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(54) **Title:** ANTIOXIDANT COMPOSITION COMPRISING PROPIONYL L–CARNITINE AND A FLAVONOID AGAINST THROMBOSIS AND ATHEROSCLEROSIS

(57) **Abstract**

A composition is disclosed which comprises as characterizing active ingredients propionyl L–carnitine and a flavonoid, typically quercetin or its 3–rutinoside, rutin, for the prevention and/or therapeutic treatment of various alterations and pathological states induced by free radicals and by thrombotic or atherosclerotic abnormalities, that may take the form of a dietary supplement, dietetic support or of an actual medicine.

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ANTIOXIDANT COMPOSITION COMPRISING PROPIONYL L-CARNITINE AND A FLAVONOID AGAINST THROMBOSIS AND ATHEROSCLEROSIS

The present invention relates to a composition for the prevention and/or treatment of thrombotic or atherosclerotic abnormalities, allergic inflammatory reactions, diseases brought about by the release of free radicals and by increased platelet aggregation.

Accordingly, the composition may take the form and exert the action of a dietary supplement or of an actual medicine, depending upon the support or preventive action, or the strictly therapeutic action, which the composition is intended to exert in relation to the particular individuals it is to be used in.

More particularly the present invention relates to an orally, parenterally, rectally, cutaneously or transdermally administrable composition which comprises in combination:

(a) propionyl L-carnitine or a pharmacologically acceptable salt thereof, possibly in combination with another "carnitine", where what is meant by "carnitine" is L-carnitine or an alkanoyl L-carnitine selected from the group comprising acetyl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or their pharmacologically acceptable salts; and

(b) a flavonoid, preferably selected from the group comprising quercetin, rutin, myricetin, myricitrin or mixtures thereof or extracts of natural vegetable products containing such flavonoids.

Here below, for the sake of brevity and simplicity of presentation, reference will be made only to quercetin as an example of a flavonoid, it being understood that the description applies equally to the other flavonoids mentioned in the present invention.

Quercetin is a naturally occurring product belonging to the group of the polyphenolic flavonoids and is present in many vegetable and plant foods such as apples, garlic, grapes and wine, hazel nuts and tea-

leaves.

Quercetin is most often present in its conjugate form with glucose as glucoside or as 3-rutinoside (rutin), forms which are capable of conditioning its intestinal absorption after ingestion into the body with food. Apples contain various quercetin glucosides, including galactosides, xylosides, arabinosides, rhamnosides and glycosides. Tea-leaves contain mainly quercetin rutinosides, whereas the quercetin derivatives contained in garlic are mainly glycosides.

In grapes and wine, on the other hand, quercetin is found both as glycoside and as aglycone.

Quercetin belongs to the group of flavonoids that recent epidemiological studies have recognised as one of the dietary factors mainly responsible for the reduced mortality due to cardiovascular accidents in populations on a Mediterranean diet or on a diet rich in vegetable or plant substances and drinks such as wine and tea,

Studies carried out analysing the "French Paradox" phenomenon, i.e. the low mortality due to cardiovascular accidents in populations on a high-calorie diet rich in proteins and lipids, have identified olive oil, and, even more so, red wine, as the dietary factors capable of accounting for this apparent contradiction. Red wine, in fact, is rich in polyphenols endowed with a substantial antioxidant activity, particularly quercetin, myricectin, resveratrol and catechins.

Since the oxidation of LDLs plays an important role in the pathogenesis of atherosclerosis, the acknowledged antiatherogenic and vascular protective effects of red wine have been attributed to the presence of these polyphenols.

In particular, quercetin has been shown to inhibit not only LDL oxidation, but also LDL aggregation, which represents an additional modification of lipoproteins.

Recently, it has been found that extensive oxidation of LDLs leads to their aggregation and that both these modified forms of LDL are present in atherosclerotic lesions.

The antioxidant activity of quercetin and its protective activity against the production of free radicals have also been confirmed by tests conducted on Fe^{2+}-dependent lipoperoxidation and on rat liver microsomes exposed to CCl_4.

Another important activity of quercetin, and one which may explain its cardio-protective activity, is its ability to affect in platelet aggregation. Quercetin, in fact, is capable of inhibiting platelet aggregation induced by thrombin or ADP as well as being capable of inhibiting platelet thromboxane synthesis and the synthesis of eicosanoids such as 12-HETE.

The inhibitory effect on platelet aggregation, and also on cyclic-AMP phosphodiasterase, may be due to its inhibition of the intracellular influx of calcium ions.

Tests on the vasorelaxant activity of quercetin, measured on the isolated aorta, have also demonstrated its ability to act as a vasodilator via enhanced nitric oxide synthesis.

To complete the pharmacological profile of quercetin, we should also recall its inhibitory activity on lipoperoxygenase and cyclo-oxygenase and their consequent allergic and inflammatory reactions, as well as its ability to potentiate prostacyclin with consequent cytoprotective and anti-inflammatory effects.

Another important characteristic of quercetin is that it is a selective inhibitor of tyrosine protein kinase and of activation of the nuclear transduction factor NFK-IKB, and thus, via this pathway, inhibits the formation of prostaglandins and cytokines as well as inhibiting tumour growth.

Numerous research studies, in fact, indicate that quercetin is capable of inhibiting the growth of leukaemic cells and the development of lung or breast tumours.

It has been demonstrated that quercetin is, in fact, a potent inhibitor of PI-kinase (1-phosphatidylinositol-4-kinase) and of PIP-kinase (phosphatidylinositol-4-phosphate-5-kinase) with consequent reduction of the second transduction messenger of the signal represented by IP3 (inositol-1,4,5-triphosphate), and its ability to inhibit tumour growth may be explained by this mechanism. Moreover, its ability to inhibit oestrone sulphatase may also be a further factor in explaining its ability to curb oestrogen-dependent tumour growth.

L-carnitine and its alkanoyl derivatives also play an important biological role in both the nutritional and therapeutic fields.

A deficiency of L-carnitine in the diet, as may occur in some cases in children, may slow down growth, which can be restored to normal by the administration of L-carnitine.

An L-carnitine deficiency in the body may lead to clinical syndromes of systemic type or syndromes confined to the myocardial or skeletal muscle systems. Among all the tissues of the body, the muscles and heart have the highest L-carnitine concentrations, which takes on very considerable physiological significance if we consider that the heart, above all, is strongly dependent for its energy requirements on the beta-oxidation of fatty acids, a process related to the presence of L-carnitine. In addition to its role as a carrier of long-chain fatty acids across the mitochondrial membrane, L-carnitine also plays an important role in blocking long-chain metabolites of acyl-CoA which may accumulate during states of tissue ischaemia and damage the sarcolemma in the muscles. It is also well known that an eccess of fatty acids during reperfusion may potentiate myocardial ischaemic damage.

L-carnitine and its alkanoyl derivates, in addition to playing a major role in the beta-oxidation of fats and in the energy production of ATP, are also capable of acting in energy production both in terms of glucose utilisation and in terms of the utilisation of branched-chain amino acids.

In the explanation of the complex pharmacological and therapeutic profile of the "carnitines", we must bear in mind not only their energy characteristics but also the data indicating their effective antioxidant action, as demonstrated by their protective effect against the lipoperoxidation of the cell phospholipid membranes as well as against the oxidative damage induced at myocardial or endothelial cell level.

It has now surprisingly been found that a composition containing a combination of the following as its characterising components:
(a) propionyl L-carnitine or a pharmacologically acceptable salt thereof, and
(b) a flavonoid selected from the group comprising quercetin, rutin, myricetin, myricitrin or mixtures thesereof,
is extremely effective in preventing and/or treating damage induced by the presence of free radicals and by increased platelet aggregation, as well as thrombotic or atherosclerotic abnormalities and allergic inflammatory reactions, as a result of the potent synergistic effect exerted by its components.

It has also been found that, advantageously, component (a) may further comprise of a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or a pharmacologically acceptable salt thereof, and that component (b) may consist of an extract of vegetable or plant products containing it.

The (a):(b) weight-to-weight ratio ranges fron 1:0.1 to 1:10.

The potent synergistic effect of the aforesaid components (a) and (b) has been ascertained by means of various pharmacological tests, some of which are reported here below.

Toxicology

It is well known that both L-carnitine and its derivatives are characterised by low toxicity and excellent tolerability. Quercetin, too, like other naturally occurring polyphenols, presents very favourable toxicity and tolerability characteristics.

The tests performed combining the various "carnitines" with quercetin have confirmed the acknowledged good toxicity and tolerability characteristics of these compounds.

In tests performed in the rat, it proved possible to administer orally in a single adminstration up to 4 g/kg of propionyl L-carnitine or the same amount of a combination of acetyl L-carnitine, propionyl L-carnitine and isolvaleryl L-carnitine in a 1:1:1 weight-to-weight ratio without any signs of toxicity being observed. Similarly, no signs of toxicity were observed with the administration of a 1 g/kg dose of quercetin.

Similar favourable results were obtained with the administration of a combination of propionyl L-carnitine or carnitine mixture plus quercetin at the same doses indicated above. Even the prolonged administration of 1 g/kg of propionyl L-carnitine or the same amount of carnitine mixture in combination with 100 mg/kg of quercetin in rats for thirty days consecutively with the diet was well tolerated and led to no detectable toxic abnormalities in the animals thus treated.

The blood cell counts and tests for various biochemical parameters (serum glucose, BUN, cholesterol, triglycerides) revealed no abnormalities worthy of note as compared to control animals, and the histological examination carried out on the main organs (liver, kidneys, heart, lungs, brain) also failed to detect any pathological abnormalities,

thus confirming the low toxicity and good tolerability of the new combination assessed in these tests as well.

Platelet aggregation tests

Blood samples taken from healthy volunteers were used for these tests.

The blood samples were treated with sodium citrate and centrifuged for 8 minutes at 100 rpm. The number of platelets was counted and brought to a fixed level of 300,000 platelets/ml by adding platelet poor plasma (PPP) where necessary.

Platelet aggregation was induced using collagen (2,5 μg/ml, 5 μg/ml) as the aggregating agent and determined photometrically according to the method described by Born (Born G.V.R., Nature, 194, 927, 1962).

Platelet aggregation was measured in baseline conditions and after 10 minutes' incubation with quercetin or propionyl L-carnitine or with a combination of quercetin and propionyl L-carnitine in the same amounts.

The propionyl L-carnitine doses were 10 μg and 20 μg/ml, while the quercetin doses were 0.1 μg and 0.25 μg/ml. Whereas propionyl L-carnitine did not prove capable of modifying the platelet aggregating action induced by collagen, quercetin at the doses used (0.25 μg) reduced it by 50%, but the inhibition reached 100% when quercetin was combined with propionyl L-carnitine, thus demonstrating the potent synergistic effect which propioyl L-carnitine and quercetin are capable of exerting when used in combination.

Antiatherosclerotic activity tests

In these tests, experimental atherosclerosis was induced in rabbits by administering 0.5% of cholesterol by weight together with the standard diet. New Zealand rabbits with a mean body weight of 2.8 kg were used

in these tests and received, together with the cholesterol-enriched diet, 400 mg/kg of propionyl L-carnitine, or 400 mg/kg of carnitine mixture (propionyl L-carnitine, acetyl L-carnitine and isovaleryl L-carnitine in a 1:1:1 weight-to-weight ratio), or 50 mg/kg of quercetin, or various combinations of these products.

After thirty days' treatment, a blood sample was taken from the central artery of the ear in each animal and used to assay the lipoproteins present according to the method described by Hatch (Hatch F.T., Advan. Lipid Res., 6, 1, 1968).

The liver was then removed from each animal and used to assay total cholesterol and triglycerides according to the method of Dehoff (Dehoff J.L., Clin. Chem., 24, 433, 1978) and Levy (Levy A., Advances in Automated Analysis, 497 - Thurman - Miami, 1972). Arteriosclerotic lesions at the level of the heart and aorta were assessed according to the Klurfield method (Klurfield D.M., J. Med., 10, 35, 1979), grading them from I to IV according to the severity of the damage detected.

The results of these tests show that both propionyl L-carnitine and the carnitine mixture are capable of reducing both the biochemical and histological parameters of experimentally induced atherosclerosis in the rabbit.

Quercetin, too, shows good inhibitory activity. The greatest degree of protective activity, however, is that achieved when carnitine and quercetin are administered in combination. In this case, in fact, the atherosclerotic lesions either do not occur at all or are only minimally detectable.

These tests, too, demonstrate the potent synergistic effect that can be achieved by the combination of carnitines, and particularly propionyl L-carnitine, plus quercetin.

Table 1

Plasma lipoprotein concentrations in hypercholesterolaemic rabbits

	VLDL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
Hypercholesterolaemic controls	1,220 ± 33.2	468 ± 22.8	25.2 ± 4.1
Propionyl L-carnitine (400 mg/kg)	855 ± 32.5	380 ± 21.5	26.4 ± 3.9
Carnitine mixture (400 mg/kg)	910 ± 41.8	345 ± 20.8	29.5 ± 4.4
Quercetin (50 mg/kg)	816 ± 37.5	298 ± 30.1	28.6 ± 3.8
Propionyl L-carnitine (400 mg/kg) + Quercetin (50 mg/kg)	318 ± 15.6	175 ± 20.2	30.8 ± 2.8
Carnitine mixture (400 mg/kg) + Quercetin (50 mg/kg)	378 ± 20.6	111 ± 10.2	31.1 ± 3.1

Table 2

Liver concentrations of total cholesterol and triglycerides in hypercholesterolaemic rabbits

	Total cholesterol (100 mg/g)	Triglycerides (mg/g)
Hypercholesterolaemic controls	1,915 ± 220	190 ± 16.3
Propionyl L-carnitine (400 mg/kg)	1,470 ± 310	165 ± 14.5
Carnitine mixture (400 mg/kg)	1,495 ± 355	145 ± 15.9
Quercetin (50 mg/kg)	1,320 ± 230	130 ± 14.5
Propionyl L-carnitine (400 mg/kg) + Quercetin (50 mg/kg)	720 ± 65	105 ± 9.62
Carnitine mixture (400 mg/kg) + Quercetin (50 mg/kg)	795 ± 72	115 ± 11.2

Anti-inflammatory activity tests

To assess the anti-inflammatory activity of the combination of propionyl L-carnitine or carnitine mixture plus quercetin, its inhibitory effect on oedema induced in the rat paw by subplantar injection of carrageenin was evaluated.

To this end, 0.1 cc of a 1% carrageenin solution (Sigma, St, Louis, USA) were injected in the subplantar zone of the rat paw. The volume of oedema of the paw was measured by means of a mercury plethysmograph at intervals of one hour over the four-hour period following injection of carrageenin. One hour prior to injection of carrageenin the animals received oral administrations either of propionyl L-carnitine (300 mg/kg and 150 mg/kg), or carnitine mixture (acetyl L-carnitine, propionyl L-carnitine, isovaleryl L-carnitine; 300 mg/kg and 150 mg/kg), or quercetin (100 mg/kg and 50 mg/kg), or various combinations of these compounds. The results of these tests indicate that whereas propionyl L-carnitine has a modest anti-oedema effect, as does quercetin, when propionyl L-carnitine or the carnitine mixture is combined with quercetin the anti-inflammatory effect becomes very marked, thus demonstrating, in this case, too, that a potent synergistic effect of quercetin and carnitines is achieved.

Table 3

Anti-inflammatory activity tests

Treatment	mg/kg	% reduction of carrageenin-induced oedema after			
		1	2	3	4 h
Propionyl L-carnitine	150	---	---	---	---
Propionyl L-carnitine	300	12 ± 0.1	10 ± 0.2	6 ± 0.5	---
Carnitine mixture	150	---	---	---	---
Carnitine mixture	300	---	12 ± 0.3	5 ± 0.7	---
Quercetin	50	8 ± 0.6	10 ± 0.2	---	---
Quercetin	100	18 ± 1.2	22 ± 2.5	20 ± 1.9	18 ± 1.5
Propionyl L-carnitine + Quercetin	150 + 50	22 ± 2.4	26 ± 3.1	25 ± 2.5	20 ± 3.9
Carnitine mixture + Quercetin	150 + 50	20 ± 3.1	25 ± 2.9	20 ± 2.5	18 ± 3.1
Propionyl L-carnitine + Quercetin	300 + 100	36 ± 4.2	39 ± 4.2	34 ± 3.8	30 ± 2.9
Carnitine mixture + Quercetin	300 + 100	37 ± 3.9	35 ± 4.7	35 ± 4.1	32 ± 3.9

Anaphylactic shock tests

These tests were performed using male albino guinea-pigs with a mean weight of 300 g; the animals received intraperitoneal injections of 1 cc of horse serum diluted 1:10.

After twenty-five days, intravenous injection of 1 cc of horse serum triggered anaphylactic shock with onset of bronchospasm and death of the animals. Five days before the shock-triggering injection, the sensitised animals were treated orally either with propionyl L-carnitine (300 mg/kg), or with carnitine mixture (300 mg/kg), or with quercetin (50 mg/kg), or with various combinations of these compounds.

It was found that the administration of the combination of propionyl L-carnitine and quercetin and the combination of carnitine mixture and quercetin is capable of protecting more than half the treated animals against death by anaphylactic shock, whereas no protective effect is observed with administration of either propionyl L-carnitine or quercetin alone, thus demonstrating that in these tests, too, there was a potent synergistic effect between carnitines and quercetin.

Table 4

Protection against anaphylactic shock.

Treatment	Surviving/treated animals
Propionyl L-carnitine (300 mg/kg)	2/10
Carnitine mixture (300 mg/kg)	1/10
Quercetin (50 mg/kg)	3/10
Propionyl L-carnitine (300 mg/kg) + Quercetin (50 mg/kg)	6/10
Carnitine mixture (300 mg/kg) + Quercetin (50 mg/kg)	5/10

Tests on leukopenia induced by mitomycin C

To evaluate the immunostimulatory effect of the combination of propionyl L-carnitine or carnitine mixture plus quercetin, the effect of these products was evaluated on the toxic and immunosuppressive activity induced by mitomycin C.

Mitomycin C (50 μg/mouse) injected intraperitoneally in mice every day for five consecutive days causes severe leukopenia which then worsens progressively up to the death of the animals which occurs after approximately 12 days.

The oral administration of propionyl L-carnitine (300 mg/kg), or of carnitine mixture (300 mg/kg), or of quercetin (100 mg/kg), or of these substances in combination, from the first day of administration of mitomycin C up to day five, inhibits the reduction of leukocytes and increases the survival time of the animals thus treated.

The protective effect is modest with administration of propionyl L-carnitine, carnitine mixture or quercetin alone, but becomes very marked with the combinations of propionyl L-carnitine and carnitine mixture plus quercetin. The results of these tests again demonstrate a protective synergistic effect of the combination of propionyl L-carnitine plus quercetin, in this case against the immunosuppressive and toxic action of mitomycin C.

Table 5

Effect on leukopenia and survival time in mice treated with mitomycin C.

Treatment	Number of leukocytes after (days)			% Rats surviving after (days)		
	5	10	12	5	10	12
Mitomycin C	5,800 ± 250	3,200 ± 310	1.200 ± 220	60	35	20
Propionyl L-carnitine	6,000 ± 310	5,400 ± 280	2,100 ± 125	60	45	30
Carnitine mixture	6,200 ± 405	4,300 ± 340	2,200 ± 270	70	35	30
Quercetin	5,600 ± 480	4,800 ± 410	2,800 ± 310	70	30	30
Propionyl L-carnitine + Quercetin	7,100 ± 410	6,200 ± 370	6,100 ± 380	90	75	65
Carnitine mixture + Quercetin	6,800 ± 510	6,000 ± 420	5,800 ±480	80	80	60

Illustrative, non-limiting examples of compositions according to the invention are reported hereinbelow.

1)	Propionyl L-carnitine	mg	500
	Quercetin	mg	250
2)	Carnitine mixture (propionyl L-carnitine mg 125, acetyl L-carnitine mg 125, isovaleryl L-carnitine mg 125)	mg	375
	Quercetin	mg	125
3)	Propionyl L-carnitine	mg	250
	Quercetin	mg	125
4)	Carnitine mixture (propionyl L-carnitine mg 75, acetyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	225
	Quercetin	mg	125

5)	Propionyl L-carnitine	mg	125
	Quercetin	mg	125
	Citroflavonoids	mg	50
	Vit. C	mg	100
	Rutin	mg	20
	CoQ_{10}	mg	10
	Vit. E	mg	5
	β-carotene	mg	5
	Manganese glycinate	mg	5
	Zinc glycinate	mg	5
	Magnesium glycinate	mg	20
	Selenium methionine	μg	50
(6)	Carnitine mixture (propionyl L-carnitine mg 100, acetyl L-carnitine mg 100, isovaleryl L-carnitine mg 100)	mg	300
	Quercetin	mg	150
	Citroflavonoids	mg	50
	Vit. C	mg	100
	Rutin	mg	20
	CoQ_{10}	mg	10
	Vit. E	mg	5
	β-carotene	mg	5
	Manganese glycinate	mg	5
	Zinc glycinate	mg	5
	Magnesium glycinate	mg	20
	Selenium methionine	μg	50

What is meant by pharmacologically acceptable salt of L-carnitine or alkanoyl L-carnitine is any salt of these active ingredients with an acid that does not give rise to unwanted toxic or side effects. These acids are well known to pharmacy experts.

Non-limiting examples of suitable salts are the following: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate; acid fumarate;

glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; orotate; oxalate, acid oxalate; sulphate, acid sulphate, trichloroacetate, trifluoroacetate and methanesulphonate.

A list of FDA-approved pharmacologically acceptable salts is given in Int. J. of Pharm. 33, (1986), 201-217; this latter publication is incorporated herein by reference.

Claims

1. A combination composition which comprises:
(a) propionyl L-carnitine or a pharmacologically acceptable salt thereof; and
(b) a flavonoid.

2. The composition of claim 1, wherein the ingredient (a) further comprises a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, valeryl L-carnitine, isovaleryl L-carnitine or their pharmacologically acceptable salts or mixtures thereof.

3. The composition of claim 1 or 2 wherein the flavonoid is selected from the group comprising quercetin, rutin, myricetin and myricitrin.

4. The composition of claims 1-3 wherein the weight ratio (a):(b) is from 1:0.1 to 1:10.

5. The composition of any of the preceding claims, wherein the ingredient (b) is in the form of vegetal extracts which contain the ingredient itself.

6. The composition of any of the preceding claims wherein the pharmacologically acceptable salt of L-carnitine or alkanoyl L-carnitine is selected from the group comprising: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; orotate; acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

7. The composition of any of the preceding claims, which further comprises vitamins, coenzymes, mineral substances and antioxidants.

8. The composition of any of the preceding claims, orally administrable, in the form of a dietary supplement.

9. The composition of any of the preceding claims, orally, parenterally, rectally, cutaneously, ocularly or transdermally administrable in the form of a medicament.

10. The dietary supplement of claim 8, for the prevention of diseases brought about by the presence of free radicals and by increased platelet aggregation, thrombotic or atherosclerotic abnormalities, allergic inflammatory reactions.

11. The medicament of claim 9, for the therapeutic treatment of diseases brought about by the presence of free radicals and by increased platelet aggregation, thrombotic or atherosclerotic abnormalities and allergic inflammatory reactions.

12. The dietary supplement of claim 10, in solid, semi-solid or liquid form.

13. The medicament of claim 11, in solid, semi-solid or liquid form.

14. The dietary supplement of claim 12, in the form of tablets, lozenges, pills, capsules, granulates or syrups.

15. The medicament of claim 13, in the form of tablets, lozenges, pills, capsules, granulates, syrups, vials or drops.

16. The composition, dietary supplement or medicament of any of the preceding claims in unit dosage form, comprising:

Propionyl L-carnitine	mg 500
Quercetin	mg 250

17. The composition, dietary supplement or medicament of any of claims 1-15 in unit dosage form, comprising:

Carnitine mixture (propionyl L-carnitine mg 125, acetyl L-carnitine mg 125, isovaleryl L-carnitine mg 125)	mg	375
Quercetin	mg	250

18. The composition, dietary supplement or medicament of any of claims 1-15 in unit dosage form, comprising:

Propionyl L-carnitine	mg	250
Quercetin	mg	125

19. The composition, dietary supplement or medicament of any of claims 1-15 in unit dosage form, comprising:

Carnitine mixture (propionyl L-carnitine mg 75, acetyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	225
Quercetin	mg	125

20. The composition, dietary supplement or medicament of any of claims 1-15 in unit dosage form, comprising:

Propionyl L-carnitine	mg	125
Quercetin	mg	125
Citroflavonoids	mg	50
Vit. C	mg	100
Rutin	mg	20
CoQ_{10}	mg	10
Vit. E	mg	5
β-carotene	mg	5
Manganese glycinate	mg	5
Zinc glycinate	mg	5
Magnesium glycinate	mg	20
Selenium methionine	μg	50

21. The composition, dietary supplement or medicament of any of claims 1-15 in unit dosage form, comprising:

Carnitine mixture (propionyl L-carnitine mg 100, acetyl L-carnitine mg 100, isovaleryl L-carnitine mg 100)	mg	300
Quercetin	mg	150
Citroflavonoids	mg	50
Vit. C	mg	100
Rutin	mg	20
CoQ_{10}	mg	10
Vit. E	mg	5
β-carotene	mg	5
Manganese glycinate	mg	5
Zinc glycinate	mg	5
Magnesium glycinate	mg	20
Selenium methionine	μg	50

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/IT 99/00351

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/22 A61K31/205 A61K35/78 A23L1/302 A23L1/30 A23L1/304

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2000	27/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

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Int. ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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