MIXTURES WHICH CAN BE ISOLATED FROM EUGENIA JAMBOLANA LAMARCK SEEDS, THEIR PREPARATION AND THE USE OF THESE MIXTURES AND SOME OF THEIR CONSTITUENTS AS MEDICAMENTS

The present invention relates to mixtures which can be isolated from Eugenia Jambolana Lamarck seeds (Myrtaceae family), medicaments containing these mixtures or some of their constituents, the use of these mixtures and constituents for the preparation of an antidiabetic medicament and their preparations.

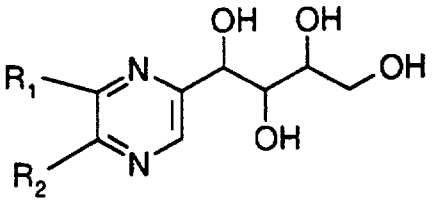
A plant extract prepared from Eugenia Jambolana seeds or bark containing a polyphenol and sterol mixed complex is described in patent FR 2,465,484.

New mixtures which can be isolated from Eugenia Jambolana Lamarck seeds, and which are free of polyphenol and sterol complex, as well as certain constituents of these mixtures endowed with hypoglycaemic properties, have now been found.

These mixtures are characterized in that they are free of polyphenol and sterol derivatives and can be isolated by grinding Eugenia Jambolana Lamarck seeds, maceration of the powder with a lower aliphatic alcohol with the use of heat, filtration, recovery of the insoluble part no longer containing polyphenol and sterol compounds, treatment of the insoluble part with an ammoniacal solution, treatment of the ammoniacal mixture with a lower aliphatic alcohol with the use of heat, filtration, recovery of the insoluble matter and drying this insoluble matter which constitutes the mixture I, then optionally treatment of the mixture I

with a water-lower aliphatic alcohol solution, filtration, partial concentration of the filtrate, purification on nonpolar adsorbent resins, partial concentration, centrifugation, ultrafiltration and isolation of the mixture II.

From the mixture II, there may also be separated sodium oxamate and the compounds of formula:



(I)

in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:

$$-CH_2-CHOH-CHOH-CH_2OH \quad (A)$$

$$-CHOH-CHOH-CHOH-CH_2OH \quad (B)$$

or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom.

Sodium oxamate has already been described by TOUSSAINT, Ann., 120, 237 (1861).

The compounds of formula (I) have already been described by KUHN et al., Ann., 644, 122-127 (1961); TSUCHIDA et al., Agr. Biol. Chem., 39 (5), 1143-1148 (1975); TSUCHIDA et al., Agr. Biol. Chem., 40 (5), 921-925 (1976); TSUCHIDA et al., Nippon Shokuhin Kogyo Gakkaishi, 37, 154-161 (1990) and AVALOS et al., tetrahedron, 49, 2655-2675 (1993).

The present invention also relates to the

process for preparing the mixture I from dried and finely ground Eugenia Jambolana Lamarck seeds.

The powder is screened, preferably with the aid of a normalized screen with holes 0.5 μm in diameter and then subjected to the following treatment:

a - maceration, with stirring, in a lower aliphatic alcohol, at a temperature of between 40 and 70°C,

b - filtration under vacuum and recovery of the insoluble matter,

c - maceration, with stirring, of the insoluble matter with a lower aliphatic alcohol at a temperature of between 40 and 70°C,

d - filtration under vacuum and removal of the alcoholic phases containing mainly the undesirable polyphenols and sterols,

e - taking up the insoluble matter in an ammoniacal solution at a temperature of between 10 and 30°C,

f - taking up the whole wet ammoniacal mass in a water-lower aliphatic alcohol solution, at a temperature of between 40 and 70°C,

g - filtration and removal of the alcoholic solution,

h - washing of the insoluble matter with a lower aliphatic alcohol, filtration and removal of the alcoholic solution,

i - recovery of the insoluble matter and drying.

In step a, the procedure is generally carried out by means of 2 to 10 litres of a lower aliphatic alcohol such as methanol or ethanol per 1 kg of screened powder. Preferably, 5 litres of ethanol with a titre of 93-95° Gay Lussac are used at 60°C for 1 hour.

The filtration of step b is preferably carried out under a vacuum of 40 kPa.

In step c, the procedure is generally carried out by means of 2 to 10 litres of a lower aliphatic alcohol such as methanol or ethanol per 1 kg of starting screened powder. Preferably, 4 litres of ethanol with a titre of 93-95° Gay Lussac are used at a temperature of 60°C for 1 hour.

The filtration of step d is preferably carried out under a vacuum of 40 kPa.

In step e, per 1 kg of starting screened powder, 750 to 1250 ml of an aqueous ammoniacal solution preferably containing 350 ml of 28% ammonium hydroxide per 1000 ml are generally used. It is particularly advantageous to use 1 litre of the aqueous ammoniacal solution and to carry out the procedure for 10 to 30 hours and, preferably, 20 hours at a temperature close to 20°C.

In step f, the wet ammoniacal mass obtained from 1 kg of starting screened powder is generally taken up, with stirring, in 2 to 10 litres of a lower aliphatic alcohol-water mixture (methanol or ethanol for example) (70/30 to 80/20 by volume) and, preferably, in 5 litres of an ethanol-water mixture (75/25 by volume), at 60°C, for 1 hour.

In step g, the filtration is preferably carried out on a cotton cloth and under a vacuum of about 80 kPa.

In step h, the washing is generally carried out with 500 to 1500 ml of a lower aliphatic alcohol

(methanol or ethanol for example) per 1 kg of starting screened powder and, preferably, with 1 litre of ethanol and the filtration is carried out on a cotton cloth and under a vacuum of about 80 kPa.

In step i, the drying is preferably carried out in the open air and protected from light.

The present invention also relates to the process for preparing the mixture II.

The mixture I obtained above is subjected to the following operations:

j - treatment of the mixture I by means of a water-lower aliphatic alcohol solution,

k - decantation and then, on the one hand, drawing off the top phase which is filtered to give the filtrate 1 and, on the other hand, treating the bottom phase with water and filtration to give the filtrate 2, pooling of the filtrates 1 and 2 and concentration to aqueous phase,

l - treatment with a nonpolar adsorbent resin and then filtration,

m - concentration of the filtrate, filtration and then ultrafiltration,

n - freeze-drying and isolation of the extract II.

In step j, 10 to 25 litres of the water-lower aliphatic alcohol solution (methanol or ethanol for example) (95/5 to 90/10 by volume) are generally used per 1 kg of the mixture I. It is preferable to carry out the procedure in 18 litres of a water-ethanol solution (17.7-0.93 by volume).

In step k, it is preferable to filter the top

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phase on a cotton cloth. It is advantageous to add, per 1 kg of the mixture I, 10 to 25 litres of water to the bottom phase and in particular 10 litres and to filter on sintered glass.

In step k, the concentration is generally carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa.

In step l, S861 resin or XAD-type resins marketed by Rhom and Hass are preferably used and the mixture is filtered on sintered glass.

In step m, the concentration is generally carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa. It is also advantageous to carry out 3 successive ultrafiltrations on 10 kd, 3 kd and 1 kd cartridges.

The present invention also relates to the process for preparing sodium oxamate and the compounds of formula (I).

The said process consists in subjecting the mixture II to the following operations:

o - chromatography of the mixture II on an infusorial earth column, recovery of the fractions containing the 4 products and pooling of these fractions into a single fraction,

p - chromatography of the fraction previously obtained on a Sephadex® column in order to obtain sodium oxamate, the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (B) and a mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a

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residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom,

q - optionally, chromatography of the mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (B) and R_2 represents a hydrogen atom by HPLC.

The chromatography of step o is carried out by means of an organic solvent such as heptane, ethyl acetate or a lower aliphatic alcohol. Preferably, a CHEM ELUT® column marketed by Prolabo is used, saturated with water and then eluted successively with heptane, a heptane-ethyl acetate mixture (50/50 by volume), ethyl acetate, an ethyl acetate-n-butanol mixture (95/5; 90/10; 80/20; 50/50; 20/80), n-butanol, and an n-butanol-water mixture (98/2 and then 95/5 by volume).

The chromatography of step p is preferably carried out by means of a water-ethanol mixture (50/50 by volume).

The chromatography of step q is generally carried out on a YMC 180DS-AQ column marketed by AIT with, as eluent, a water containing 0.1% of formic acid mixture.

In the preceding definitions and those which follow, the lower aliphatic alcohols preferably contain 1 to 4 carbon atoms.

The medicaments containing the mixtures I or II or sodium oxamate or one or more compounds of formula

(I) generally form part of the invention.

The present invention also relates to the use of the mixtures I and II, of sodium oxamate and of the compounds of formula (I) or a mixture of these with the preparation of medicaments for the treatment or prevention of diabetes and of the complications of diabetes.

The following examples illustrate the invention.

EXAMPLE 1 :Preparation of the mixture I

Eugenia Jambolana Lamarck seeds are dried in the open air, protected from light, and then finely ground. The powder thus obtained is screened with the aid of a screen of mesh 0.5 μm. 1 kg of screened powder is macerated, with mechanical stirring, in 5 litres of ethanol with a titre of 93-95° Gay Lussac, for one hour at 60°C. After filtration under vacuum, the insoluble matter is further treated under the same conditions with 4 litres of ethanol of the same titre at 60°C for a further one hour. The two ethanolic extracts containing mainly the undesirable polyphenol and sterol complex are removed. After complete filtration, the insoluble matter is taken up in 1 litre of ammoniacal solution (28 % NH_4OH 350 ml and distilled H_2O in sufficient quantity to obtain 1 litre of solution) and the mixture is left in contact for about 20 hours at a temperature close to 20°C. The wet ammoniacal mass is allowed to macerate again in 5 litres of the ethanol of titre 93 to 95° Gay Lussac-water mixture (75/25 by

volume), with mechanical stirring, for 1 hour at 60°C. The insoluble matter is filtered and it is washed with 1 litre of ethanol of the same titre; the filtrate and the washings are removed. The final insoluble matter is dried in the open air and protected from light. The mixture I is thus obtained in the form of a powder which is free of polyphenol and sterol derivatives. The yield from the pulverized and screened seeds is 80%.

EXAMPLE 2 - Preparation of the mixture II

1 kg of the mixture I obtained in Example 1, in a solution containing 17.7 litres of water and 0.93 litre of ethanol, is stirred for 3 hours. After decantation overnight, on the one hand, the top phase (13.5 litres) is drawn off and then filtered on a cotton cloth in a 7-litre filter (Schott) to give the filtrate 1 (13.5 litres) and, on the other hand, the bottom phase is stirred for 1 hour with 20 litres of water, filtered on No. 3 sintered glass to give the filtrate 2 (24 litres). The filtrates 1 and 2 are pooled and then concentrated in aqueous phase (33.5 litres) in a thermosiphon concentrator (Schott) at 35°C under a vacuum of 0.4 kPa. The concentrate is stirred for one hour with 2.5 litres of S861 resin (Rhom and Haas) and then filtered on No. 3 sintered glass. The filtrate is concentrated in a thermosiphon concentrator (Schott) at 35°C and then under a vacuum of 0.4 kPa to 5.5 litres. The concentrate is centrifuged in a tubular centrifuge (centrifugal force 62000 g) and filtered on a 0.22 μm filter (Gelman suporcap 100 type) pump. After

3 successive ultrafiltrations on 10 Kd, 3 Kd and 1 Kd cartridges and freeze-drying, 25 g of the mixture II are obtained in the form of a dark brown hygroscopic powder.

EXAMPLE 3 - Constituents obtained from the mixture II

525 mg of the mixture II obtained in Example 2 in solution in 1.1 ml of milli Q-filtered water are chromatographed on a CHEM ELUT® column marketed by PROLABO, 50 cm in height and with a diameter of 1 cm, saturated with milli Q-filtered water. The elution is carried out with heptane using increasing gradients of ethyl acetate and then of n-butanol, of n-butanol/hydrochloric acid and of water (fraction 1 : heptane; fraction 2 : heptane/ethyl acetate (50/50 by volume); fractions 3-4 : ethyl acetate; fractions 5-6 : ethyl acetate/n-butanol (95/5 by volume), fractions 7-8 : ethyl acetate/n-butanol (90/10 by volume), fractions 9-10 : ethyl acetate/n-butanol (80/20 by volume); fractions 11-12 : ethyl acetate/n-butanol (50/50 by volume), fractions 13-14 : ethyl acetate/n-butanol (20/80 by volume), fractions 15-16 : n-butanol, fractions 17-18 : n-butanol/water (98/2 by volume), fractions 19-21 : n-butanol/water (95/5 by volume). 50 ml fractions are collected. Fractions 19 to 21 are combined and concentrated to dryness under reduced pressure. 108 mg of a fraction is thus obtained which is chromatographed on a Sephadex® LH20 column marketed by Pharmacia (height 100 cm, diameter 1 cm) produced with a methanol-water mixture (50-50 by volume). The

elution is carried out with the same eluent mixture; 1 ml fractions are collected.

1 - Fractions 88 to 91 are combined and concentrated to dryness. 14.4 mg of a product are obtained, which product gives, upon crystallization from 0.5 ml of ethanol, 2 mg of 2,5-di-(tetrahydroxybutyl)pyrazine in the form of white crystals whose characteristics are the following:

- optical rotation $[\alpha]^{20}$ (Na 589) = -137° ± 2.0 (dimethyl sulphoxide; c=0.5),
- infrared spectrum produced on a Nicolet 60SX-R apparatus in solution in KBr, main characteristic absorption bands: 3281 cm^{-1} (ν bound OH groups including H_2O), 2972+2940+2901+2880 cm^{-1} (ν CH of the CH_2 and CHOH groups), 2733 cm^{-1} (ν bound OH groups), 1635 cm^{-1} (deformations of the OH groups, including H_2O), 1491 cm^{-1} (ν C=C and C=N of the pyrazine nucleus), 1449 cm^{-1} (ν C=C and C=N of the pyrazine nucleus + deformations of the OH groups), 1413 cm^{-1} (deformations of the OH groups), 1343 cm^{-1} (ν C=C and C=N of the pyrazine nucleus), 1309+1290+1251+1215+1181+1161+1123 cm^{-1} (deformations of the CH groups), 1092 cm^{-1} (ν CO of the secondary alcohols), 1048+1035 cm^{-1} (ν CO of the primary alcohols + pyrazine nucleus), 947+899+854 cm^{-1} (secondary alcohols), 877 cm^{-1} (ν CH of the pyrazine nucleus), 727 cm^{-1} (pyrazine nucleus + deformations of the OH groups), 639 cm^{-1} (pyrazine nucleus), 607+531 cm^{-1} broad (deformations of the OH groups), 451+411 cm^{-1} (pyrazine nucleus),
- mass spectrum performed on a FINNIGAN TSQ46

apparatus, mass ionization mode M/z=321 (MH)+,

- ^{1}H NMR spectrum (600 MHz, DMSO, chemical shift in ppm): 3.40 and 3.61 (2 mts, 2H each : CH_2 at position 4', 4"); 3.58 (2 mts, 2H each : CH at position 2', 2", 3', 3"); 4.36 (broad t, 2H : OH at position 4', 4"); 4.40 (d, J=7.2 Hz, 2H : OH at position 2', 2"); 4.63 (d, J=4.8 Hz, 2H : OH at position 3', 3"); 4.95 (dd J=6.0 and 0.6 Hz, 2H : CH at position 1', 1"); 5.30 (d, J=6.0 Hz, 2H : OH at position 1', 1"); 8.61 (s, 2H, CH at position 3 and 6),

- ultraviolet spectrum : λ max = 275 nm (ϵ=8260); 206 nm (ϵ=10220) (c=19 mg/ml; water), λ max = 276 nm (ϵ=7960); 206 nm (ϵ=9920) (c=19 mg/ml; HCl 0.1N), λ max = 275 nm (ϵ=7690); (c=19 mg/ml; KOH 0.1N),

- HPLC on Y.M.C. 180DS-AQ column of 150x4.6 mm (batch AIT/DE940377) marketed by AIT, isocratic elution H_2O +0.1% formic acid with a flow rate of 1 ml/min, UV detection at 270 nm, retention time : 2 min 32 s.

2 - Fractions 92 and 93 are combined and concentrated to dryness. 9 mg of a fraction are obtained, which fraction gives, upon crystallization from 0.5 ml of ethanol, 1.2 mg of sodium oxamate having the same characteristics as those described by TOUSSAINT, Ann., 120, 237 (1861).

3 - Fractions 94 to 97 are combined and concentrated to dryness. 25.9 mg of a fraction are obtained, which fraction gives, upon crystallization from 0.5 ml of ethanol, 6.2 mg of a mixture of 2-(tetrahydroxybutyl)-5-(2',3',4'-trihydroxybutyl)pyrazine and 2-(tetrahydroxybutyl)-6-

(2',3',4'-trihydroxybutyl)pyrazine which is further separated by HPLC on a Y.M.C. 180DS-AQ column of 150x4.6 mm (batch AIT/DE940377); isocratic elution H_2O +0.1% formic acid with a flow rate of 1 ml/min, UV detection at 270 nm.

5.2 mg of 2-(tetrahydroxybutyl)-5-(2',3',4'-trihydroxybutyl)pyrazine are thus obtained, which has the following characteristics:

- optical rotation $[\alpha]^{20}$ (Na 589) = -116.3° ± 1.7 (dimethyl sulphoxide; c=0.5),
- infrared spectrum performed on a Nicolet 60SX-R apparatus in solution in KBr, main characteristic absorption bands at 3398 cm^{-1} (ν bound OH groups including H_2O), 2951+2922+2891 cm^{-1} (ν CH of the CHOH groups), 2761 cm^{-1} (ν bound OH groups), 1636 cm^{-1} (deformations of the OH groups, including H_2O), 1483+1463 cm^{-1} (ν C=C and C=N of the pyrazine nucleus), 1411 cm^{-1} (deformation of the OH groups), 1367+1328+1270+1227+1191 cm^{-1} (deformation of the CH groups), 1071 cm^{-1} (ν CO of the secondary alcohols), 1041 cm^{-1} (ν CO of the primary alcohols + pyrazine nucleus), 943+897 cm^{-1} (secondary alcohols), 869 cm^{-1} (ν CH of the pyrazine nucleus), 645 cm^{-1} (CH of the pyrazine nucleus), 607 cm^{-1} broad (deformations of the OH groups), 446+409 cm^{-1} (pyrazine nucleus),
- mass spectrum performed on a FINNIGAN TSQ46 apparatus, mass ionization mode M/z=305 (MH)+,
- ^1H NMR spectrum (600 MHz, DMSO, chemical shift in ppm): 2.70 and 3.04 (2 dd, J=9.0 and 15.0 Hz and J=3.0 and 15.0 Hz, 1H each : CH_2 at position 1"); between 3.30

and 3.45 (mts, CH at position 3", 4', 4"); between 3.53 and 3.65 (mts, 4H : CH at position 2', 3', 4', 4"), 3.73 (mt, 1H : CH at position 2"); 4.37 (broad t, 1H : OH at position 4'); 4.42 (mt, 2H : OH at position 2' and 4"); 4.60 (d, J=6 Hz, 1H : OH at position 2"); 4.63 (d, J=6 Hz, 1H : OH at 3'); 4.67 (d, J=6 Hz, 1H : OH at position 3"); 4.92 (dd J=6.0 and 0.6 Hz, 1H : CH at position 1'); 5.30 (d, J=6.0 Hz, 1H : OH at position 1'); 8.39 (s, 1H : CH at position 6); 8.61 (s, 1H : CH at position 3),

- ultraviolet spectrum : λ max = 276 nm (ϵ=7756) ; 206 nm (ϵ=8738) (c=19 mg/ml; water), λ max = 277 nm (ϵ=7218); 208 nm (ϵ=7171) (c=19 mg/ml; HCl 0.1 N), λ max = 276 nm (ϵ=7467) (c=19 mg/ml; KOH 0.1N),

- HPLC on Y.M.C. 180DS-AQ column of 150×4.6 mm (batch AIT/DE940377) marketed by AIT, isocratic elution H_2O +0.1% formic acid with a flow rate of 1 ml/min, UV detection at 270 nm, retention time : 3 min 75 s

and 1 mg of 2-(tetrahydroxybutyl)-6-(2',3',4'-trihydroxybutyl)pyrazine which has the following characteristics:

- ^1H NMR spectrum (600 MHz, DMSO, chemical shift in ppm): 2.70 and 3.04 (2 dd, J=9.0 and 15.0 Hz and J=3.0 and 15.0 Hz, 1H each : CH_2 at position 1"); between 3.30 and 3.45 (mts, CH at position 3", 4', 4"); between 3.53 and 3.65 (mts, 4H : CH at position 2', 3', 4', 4"), 3.73 (mt, 1H : CH at position 2"); 4.37 (broad t, 1H : OH at position 4'); 4.42 (mt, 2H : OH at position 2' and 4"); 4.60 (d, J=6 Hz, 1H : OH at position 2"); 4.63 (d, J=6 Hz, 1H : OH at 3'); 4.67 (d, J=6 Hz, 1H : OH at

position 3"); 4.92 (dd J=6.0 and 0.6 Hz, 1H : CH at position 1'); 5.30 (d, J=6.0 Hz: 1H, OH at position 1'); 8.31 (s, 1H : CH at position 5); 8.53 (s, 1H : CH at position 3),

- HPLC on Y.M.C. 180DS-AQ column of 150x4.6 mm (batch AIT/DE940377) marketed by AIT, isocratic elution H_2O +0.1% formic acid with a flow rate of 1 ml/min, UV detection at 270 nm, retention time : 3 min 61 s.

The hypoglycaemic activity of the mixtures I and II, of sodium oxamate and of the compounds of formula (I) have been determined in mice made diabetic with streptozocin and in normal mice with post-prandial hyperglycaemia according to the following procedures:

I - Mice made diabetic with streptozotocin

Swiss albino mice weighing between 22 and 25 g are made diabetic with streptozotocin administered by intraperitoneal injection at a dose of 210 or 265 mg/Kg of mouse, diluted in a citrate buffer at a concentration such that each mouse receives 0.2 ml of the solution on day 1 (D1). 3 to 4 days later, a check is made on 2 to 3 mice to see if the diabetes is established (glycaemia greater than 7.2 mmol/litre (130 mg per 100 ml). The glycaemia is then measured after starving for 4 hours. If the mice have become diabetic, they are divided into batches of 5 to 7 mice. Each of the batches receives, from D1 and daily, a selected dose of product. The administration is made once a day and at a fixed time, by gastric intubation and in a volume of 0.4 ml of distilled water as

vehicle. Two batches of controls are made up:

- one batch of untreated diabetic mice
- one batch or normal mice

These two batches of controls receive 0.4 ml of vehicle by gastric intubation and simultaneously with the treated mice.

The treatment lasts for 4 days. On the 5th day (D5), there is no administration of product. After fasting for 4 hours, the final glycaemias are measured.

II - Normal mice with post-prandial hyperglycaemia

Swiss albino mice weighing between 22 and 25 g are made to have post-prandial hyperglycaemia by the following procedure:

- fasting 2 hours
- food in excess for 1 hour
- fasting 2 hours

The glycaemia is measured at the end of the last two hours of fasting, which constitutes the glycaemia at time T0. The mice are then divided into homogeneous batches according to the measured glycaemias. The products to be evaluated are administered without delay by gastric intubation in 0.4 ml of distilled water. The control batch receives the excipient (0.4 ml of distilled water). After one hour, the final glycaemias are measured which constitute the glycaemia at time T60.

Results obtained on the glycaemia of mice made diabetic with streptozotocin

PRODUCTS mg/mouse/day	NUMBER OF MICE	GLYCAEMIA AT D1 mg/100 ml	GLYCAEMIA AT D5 mg/100 ml	% inhibition
Sodium oxamate (0.5 mg)	5	153.40±11.53	89.90±13.94	-41.46
Mixture II (0.5 mg)	5	270.50±58.72	117.50±17.35	-56.56
2-(tetrahydroxybutyl)-5-(2',3',4'-trihydroxybutyl)-pyrazine (0.5 mg)	5	304.25±99.35	164.50±95.13	-45.93
2-(tetrahydroxybutyl)-5-(2',3',4'-trihydroxybutyl)-pyrazine and 2-(tetrahydroxy-butyl)-6-(2',3',4'-trihydroxybutyl)pyrazine (50/50) (0.25 mg)	6	320.83±130.30	174.00±97.74	-45.77
Controls	5	221.66±50.17	210.33±20.07	-5.11

Results obtained on the glycaemia of normal mice with post-prandial hyperglycaemia

PRODUCTS mg/mouse/day	NUMBER OF MICE	GLYCAEMIA AT T0 mg/100 ml	GLYCAEMIA AT T60 mg/100 ml	% inhibition
Mixture I (5 mg)	5	129.50±29.06	87.60±14.16	-32.35
Sodium oxamate (0.5 mg)	15	136.46±23.69	102.93±20.95	-24.57
Mixture II (0.5 mg)	15	133.93±17.50	105.60±16.91	-21.15
2,5-di(tetrahydroxybutyl) pyrazine (0.5 mg)	10	136.25±16.92	102.41±14.12	-24.83
2-(tetrahydroxybutyl)-5-(2',3',4'-trihydroxy-butyl)pyrazine (0.5 mg)	10	128.75±21.23	90.50±19.55	-29.70
2-(tetrahydroxybutyl)-5-(2',3',4'-trihydroxy-butyl)pyrazine and 2-(tetrahydroxybutyl)-6-(2',3',4'-trihydroxybutyl)pyrazine (50/50) (0.25 mg)	5	126.60±17.03	100.60±16.88	-20.53
Controls	10	137.83±13.99	130.50±20.23	-5.32

The mixtures according to the invention, the sodium oxamate and the compounds of formula (I) have a low toxicity. Their LD_{50} is greater than 2000 mg/kg orally in mice.

The mixtures according to the invention, the sodium oxamate and the compounds of formula (I) reduce the glycaemia in a diabetic subject and are therefore useful in the treatment of diabetes and the complications of diabetes.

When these products are used in monotherapy in the treatment of diabetes, there is no risk of hypoglycaemia. They are true antidiabetic agents. It appears that this effect results from a peripheral increase in glucose. The products do not significantly stimulate the secretion of insulin but the presence of small quantities of insulin is necessary for their action.

In sand rats (Psammomys obesus) which are spontaneously diabetic in captivity, the products decrease hyperglycaemia, prevent or decrease cataract and restore a degree of fertility.

In human therapy, these products are therefore useful in the prevention and treatment of diabetes and especially type II diabetes (NID diabetes) not exhibiting acetonuria, obese diabetes, diabetes at the age of about fifty, metaplethoric diabetes, diabetes affecting the elderly and mild diabetes. They can be used as a supplement to insulin therapy (because of their insulin-potentiating activity) in insulin-dependent diabetes where they make it possible to

gradually reduce the dose of insulin, unstable diabetes, insulin-resistant diabetes, and as a supplement to hypoglycaemic sulphamides when these do not provide a sufficient decrease in glycaemia. These products can also be used in the complications of diabetes such as hyperlipaemias, lipid metabolism disorders, dyslipaemias and obesity. They are also useful in the prevention and treatment of the lesions of atherosclerosis and their complications (coronopathies, myocardial infarction, cardiomyopathies, progression of these three complications into left ventricular insufficiency, various arteriopathies, arteritis of the lower limbs with claudication and progression into ulcers and gangrene, cerebral vascular insufficiency and its complications and sexual impotence of vascular origin), diabetic retinopathy and all its manifestations (increase in capillary permeability, dilation and capillary thrombosis, microaneurysms, arteriovenous shunt, venous dilation, punctiform and macular haemorrhages, exudates, macular oedemas, manifestations of proliferative retinopathy: neovessels, proliferative retinitis scars, haemorrhages of the vitreous body, retinal detachment), diabetic cataract, diabetic neuropathy in its various forms (peripheral polyneuropathies and its manifestations such as paresthesias, hyperesthesias and pain, mononeuropathies, radiculopathies, autonomous neuropathies, diabetic amyotrophies), the manifestations of diabetic foot (ulcers of the lower

extremities and of the foot), diabetic nephropathy in its two diffuse and nodular forms, atheromatoses (rise in HDL lipoproteins promoting the elimination of cholesterol from the atheroma plaques, decrease in the LDL lipoproteins, decrease in the LDL/HDL ratio, inhibition of oxidation of the LDLs, decrease in platelet adhesiveness), hyperlipaemias and dyslipaemias (hypercholesterolaemias, hypertriglyceridaemias, normalization of the fatty acid level, normalization of the uricaemia, normalization of the A and B apoproteins), cataracts, high blood pressure and its consequences.

The medicaments according to the invention consist of a mixture according to the invention, sodium oxamate, a compound of formula (I) or a combination of these products, in the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product which may be inert or physiologically active. The medicaments according to the invention can be used orally, parenterally, rectally or topically.

As solid compositions for oral administration, there may be used tablets, pills, powders (gelatine capsules, cachets) or granules. In these compositions, the active ingredient according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under an argon stream. These compositions may also comprise substances other than the diluents, for example one or more lubricants such as magnesium stearate or talc, a

colorant, a coating (sugar-coated tablets) or a glaze.

As liquid compositions for oral administration, there may be used pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil. These compositions may comprise substances other than the diluents, for example wetting, sweetening, thickening, flavouring or stabilizing products.

The sterile compositions for parenteral administration may preferably be solutions in aqueous or nonaqueous form, suspensions or emulsions. As solvent or vehicle, there may be used water, propylene glycol, polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate or other suitable organic solvents. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization can be performed in several ways, for example by aseptizing filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene

glycols.

The compositions for topical administration may be for example creams, lotions, collyria, collutoria, nasal drops or aerosols.

The doses depend on the desired effect, the duration of treatment and the route of administration used; they are generally between 150 mg and 600 mg per day via the oral route for an adult with unit doses ranging from 50 mg to 200 mg of active substance.

In general, the doctor will determine the appropriate dosage according to the age, weight and all the other factors specific to the subject to be treated.

The following examples illustrate compositions according to the invention:

EXAMPLE A

Gelatine capsules in doses of 50 mg of active product having the following composition are prepared according to the usual technique:

- Active product..... 50 mg
- Cellulose..... 18 mg
- Lactose..... 55 mg
- Colloidal silica..... 1 mg
- Sodium carboxymethyl starch..... 10 mg
- Talc..... 10 mg
- Magnesium stearate..... 1 mg

EXAMPLE B

Tablets in doses of 50 mg of active product

having the following composition are prepared according to the usual technique:

- Active product..... 50 mg
- Lactose..... 104 mg
- Cellulose..... 40 mg
- Polyvidone..... 10 mg
- Sodium carboxymethyl starch..... 22 mg
- Talc..... 10 mg
- Magnesium stearate..... 2 mg
- Colloidal silica..... 2 mg
- Hydroxymethylcellulose, glycerine, titanium oxide (72-3.5-24.5) qs 1 finished film-coated tablet containing 245 mg

EXAMPLE C

An injectable solution containing 50 mg of active product having the following composition is prepared:

- Active product..... 50 mg
- Benzoic acid..... 80 mg
- Benzyl alcohol.....0.06 ml
- Sodium benzoate..... 80 mg
- Ethanol at 95%.....0.4 ml
- Sodium hydroxide..... 24 mg
- Propylene glycol.....1.6 ml
- Water.....qs... 4 ml



CLAIMS

1. Mixtures free of polyphenol and sterol derivatives and which can be isolated by grinding Eugenia Jambolana Lamarck seeds, maceration of the powder with a lower aliphatic alcohol with the use of heat, filtration, recovery of the insoluble part no longer containing polyphenol and sterol compounds, treatment of the insoluble part with an ammoniacal solution, treatment of the ammoniacal mixture with a lower aliphatic alcohol with the use of heat, filtration, recovery of the insoluble matter and drying this insoluble matter which constitutes the mixture I and optionally treatment of the mixture I with a water-lower aliphatic alcohol solution, filtration, partial concentration of the filtrate, purification on non-polar adsorbent resins, partial concentration, centrifugation, ultrafiltration and isolation of the mixture II.

2. Process for preparing the mixture I according to claim 1, characterized in that Eugenia Jambolana Lamarck seeds are dried, finely ground, screened and the powder obtained is subjected to the following treatment:

a - maceration, with stirring, in a lower aliphatic alcohol, at a temperature of between 40 and 70°C,

b - filtration under vacuum and recovery of the insoluble matter,

c - maceration, with stirring, of the insoluble matter with a lower aliphatic alcohol at a temperature of between 40 and 70°C,

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d - filtration under vacuum and removal of the alcoholic phases containing mainly the undesirable polyphenols and sterols,

e - taking up the insoluble matter in an ammoniacal solution at a temperature of between 10 and 30°C,

f - taking up the whole wet ammoniacal mass in a water-lower aliphatic alcohol solution, at a temperature of between 40 and 70°C,

g - filtration and removal of the alcoholic solution,

h - washing of the insoluble matter with a lower aliphatic alcohol, filtration and removal of the alcoholic solution,

i - recovery of the insoluble matter and drying the mixture I.

3. Process according to claim 2, for which, in step a, the procedure is carried out by means of 2 to 10 litres of a lower aliphatic alcohol per 1 kg of screened powder.

4. Process according to either of claims 2 and 3, for which, in step a, 5 litres of ethanol with a titre of 93-95° Gay Lussac are used at 60°C for 1 hour.

5. Process according to one of claims 2 to 4, for which the filtration of steps b and d are carried out under a vacuum of 40 kPa.

6. Process according to one of claims 2 to 5, for which, in step c, the procedure is carried out by means of 2 to 10 litres of a lower aliphatic alcohol per 1 kg of starting screened powder.

7. Process according to one of claims 2 to 6, for which, in step c, 4 litres of ethanol with a

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titre of 93-95° Gay Lussac are used at a temperature of 60°C for 1 hour.

8. Process according to one of claims 2 to 7, for which, in step e, 750 to 1250 ml of an aqueous ammoniacal solution are used per 1 kg of starting screened powder.

9. process according to one of claims 2 to 8, for which, in step e, per 1 kg of starting screened powder, 1 litre of aqueous ammoniacal solution containing 35 ml of 28% ammonium hydroxide is used and the procedure is carried out at a temperature close to 20°C for 10 to 30 hours hours.

10. Process according to one of claims 2 to 9, for which, in step f, the wet ammoniacal mass obtained from 1 kg of starting screened powder is taken up in 2 to 10 litres of a water-lower aliphatic alcohol solution.

11. Process according to one of claims 2 to 10, for which, in step f, the procedure is carried out in 5 litres of an ethanol-water mixture (75/25 by volume), at 60°C for 1 hour.

12. Process according to one of claims 2 to 11, for which, in step h, the washing is carried out with 500 to 1500 ml of a lower aliphatic alcohol per 1 kg of starting screened powder.

13. Process according to one of claims 2 to 12, for which, in step h, the washing is carried out with 1 litre of ethanol and the filtration is carried out on a cotton cloth and under a vacuum of about 80 kPa.

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14. Process according to one of claims 2 to 12, for which, in step i, the drying is carried out in the open air and protected from light.

15. Process for preparing the mixture II according to claim 1, for which the mixture I according to claim 1 is subjected to the following operations:

j - treatment of the mixture I according to claim 1 by means of a water-lower aliphatic alcohol solution,

k - decantation and then, on the one hand, drawing off the top phase which is filtered to give the filtrate 1 and, on the other hand, treating the bottom phase with water and filtration to give the filtrate 2, pooling of the filtrates 1 and 2 and concentration to aqueous phase,

l - treatment with a nonpolar adsorbent resin and then filtration,

m - concentration of the filtrate, filtration and then ultrafiltration,

n - freeze-drying and isolation of the extract II.

16. Process according to claim 15, for which, in step j, 10 to 25 litres of the water-lower aliphatic alcohol solution (95/5 to 90/10 by volume) are used per 1 kg of the mixture I per 1 kg of the mixture I.

17. Process according to either of claims 15 and 16, for which, in step j, 18 litres of a water-ethanol solution (17.7-0.93 by volume) are used.

18. Process according to one of claims 15 to 17, for which, in step k, the top phase is filtered on a cotton cloth and 10 to 25 litres of water are added

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to the bottom phase per 1 kg of the mixture I and the mixture is filtered on sintered glass.

19. Process according to one of claims 15 to 18, for which, in step k, the concentration is generally carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa.

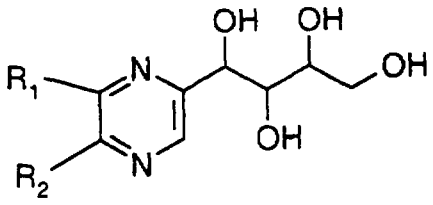
20. Process according to one of claims 15 to 19, for which, in step l, S861 resin or XAD-type resins marketed by Rhom and Hass are used and the mixture is filtered on sintered glass.

21. Process according to one of claims 15 to 20, for which, in step m, the concentration is carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa.

22. Process according to one of claims 15 to 21, for which, in step m, 3 successive ultrafiltrations are carried out on 10 kd, 3 kd and 1 kd cartridges.

23. Process for preparing sodium oxamate and the compounds of formula:

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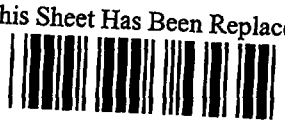
(I)

in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:

$-CH_2-CHOH-CHOH-CH_2OH$ (A)

$-CHOH-CHOH-CHOH-CH_2OH$ (B)

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or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom for which the mixture II according to claim 1 is subjected to the following operations:

o - chromatography of the mixture II according to the invention on an infusorial earth column, recovery of the fractions containing the 4 products and pooling of these fractions into a single fraction,

p - chromatography of the fraction previously obtained on a Sephadex® column in order to obtain sodium oxamate, the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (B) and a mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom,

q - optionally, chromatography of the mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom by HPLC.

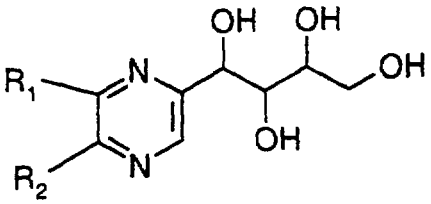
24. Process according to claim 23, for which the chromatography of step o is carried out on a CHEM ELUT® column marketed by Prolabo, saturated with water and then eluted successively with heptane, a heptane-ethyl acetate mixture (50/50 by volume), an ethyl acetate-n-butanol mixture (95/5; 90/10; 80/20; 50/50; 20/80 and then 0/100 by volume) and an n-butanol-water mixture (98/2 and then 95/5 by volume).

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25. Process according to claim 24, for which the chromatography of step p is carried out by means of a water-ethanol mixture (50/50 by volume).

26. Process according to claim 24, for which the chromatography of step q is carried out on a YMC 180DS-AQ column marketed by AIT with, as eluent, a water containing 0.1% of formic acid mixture.

27. Medicaments characterized in that they contain, as active ingredient, a mixture I according to claim 1 or a mixture II according to claim 1 or sodium oxamate or one or more compounds of formula:



(I)

in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:

$$-CH_2-CHOH-CHOH-CH_2OH \qquad (A)$$

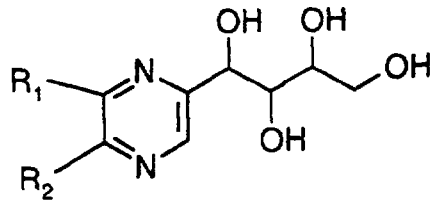
$$-CHOH-CHOH-CHOH-CH_2OH \qquad (B)$$

or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom and one or more excipients.

28. Use of a mixture I according to claim 1 or a mixture II according to claim 1 or sodium oxamate or one or more compounds of formula:

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(I)

in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:

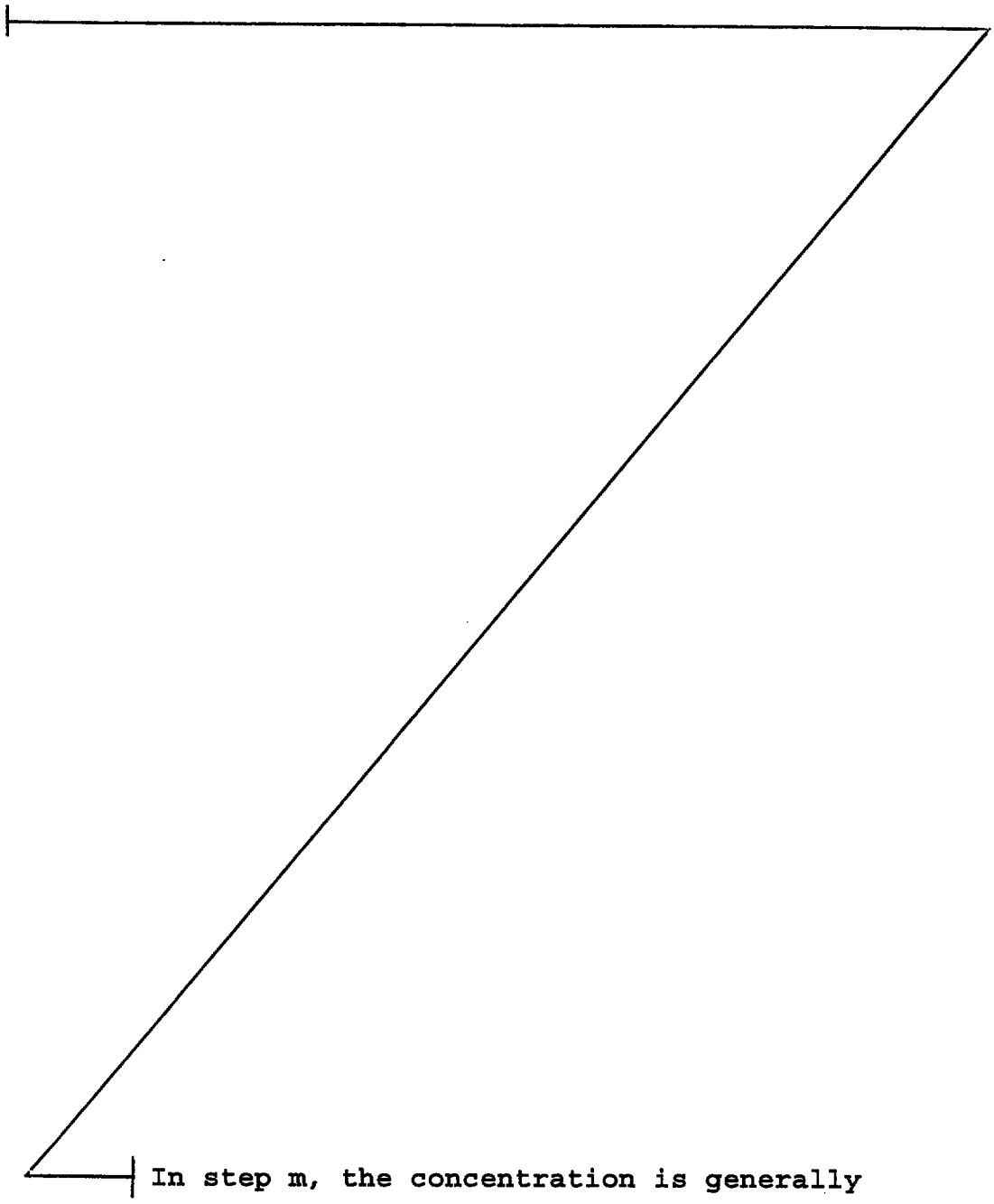
$-CH_2-CHOH-CHOH-CH_2OH$ (A)

$-CHOH-CHOH-CHOH-CH_2OH$ (B)

or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom for the preparation of a medicament for the prevention and treatment of diabetes and of the complications of diabetes.

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In step m, the concentration is generally carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa. It is also advantageous to carry out 3 successive ultrafiltrations on 10 kDA, 3 kDa and 1 kDa cartridges.

The present invention also relates to the process for preparing sodium oxamate and the compounds of formula (I).

The said process consists in subjecting the mixture II to the following operations:

o - chromatography of the mixture II on an infusorial earth column, recovery of the fractions containing the 4 products and pooling of these fractions into a single fraction,

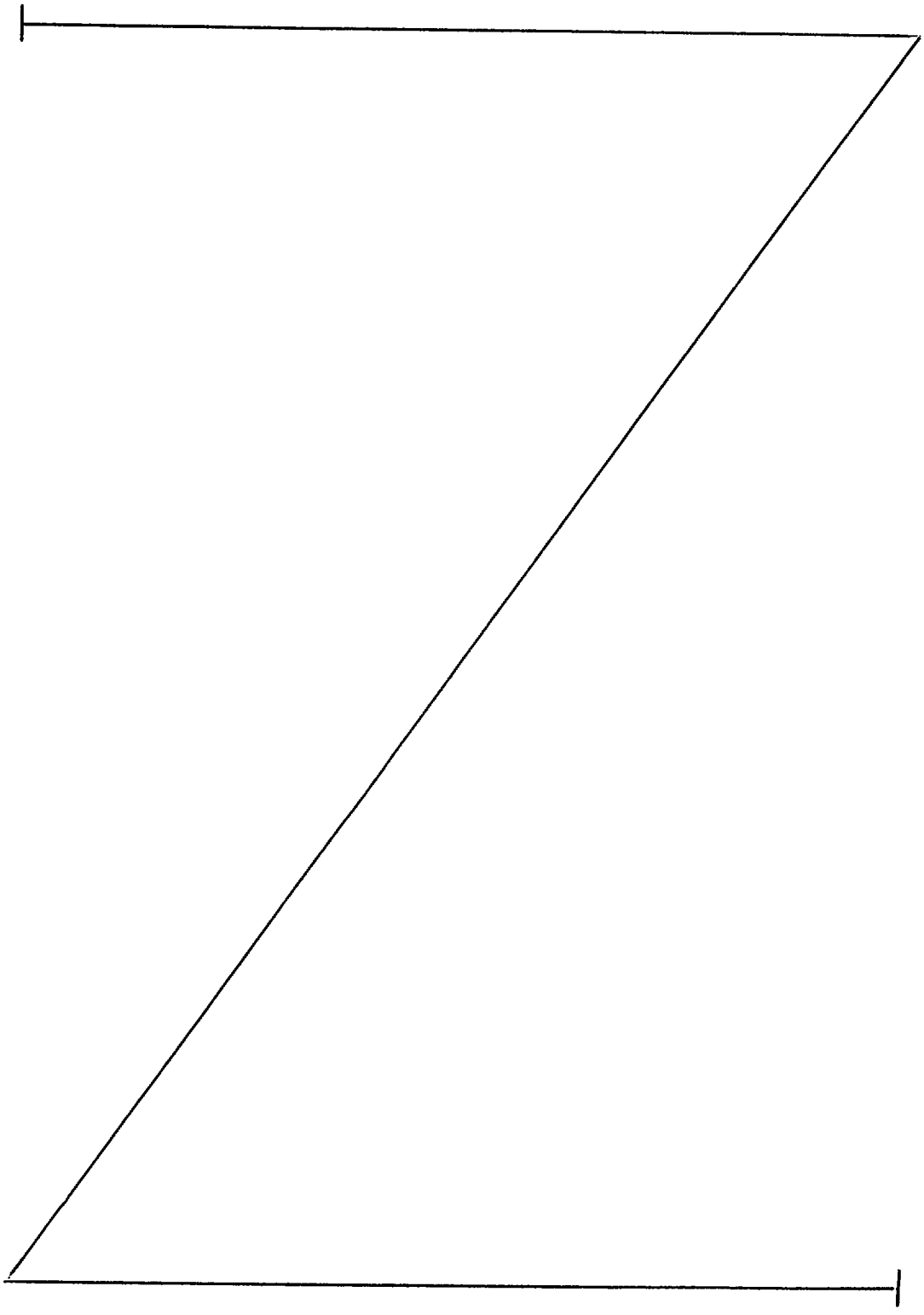
p - chromatography of the fraction previously obtained on a Sephadex® column in order to obtain sodium oxamate, the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (B) and a mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom,

q - optionally, chromatography of the mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom by HPLC.

The chromatography of step o is carried out by means of an organic solvent such as heptane, ethyl acetate or a lower aliphatic alcohol. Preferably, a CHEM ELUT® column marketed by Prolabo is used, saturated with water and then eluted successively with heptane, a heptane-ethyl acetate mixture (50/50 by volume), ethyl acetate, an ethyl acetate-n-butanol mixture (95/5; 90/10; 80/20; 50/50; 20/80), n-butanol,

and an n-butanol-water mixture (98/2 and then 95/5 by volume).

The chromatography of step p is preferably carried out by means of a water-ethanol mixture (50/50 by volume).



CLAIMS

1. Mixtures free of polyphenol and sterol derivatives and which can be isolated by grinding Eugenia Jambolana Lamarck seeds, maceration of the powder with a lower aliphatic alcohol with the use of heat, filtration, recovery of the insoluble part no longer containing polyphenol and sterol compounds, treatment of the insoluble part with an ammoniacal solution, treatment of the ammoniacal mixture with a lower aliphatic alcohol with the use of heat, filtration, recovery of the insoluble matter and drying this insoluble matter which constitutes the mixture I and optionally treatment of the mixture I with a water-lower aliphatic alcohol solution, filtration, partial concentration of the filtrate, purification on non-polar adsorbent resins, partial concentration, centrifugation, ultrafiltration and isolation of the mixture II.

2. Process for preparing the mixture I according to claim 1, characterized in that Eugenia Jambolana Lamarck seeds are dried, finely ground, screened and the powder obtained is subjected to the following treatment:

a - maceration, with stirring, in a lower aliphatic alcohol (1-4C), at a temperature of between 40 and 70°C,

b - filtration under vacuum and recovery of the insoluble matter,

c - maceration, with stirring, of the insoluble matter

with a lower aliphatic alcohol (1-4C) at a temperature of between 40 and 70°C,

d - filtration under vacuum and removal of the alcoholic phases containing mainly the undesirable polyphenols and sterols,

e - taking up the insoluble matter in an ammoniacal solution at a temperature of between 10 and 30°C,

f - taking up the whole wet ammoniacal mass in a water-lower aliphatic alcohol (1-4C) solution, at a temperature of between 40 and 70°C,

g - filtration and removal of the alcoholic solution,

h - washing of the insoluble matter with a lower aliphatic alcohol (1-4C), filtration and removal of the alcoholic solution,

i - recovery of the insoluble matter and drying the mixture I.

3. Process according to claim 2, for which, in step a, the procedure is carried out by means of 2 to 10 litres of a lower aliphatic alcohol per 1 kg of screened powder.

4. Process according to either of claims 2 and 3, for which, in step a, 5 litres of ethanol with a titre of 93-95° Gay Lussac are used at 60°C for 1 hour.

5. Process according to one of claims 2 to 4, for which the filtration of steps b and d are carried out under a vacuum of 40 kPa.

6. Process according to one of claims 2 to 5, for which, in step c, the procedure is carried out by means of 2 to 10 litres of a lower aliphatic alcohol

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per 1 kg of starting screened powder.

7. Process according to one of claims 2 to 6, for which, in step c, 4 litres of ethanol with a titre of 93-95° Gay Lussac are used at a temperature of 60°C for 1 hour.

8. Process according to one of claims 2 to 7, for which, in step e, 750 to 1250 ml of an aqueous ammoniacal solution are used per 1 kg of starting screened powder.

9. process according to one of claims 2 to 8, for which, in step e, per 1 kg of starting screened powder, 1 litre of aqueous ammoniacal solution containing 350 ml of 28% ammonium hydroxide is used and the procedure is carried out at a temperature close to 20°C for 10 to 30 hours hours.

10. Process according to one of claims 2 to 9, for which, in step f, the wet ammoniacal mass obtained from 1 kg of starting screened powder is taken up in 2 to 10 litres of a water-lower aliphatic alcohol solution.

11. Process according to one of claims 2 to 10, for which, in step f, the procedure is carried out in 5 litres of an ethanol-water mixture (75/25 by volume), at 60°C for 1 hour.

12. Process according to one of claims 2 to 11, for which, in step h, the washing is carried out with 500 to 1500 ml of a lower aliphatic alcohol per 1 kg of starting screened powder.

13. Process according to one of claims 2 to

12, for which, in step h, the washing is carried out with 1 litre of ethanol and the filtration is carried out on a cotton cloth and under a vacuum of about 80 kPa.

14. Process according to one of claims 2 to 12, for which, in step i, the drying is carried out in the open air and protected from light.

15. Process for preparing the mixture II according to claim 1, for which the mixture I according to claim 1 is subjected to the following operations:

j - treatment of the mixture I according to claim 1 by means of a water-lower aliphatic alcohol (1-4C) solution,

k - decantation and then, on the one hand, drawing off the top phase which is filtered to give the filtrate 1 and, on the other hand, treating the bottom phase with water and filtration to give the filtrate 2, pooling of the filtrates 1 and 2 and concentration to aqueous phase,

l - treatment with a nonpolar adsorbent resin and then filtration,

m - concentration of the filtrate, filtration and then ultrafiltration,

n - freeze-drying and isolation of the extract II.

16. Process according to claim 15, for which, in step j, 10 to 25 litres of the water-lower aliphatic alcohol solution (95/5 to 90/10 by volume) are used per 1 kg of the mixture I.

17. Process according to either of claims 15

and 16, for which, in step j, 18 litres of a water-ethanol solution (17.7-0.93 by volume) are used.

18. Process according to one of claims 15 to 17, for which, in step k, the top phase is filtered on a cotton cloth and 10 to 25 litres of water are added to the bottom phase per 1 kg of the mixture I and the mixture is filtered on sintered glass.

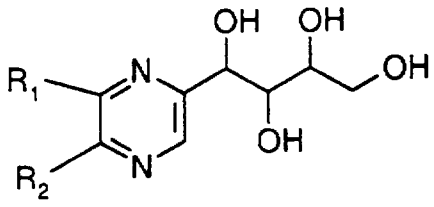
19. Process according to one of claims 15 to 18, for which, in step k, the concentration is generally carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa.

20. Process according to one of claims 15 to 19, for which, in step l, S861 resin or XAD-type resins marketed by Rhom and Hass are used and the mixture is filtered on sintered glass.

21. Process according to one of claims 15 to 20, for which, in step m, the concentration is carried out in a thermosiphon concentrator at a temperature of 35°C under a vacuum of 0.4 kPa.

22. Process according to one of claims 15 to 21, for which, in step m, 3 successive ultrafiltrations are carried out on 10 kDa, 3 kDa and 1 kDa cartridges.

23. Process for preparing sodium oxamate and the compounds of formula:



(I)

in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:



$$-CH_2-CHOH-CHOH-CH_2OH \quad (A)$$

$$-CHOH-CHOH-CHOH-CH_2OH \quad (B)$$

or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom for which the mixture II according to claim 1 is subjected to the following operations:

o - chromatography of the mixture II according to the invention on an infusorial earth column, recovery of the fractions containing the 4 products and pooling of these fractions into a single fraction,

p - chromatography of the fraction previously obtained on a Sephadex® column in order to obtain sodium oxamate, the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (B) and a mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom,

q - optionally, chromatography of the mixture of the compound of formula (I) for which R_1 represents a hydrogen atom and R_2 represents a residue (A) and of the compound of formula (I) for which R_1 represents a residue (A) and R_2 represents a hydrogen atom by HPLC.

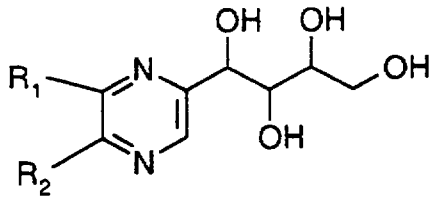
24. Process according to claim 23, for which

the chromatography of step o is carried out on a CHEM ELUT® column marketed by Prolabo, saturated with water and then eluted successively with heptane, a heptane-ethyl acetate mixture (50/50 by volume), an ethyl acetate-n-butanol mixture (95/5; 90/10; 80/20; 50/50; 20/80 and then 0/100 by volume) and an n-butanol-water mixture (98/2 and then 95/5 by volume).

25. Process according to claim 24, for which the chromatography of step p is carried out by means of a water-ethanol mixture (50/50 by volume).

26. Process according to claim 24, for which the chromatography of step q is carried out on a YMC 180DS-AQ column marketed by AIT with, as eluent, a water containing 0.1% of formic acid mixture.

27. Medicaments characterized in that they contain, as active ingredient, a mixture I according to claim 1 or a mixture II according to claim 1 or sodium oxamate or one or more compounds of formula:



(I)

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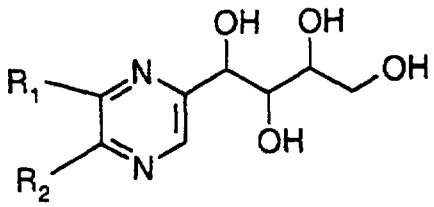
in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:

$-CH_2-CHOH-CHOH-CH_2OH$ (A)

$-CHOH-CHOH-CHOH-CH_2OH$ (B)

or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom and one or more excipients.

28. Use of a mixture I according to claim 1 or a mixture II according to claim 1 or sodium oxamate or one or more compounds of formula:



(I)

in which either R_1 represents a hydrogen atom and R_2 represents a chain of formula:

$-CH_2-CHOH-CHOH-CH_2OH$ (A)

$-CHOH-CHOH-CHOH-CH_2OH$ (B)

or R_1 represents a chain of formula (A) and R_2 represents a hydrogen atom for the preparation of a medicament for the prevention and treatment of diabetes and of the complications of diabetes.

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(54) Title: MIXTURES DERIVED FROM GRAINS OF EUGENIA JAMBOLANA LAMARCK, PREPARATION AND USE OF SAID MIXTURES AND SOME OF THEIR CONSTITUENTS AS MEDICAMENTS

(54) Titre: MELANGES ISOLABLES A PARTIR DE GRAINES D'EUGENIA JAMBOLANA LAMARCK, LEUR PREPARATION ET L'UTILISATION DE CES MELANGES ET CERTAINS DE LEURS CONSTITUANTS COMME MEDICAMENTS

(57) Abstract

The present invention relates to mixtures which can be isolated from grains of Eugenia Jambolana Lamarck, the preparation of such mixtures, the medicaments containing said mixtures or constituents of said mixtures, and the use of these mixtures and constituents for the preparation of a medicament.

(57) Abrégé

La présente invention concerne des mélanges isolables à partir de graines d'Eugénia Jambolana Lamarck, leur préparation, les médicaments contenant ces mélanges ou des constituants de ces mélanges et l'utilisation de ces mélanges et constituants pour la préparation d'un médicament.

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