STEVENS, Ian**; Potter Clarkson LLP, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(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, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** USE OF COCOA EXTRACT

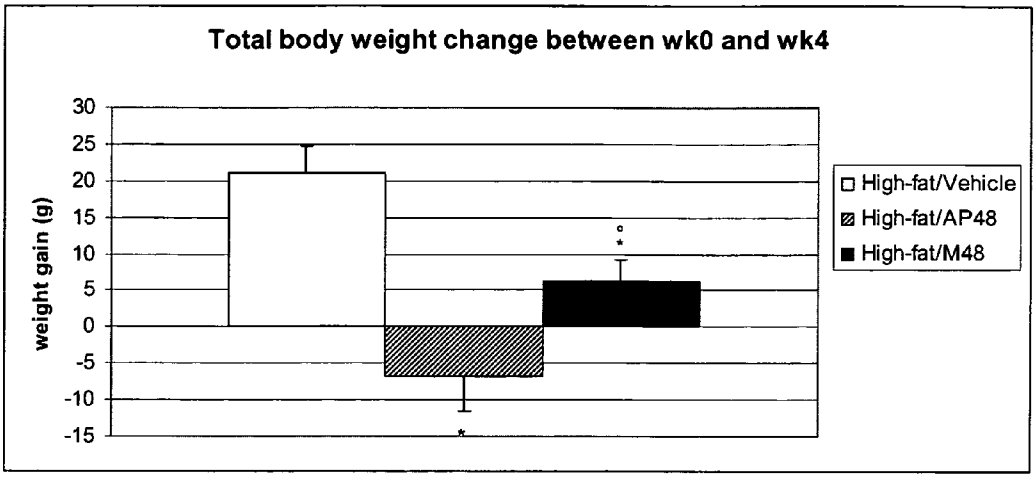

Fig 1

(57) **Abstract:** A cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment for no more than three days, having a polyphenol content of more than 25% by weight, may be used in the treatment or alleviation of obesity.

WO 2008/131910 A1

USE OF COCOA EXTRACT

This invention relates to a cocoa extract and to its uses. In particular, the invention relates to uses for cocoa extracts in the treatment or alleviation of obesity.

Chocolate and cocoa are popularly claimed to have a plethora of positive effects, including stimulant, relaxant, euphoriant, aphrodisiac, tonic and antidepressant properties. However, the scientific basis for these claims has been elusive. Certainly, depression may in some individuals lead to a craving for sweet foods, and people may receive a transitory uplift in mood from the pleasure of consuming chocolate or from relief of hypoglycemia due to consumption of the sugar in the chocolate. However, the various chemicals in chocolate (other than sugar) suggested to have potentially psychoactive or mood altering effects are generally not present at pharmacologically effective levels.

Cocoa for the production of chocolate is made from the dried and partially fermented seeds of the cacao tree. The harvested cacao pods are opened, the pulp and cocoa beans are removed, and the rind is discarded. The pulp and beans are then piled in heaps, placed in bins, or laid out on grates for usually 6-7 days, during which time the thick pulp liquifies as it ferments. The fermented pulp trickles away, leaving the cocoa beans behind to be collected, dried and further processed to make cocoa butter and cocoa powder. In some instances, the product is treated with alkali to reduce the acidity of the powder. Fermentation is important for the quality and flavor of the beans, which originally have a strong bitter taste. Unfermented or underfermented cocoa beans have a flavor similar to raw potatoes, are very susceptible to mildew and fungal growth, and therefore are not used in the manufacture of chocolate for food consumption. The cocoa bean without its shell is known as a "cocoa nib".

Cocoa is known to contain polyphenols and other biologically active compounds such as xanthines, including theobromine and caffeine.

Obesity is a condition in which the natural energy reserve, stored in the fatty tissue of humans and other mammals, is increased to a point where it is associated with certain health conditions or increased mortality. Although obesity is an individual clinical condition, it is increasingly viewed as a serious and growing public health problem.

Cocoa extracts containing polyphenols have been proposed for a number of uses. For example, WO 96/010404 describes cocoa extracts containing proanthocyanidins that are said to be anti-neoplastic. US 7,122,574 discloses polyphenol-containing cocoa extracts that can be used for treating hypertension. WO 03/079998 states that cocoa extracts containing polyphenols can be used in the treatment of diseases involving defective gap junctional communication.

Actives in cocoa extracts other than polyphenols have also been used in an attempt to achieve physiological effects. For example, US 6,927,280 discloses a cocoa albumin and its uses. US 7,115,285 relates to a composition, comprising theobromine or a salt thereof, for suppressing appetite and cravings for substances such as nicotine, coffee, sweets or chocolate while improving energy and enhancing mood. WO 2007/042745 discloses a composition comprising chocolate which is enhanced with theobromine and reviews the active components in chocolate, stating that cocoa contains a number of chemical substances whose influence on human and/or animal physiology is not fully understood, including phenylethylamine and tyramine which act as neurotransmitters and may effect mood swing by causing an emotional high, which can be associated with a feeling of alertness and contentment.

US 7,122,574 discloses a polyphenol-containing cocoa extract and numerous applications for it, including an effect on satiety. The extracts were made from defatted cocoa material.

WO 98/09533 describes cocoa components having enhanced levels of cocoa polyphenols. US 2004/0096566 relates to a method for obtaining cocoa bean polyphenol extracts.

US 2004/0005347 relates to a composition and method for treating several disorders including obesity, that involves the use of cocoa or one of its active components together with a dopamine D2 receptor agonist.

US 2003/0206981 describes compositions comprising dietary fibre extracted from cocoa bean husks. The compositions are stated as being useful in the treatment of metabolic disorders.

EP-A-1609466 states that a composition in tablet form comprising cinnamon leaf oil, ginger extract, oleoresin or oil, turmeric extract oil and/or oleoresin, cocoa extract, citric acid, citrus essential oils, and a white kidney bean protein fraction with alpha amylase inhibitory activity, can be used for treating overweight humans and animals. The cocoa extract contains 6% theobromine but it is not clear how it is produced.

US 2006/0210653 relates to compositions for increasing a person's natural metabolic rate. A cocoa extract is one of the many possible extracts described but there is no indication as to how it is produced.

US 2006/0204599 relates to a dietary supplement derived from *Acacia* for maintaining weight loss.

US 2006/0134230 discloses a weight loss composition comprising several extracts, including a cocoa extract. The cocoa extract contains theobromine but there is no indication as to how it is produced.

WO 02/14251 describes a method for obtaining cocoa bean polyphenol extracts by solvent extraction of fresh cocoa beans. The extracts have cosmetic, food and therapeutic uses and may contain increased levels of beta-sitosterol.

WO 2007/082703 relates to the use of cocoa polyphenols, which may be produced by the method described in WO 02/14251, in beer production.

FR-A-2885050 describes a slimming cosmetic and/or pharmaceutical composition comprising a cocoa extract containing polyphenols for the treatment of adipocytes of the skin.

There remains a need for compositions that are useful in the treatment or alleviation of obesity, particularly compositions that are derived from natural products. There also remains a need for compositions having these benefits that can be readily incorporated into formulations for oral consumption. For example, the compositions for incorporation into foods and beverages are desirably readily dispersible and impart a good appearance to the product, in terms of colour and/or texture.

According to the invention, there is provided a cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment for no more than three days, having a polyphenol content of more than 25% by weight, for use in the treatment or alleviation of obesity.

In another aspect, the invention provides the use of a cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment for no more than three days, having a polyphenol content of more than 25% by weight, in the manufacture of a medicament for use in the treatment or alleviation of obesity.

In a further aspect, the invention provides a method for the treatment or alleviation of obesity, comprising administering an effective amount of a cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment no more than three days, having a polyphenol content of more than 25% by weight.

It has been found that the extracts according to the invention, prepared from non-defatted cocoa beans which have not been fermented or have been fermented for a short time, such as less than three days, have advantages in terms of their effect in

treating obesity. This was surprising. Most of the known cocoa extracts that are asserted as having physiological effects are derived from defatted and/or fermented beans, which are often also roasted.

The extract of the invention is typically a brown-coloured, free-flowing powder. Usually, the extract will have no noticeable odour.

The extract of the invention preferably has a polyphenol content of at least 27% by weight, more preferably at least 30% by weight, even more preferably at least 40% by weight, such as at least 45% by weight. The upper limit for the polyphenol content is typically about 70% by weight. Thus, preferred amounts of polyphenol include from 30% to 70%, from 35% to 70%, from 40% to 70%, from 45% to 65% and from 45% to 60%, the percentages being by weight of the extract. The percentages of polyphenols are preferably expressed as gallic acid equivalents, according to the Folin-Ciocalteu method (e.g., as described in Singleton VL, Orthofer R, Lamuela-Raventos RM. Analysis of total phenols and other oxidation substrates and antioxidants by means of Folin-Ciocalteu reagent. Meth Enzymol 1999; 99: 152-178).

Polyphenols in the extracts of the invention typically comprise monomers and oligomers. Preferably, the extracts of the invention comprise up to 10% by weight of each of monomers, dimers, trimers, tetramers, pentamers, hexamers, heptamers, octamers, nonamers and decamers, and higher oligomers in an amount of up to 15% by weight. More preferably, extracts of the invention comprise, by weight of the extract, 5-10% monomers (preferably including at least 5% epicatechin), 5-10% dimers, 5-10% trimers, 2-8% tetramers, 2-8% pentamers, 2-8% hexamers, 0.5-5% heptamers, 0.1-4% octamers, 0.1-3% nonamers and 0.05-2% decamers, and 5-12% higher oligomers.

Extracts of the invention may contain xanthines (preferably methylxanthines), such as caffeine and theobromine. Caffeine may be present together with theobromine, typically at a weight ratio of theobromine to caffeine in the range of from 20:1 to 5:1. In one embodiment of the invention, the theobromine content is at least 5% by

weight, and preferably from 5 to 11% by weight. In this embodiment, the composition preferably has a weight ratio of from 7:1 to 12:1 polyphenol:theobromine. In an alternative embodiment, the extract may be treated, for example with supercritical carbon dioxide, to lower the theobromine content and the content of other xanthines that may be present. A method for lowering the content of theobromine in extracts of this type is described in Example 2.3 of WO 2007/082703, the contents of which are incorporated herein by reference. In this alternative embodiment, the extract has a theobromine content of less than 5% by weight, such as less than 4.5% by weight, for example from 0.1 to 4% by weight.

The extracts of the invention are prepared from cocoa beans that are non-defatted and have not been fermented or have been allowed to ferment for no more than three days. The cocoa beans will typically not have been roasted. Thus, the cocoa beans that are used as the starting material for the production of the extracts of the invention are very different from the cocoa beans that are used to produce cocoa powder and chocolate. Typically, the extracts are prepared from cocoa nibs which are deshelled cocoa beans that are unfermented and non-roasted.

The cocoa beans are preferably obtained by a process that comprises: harvesting and hulling cocoa beans; preventing fermentation of the beans or allowing the beans to ferment for no more than three days (more preferably less than two days, even more preferably less than one day) before halting the fermentation process by drying.

The fat content of the non-defatted cocoa beans, or of the cocoa nibs, that are used in the invention, is typically greater than 30% by weight, more preferably greater than 35% by weight, even more preferably greater than 40% by weight, such as greater than 45% by weight; for example, greater than 50% by weight.

Extracts of the invention are preferably obtainable by solvent extraction of the cocoa beans. The solvent is preferably selected from C1 to C6 alcohols or C1 to C6 ketones, and mixtures thereof, optionally in admixture with water, such as, for example, ethanol, acetone, 2-butanol, 2-propanol and mixtures thereof, optionally

in admixture with water. A particularly preferred solvent comprises a mixture of water and acetone in a weight ratio of water:acetone of from 1:1 to 1:9. Preferably, solvent extraction is carried out using a counter current process for a time and at a temperature to achieve the desired degree of extraction, typically from one hour to 2 days at from 20 to 60 °C. After extraction, the liquid solvent extract is evaporated to remove a part of the solvent and then spray dried. To improve its solubility, the extract powder is preferably agglomorated in a fluidised bed. The xanthine (and theobromine) content of the extract may be reduced by extraction with super-critical carbon dioxide after the solvent has been removed.

Processes that may be used for producing the extracts of the invention are described in WO 2007/082703 and WO 02/14251, the contents of which are incorporated herein by reference.

Extracts of the invention preferably comprise less than 2% by weight phenylethylamine.

Extracts of the invention may comprise other components derived from the cocoa beans such as protein and sugars. Typically, the extracts comprise from 15 to 40% by weight protein, such as from 20 to 30% by weight protein. The extracts may comprise from 2 to 12% by weight sugars, such as from 4 to 10% by weight sugars.

The extracts of the invention comprise cocoa fats. The term "fats" as used in this context includes lipid material in cocoa beans such as sterols, lipids and phospholipids, as well as mono-glycerides and di-glycerides. Without wishing to be bound by theory, it is believed that these one or more components of the cocoa fats contribute to the beneficial physiological effects of the extracts of the invention. Preparing the extracts of the invention from cocoa beans which have not been defatted or fermented for any substantial length of time increases the amounts of these fat components compared to extracts from defatted beans or beans that have been fermented.

Preferably, the extracts of the invention comprise from 0.1 to 10% by weight of cocoa fats, such as from 0.2 to 8%, or from 0.3 to 7%, or from 0.5 to 5%, or from 0.7 to 3%, by weight of cocoa fats. Preferably, the cocoa fats are non-triglyceride lipids.

An example of a preferred extract of the invention comprises:

(i) from 35 to 70% by weight cocoa polyphenols;

(ii) from 1 to 10% by weight xanthines;

(iii) less than 2% by weight phenylethylamine; and

(iv) from 0.1 to 10% by weight of cocoa fats.

Another extract of the invention comprises by weight 50-60% polyphenols, 7-10% theobromine, and less than 2% phenylethylamine. For example, this extract may comprise by weight 54-58% polyphenols, 8-9% theobromine, and 0.5-1.5% phenylethylamine. In these compositions, the fat content is preferably no more than 1% and/or the sugar content is no more than 3%.

One or more extracts of the invention may be admixed to form a mixed extract composition.

The extracts are used in the invention to treat or alleviate obesity (preferably in a human). The term "obesity" is used herein to refer to obese and overweight condition. These conditions may be determined by measuring body mass index, waist to hip ratio or body fat. The extracts of the invention do not rely for their action on a satiety effect or on appetite suppression or on an anti-depressive or mood enhancement effect. Instead, and without wishing to be bound by theory, it is believed that the extracts have the effect of increasing metabolism and/or the rate at which fat is burned by the subject. Therefore, the invention provides the treatment or alleviation of obesity by increasing metabolism and, in another aspect, relates to the use of the extracts for increasing metabolic rate.

Extracts and compositions of the invention preferably do not contain a dopamine D2 receptor agonist added to the cocoa extract (e.g., from a plant extract other than a cocoa extract).

The extracts of the invention are preferably formulated for oral consumption. For example, the extract may be provided as part of a foodstuff or confectionery product. Typically, the extract will be included in the foodstuff or confectionery product in an amount of from 0.1% to 50% by weight, such as from 0.5% to 10% by weight.

Foodstuffs and confectionery products include, for example, those having a fat continuous phase as well as those having a water continuous phase. Foodstuffs include foods and beverages.

Beverages include those adapted for consumption hot or cold. Beverages include one or more additives selected from sweeteners, flavouring agents, colouring agents, stabilisers and preservatives. Beverages will typically comprise from 50% to 99% water. Beverages will typically comprise the extracts of the invention dispersed and/or suspended therein. The extract of the invention may be formulated as a powder which can be converted to a beverage on the addition of water and mixing.

Foodstuffs typically comprise one or more of protein, fat and carbohydrate. Foodstuffs include dairy products and confectionery products. A preferred foodstuff comprises vegetable fat and/or cocoa butter. Particularly preferred foodstuffs include chocolate and chocolate-like products comprising cocoa solids and sugar. For example, the extracts of the invention may be included in conventional chocolate or chocolate-like products in amounts of from 0.1% to 50% by weight, such as from 0.5% to 25% by weight.

Chocolate or chocolate-like products preferably comprise one or more components selected from the group consisting of cocoa materials, sugars, sugar substitutes, milk powders, fat, emulsifier, flavouring agents and mixtures thereof.

Preferably, the cocoa materials are selected from cocoa powder, cocoa mass, cocoa liquor, cocoa butter and mixtures thereof. Milk powders include, for example, skimmed milk powder, whey powder and derivatives thereof, full cream milk powder and mixtures thereof. Suitable sugars include sucrose, fructose, glucose and dextrose and mixtures thereof (with sucrose being preferred). Sugar substitutes preferably include inulin, dextrin, isomaltulose, polydextrose and maltitol and mixtures thereof. Fats include butter fat or fractions thereof, palm oil or fractions thereof, coconut or fractions thereof, palm kernel oil or fractions thereof, liquid oils (for example, sunflower oil and/or rapeseed oil), interesterified mixtures of the above fats or fractions or hardened components thereof, or mixtures thereof. Emulsifiers include lecithin, fractionated lecithin and PGPR or mixtures thereof. Flavouring agents include vanilla and caramel or mixtures thereof.

Chocolate and chocolate-like products may comprise one or more food additives such as biscuit, nuts (whole or pieces), crispies, sponge, wafer or fruit, such as cherries, ginger and raisins or other dried fruit. These additives are normally embedded in the product.

Alternatively, the extract may be provided as a pharmaceutical composition or supplement.

Pharmaceutical compositions are preferably in the form of tablets, pills, capsules, caplets, multiparticulates including: granules, beads, pellets and micro-encapsulated particles; powders, elixirs, syrups, suspensions and solutions. Pharmaceutical compositions will comprise a pharmaceutically acceptable diluent or carrier. Pharmaceutical compositions are preferably adapted for administration parenterally (e.g., orally). Orally administrable compositions may be in solid or liquid form and may take the form of tablets, powders, suspensions and syrups. Optionally, the compositions comprise one or more flavouring and/or colouring agents. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The pharmaceutial compositions of the invention may contain 0.1-99% by weight of the extract.

Supplements may, for example, comprise the extract in liquid form (e.g., as a solution, dispersion or suspension) and/or encapsulated in a capsule. Supplements (which term includes dietary and nutritional products) may take the form of a soft gel or a hard capsule comprising an encapsulating material, preferably selected from the group consisting of gelatin, glycerol, starch, modified starch, starch derivatives such as glucose, sucrose, lactose and fructose. The encapsulating material may optionally contain cross-linking or polymerizing agents, stabilizers, antioxidants, light absorbing agents for protecting light-sensitive fills, preservatives and the like. Preferably, the amount of the extract in the food supplements is from 1 mg to 1000 mg (such as from 50 to 500 mg).

As used herein, the term "effective amount" refers to the amount of an extract or composition which is effective, upon single or multiple dose administration to a patient, in treating obesity. An effective amount of the extracts of the invention, is in general, about 0.1 to 20 g/day, e.g., 1-10 g/day for an adult human, most preferably from 0.5 to 5 g/day. The daily dose may be administered once per day, or in divided doses. The extract can be administered orally, transdermally or rectally, preferably orally. An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

The following non-limiting examples illustrate the invention and do not limit its scope in any way. In the examples and throughout this specification, all percentages, parts and ratios are by weight unless indicated otherwise.

Example 1

Evaluation of the anti-obesity effect of cocoa polyphenol extract in female Sprague-Dawley rats on a high fat diet.

Extract

The extract was prepared by extraction of cocoa nibs (deshelled cocoa beans unfermented and non-roasted) in a counter-current process with the use of a 70/30 mixture of acetone/water. The liquid extract is evaporated and then spray-dried. To improve solubility, the extract powder is agglomorated in a fluidised bed.

The extract had the following composition (% by weight):

Polyphenols	47.5
Ash	4.3
Xanthines	6.9
Moisture	3.5
Fat	1.5
Sugars	6.1
Proteins	24.5
Fibres	5.5
Others	0.2

The polyphenol content (as % by weight of total polyphenols) was as follows:

Monomers	8.2 (7.15% epicatechin and 1.04% catechin)
Dimers	7.1

Trimers	7.3
Tetramers	4.4
Pentamers	3.8
Hexamers	3.5
Heptamers	1.4
Octamers	0.9
Nonamers	1.1
Decamers	0.4
Higher	9.5

No gallic acid or gallic acid derivatives were detected.

Treatment

Testing was carried out using 24 female Sprague-Dawley rats. A daily dose of cocoa polyphenol extract of 48 mg/kg body weight (BW) (n=12) or a placebo (spring water 10 ml/kg BW) (n=12) was given for 4 weeks on a high fat diet (31% lard and 3% soybean oil). The cocoa polyphenolic extract (48 mg/kg BW) displayed an anti-obesity effect by limiting significantly the body weight gain of rats, without affecting food and water consumption and by significantly reducing the gain of fat mass. The effect on CPT-1 expression (enzymes) underpins the hypothesis of a higher catabolism of fat. BW at week 4 is 7% lower in the cocoa polyphenol group compared to the BW at week 4 in the placebo group.

	Placebo	Cocoa polyphenol extract
BW wk 0 (g)	283 +/- 14.1 a	281.8+/-13.8 a
BW wk 4 (g)	311.8 +/- 11.0 a	288.9 +/- 13.8 b
TG (g)	28,1 +/- 6.8 a	7,2 +/- 2.4 b
TFI wk 0(g/kg BW)	45	45
TFI wk 4 (g/kg BW)	40	40
Water intake wk 0 (g/kg BW)	60	60
Water intake wk 4 (g/kg BW)	60	55
Fat mass difference wk4 vs wk 0 (%)	0.72 ± 0.25 a	0.04 ± 0.45 b
CPT-1 (nmol/min/mg)	6,03 +/-1,02 a	9,54 +/- 0,98 b

TG: total gain, TFI: total feed intake, CPT-1: carnitine palmitoyltransferase, a different letter in one row indicates a statistically significant difference with $P<0.05$

Example 2

Comparison of Defatted and Non-defatted Cocoa Polyphenol Extracts

A defatted polyphenolic extract was prepared as follows.

Defatted cocoa cakes were ground in a homogenizer (Waring blender) and a portion of hexane was added. The mixture was stirred for 30 minutes at room temperature and at about 400 rpm. After 30 minutes, this mixture was filtered through a glass filter type 3. The residue was recuperated and dried under high vacuum using an oil pump. This residue was extracted with another amount of hexane using the same extraction conditions. The residue was recuperated and dried under high vacuum for further extraction using acetone/water. The cocoa powder, that was recuperated on the filter after two hexane extractions and dried under high vacuum, was extracted using a mixture of acetone/water (1/1, v/v) with

0.5% acetic acid added (pH = 3). This mixture was stirred for 30 minutes at room temperature and at about 400 rpm. After 30 minutes, this mixture was filtered through a glass filter type 3. The residue was recuperated and extracted with an additional amount of a mixture of acetone/water (1/1, v/v) with 0.5% acetic acid added (pH = 3) using the same extraction conditions. The filtrates were combined and the solvent was removed under vacuum with a rotavapor. The remaining water fraction was lyophilized for 48h. The extract had a polyphenol content (Folin) of 31.75%.

A cocoa polyphenolic extract of the invention was prepared from non-defatted cocoa beans generally as described in Example 1 but having a comparable polyphenol content to the extract from defatted beans.

The cocoa polyphenolic extract of the invention (referred to as AP48) and the cocoa polyphenolic extract from defatted cocoa beans (referred to as M48) were both orally administered at the dose of 48 mg/kg BW for 4 weeks to obesity induced female Sprague-Dawley rats.

Body weight and final body fat mass were determined before and after treatment and the results were as follows.

Body weight evolution over 4 weeks (starting at wk0 and finishing at wk4) on a high-fat diet is shown in the following table and the results are depicted in Figure 1.

	High-fat/Vehicle (n=12)	High-fat/AP48 (n=12)	High-fat/M48 (n=12)
BW wk 0 (g)	255.5 ± 4.4	254.2 ± 3.2	254.3 ± 3.3
BW wk 4 (g)	276.6 ± 2.7	248.6 ± 4.5	260.5 ± 2.9
Wk4:Post-hoc unpaired t-test (*vs.* High-fat/Vehicle) *Significance*		t = 5.45 *P* < 0.0001	t = 4.05 *P* = 0.0005
Wk4:Post-hoc unpaired t-test (*vs.* High-fat/AP48) *Significance*			t = 2.27 *P* = 0.034

BW: body weight

The results for body fat (%) evolution over 4 weeks on a high-fat diet are shown in the following table and are depicted in Figure 2.

	High-fat/Vehicle (n=12)	High-fat/AP48 (n=12)	High-fat/M48 (n=12)
Fat mass wk 0 (%)	5.55 ± 0.16	5.42 ± 0.13	5.49 ± 0.14
Fat mass wk 4 (%)	6.44 ± 0.08	5.09 ± 0.19	5.84 ± 0.17
Wk4: Post-hoc unpaired t-test (*vs.* *Significance*		t = 7.01 *P* < 0.0001	t = 3.18 *P* = 0.004
Wk4Post-hoc unpaired t-test (*vs.* High-fat/AP48) *Significance*			t = 2.97 *P* = 0.008

Both extracts reduced the effects of induced obesity by limiting significantly the increase of body weight and by inhibiting or limiting the increase of body fat mass. Greater effects were observed with the extract of the invention in all of the parameters measured.

Claims

1. A cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment for no more than three days, having a polyphenol content of more than 25% by weight, for use in the treatment or alleviation of obesity by oral administration.

2. Extract as claimed in Claim 1 having a polyphenol content of at least 30% by weight.

3. Extract as claimed in Claim 1 having a polyphenol content of from 30 to 70% by weight.

4. Extract as claimed in any one of Claims 1 to 3 having a theobromine content of at least 5% by weight.

5. Extract as claimed in any one of Claims 1 to 3 having a theobromine content of less than 5% by weight.

6. Extract as claimed in any one of the preceding claims, which is obtainable by solvent extraction of the cocoa beans.

7. Extract as claimed in Claim 6, wherein the solvent is selected from C1 to C6 alcohols or ketones, and mixtures thereof, optionally in admixture with water.

8. Extract as claimed in Claim 7, wherein the solvent is selected from ethanol, acetone, 2-butanol, 2-propanol and mixtures thereof, optionally in admixture with water.

9. Extract as claimed in any one of the preceding claims, comprising less than 2% by weight phenylethylamine.

10. Extract as claimed in any one of the preceding claims, comprising from 0.1 to 10% by weight of cocoa fats.

11. Extract as claimed in Claim 10, comprising from 0.2 to 5% by weight of cocoa fats.

12. Extract as claimed in Claim 10 or Claim 11, wherein the cocoa fats are non-triglyceride lipids.

13. Extract as claimed in any one of the preceding claims comprising

(i) from 35 to 70% by weight cocoa polyphenols;

(ii) from 1 to 10% by weight xanthines;

(v) less than 2% by weight phenylethylamine; and

(vi) from 0.1 to 10% by weight of cocoa fats.

14. Extract as claimed in any one of the preceding claims, comprising from 15 to 40% by weight protein.

15. Extract as claimed in any one of the preceding claims, comprising from 2 to 12% by weight sugars.

16. Extract as claimed in any one of the preceding claims which is provided as part of a food or confectionery product.

17. Extract as claimed in any one of the preceding claims which is provided as a pharmaceutical composition or supplement.

18. Use of a cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment no more than three days, having a polyphenol content of more than 25% by weight, in the manufacture of a composition for use in the treatment or alleviation of obesity by oral administration.

19. Method for the treatment or alleviation of obesity, comprising orally administering an effective amount of a cocoa extract obtainable by the extraction of non-defatted cocoa beans which have not been fermented or have been allowed to ferment no more than three days, having a polyphenol content of more than 25% by weight.

20. Use as claimed in Claim 18 or method as claimed in Claim 19, wherein the extract has a polyphenol content of at least 30% by weight.

21. Use as claimed in Claim 18 or method as claimed in Claim 19, wherein the extract is an extract as defined in any one of Claims 2 to 17.

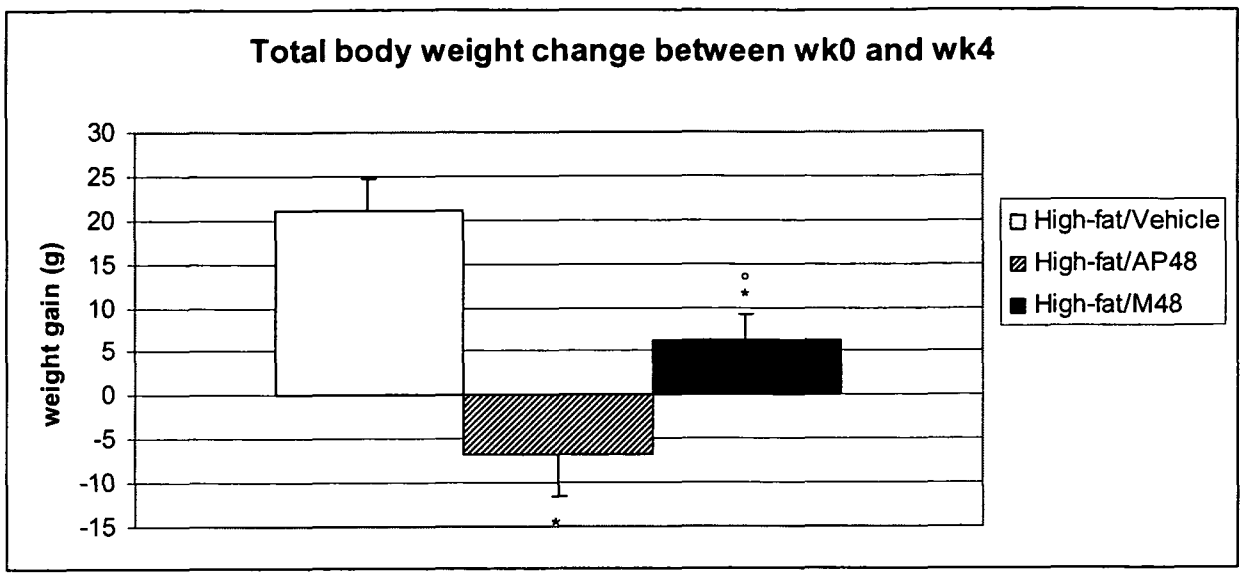
Total body weight change between wk0 and wk4
weight gain (g)
30
25
20
15
10
5
0
-5
-10
-15
High-fat/Vehicle
High-fat/AP48
High-fat/M48

Fig 1

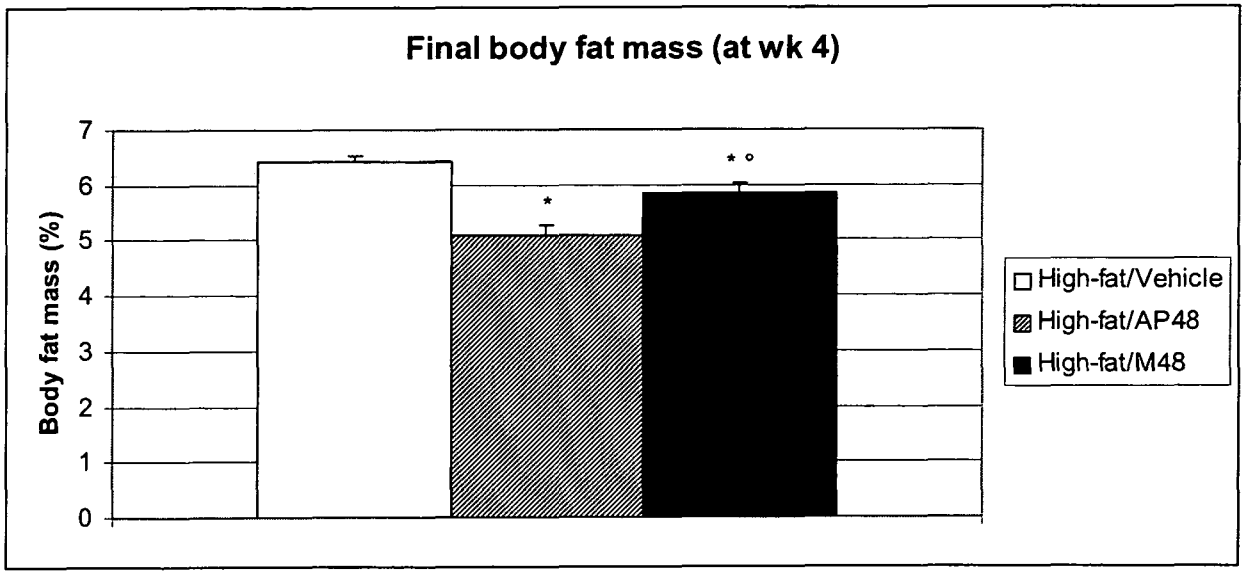
Final body fat mass (at wk 4)
Body fat mass (%)
7
6
5
4
3
2
1
0
High-fat/Vehicle
High-fat/AP48
High-fat/M48

Fig 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/003322

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/185 A61P3/04

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, PASCAL, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/14251 A (BARRY CALLEBAUT FRANCE [FR]; LECOUPEAU JEAN PAUL [FR]; VERCAUTEREN JOS) 21 February 2002 (2002-02-21) claims 1,4,8,14	1-21
Y	WO 98/09533 A (MARS INC [US]; KEALEY KIRK S [US]; SNYDER RODNEY M [US]; ROMANCZYK LEO) 12 March 1998 (1998-03-12) page 12, column 13	1-21
Y	WO 2006/128259 A (HORIZON SCIENCE PTY LTD [AU]; KANNAR DAVID [AU]; KITCHEN BARRY JAMES [) 7 December 2006 (2006-12-07) claims 14-16,27,28	1-21

-/--

[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 document 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
6 August 2008	19/08/2008

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Thalmair-De Meyere

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/003322

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR 2 885 050 A (NUXE SA LAB [FR]) 3 November 2006 (2006-11-03) the whole document	1-21
Y	DATABASE WPI Week 199738 Thomson Scientific, London, GB; AN 1997-403398 XP002486401 & CN 1 113 114 A (QIN G) 13 December 1995 (1995-12-13) abstract	1-21
Y	MATSUI N ET AL: "Ingested cocoa can prevent high-fat diet-induced obesity by regulating the expression of genes for fatty acid metabolism" NUTRITION, NUTRITION, BURBANK, CA, US, vol. 21, no. 5, 1 May 2005 (2005-05-01), pages 594-601, XP004863906 ISSN: 0899-9007 the whole document	1-21
Y	ETENG M U ET AL: "Theobromine rich cocoa powder induces weight loss and changes in lipid profile of obese Wistar rats" 1 September 2006 (2006-09-01), DISCOVERY AND INNOVATION,, PAGE(S) 191 - 196 , XP009102531 ISSN: 1015-079X the whole document	1-21
Y	BERNAERT H: "The nutritional aspects of chocolate" FOOD SCIENCE AND TECHNOLOGY TODAY, LONDON, vol. 20, no. 4, 1 January 2006 (2006-01-01), pages 17,19-20, XP009102538 ISSN: 0950-9623 page 19 - page 20	1-21
Y	BERNAERT H: "Chocolate is good for you. The sweet truth about chocolate" AGRO FOOD INDUSTRY HI-TECH, TEKNOSZIENZE, MILAN, IT, vol. 17, no. 1, 1 January 2006 (2006-01-01), pages 22-23, XP009102628 the whole document	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/003322

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/003322

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0214251 A	21-02-2002	AU 8413801 A	25-02-2002
		BR 0113198 A	08-07-2003
		CA 2418984 A1	21-02-2002
		EP 1309532 A1	14-05-2003
		FR 2812873 A1	15-02-2002
		JP 2005506948 T	10-03-2005
		MX PA03001292 A	30-07-2004
		US 2004096566 A1	20-05-2004
		US 2007258920 A1	08-11-2007
WO 9809533 A	12-03-1998	AU 750621 B2	25-07-2002
		AU 4336997 A	26-03-1998
		BR 9713194 A	31-10-2000
		CA 2264822 A1	12-03-1998
		CN 1235518 A	17-11-1999
		EP 1842431 A1	10-10-2007
		EP 1014804 A1	05-07-2000
		HK 1023038 A1	24-09-2004
		IL 128848 A	14-08-2002
		JP 2001500016 T	09-01-2001
		JP 3977726 B2	19-09-2007
		JP 2003204758 A	22-07-2003
		JP 2006034291 A	09-02-2006
		RU 2242880 C2	27-12-2004
		US 6194020 B1	27-02-2001
		US 6372267 B1	16-04-2002
		US 6015913 A	18-01-2000
WO 2006128259 A	07-12-2006	CA 2608865 A1	07-12-2006
		CN 101203270 A	18-06-2008
		EP 1885453 A1	13-02-2008
FR 2885050 A	03-11-2006	NONE	
CN 1113114 A	13-12-1995	NONE	