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(54) Titre : EXTRAITS DE CYNARA SCOLYMUS DESTINES AU TRAITEMENT DE LA DYSLIPIDEMIE, L'HYPERGLYCEMIE, L'HYPERCHOLESTEROLEMIE, L'HYPERTENSION OU LA STEATOSE HEPATIQUE

(54) Title: CYNARA SCOLYMUS EXTRACTS FOR THE TREATMENT OF DYSLIPIDAEMIA, HYPERGLYCAEMIA, HYPERCHOLESTEROLAEMIA, HYPERTENSION OR HEPATIC STEATOSIS

(57) Abrégé/Abstract:
The present invention relates to the preparation of Cynara scolymus leaf extracts, which are useful for the prevention and treatment of dyslipidaemia, in particular to increase HDL cholesterol in patients at cardiovascular risk. Said extracts are useful to normalise the lipid and carbohydrate balances and significantly increase the value of HDL cholesterol by favourably changing the LDL/HDL ratio, especially in post-infarction patients with drug-induced dyslipidaemia.

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(54) **Title**: CYNARA SCOLYMUS EXTRACTS FOR THE TREATMENT OF DYSLIPIDAEMIA

(57) **Abstract**: The present invention relates to the preparation of Cynara scolymus leaf extracts, which are useful for the prevention and treatment of dyslipidaemia, in particular to increase HDL cholesterol in patients at cardiovascular risk. Said extracts are useful to normalise the lipid and carbohydrate balances and significantly increase the value of HDL cholesterol by favourably changing the LDL/HDL ratio, especially in post-infarction patients with drug-induced dyslipidaemia.

CYNARA SCOLYMUS EXTRACTS FOR THE TREATMENT OF DYSLIPIDAEMIA, HYPERGLYCAEMIA, HYPERCHOLESTEROLAEMIA, HYPERTENSION OR HEPATIC STEATOSIS.

Summary of the invention

The present invention relates to the preparation of a novel extract of *Cynara scolymus* with a high content of flavonoids and sesquiterpenes, produced from the leaves of selected cultivars. The extracts of the invention increase the HDL cholesterol and are useful in the treatment of dyslipidaemia in patients at cardiovascular risk. As well as normalising the lipid and carbohydrate balance, the extracts of the invention are also useful to regulate dyspepsia and non-alcoholic liver steatosis. In particular, the extracts have provided to increase the HDL cholesterol value significantly in patients with below-average parametric values, by favourably changing the LDL/HDL ratio.

The present invention also relates to an extract of the leaves of *Cynara* species varieties having a caffeoylquinic acid content of 30 to 45%, a flavonoid content of 8 to 16% and a cynaropicrin content of 10 to 18%.

The present invention also relates to a pharmaceutical composition containing the extract as defined herein as the active ingredient, in admixture with at least one excipient or carrier.

The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for the treatment of hyperglycaemia, hypercholesterolaemia, hypertension or hepatic steatosis in a patient in need thereof.

The present invention also relates to a use of the extract as defined herein

or the composition as defined herein, for the preparation of a medicament for the treatment of hyperglycaemia, hypercholesterolaemia, hypertension or hepatic steatosis in a patient in need thereof.

The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for increasing HDL cholesterol in a patient in need thereof.

The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for the preparation of a medicament for increasing HDL cholesterol in a patient in need thereof.

The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for the treatment of metabolic syndrome in a patient at cardiovascular risk.

The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for the preparation of a medicament for the treatment of metabolic syndrome in a patient at cardiovascular risk.

The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for the treatment of dyslipidaemia in a patient at cardiovascular risk.

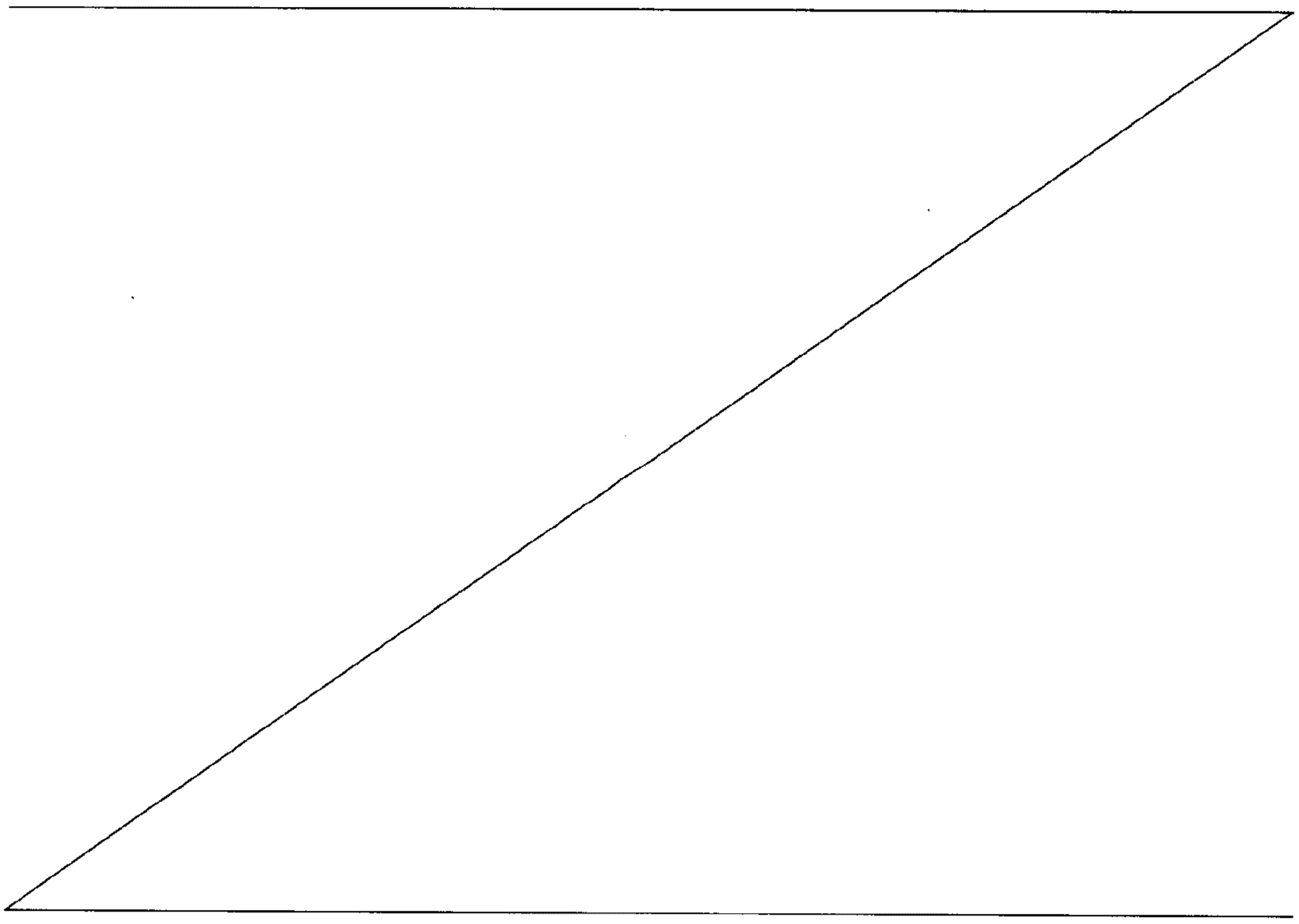
The present invention also relates to a use of the extract as defined herein or the composition as defined herein, for the preparation of a medicament for the treatment of dyslipidaemia in a patient at cardiovascular risk.

Prior art

Globe artichoke (*Cynara scolymus*) extracts are known for their choleretic,

cholagogic, anti-dyspepsia and mildly cholesterol-reducing action; the cholesterol reduction is modest (not more than approx. 10%). The published studies differ in terms of quality of protocols and composition of the extracts used.

Obtaining *Cynara scolymus* extracts presents major problems of reproducibility, because the active ingredient content is not uniform from preparation to preparation. Evaluating the therapeutic activity of the extracts is therefore problematic, and comparisons with other known drugs are difficult, if not impossible. The low reproducibility of the extracts is due to a number of factors, such as the choice of the plant biomass and the conditions used in drying and in the extraction process. The production of the biomass is critical because the drying conditions, which are essential to maintain the active ingredient content, depend on the growing period of the plant.



The active components of artichoke extracts are caffeoylquinic acids, which perform a choleretic, blood-sugar reducing and liver-protecting effect; flavonoids, which perform a hypolipaemic action associated with cholesterol synthesis, and cynaropicrin, which performs an anti-inflammatory action due to interaction with nuclear factor NFkB and TNF-α.

Description of the invention

It has now been found that an extract with an active ingredient content that guarantees marked, constant therapeutic activity can be obtained from the leaves of selected artichoke cultivars. It has also been found that the cynaropicrin present in the extract of the invention also acts at hepatic level on the enzymes that regulate HDL biosynthesis.

Young leaves of the selected artichoke cultivar, preferably *Cynara scolymus* or *Cynara carduncolus,* preferably *Cynara scolymus*, are used to prepare the extract of the invention. It is preferable to use the leaves about a month after the germination of the seeds or after transplanting the seedlings. The *Cynara* species are preferably produced using organic agriculture techniques, avoiding the use of pesticides and monitoring their absence in the growing medium, as pesticide removal would be impossible without simultaneously prejudicing the content of active lipophilic ingredients responsible for modulating the formation of HDL lipoproteins.

A particularly preferred variety of artichoke is the spiny purple variety of *Cynara scolymus*. A plant biomass, easily dried at temperatures of between 60 and 100°C, preferably 80°C, is obtained from the plant, grown to a foliage height of 20 cm.

The selected cultivar must preferably have a 3.8% content of caffeoylquinic acids, 1.5% luteolin flavonoids and 3% cynaropicrin. After drying, the biomass is extracted by known methods, described, for example, in WO 2007/006391 and WO 2008/107183.

The extracts obtained have a caffeoylquinic acid content of between 30 and 45%, preferably 35 ± 2%, a flavonoid content of 8 to 16%, preferably 12 ± 2%, and a cynaropicrin content of 10 to 18%, preferably 13 ± 2%.

Said extracts have demonstrated an unexpected activity in reducing total cholesterol, LDL cholesterol and blood glucose, and increasing cHDL. More specifically, the extract significantly reduces the fasting blood glucose, total cholesterol and LDL cholesterol levels by 20%, increases diuresis, thus helping to reduce the blood pressure, and contributes to reducing liver steatosis.

In particular, it should be emphasised that an unexpectedly high increase in HDL cholesterol is observed in both hyperlipaemic individuals and those with below-normal HDL cholesterol resulting from statin treatment or cholesterol-lowering drugs. Modest, erratic increases in HDL cholesterol following the administration of *Cynara scolymus* extracts have been reported in the literature, but without any evidence of reproducibility or consistency. In fact, these studies (Naturmed, 13, 17-24,1998, Arzneim - Forschung, 50, 260-65, 2000, The Cochrane Library, 2002, Issue 3) report contradictory data of low practical relevance.

Conversely, experimentation with the compositions of the invention indicates a reduction of approx. 20% in total cholesterol and LDL cholesterol, and a significant increase of 19% in HDL cholesterol. This increase, which was found to be constant over time on a case study of patients with total cholesterol ranging from 200 to 280 mg/dl, is not observed with known herbal preparations.

The extract of the invention has also proved effective on various parameters in patients suffering from metabolic syndrome, where normalisation of parameters such as blood glucose, lipid parameters and hypertension was observed.

The extracts of the invention will be formulated in suitable administration forms such as capsules or normal or gastroprotected tablets.

The preferred carriers are oils rich in ω-3 fatty acids which facilitate absorption of the cynaropicrin present in the extract.

According to a further aspect, the compositions of the invention may be administered in combination with other substances having a useful or complementary activity.

The compositions of the invention will be formulated according to conventional methods, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA. In particular, the compositions of the invention will be formulated according to conventional plant ingredient formulation techniques, which require particular care to be taken to avoid interactions with the excipients and the capsule matrices. Examples of oral formulations are tablets, dragées, soft and hard gelatin capsules, and cellulose capsules. The average dose corresponds to 100-500 mg of extract one to three times a day.

The following examples illustrate the invention in greater detail.

Example 1 - Cellulose capsules suitable to contain oils

Unit composition:

Cynara scolymus extract	200 mg
Glyceryl monostearate	10 mg
Linseed oil	q.s. for 800 mg
Soya lecithin	10 mg

Example 2 - Soft gelatin capsules

Unit composition:

Cynara scolymus extract	300 mg
Glyceryl monostearate	10 mg
Linseed oil	q.s. for 700 mg
Soya lecithin	10 mg

Example 3 - Tablets

Unit composition:

Cynara scolymus extract	200 mg
Microcrystalline cellulose	300 mg
Lactose	190 mg
Silicon dioxide	5 mg
Magnesium stearate	5 mg

CLAIMS

1. An extract of the leaves of *Cynara* species varieties having a caffeoylquinic acid content of 30 to 45%, a flavonoid content of 8 to 16% and a cynaropicrin content of 10 to 18%.

2. The extract according to claim 1, wherein the caffeoylquinic acid content is 35 ± 2%, the flavonoid content is 12 ± 2% and the cynaropicrin content is 13 ± 2%.

3. The extract according to claim 1 or 2, obtained from young leaves of *Cynara scolymus* or *Cynara carduncolus* cultivars.

4. The extract according to claim 3, obtained from *Cynara scolymus* cultivars.

5. The extract according to claim 4, wherein the cultivar is the spiny purple variety.

6. The extract according to any one of claims 1 to 5 for use in the pharmacological treatment of hyperglycaemia, hypercholesterolaemia, hypertension or hepatic steatosis.

7. The extract according to any one of claims 1 to 5 for use to increase HDL cholesterol.

8. A pharmaceutical composition containing the extract as defined in any one of claims 1 to 5 as the active ingredient, in admixture with at least one excipient or carrier.

9. The composition according to claim 8, wherein the carrier is an oil comprising omega-3 unsaturated fatty acids.

10. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the treatment of hyperglycaemia, hypercholesterolaemia, hypertension or hepatic steatosis in a patient in need thereof.

11. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the preparation of a medicament for the treatment of hyperglycaemia, hypercholesterolaemia, hypertension or hepatic steatosis in a patient in need thereof.

12. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for increasing HDL cholesterol in a patient in need thereof.

13. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the preparation of a medicament for increasing HDL cholesterol in a patient in need thereof.

14. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the treatment of metabolic syndrome in a patient at cardiovascular risk.

15. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the preparation of a medicament for the treatment of metabolic syndrome in a patient at cardiovascular risk.

16. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the treatment of dyslipidaemia in a patient at cardiovascular risk.

17. Use of the extract as defined in any one of claims 1 to 5 or the composition as defined in claim 8 or 9, for the preparation of a medicament for the treatment of dyslipidaemia in a patient at cardiovascular risk.