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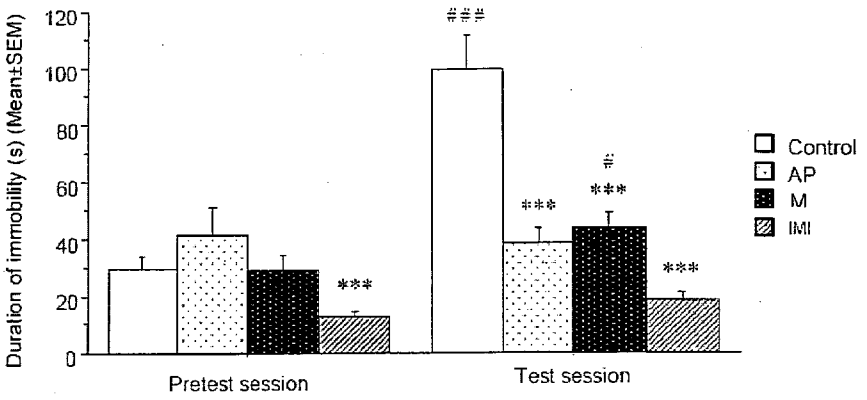


Dunnett't-test: ***P<0.005 (*vs.* Control in each session).
Paired t-test: #P<0.05; ###P<0.001 (Pretest *vs.* Test).

AP is an extract of the invention
M is an extract from defatted cocoa

FIGURE 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 prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine.

WO 2008/131911 A1

COCOA EXTRACT AND USE THEREOF

This invention relates to a cocoa extract and to its uses. In particular, the invention relates to uses for cocoa extracts in the treatment and prophylaxis of, for example, depression, anxiety or addiction, and for mood enhancement.

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.

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.

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

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 6,174,542 describes chocolate containing dietary supplements for treating, preventing, alleviating or managing symptoms associated with premenstrual syndrome (PMS) in women.

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.

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.

There remains a need for compositions that can beneficially affect disorders such as depression, anxiety or addiction, and that are useful for mood enhancement, 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 prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine.

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 prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism,

tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine.

In a further aspect, the invention provides a method for the treatment or prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine, 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.

A preferred aspect of the invention involves mood enhancement in a person not suffering from any diagnosed clinical depression or anxiety.

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 certain disorders. 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.

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 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 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.

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.

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 agglomerated 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.

Extracts of the invention are particularly useful for the treatment or prophylaxis of dysphoria. Preferably, the condition is not associated with any diagnosed clinical depression or anxiety.

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).

The extracts of the invention are useful in the treatment of dysphoria, depression (including major depressive disorder, dysthymia, adjustment disorder with depressed mood, and depression associated with bipolar disorder), anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine. The extract is moreover useful to enhance mood in persons not suffering from clinical depression or other disorder. In particular, when the condition to be treated is depression: in the treatment of depression, the invention may further comprise administering to the patient (preferably a human) an

effective amount of an antidepressant, such as a selective serotonin reuptake inhibitor (SSRI). Preferably, the SSRI is selected from fluoxetine, duloxetine, venlafaxine, citalopram, fluvoxamine, sertraline, and paroxetine.

As used herein, the term "patient" refers to a mammal such as a dog, cat, guinea pig, mouse, rat, monkey, or human being. It is understood that a human being is the preferred patient.

As used herein, the term "treating" or "treatment" means to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder.

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 the patient suffering from the named disorder. 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, e.g., ca. 10 – 100 mg/kg/day, 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 dosages of the drugs that may be co-administered with the extract may be determined by the physician in charge of the case, using knowledge of the drugs,

the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred human dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs: Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day; Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day; Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day; Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day; Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day; Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day; Paroxetine: from about 5 to about 100 mg once/day; preferred, from about 50 to about 300 mg once/day. In more general terms, one would create a combination of the present invention by choosing a dosage of SRI according to the spirit of the above guideline, and choosing a dosage of the extract in the ranges taught above. The adjunctive therapy of the present invention is carried out by administering a SRI together with the extract in any manner which provides effective levels of the two compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately. The benefit of the adjunctive therapy is that it is believed to augment the increase in availability of serotonin, norepinephrine and dopamine caused by the SSRI compounds, resulting in improved activity in treating the various conditions described above. The increase in availability of serotonin is particularly important and is a preferred aspect of the invention. Further, the invention may provide a more rapid onset of action than is usually provided by treatment with the SSRI alone.

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

Effect of Cocoa Polyphenolic Extract (CPE) in rat model for depression

Male Wistar-Unilever rats (HsdCpb:WU) (Harlan, Horst, The Netherlands), weighing 200 to 225 g are weighed and randomly divided into 4 groups (n=12). Cocoa extract according to the invention comprising by weight 54-58% polyphenols, 8-9% theobromine, and 0.5-1.5% phenylethylamine is dissolved in spring water and stirred until homogenization just before its administration at the doses of 24 and 48 mg/kg BW, PO, in a volume of administration of 10 ml/kg BW. Rats are separated into the following groups:

- Control: vehicle;
- IMI: Imipramine 15 mg/kg BW, PO (1x15 mg/kg);
- CPE 24: 24 mg/kg BW, PO (2x12 mg/kg);
- CPE 48: 48 mg/kg BW, PO (2x24 mg/kg).

The test product is orally administered for 14 days twice a day (2x12 and 2x14 mg/kg BW) in the morning and in the afternoon. Imipramine (Sigma, France) was stored at room temperature and prepared fresh before testing. It is dissolved in spring water and stirred until homogenization just before its administration at a dose of 15 mg/kg BW, PO, in a volume of administration of 10 ml/kg. Imipramine is administered once a day.

An open field (40 cm high x 60 cm in diameter) divided into 9 areas (8 equal squares and the central zone) is used for the measurement of locomotor and behavioral activity, to exclude the possibility that immobility is due to locomotion

problems. The experimental devices for the forced swimming test are plexiglas cylinders (50 cm high x 20 cm in diameter) filled to 30 cm depth with water at 25°C. In the slightly lit test room, a CCD-TV camera allows the rats to be observed and filmed on VHS-videotapes from a neighbouring room. During the experimental period, rats are weighed 3 times per week, i.e. Monday, Wednesday and Friday. Each rat is individually placed for 3 min in the center of the open field device 5 hours after the 13th treatment and 15 min before the forced swim test pretest session. This test is performed in order to test the effects of the products used on the locomotor activity of the animals and confirm that the results in the forced swim relate to the animal's mental state as opposed to locomotor ability. Immobility is defined as absence of swimming activity other than that necessary to keep the rat's head above the water. Imipramine (15 mg/kg BW, PO) is used as the antidepressant reference substance.

The test product and the vehicle are orally administered for 14 days, twice a day in the morning and in the afternoon. On D13, the products are administered just after the pretest session which lasted 15 minutes. On D14 the products are administered five hours and one hour prior to the forced swimming test. The test session lasts 5 minutes. The first five minutes of the initial 15-min swimming pretest and the 5-min swimming test session are videotaped for scoring the duration of immobility. Imipramine (15 mg/kg BW, PO) is used as the antidepressant reference substance.

The results of such an experiment were as follows:

a. No significant differences were observed in body weight between control, CPE 24 and CPE 48 treated-groups all along the experimental period. The body weight of IMI group was significantly lower than those of the other treated-groups from D5 to D14.
b. Neither administration of Imipramine nor CPE showed significant differences in any overt behavioral changes or motor dysfunction in the open field test.
c. Imipramine and CPE, at the two doses tested, significantly reduced the durations of immobility in comparison with vehicle in the

forced swimming test. ANOVA showed a significant difference among the durations of immobility during the pretest session of the four treatment groups [F(3,44)=3.45; P=0.02]. During the pretest session, only Imipramine significantly reduced the duration of immobility after a 13 day-period of treatment in comparison with vehicle (Dunnett's t test: t=3.00; P=0.007). During the test session, ANOVA showed a significant difference among the durations of immobility of the four treatment groups [F(3,44)=13.73; P<0.0001]. Imipramine and CPE at the doses of 24 and 48 mg/kg significantly reduced the durations of immobility in comparison with vehicle (Dunnett's t test: t=4.32; P=0.0003, t=3.48; P=0.002 and t=3.53; P=0.002, respectively). In addition, the duration of immobility significantly increased in Control group, while it significantly decreased in Imipramine, CPE 24 and CPE 48 treated-groups.

Effects of Imipramine and CPE on depression

(Mean±SEM)

Products	**Control** - (n=12)	**CPE24** 24 mg/kg (n=12)	**CPE48** 48 mg/kg (n=12)	**IMI** 15 mg/kg (n=12)
Pretest	39.54 ± 4.86	42.96 ± 5.84	42.29 ± 7.15	21.25 ± 3.70
Test	124.42 ± 26.33	30.29 ± 6.24	29.29 ± 5.85	10.33 ± 1.79
Paired t-test (2 tailed) Significance	t=3.22 P=0.008	t=5.16 P=0.0003	t=2.66 P=0.02	t=2.75 P=0.02

These results suggest that the extract displays an antidepressant-like profile without any observed side effects in our experimental conditions.

Example 2

Comparison of Cocoa Polyphenolic Extract of the Invention with Cocoa Polyphenolic Extract From Defatted Cocoa Beans

An investigation was carried out into the effect of the cocoa polyphenolic extracts of the invention compared to the effect of a cocoa polyphenolic extract obtained from defatted cocoa beans.

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 WO 02/14251 having a comparable polyphenol content to the extract from defatted beans.

The antidepressant-like effects the extract of the invention and the extract from defatted cocoa beans were compared by administering the extracts at the dose of 24 mg/kg BW for 14 days to male Wistar-Unilever rats, in the forced swimming test. The test products and a vehicle (spring water) were orally administered at the half dose for 12 days, twice a day in the morning and in the afternoon. On D13, the products were administered at the total dose just after the pretest session which lasted 15 minutes. On D14 the products were administered at the total dose five hours and one hour prior to the forced swimming test session that lasted 5 minutes. The first five minutes of the initial 15 minute swimming pretest and the 5 minute swimming test session were videotaped for scoring the duration of immobility. Imipramine (15 mg/kg BW, PO) was used as the antidepressant reference substance.

The results are shown in the table below and are depicted in Figure 1.

Effects of Cocoa Extracts and Imipramine (IMI) on immobility(s) in the forced swimming test (Mean±SEM)

Products	Control – (n=12)	Extract of the Invention 24 mg/kg (n=12)	Defatted Extract 24 mg/kg (n=12)	IMI 15 mg/kg (n=12)
Pretest	29.71 ± 4.31	41.83 ± 9.31	29.38 ± 5.04	12.92*** ± 3.07
Test	99.38 ± 12.09	38.50*** ± 5.45	43.96*** ± 5.03	18.25*** ± 3.07
Paired t-test (2 tailed) Significance	t=5.41 P=0.0002	t=0.53 NS	t=2.86 P=0.016	t=1.82 NS

Dunnett's test (vs. Control): ***P<0.001.

These results suggest that the extract of the invention displays a similar antidepressant-like profile to that of Imipramine and that the extract of the invention shows an antidepressant-like effect, which is more effective than that of the defatted extract.

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 prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine.

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, for the treatment or prophylaxis of dysphoria.

7. Extract as claimed in any one of the preceding claims, wherein the condition is not associated with any diagnosed clinical depression or anxiety.

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

9. Extract as claimed in Claim 8, wherein the solvent is selected from C1 to C6 alcohols or ketones, and mixtures thereof, optionally in admixture with water.

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

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

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

13. Extract as claimed in Claim 12, comprising from 0.2 to 5% by weight of cocoa fats.

14. Extract as claimed in Claim 12 or Claim 13, wherein the cocoa fats are non-triglyceride lipids.

15. 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.

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

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

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

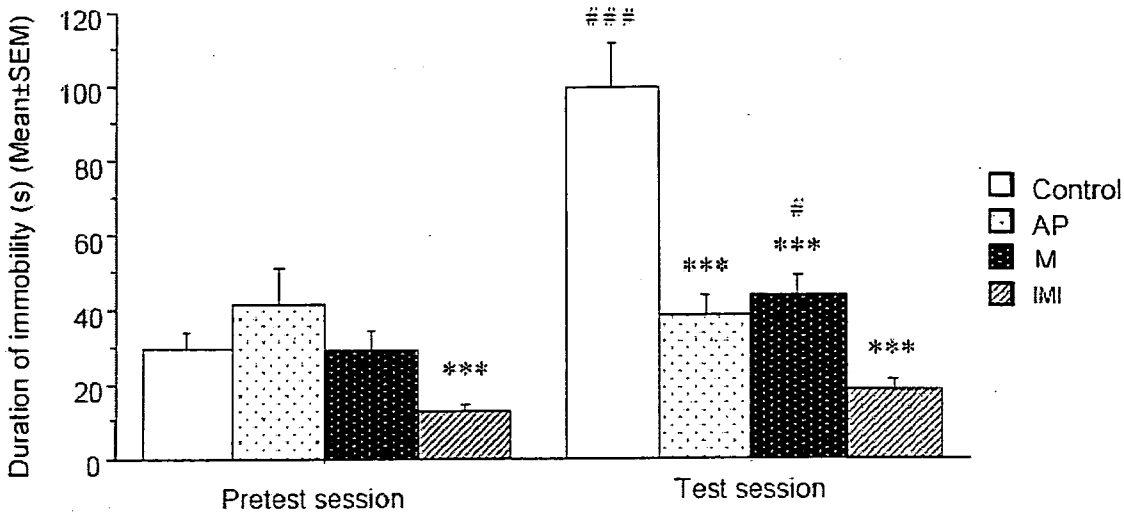
19. Extract as claimed in any one of the preceding claims which is provided as a pharmaceutical composition or supplement.

20. 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 medicament for use in the treatment or prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine.

21. Method for the treatment or prophylaxis of a condition selected from dysphoria, depression, anxiety, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, alcoholism, tobacco addiction, obsessive-compulsive disease, panic disorder, premenstrual syndrome, and migraine, 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.

22. Use as claimed in Claim 20 or method as claimed in Claim 21, wherein the extract has a polyphenol content of at least 30% by weight.

23. Use as claimed in Claim 20 or method as claimed in Claim 21, wherein the extract is an extract as defined in any one of Claims 2 to 19.



Dunnett't-test: ***P<0.005 (*vs.* Control in each session).

Paired t-test: #P<0.05; ###P<0.001 (Pretest *vs.* Test).

AP is an extract of the invention
M is an extract from defatted cocoa

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/003323

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/185

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, 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	1-23
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	1-23
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	1-23

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

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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
26 August 2008	03/09/2008

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/EP2008/003323

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	1-23
Y	DATABASE WPI Week 199738 Thomson Scientific, London, GB; AN 1997-403398 XP002487176 & CN 1 113 114 A (QIN G) 13 December 1995 (1995-12-13) abstract	1-23
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	1-23
Y	ETENG M U ET AL: "Theobromine rich cocoa powder induces weight loss and changes in lipid profile of obese Wistar rats" DISCOVERY AND INNOVATION,, vol. 18, no. 3, 1 September 2006 (2006-09-01), pages 191-196, XP009102531 ISSN: 1015-079X the whole document	1-23
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	1-23
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	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/003323

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 21-23 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/EP2008/003323

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