Abstract: A substantially pure fatty acid monoester of an estrogen, where the fatty acid is a conjugated linoleic acid or a fatty acid of at least eighteen carbons with at least two double bonds arranged in a conjugated system. It also discloses compositions which contain the monoester and use thereof for the treatment and/or prophylaxis of diabetes mellitus type 2, hyperlipidemia, metabolic syndrome, obesity and excess weight. The substantially pure monoester of conjugated linoleic acid of an estrogen allows treating the indicated diseases due to their capacity to decrease insulin resistance. The oral administration of said compound facilitates the treatment thereof.
DESCRIPTION
"MONOESTERS OF ESTROGENS WITH CONJUGATED LINOLEIC ACID AND USES THEREOF"

Technical field of the invention

The present invention relates to substantially pure monoesters of conjugated fatty acids and an estrogen. It also relates to pharmaceutical and/or cosmetic compositions which contain them, as well as to their uses.

Background of the invention

Oleoyl estrone is a compound product of the condensation of the estrogen called estrone or 3-hydroxyestra-1,3,5(10)-trien-17-one, with the fatty acid called oleic acid or cis-9 octadecenoic acid.

EP0771817 discloses that oleoyl estrone (OE) is a compound with the capacity to treat obesity and/or weight problems in mammals. EP1380300 also discloses the use of OE for the preparation of a drug for the treatment and/or prophylaxis of a metabolic disease selected from diabetes mellitus type 2, hyperlipidemia and metabolic syndrome or syndrome X.

The disease known as diabetes mellitus type 2, also called non-insulin-dependent diabetes mellitus (NIDDM), could be defined as inability by the insulin hormone circulating in the blood to act or promote the uptake of blood glucose in the tissues, whereby, consequently, the levels of this blood sugar remain high. It is said that insulin resistance is produced in NIDDM. Generally, diabetes mellitus type 2 entails less severe effects than diabetes mellitus type 1 or insulin-dependent, where there is a defect in the hormone production by the pancreatic cells responsible for it. But, however, the hyperglycemia and hyperinsulinemia typical of diabetes mellitus type 2, are usually accompanied by other physiological dysfunctions such as arterial hypertension and/or hyperlipidemia, which contributes to making this pathology worse. These symptoms of hyperglycemia and hyperinsulinemia with arterial hypertension and/or hyperlipidemia and obesity is also known with the name of metabolic syndrome.

Numerous efforts are being made to localize active ingredients which are useful for the treatment of these diseases, many seeking compounds which intervene in the metabolism of degradation and/or mobilization of lipids or in the regularization of the glycosides metabolism.

An example of this are conjugated linoleic acids (CLA). Conjugated linoleic
acid or CLA means any fatty acid of eighteen or more carbons with at least two double bonds arranged so that a double bond alternates with a single bond. CLA relates more specifically to a family of eight geometric isomers of the linoleic acid (cis,cis-9,12-octadecadienoic acid), which is preferably found in meat and dairy products. Thus, CLA has different isomers of C18:2, the most typical being cis9-trans11 acid or cis,trans-9,11-octadecadienoic acid and trans10-cis12 acid or trans,cis-10,12-octadecadienoic acid.

Although said isomers of octadecadienoic acid with two conjugated double bonds are called linoleic acid (conjugated), in fact the linoleic acid is a specific and defined chemical species: an unsaturated omega-6 fatty acid, whose molecular formula is C_{18}H_{32}O_{2} and with double bonds in cis in carbons 9 and 12, i.e. the linoleic acid is not a conjugated linoleic acid.

It has been observed that the CLA intervenes in some physiological processes, such as cellular growth, specifically inhibiting the growth, for which purpose its use has been suggested for the treatment of cancer and obesity (Pariza MW, Park Y, Cook ME. Conjugated linoleic acid and the control of cancer and obesity. Toxicol Sci 1999; 52: 107-110, Lee KW, Lee HJ, Cho HY, Kim YJ. Role of the conjugated linoleic acid in the prevention of cancer. Crit Rev Food Sci Nutr 2005; 45: 135-144, Wang YM, Jones PJH. Conjugated linoleic acid and obesity control: efficacy and mechanisms, Int J Obesity 2004; 28: 941-955, Wang YM et al. Isomer specific anti-obese and hypolipidemic properties of conjugated linoleic acid in obese OLETF rats. Biosci Biotechnol Biochem 2006; 70: 355-362). Thus, many of the effects of the CLA are derived from its capacity to inhibit cell proliferation and induce apoptosis. CLA is present in multiple functional foods, which are used to decrease body fat, but which entail undesired secondary effects and are not always successful.

Specifically Wang YM et al. have determined that the CLA trans10-cis12 isomer induces an effect of significant weight loss. In comparison with oleic acid, the carboxyl group and the double bond in cis of the aforementioned CLA isomer are at a greater distance, specifically twelve carbons, than the distance between the same functional group and bond type than in oleic acid, that are separated by just nine carbons.

Recent studies have also demonstrated that the CLA promotes hyperinsulinemia and insulin resistance (Poirier H et al. Hyperinsulinemia triggered by dietary conjugated linoleic acid is associated with decrease in leptin and adiponectin plasma levels and pancreatic beta cell hyperplasia in the mouse.


Controlling the levels of insulin circulating in blood is of evident importance in the aforementioned diseases, for which purpose numerous efforts are being carried out to localize molecules which permit said control or which improve the effects of the already known drugs. Any substance which permits controlling or treating excess weight and obesity in mammals is also of interest.

Researchers have discovered that, surprisingly, the substitution of oleic acid by a conjugated linoleic acid, in the oleoyl-estrone molecule, leads to a new molecule with very promising pharmacological actions, much more effective than current drugs and which permits controlling insulin blood levels with greater sensitivity. Furthermore, said molecules are advantageous for the treatment of excess weight and/or obesity.

Explanation of the invention

The present invention has the object of a substantially pure fatty acid monoester of an estrogen, where the estrogen is estrone; and the fatty acid is a fatty acid of at least eighteen carbons with at least two double bonds arranged in a conjugated system.

Another object of the present invention is a substantially pure fatty acid monoester of an estrogen, where the estrogen is estrone and the fatty acid is a conjugated linoleic fatty acid, i.e. a fatty acid of at least eighteen carbons, with at least two double bonds separated by a single bond.

A conjugated fatty acid is defined as a molecule with a carboxyl group and an aliphatic chain which comprises two or more double bonds between carbons, said bonds being arranged according to a conjugated system, i.e. between carbon atoms covalently bonded together by a single and a multiple bond, double or triple, which are alternated.
The substantially pure fatty acid monoester of an estrogen according to the invention is characterized in that the estrogen is estrone and the conjugated fatty acid of at least eighteen carbons is a conjugated linoleic acid selected from the group consisting of: cis,cis-9,11-octadecadienoic acid; cis, trans-9,11-octadecadienoic acid; trans, cis-9,11-octadecadienoic acid; trans,trans-9,11-octadecadienoic acid; cis,cis-10,12-octadecadienoic acid; cis,trans-10,12-octadecadienoic acid; trans,cis-10,12-octadecadienoic acid; and trans,trans-10,12-octadecadienoic acid.

Preferably, the fatty acid monoester of an estrogen is the monoester of estrone with the conjugated linoleic acid trans,cis-10,12-octadecadienoic, in accordance with formula I.

Another object of the invention is a pharmaceutical and/or cosmetic composition which comprises a therapeutically and/or cosmetically effective quantity of a fatty acid monoester of an estrogen, where the estrogen is estrone and the fatty acid is a fatty acid of at least eighteen carbons with at least two double bonds arranged in a conjugated system, and the appropriate quantities of excipients for the desired administration route.

The pharmaceutical and/or cosmetic composition object of the invention is characterized in that it comprises a therapeutically and/or cosmetically effective quantity of a fatty acid monoester of an estrogen, where the estrogen is estrone and the fatty acid is a conjugated linoleic acid.

According to another characteristic of the invention, the pharmaceutical and/or cosmetic composition comprises a substantially pure fatty acid monoester of an estrogen, where the estrogen is estrone and the conjugated linoleic fatty acid is a fatty acid selected from the group consisting of: cis,cis-9,11-octadecadienoic acid; cis, trans-9,11-octadecadienoic acid; trans, cis-9,11-octadecadienoic acid; trans,trans-9,11-octadecadienoic acid; cis,cis-10,12-octadecadienoic acid; cis,trans-10,12-octadecadienoic acid; trans,cis-10,12-octadecadienoic acid; and trans,trans-10,12-octadecadienoic acid.
Preferably, the pharmaceutical and/or cosmetic composition comprises the monoester of estrone with the conjugated linoleic acid trans,cis-10,12-octadecadienoic, in accordance with formula I.

The composition according to the invention is characterized in that it is for oral administration and the fatty acid monoester of an estrogen is in pure form or suspended in a lipophilic emulsion in the form of emulsion or solution.

Preferably, the composition is in the form of gel, capsules or tablets.

A further object of the present invention is the use of a fatty acid monoester of an estrogen, where the estrogen is estrone and the fatty acid is a fatty acid of at least eighteen carbons with at least two double bonds arranged in a conjugated system, preferably a conjugated linoleic acid, for the preparation of a drug for the treatment and/or prophylaxis of obesity and/or excess weight in mammals.

According to another characteristic of the invention, the fatty acid monoester of an estrogen, where the estrogen is estrone and the conjugated linoleic fatty acid is an acid selected from the group consisting of cis,cis-9,11-octadecadienoic acid; cis, trans-9,11-octadecadienoic acid; trans, cis-9,11-octadecadienoic acid; trans, trans-9,11-octadecadienoic acid; cis,cis-10,12-octadecadienoic acid; cis,trans-10,12-octadecadienoic acid; trans,cis-10,12-octadecadienoic acid; and trans,trans-10,12-octadecadienoic acid, is used for the preparation of a drug for the treatment and/or prophylaxis of obesity and/or excess weight in mammals.

Preferably, the monoester of estrone with the conjugated linoleic acid trans,cis-10,12-octadecadienoic, in accordance with formula I, is used for the preparation of a drug for the treatment and/or prophylaxis of obesity and/or excess weight in mammals.

A further object of the invention is the use of a fatty acid monoester of an estrogen, where the estrogen is estrone and the fatty acid is a fatty acid of at least eighteen carbons with at least two double bonds arranged in a conjugated system, preferably a conjugated linoleic acid, for the preparation of a drug for the treatment and/or prophylaxis of a mammal that suffers from a disease related to the metabolic syndrome, selected from diabetes mellitus type 2, hyperlipidemia, glucose intolerance, hyperinsulinemia or insulin resistance, or a combination thereof.

According to another characteristic of the invention, the fatty acid monoester of an estrogen, where the estrogen is estrone and the conjugated linoleic fatty acid selected from the group consisting of cis,cis-9,11-octadecadienoic acid; cis,trans-9,11-octadecadienoic acid; trans, cis-9,11-octadecadienoic acid; trans,trans-9,11-octadecadienoic acid; cis,cis-10,12-octadecadienoic acid; cis,trans-10,12-octadecadienoic acid;...
octadecadienoic acid; trans,cis-10,12-octadecadienoic acid; and trans,trans-10,12-
octadecadienoic acid, is used for the preparation of a drug for the treatment and/or
prophylaxis of a mammal that suffers from a disease related to the metabolic
syndrome, selected from diabetes mellitus type 2, hyperlipidemia, glucose
intolerance, hyperinsulinemia or insulin resistance, or a combination thereof.

Preferably, the monoester of estrone with the conjugated linoleic acid
trans,cis-10,12-octadecadienoic, in accordance with formula I, is used for the
preparation of a drug for the treatment and/or prophylaxis of a mammal that suffers
from a disease related to the metabolic syndrome, selected from diabetes mellitus
type 2, hyperlipidemia, glucose intolerance, hyperinsulinemia or insulin resistance,
or a combination thereof.

In accordance with a particular embodiment of the invention, the metabolic
disease is insulin resistance which constitutes the basis of diabetes mellitus type 2.

According to another embodiment of the invention, the metabolic disease is
hyperlipidemia. Within hyperlipidemia, the fatty acid monoester of estrone is used for
the preparation of a drug for the treatment and/or prophylaxis of
hypertriglyceridemia, hypercholesterolemia and hyperlipoproteinemia.

In accordance with another particular embodiment, the metabolic disease is
the metabolic syndrome associated with glucose intolerance, hyperlipidemia,
hyperinsulinemia, and/or insulin resistance.

The use of the fatty acid monoester of an estrogen according to the invention
is characterized in that it is for a mammal and, specifically, a human being.

**Brief description of the drawings**

The following figures are related and are obtained from the experiments
stated below to exemplify the efficacy of the new molecules or new fatty acid
monoesters of an estrogen, specifically estrone and conjugated linoleic fatty acid.
Therein:

Fig. 1 corresponds to a graphic which compares the change in body weight
in male Wistar rats treated with monoester of estrone and oleic acid (oleoyl estrone
-OE) or with monoester of estrone and conjugated linoleic acid (conjugated
linoleoyl-estrone - CLE). C: control; CLE: treated with CLE and OE: treated with OE:

Fig. 2 is a graphic which represents the food consumption per gram and day
with respect to the days of treatment with CLE, OE or without treatment (Control: C);

Fig. 3 represents the balance of energy calculated for each group of the
experiment. Ei: Supply or intake of energy; Is: Energy storage; and Ee: Energy
expenditure. The columns represent the energy expenditure in watts (W) of six animals per each group. They also indicate the contribution or consumption of food and the reserves of internal energy; and

Fig. 4 corresponds to a bar diagram where the effects of OE and CLE have been compared on those physiological parameters which show significant differences with respect to the controls (C). The data represent the effect of CLE on percentages of the effects of OE.

Detailed description of the invention

Examples

Example 1: Effect of CLE on body weight. Comparison with OE.

Male Wistar rats, 45 days old (Harlan-Interfauna, Sant FeNu de Codines, Barcelona) were used to determine the effects of the monoester of estrone with conjugated linoleic acid (CLE), on body weight. The rats were maintained in standard housing conditions in collective enclosures and they were fed "ad libitum" during five weeks with a modified cafeteria diet. At the end of this period, the animals had excess weight. The rats were then fed with maintenance fodder for rats (Panlab, Barcelona, Spain).

For the experiment, the rats were used when they were 90 days old and weighed 330 to 390 grams. This protocol managed to achieve an accumulation of around 17% of the body weight in the form of fat, which represents approximately double the fat content of this type of rat and for this age. This experimental model is comparable with a human with excess weight.

All animals received 0.2 ml of sunflower oil daily at the start of the cycle and were maintained under standard conditions, with the possibility of freely accessing the food. Their weights and food consumption were noted daily.

Four groups of six animals were selected at random:

Group 1: Zero-time controls.
Group 2: Controls (C).
Group 3: Rats that received oleoyl estrone (OE) daily at a dose of 10 nmol per gram of weight of the rat.
Group 4: Rats that received conjugated (trans 10-cis12) linoleoyl estrone (CLE) at the same dose as group 3.

The rats of group 1 were sacrificed and processed to obtain the proportions
of the components at zero time.

The experiment lasted 10 days. At the end of it, the rats were sacrificed by decapitation and the blood was collected for it to coagulate. The serum was separated and stored at -80°C.

The rats were dissected, removing the content of the stomach and intestines. The tract and the organs were heat treated in the autoclave and were homogenized. The rat paste obtained was used to estimate the lipid and energy content (an adiabatic calorimeter of type C-7000 Ika, Heitersheim, Germany was used). The percentages of the body composition of the control animals were used to determine the absolute content in lipids, proteins and energy of the rats at the start of the experiment, applying these values to their initial weight. The measurement of the body weight and the composition of the rats at the end of the study was used to determine the changes in body size and in the composition, caused by the 10 days of treatment.

The energy supply was estimated from the food consumed, which contained metabolizable energy of 13.3 kJ/g; the reservation or storage of energy was the difference between the estimated energy on day 0 and the energy content at day 10. The average energy consumed was calculated as the difference between energy supply and energy store.

The serum was used to measure the following parameters: glucose, non-esterified fatty acids (NEFA), total triacylglycerols, total cholesterol, urea, insulin, leptin and adiponectin.

Statistical comparisons were established between the groups using ANOVA algorithms and the Tukey's post-hoc test.

As illustrated in Fig. 1, the weight loss of the animals that received CLE (1.0% per day with respect to the controls) was similar to the weight loss in animals that received OE (1.3% daily with respect to the controls). Evidently, the controls gained weight (0.2% per day).

In attached Table 1, which shows the body composition of the rats treated during 10 days with CLE or OE, it is gathered that the weight loss both in the animals that received OE and in those that received CLE was the result of a loss of lipids whilst the quantity of body protein remained without changes. The animals reduced their size, losing with it a very significant quantity of total body energy, specifically 24.0% in CLE and 29.3% in OE. Nevertheless, the energy density (kJ/g) was compensated due to the maintenance of its protein content.
**Table i:**
The details correspond to the mean ± the standard error of the average of 6 different animals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>units</th>
<th>Control</th>
<th>OE</th>
<th>CLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight day 0</td>
<td>g</td>
<td>381±16</td>
<td>380±9</td>
<td>364±16</td>
</tr>
<tr>
<td>Body weight variation</td>
<td>g/day</td>
<td>+0.8±0.4</td>
<td>-5.3±1.0</td>
<td>-3.4±0.2</td>
</tr>
<tr>
<td>Energy content at day 10</td>
<td>kJ/g</td>
<td>11.63±0.5</td>
<td>9.92±0.7</td>
<td>9.44±0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Energy content at day 10</td>
<td>MJ</td>
<td>4.55±0.38</td>
<td>3.27±0.32</td>
<td>3.12±0.19</td>
</tr>
<tr>
<td>Variation in energy content</td>
<td>% respect initial</td>
<td>4.4±6.5</td>
<td>-29.3±4.4</td>
<td>-24.0±5.9</td>
</tr>
<tr>
<td>Lipid content at day 10</td>
<td>g/kg</td>
<td>196±18</td>
<td>135±20</td>
<td>131±10</td>
</tr>
<tr>
<td>Lipid content at day 10</td>
<td>g</td>
<td>77.2±10.0</td>
<td>44.9±7.6</td>
<td>43.5±4.3</td>
</tr>
<tr>
<td>Variation in lipid content</td>
<td>% respect initial</td>
<td>10.5±10.0</td>
<td>-42.9±4.9</td>
<td>-33.1±7.9</td>
</tr>
<tr>
<td>Protein content at day 10</td>
<td>g/kg</td>
<td>168±4</td>
<td>188±5</td>
<td>191±8</td>
</tr>
<tr>
<td>Protein content at day 10</td>
<td>g</td>
<td>65.0±1.9</td>
<td>61.3±2.4</td>
<td>63.0±3.6</td>
</tr>
<tr>
<td>Variation in protein content</td>
<td>% respect initial</td>
<td>2.0±3.5</td>
<td>-1.1±3.8</td>
<td>3.0±5.6</td>
</tr>
</tbody>
</table>

The details correspond to the mean ± the standard error of the average of 6 different animals.

Fig. 2 represents the food consumption both in the animals that received CLE and those that received OE. From them, it was observed that each group followed a very different pattern, being the median of the controls of 18.610.1 grams per day during the 10-day period, those of group OE of 81 0.2 and those of group CLE of 10.310.2.

Finally, Fig. 3 represents the calculated energy balance. From this, it is gathered that there are no differences in the energy expenditure value (Ee). This is due to the fact that the modifications in the energy supply are compensated by the body reserves.

**Example 2:** Effect of CLE on metabolites and circulating hormones. Comparison with the OE

From the blood obtained and treated as indicated in Example 1, the parameters that appear listed in Table 2 were analysed for each one of the trial groups.
Table 2:
The details correspond to the mean ± the standard error of the mean of 11-12 different animals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>units</th>
<th>Control</th>
<th>OE</th>
<th>CLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>mM</td>
<td>7.74±0.9</td>
<td>6.96±0.15</td>
<td>6.93±0.30</td>
</tr>
<tr>
<td>Urea</td>
<td>mM</td>
<td>6.68±0.15</td>
<td>7.20±0.39</td>
<td>6.96±0.39</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>µM</td>
<td>1679±82</td>
<td>418±50</td>
<td>605±60</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>mM</td>
<td>1.63±0.08</td>
<td>0.54±0.10</td>
<td>0.61±0.05</td>
</tr>
<tr>
<td>NEFA</td>
<td>µM</td>
<td>399±32</td>
<td>433±40</td>
<td>452±49</td>
</tr>
<tr>
<td>Insulin</td>
<td>pM</td>
<td>574±79</td>
<td>334±75</td>
<td>203±49</td>
</tr>
<tr>
<td>Leptin</td>
<td>pM</td>
<td>47.1±1.9</td>
<td>21.4±3.3</td>
<td>16.8±3.3</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>nM</td>
<td>80.1±5.1</td>
<td>62.4±4.8</td>
<td>62.5±3.4</td>
</tr>
</tbody>
</table>

From this Table 2 it is gathered that the blood glucose levels (glycemia) decreased and in the same proportion, with respect to the controls, both of group OE and group CLE. Also the triacylglycerols and the circulating cholesterol decreased in groups CLE and OE in relation to the controls, the effect being more marked in OE than in CLE. Nevertheless, no significant differences were observed in the values of urea and non-esterified fatty acids (NEFA) in blood.

In contrast, the insulin levels were greater in the Control group than in the other two groups and, surprisingly, in group CLE the quantity of insulin in blood was less than that of the controls.

The other hormones, leptin and adiponectin, are found in lower proportion than in groups OE and CLE with respect to the controls, although they decrease in a similar proportion.

From these Examples 1 and 2, it is clearly and univocally gathered that, although the oral administration of the monoester of estrone with conjugated linoleic acid (conjugated linoleoyl-estrone) in a model of rats with excess weight leads to similar results to those obtained with the oral administration of oleoyl estrone (OE), the effect of CLE on insulin sensitivity is greater than the effect caused by OE, since both molecules have the same glycemia levels, but with CLE said glycemia levels are achieved with a lower circulating insulin level.

The similarity between the effects of CLE and OE at the same dose, in relation to the mobilization of fat or the blood levels of pectin and adiponectin, suggests that the monoester of estrone with conjugated linoleic acid acts through the same channel as oleoyl estrone. That is to say, both molecules promote a decrease in food consumption, the maintenance of thermogenesis, the mobilization
of lipids in the adipose tissues, the decrease in circulating lipids, especially cholesterol and the saving of proteins and glucose by the decrease in insulin resistance.

Furthermore, it should be postulated that the absorption and transport of CLE is performed through the same channels and carriers as OE.

It is hypothesized that the high number of widely distributed non-specific esterases hydrolyze the estrone ester with conjugated linoleic acid (CLE) to release the conjugated linoleic acid or CLA to the tissues.

The ubiquity of the oleic acid and its arrangement for the cells is very different to those of the CLA, whose effects in cell proliferation and cancer have already been disclosed. It can be speculated that the absorption of CLE in the stomach and in the intestine will be similar to that of the OE, due to its similar structure, to the little specificity of the intestinal esterases and because similar effects were observed in Examples 1 and 2. Assuming that the kinetics of the CLE (degradation to estrone and conjugated fatty acid) is similar to that of the OE, no immediate significant effects should be expected, because the level of conjugated linoleic acid (CLA) derived from the CLE obtained would be much lower than that required to observe effects in the cell dynamics, since it requires greater doses of CLA when it is administered to achieve the described pharmacological effects (Rahman SM, et al. Effects of short-term administration of conjugated linoleic acid on lipid metabolism in white and brown adipose tissues of starved/reted Otsuka Lonh-Evans Tokushima fatty rats. Food Res Int 2001; 34:515-520). Thus, to justify the results obtained in the present trial, we should think of the possibility that the quantity of CLA that reaches the target cells specifically acquires high local concentrations that induce the effects different to those generated by OE. This concentrator effect avoids the drug dispersion observed with its direct administration, so that the similarity of the structure of the CLE with the OE permits a very direct application, with less quantity of agent and specifically applied to the target cells on which it acts.

The effects observed with CLE contrast, therefore, with the independent actions of CLA, that by itself promotes the decrease in insulin sensitivity. Oleoyl estrone reduces the insulin levels and, therefore, it is expected that the combination of an oleoyl estrone type activity and an additional effect of CLA cause a reduction in the efficacy of insulin in comparison with the oleoyl estrone administered alone.

Nevertheless, the results of Examples 1 and 2 demonstrate the opposite, i.e. they lead to an improvement in the effects of the oleoyl estrone (OE).
The effects of CLA in relation to insulin resistance are still not very clear and it is postulated that the oxidative stress induced by the fatty acids intervenes.

Therefore, the "type OE" effects of the CLE result in a potent mobilization of fat from the adipose tissue and its subsequent oxidation in the muscle, which justifies its use against obesity and excess weight. The levels of NEFA and lipids in the blood do not change despite their increased exchange. Thus, from all of this it can be inferred that the possible effects of CLE on the fatty acid dynamics on a cell level may be due to the fact that the CLA obtained once the CLE molecule has been hydrolyzed finds an environment which favours the inhibition of its actions or effects known to date. Contrarily, during the apoptosis processes it may be the case that the "type OE" effects of the CLE molecule are increased, decreasing the number of cells in adipose tissue and decreasing the corresponding release of cytokines promoting insulin resistance. Furthermore, there exist several indications that suggest that this fact may be due to a positive synergic effect among the CLA effects and the "type OE" effect of the CLE molecule since, at least, the levels of leptin decrease more markedly with CLE than with OE.

In any case, the decrease in blood leptin and the increase in adiponectin caused by CLE are similar to those promoted by the OE molecule alone.

Fig. 4 compares the effects of OE and CLE on several parameters which have significant differences with respect to the controls. CLE induces greater effects in the levels of insulin and leptin than OE. The effects on cholesterol, glucose and adiponectin are similar for both compounds. Finally, the decrease in food consumption, energy loss and triacylglycerols and circulating lipids in general, caused by the administration of CLE, are somewhat less than the same effects caused by OE, although they maintain their efficacy. Nevertheless, this relatively lower capacity to mobilize lipids does not affect other parameters, such as their hypercholesterolemia effects or the modulation of the adiponectin levels, or the normalization of the glycemia.

Thus, the monoester of conjugated linoleic acid of estrone (CLE) seems to produce a greater decrease in the leptin and insulin levels than the oleoyl estrone (OE). This fact can be explained by the CLA action and the "mimetic or type OE effect" in the target tissues. We can thus state that the monoester of estrone with conjugated linoleic acid (CLE) represents a considerable improvement with respect to the oleoyl estrone (OE) on its effects on insulin resistance, showing a greater efficacy in cytokine control.

Furthermore, we can speak of a considerable effect in the treatment of
obesity and/or excess weight, also derived from the dual behaviour of the CLE molecule, first by action as “analogous or mimetic of OE”, although somewhat less effective in this respect if it is calculated on a molar base, and then by the localized release in the target cells of the CLA.

It is again highlighted that the tests carried out to obtain pharmacological data have been performed with experiments with animal models of human diseases, for which the conclusions drawn are applicable to the latter.

In aforementioned Examples 1 and 2, the monoester of estrone with conjugated linoleic acid referred to corresponds to the monoester of estrone with the conjugated linoleic acid trans,cis-10,12-octadecadienoic or 10trans-12cis-linoleoyl-estrone according to formula I.

In any case, any of the stereoisomeric variants described above as conjugated linoleic fatty acid have similar effects. That is to say, the other conjugated linoleic acids selected from cis, cis-9,11-octadecadienoic acid; cis, trans-9,11-octadecadienoic acid; trans, cis-9,11-octadecadienoic acid; trans,trans-9,11-octadecadienoic acid; cis,cis-10,12-octadecadienoic acid; cis,trans-10,12-octadecadienoic acid; and trans,trans-10,12-octadecadienoic acid.

We should also expect a similar behaviour with the monoesters of estrone with conjugated linoleic fatty acid with more than two conjugated carbon-carbon double bonds. In the same way, we should also expect a similar behaviour with fatty acid monoesters of an estrogen, where the estrogen is estrone and the fatty acid is a fatty acid of more than eighteen carbons with at least two double bonds arranged in a conjugated system, for example a monoester of estrone and conjugated eicosatetraenoic acid.

With the results obtained in these Examples 1 and 2, it is clearly demonstrated that the monoester of estrone and conjugated linoleic acid (CLE) is useful for the preparation of a drug for the treatment and/or prophylaxis of a human that suffers from a disease from among the following: diabetes mellitus type 2; hyperlipidemia; and Metabolic syndrome, associated to glucose intolerance, hyperinsulinemia or insulin resistance.

In all these pathologies the so-called insulin resistance effect is produced, or in other words, the insulin hormone in the blood is incapable of promoting the uptake of glucose from the blood to the tissues. For this reason, the surprising effect of the monoester of estrone with conjugated linoleic acid (CLE), stated in Examples 1 and 2 of the present invention and according to which the CLE is capable of controlling the blood insulin levels with greater sensitivity and proportion, are useful for the
preparation of a drug for the treatment or prophylaxis of the aforementioned diseases.

As pharmaceutical and/or cosmetic compositions that contain monoester of estrone with conjugated linoleic acid (CLE) with the pharmaceutically acceptable excipients, preparations are produced with the suitable quantities of the active ingredient and the compounds useful for the correct formulation and preservation thereof. Thus, excipients are used such as methylparaben or propylparaben, or carrier vehicles of the active ingredient such as sunflower or soy oil.

Evidently, all those known by persons skilled in the art are also useful as carrier vehicles of the active ingredient, such as systems of liposomes, microcapsules or nanocapsules, etc.

These compositions are formulated, preferably, so that they can be orally administered as drinkable preparations, such as gels or in tablets or capsules. For its oral administration, the monoester of estrone with conjugated linoleic acid is very advantageous in comparison with the majority of the drugs that are currently administered to persons who suffer from any of the aforementioned diseases. Thus, for example, the drugs administered can be substituted by injection (injectable) in the case of diabetes mellitus type 2.
1. A substantially pure fatty acid monoester of an estrogen, where the estrogen is estrone; and the fatty acid is a fatty acid of at least eighteen carbons with at least two double bonds arranged in a conjugated system.

2. The substantially pure fatty acid monoester of an estrogen according to claim 1, where the estrogen is estrone; and the fatty acid is a conjugated linoleic fatty acid.

3. The substantially pure fatty acid monoester of an estrogen according to any of preceding claims 1 or 2, where the estrogen is estrone; and the conjugated linoleic acid selected from the group consisting of: cis, cis-9,11-octadecadienoic acid; cis, trans-9,11-octadecadienoic acid; trans, cis-9,11-octadecadienoic acid; trans, trans-9,11-octadecadienoic acid; cis,cis-10,12-octadecadienoic acid; cis.trans-10,12-octadecadienoic acid; trans,cis-10,12-octadecadienoic acid; and trans.trans-10,12-octadecadienoic acid.

4. The monoester according to any one of the preceding claims 1 to 3, which is the monoester of estrone with the conjugated linoleic acid trans,cis-10,12-octadecadienoic.

5. The monoester according to any one of claims 1 to 4, which is a compound according to the formula (I).

6. A pharmaceutical and/or cosmetic composition which comprises a therapeutically and/or cosmetically effective quantity of a fatty acid monoester of an estrogen as defined in any one of claims 1 to 5, and appropriate quantities of excipients useful for the desired administration route.
7.- The composition according to claim 6, where the route of administration is oral and the fatty acid monoester of an estrogen is suspended in a lipophilic medium, typically lipidic, in the form of emulsion or solution.

8.- The composition according to any one of claims 6 or 7, characterized in that it is in the form of gel, capsules or tablets.

9.- Use of a fatty acid monoester of an estrogen as defined in any one of claims 1 to 5, for the preparation of a drug for the treatment and/or prophylaxis of obesity and/or excess weight in mammals.

10.- Use of a fatty acid monoester of an estrogen as defined in any of claims 1 to 5, for the preparation of a drug for the treatment and/or prophylaxis of a mammal that suffers from a metabolic disease selected from the group consisting of diabetes mellitus type 2, hyperlipidemia, and metabolic syndrome associated to glucose intolerance, hyperinsulinemia or insulin resistance.

11.- The use according to claim 10, where the metabolic disease is diabetes mellitus type 2 or any pathology associated to insulin resistance and/or glucose intolerance.

12.- The use according to claim 10, where the metabolic disease is a hyperlipidemia consisting of a hyperlipoproteinemia and/or hypertriacylglycerolemia and/or hypercholesterolemia.

13.- The use according to claim 10, where the metabolic disease is the metabolic syndrome.

14.- The use according to any one of claims 9 to 13, where the mammal is a human.
FIG. 1

Variation in the body weight (% respect to the initial)

Time (days)

FIG. 2

Food consumption (g/day)

Time (days)
FIG. 3

FOOD CONSUMPTION
BODY LIPIDS
BODY ENERGY
TRIACYLGLYCEROLS
COLESTEROL IN SERUM
GLUCOSA IN SERUM
INSULIN IN SERUM
LEPTIN IN SERUM
ADIPONECTIN IN SERUM

FIG. 4