Antioxidant, antiproliferous composition, comprising a carnitine and a carotenoid.

The present invention relates to a composition for the prevention and/or treatment of diseases brought about by the presence of free radicals due to environmental pollution and by lipoperoxidation phenomena of atherosclerotic, vascular, cardiac or cerebral kind; of proliferative alterations of tissues comprising prostatic, uterine, mammary or colon tissues; sight and retina alterations comprising cataract and macular degeneration of the retina.

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 a composition that can be administered orally, parenterally, rectally, transdermally or by ocular instillation, 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 carotenoid, preferably selected from the group comprising of lycopene, α-carotene, β-carotene, zeaxanthin, cryptoxanthin, lutein or mixtures thereof or extracts of natural vegetable products containing such carotenoids, typically tomato extracts (*Lycopersicon esculentum*).

The carotenoids are a group of long-chain vegetable pigments of a terpenic nature (tetraterpenes) containing up to 40 carbon atoms with a conjugated system of double bonds. Carotenoids are present in superior plants, in chloroplasts and in those plastids located in the

regions of the plant where chlorophyll is absent (some roots and many flowers and fruits, such as, for example, tomatoes, in which they increase during ripening); they are also to be found in blue algae, in some photosynthetic bacteria and in some fungi. Carotenoids play a complementary role to chlorophyll in photosynthesis, absorbing some light rays and transmitting the energy to the chlorophyll itself.

Though more than six hundred carotenoids are present in the vegetable world, only forty of these are present in the human diet and only fourteen are absorbed in the gut, the remainder consisting of non-absorbable epoxides. The most common of these fourteen are lycopene, α-carotene, β-carotene, lutein, zeaxanthin and the β-cryptoxanthins.

Lycopene presents eleven linearly conjugated double bonds (whereas β-carotene presents nine) and is the carotenoid with the longest chain of linearly conjugated double bonds.

A relationship has also been claimed between this particular structure and its greater potency as an antioxidising agent.

Though metabolic interactions exist between lycopene and β-carotene, lycopene cannot transform itself in the body into β-carotene, which is characterised by a trimethylcyclohexanyl ring on the two sides of the carbon chain.

β-carotene, on the other hand, is capable of transforming itself through reduction of the chain to *trans*-retinol and retinoic acid and of acting as provitamin A.

These compounds are characterised by substantial antioxidising capacity, but among them lycopene is the one which presents the greatest ability to block singlet oxygen, which is more than twice that of β-carotene, for instance.

Lycopene is absorbed by the body, particularly in the presence of fat and is found in the blood and tissues in its two isomeric forms, *cis*- and *trans*-lycopene.

Like all carotenoids, lycopene cannot be synthesised by the body, but must be ingested with food.

There are many foods containing carotenoids, including papaya, pink grapefruit, spinach, apricots, milk and eggs, but it is above all tomatoes which contain the largest amount of lycopene.

In addition to its substantial antioxidising capacity, the interest in lycopene is due to the results of a number of epidemiological studies which have shown that a carotenoid with provitamin A action such as β-carotene may itself exert a protective effect on some forms of tumours, without having to be transformed into retinol. Numerous prospective and retrospective investigations have revealed an inverse correlation between the consumption of vegetables and fruit rich in carotene or high plasma concentrations of carotene and tumour risk, particularly for lung tumours. These results were attributed to carotenoids only as precursors of vitamin A. However, recent clinical tests have shown that taking β-carotene alone with the diet affords no benefit in terms of tumour risk as compared to populations whose diets are devoid of this vitamin.

The same negative results were obtained in groups of smokers or of individuals at risk for asbestosis. More thorough processing of these data revealed that carotenoids other than β-carotene could contribute towards achieving the protective effect detected with other tests.

What particularly characterises lycopene and what is believed to underlie the favourable biological effects it is capable of exerting in the body, is its potent antioxidising action most notably against singlet oxygen, which is one of the most reactive oxygen products in producing free radicals. In addition to its action against singlet oxygen, lycopene

is also extremely active in protecting cells and tissues from other reactive species of oxygen such as hydrogen peroxide and nitrous oxide.

These particular activities of lycopene, which put it in the foreground among all the other natural antioxidants may partly account for the beneficial health-promoting effects which the intake of lycopene with the diet is capable of exerting.

It has been found, in fact, that subjects suffering from myocardial infarction, as well as those potentially at risk owing to the presence of high blood concentrations of cholesterol or triglycerides, present very low blood concentrations both of β-carotene and, particularly, lycopene as compared to control subjects. That this may be related to the anti-lipoperoxidative effect exerted by lycopene also emerges from research demonstrating that lycopene is present in LDLs and may prevent their oxidation.

It has been confirmed that the antilipoperoxidative effect of lycopene is also superior to that of β- and α-carotene when measured on cell cultures (C3H/10T1/2 cells) where it prevents their neoplastic transformation. The antilipoperoxidative activity of lycopene also explains its ability to prevent atherosclerosis and atherosclerotic vascular damage and also, in conjunction with its IGF-inhibiting and junctional intracellular communication enhancing activity, tumour cell proliferation.

Lycopene is the most potent of the carotenoids in inhibiting the spontaneous development of breast tumours in the rat and the growth of leukaemic cells (H1-60 promyelocytic leukaemia cell line) as well as rat glioma C-6 cells *in vitro* or the neoplastic transformations induced by chemical agents.

Epidemiological studies have demonstrated an inverse correlation between lycopene intake with the diet and the risk of developing prostate tumour, so much so that lycopene can be identified as a means

of prevention in this particular disease. The same is true of the risk of breast and lung tumours.

Another disease in which lycopene, like lutein and zeaxanthin, may exert a preventive action is age-related macular degeneration of the retina (AMD).

L-carnitine and its alkanoyl derivatives are well known for the important role they are capable of playing at metabolic level, particularly with regard to oxidation and to fatty acid utilisation through β-oxidation.

L-carnitine, in fact, whether taken with the diet or synthesised by the body, is concentrated by the blood in the organs which are metabolically most active in the utilisation of fatty acids, such as the skeletal muscles and heart.

An L-carnitine deficiency may give rise to myopathies, whereas the oral administration of L-carnitine improves the clinical status of such myopathies. In the mitochondrial oxidation of glucose, too, L-carnitine performs an important function in energy production, with the result that adequate levels of L-carnitine are necessary for normal energy metabolism at cardiac and muscular level.

Its administration improves resistance to stress in subjects suffering from coronary insufficiency, as well as coronary flow itself and the clinical effects of cardiac decompensation.

Other biological properties of L-carnitine and its derivatives, particularly propionyl L-carnitine, are its ability to stabilise the cell membranes and to protect them against lesions induced by oxidative processes.

Surprisingly, it has now been found that a composition containing as its characterising components a combination of:

(a) propionyl L-carnitine or a pharmacologically acceptable salt thereof, and
(b) a carotenoid chosen from the group consisting of lycopene, α-carotene, β-carotene, zeaxanthin, cryptoxanthin, lutein or mixtures thereof,
is extremely effective in the prevention and/or treatment of damage induced by the presence of free radicals due to environmental pollution and by lipoperoxidation phenomena of an atherosclerotic, vascular, cardiac or cerebral nature; of proliferative abnormalities of tissues including prostate, uterine, mammary and colon tissue; and of visual and retinal disorders including cataracts and macular degeneration of the retina, as a result of the potent synergistic effect exerted by its components.

It has also been found that component (a) may advantageously further comprise a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or their pharmacologically acceptable salts or mixtures thereof and that component (b) may consist in an extract of vegetable products containing it, such as, for example, tomato (*Lycopersicon esculentum*, Solanaceae family) extract.

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

Toxicological tests

Both carnitine and its derivatives and lycopene and the other carotenoids such as lutein, zeaxanthin and cryptoxanthin, as well as β-carotene, present low toxicity and are well tolerated, particularly when administered orally.

These favourable characteristics have been confirmed in tests performed by administering to rats high doses of either L-carnitine (1 g/kg), or propionyl L-carnitine (1 g/kg), or L-carnitine (250 mg/kg) plus propionyl L-carnitine (250 mg/kg) plus acetyl L-carnitine (250 mg/kg)

plus isovaleryl L-carnitine (250 mg/kg), and also by administering 50 mg/kg of lycopene or 1 g/kg of natural tomato extract containing 5% lycopene.

Also the combination of 1 g/kg of propionyl L-carnitine and 50 mg/kg of lycopene administered orally to rats proved to be well tolerated and caused no mortality in the animals thus treated.

The same is true of the results for the administration of the carnitine mixture (L-carnitine 250 mg/kg, plus acetyl L-carnitine 250 mg/kg, plus propionyl L-carnitine 250 mg/kg, plus isovaleryl L-carnitine 250 mg/kg) in combination with lycopene at the dose of 50 mg/kg.

Similar favourable results were obtained with the daily oral administration in rats over a prolonged period (30 days) either of propionyl L-carnitine (500 mg/kg), or the mixture of the various carnitines (L-carnitine 150 mg/kg, plus acetyl L-carnitine 150 mg/kg, plus propionyl L-carnitine 150 mg/kg, plus isovaleryl L-carnitine 150 mg/kg) in combination with 25 mg/kg of lycopene.

At the end of day thirty, the rats thus treated presented no mortality or signs of toxicity. Chemico-physical test findings, red blood cell counts and white blood cell counts were normal in the treated animals, as were the results of histological examinations performed on the main organs at the end of treatment.

Tests on isolated liver cells intoxicated with carbon tetrachloride

To assess the antioxidising and protective activity against free radicals exerted by the compositions according to the invention described herein, their effects on intoxication induced by carbon tetrachloride were assayed on an isolated liver cell culture.

It is well known that carbon tetrachloride (CCl_4) induces lipoperoxidation of the cell membranes which may lead to necrosis of

the cells.

These tests, performed on a culture of rat liver cells, demonstrated that the lipoperoxidative and toxic effect of CCl_4 related to the release of free radicals can be reduced by the presence in the culture of the carnitine mixture (100 mg L^{-1}) consisting of L-carnitine, acetyl L-carnitine, propionyl L-carnitine and isovaleryl L-carnitine in a weight-to- weight ratio to one another of 1:1, or of propionyl L-carnitine (100 mg L^{-1}), especially when combined with lycopene (20 mg L^{-1}) or tomato extract containing 5% lycopene.

For the purposes of performing these tests, the liver cells taken from rat liver were isolated using the method described by Seglen (Seglen F.O., Meth. Cell. Biol. Chem., 264, 4747, 1989).

The lesions on the cell membrane induced by CCl_4 and the protective effect exerted by the carnitine mixture or by propionyl L-carnitine or by lycopene, as well as by their combination, were evaluated by assaying both alanine aminotransferase (AlaAT) and aspartate aminotransferase (aspaAT) on the supernatant fluid of the cell cultures (Beckman 700-Encore 2 Auto-biochemistry Assay System).

To assess the protection afforded against the lipoperoxidative effect of CCl_4, malonylaldehyde was measured using the thiobarbituric acid method (Ohkawa H. Anal. Biochem., 95, 351, 1979).

Cytology of liver cells at the end of treatment was examined after fixation in formalin or in glutaraldehyde under both the light and electronic microscopes. Examination of the results of these tests revealed that there was a surprising degree of synergism both between the carnitine mixture and lycopene and between propionyl L-carnitine and lycopene in protecting the liver cells against lesions of the membrane and against CCl_4-induced lipoperoxidation.

This synergism between carnitines, particularly propionyl L-carnitine, and lycopene is also evident from the measurement of malonylaldehyde, a marker of the lipoperoxidative effect.

Cytological examination of the liver cells confirms the reduction in necrotic cells after treatment with propionyl L-carnitine and lycopene; however, at ultrastructural examination particularly, whereas the cells in the control group (CCl_4) presented haemochrome abnormalities, irregular nuclear membranes, disappearance of the mitochondrial crests in the mitochondria and reduction in the number of ribosomes, those cells which had been exposed not only to CCl_4, but also to carnitines and lycopene, presented unexpectedly intact cell membranes and nuclei, and regular heterochromatins, as well as regular mitochondria and number of ribosomes.

The normalization of the cytological appearances was surprisingly marked in the liver cells exposed to the combined activity of the carnitine mixture and lycopene, whereas the effects of the single compounds alone, not in combination, were unremarkable, thus demonstrating a marked synergism between carnitines and lycopene.

Table 1

Alanine aminotransferase concentrations (AlaAT nmol·min^{-1}) in supernatant of liver cell cultures exposed to CCl_4 (controls) and to the carnitine mixture or to propionyl L-carnitine or to natural tomato carotenoid extracts or lycopene alone or in various combinations (C = carnitine mixture; P = propionyl L-carnitine; TE = natural tomato extract; L = lycopene).

Time in hrs	4	8	16
Controls	24.6 ± 2.1	26.8 ± 2.3	30.5 ± 4.5
C	20.6 ± 3.2	21.9 ± 3.3	26.4 ± 2.8
P	19.4 ± 2.1	22.3 ± 3.1	25.7 ± 3.7
TE	22.3 ± 1.8	24.3 ± 2.7	24.7 ± 2.9
L	22.1 ± 2.1	20.6 ± 2.4	23.6 ± 2.1
C + TE	11.9 ± 1.9	8.6 ± 1.1	5.1 ± 1.7
C + L	12.2 ± 1.8	10.5 ± 1.5	5.4 ± 1.9
P + L	11.5 ± 2.1	9.9 ± 2.4	6.2 ± 1.5

Table 2

Aspartate aminotransferase concentrations (AspaAT nmol·min^{-1}) in supernatant of liver cell cultures exposed to CCl_4 (controls) and to the carnitine mixture or to propionyl L-carnitine or to natural tomato carotenoid extracts or lycopene alone or in various combinations (C = carnitine mixture; P = propionyl L-carnitine; TE = natural tomato extract; L = lycopene).

Time in hrs	4	8	16
Controls	8.5 ± 0.6	10.9 ± 1.1	12.1 ± 1.5
C	8.1 ± 0.9	9.9 ± 0.8	9.8 ± 1.1
P	8.9 ± 0.9	9.2 ± 1.2	9.1 ± 1.7
TE	8.2 ± 0.8	9.1 ± 0.9	9.0 ± 1.2
L	8.8 ± 1.8	8.9 ± 0.9	9.0 ± 1.2
C + TE	5.4 ± 0.7	3.2 ± 0.9	3.0 ± 0.5
C + L	5.6 ± 1.1	3.1 ± 0.8	3.5 ± 1.2
P + L	5.5 ± 0.9	3.5 ± 1.2	3.2 ± 0.8

Experimentally induced cataract tests

Since, among the factors responsible for ocular cataracts, reference is made not only to impaired glucose metabolism, but also to free radicals and lipid lipoperoxidation, in view of their pathogenetic importance, together with dysfunctions of the blood supply to the retina, we experimentally induced the occurrence of ocular cataracts in rats by means of a diet rich in galactose according to the method described by Gabbay (Gabbay K.H., N. Engl. J. Med., 288, 831, 1973).

After about eight days of this treatment, lens opacification is obtained in the rat which, in terms of its severity, is classified in increasing order as stage I, II and III according to the method described by Sippel (Sippel T.O., Invest. Ophthalmol., 5, 568, 1966). The results obtained in these tests demonstrate that the administration for eight days, along with galactose, of the carnitine mixture (400 mg/kg orally of a combination of L-carnitine, acetyl L-carnitine, propionyl L-carnitine and isovaleryl L-carnitine in identical weight amounts to one another) or of propionyl L-carnitine (400 mg/kg) or of lycopene (5 mg/kg) or of natural tomato extract containing 5% lycopene (100 mg/kg) or of these

products in combination reduced the severity of the ocular lesions induced by galactose. But the occurrence of lens opacification was inhibited almost completely when, during the eight-day galactose treatment period, combinations of carnitine mixture and lycopene or of propionyl L-carnitine and lycopene were simultaneously administered to the experimentally treated rats.

Table 3

Lens opacification inhibition tests in galactosaemic rats treated with carnitine mixture, propionyl L-carnitine, natural tomato carotenoid extract, and lycopene, or with various combinations of these (groups of 20 rats).

Treatment mg/kg	Degree of ocular lens opacification (number of lenses examined)		
	I	II	III
Controls	0	10	10
Carnitine mixture (400 mg/kg)	0	15	5
Propionyl L-carnitine (400 mg/kg)	0	12	8
Natural tomato carotenoid extract (100 mg/kg)	8	8	4
Lycopene (5 mg/kg)	6	4	10
Carnitine mixture (400 mg/kg) + natural tomato carotenoid extract (100 mg/kg)	12	8	0
Carnitine mixture (400 mg/kg) + lycopene (5 mg/kg)	12	6	2
Propionyl L-carnitine (400 mg/kg) + natural tomato carotenoid extract (100 mg/kg)	14	6	0
Propionyl L-carnitine (400 mg/kg) + lycopene (5 mg/kg)	15	6	0

Experimental atherosclerosis tests in rabbits

In these tests, the effects of the carnitine mixture, propionyl L-carnitine, lycopene and natural tomato extract containing 5% lycopene, alone or in various combinations, on experimentally induced atherosclerosis in the rabbit were evaluated.

For these tests a group of New Zealand rabbits with a mean weight of 2.9 kg were used, to whose standard diet 0.5% by weight of cholesterol was added for 30 consecutive days. Every day the same animals received with their cholesterol-enriched diet a dose corresponding to 400 mg/kg of carnitine mixture (combination of L-carnitine, acetyl L-carnitine, propionyl L-carnitine and isovaleryl L-carnitine in identical weight amounts to one another), or 400 mg/kg of propionyl L-carnitine, or 5 mg/kg of lycopene, or 100 mg/kg of natural tomato extract containing 5% lycopene, or the same products in various combinations. At the end of day thirty of treatment, blood samples were taken from the central artery of the ear of each animal and used for assaying the lipoproteins present according to the Hatch method (Hatch F.T., Adv. Lipid Res., 6, 1, 1968).

The animals were then sacrificed and the liver was taken from each of them and used for assaying total cholesterol and triglycerides according to the Dehoff and Levy methods, respectively [Dehoff J.L., Clin. Chem., 24, 433, 1978; Levy A., Advances in Automated Analysis (Technicon Corp.) 497, Thurman, Miami 1972]. The aorta and heart were also isolated and used to evaluate the presence of atherosclerotic lesions according to the Klurfeld method (Klurfeld D.M., J. Med., 10, 35, 1979) rating lesions from I to IV according to severity.

The results of these tests indicate that both the carnitines and also, to a lesser extent, lycopene exert a protective effect on the increases in cholesterol and triglycerides induced in rabbits by the hyperlipidic diet, but that it is only with their combined use that a clear result of practically complete protection is achieved.

The animals treated with the combination of carnitines and lycopene, in fact, show a degree of protection not achievable by summation of the effects produced by the individual products in isolation. The results of these tests also demonstrate a marked synergism of effects exerted by the compositions according to the invention described herein.

Table 4

Tests in hypercholesterolaemic rabbits
Plasma lipoprotein concentrations

	VLDL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
HC	1,119 ± 295	485 ± 19.9	23.1 ± 6.5
CM	755 ± 10.9	306 ± 15.5	28.5 ± 5.5
TE	880 ± 105	295 ± 20.7	30.1 ± 4.2
p	805 ± 95	280 ± 22.5	29.5 ± 6.2
L	715 ± 80	260 ± 28.5	29.3 ± 5.5
CM + TE	290 ± 45	155 ± 16.5	35.5 ± 3.9
CM + L	240 ± 25	96 ± 9.4	31.2 ± 2.9
P + TE	250 ± 30	105 ± 15.5	36.9 ± 3.5
P + L	220 ± 20	90 ± 10.5	32.1 ±3.1

HC = hypercholesterolaemic controls
CM = carnitine mixture
TE = natural tomato carotenoid extract
P = propionyl L-carnitine
L = lycopene

Table 5

Tests in hypercholesterolaemic rabbits
Liver concentrations of total cholesterol and triglycerides

	Total cholesterol (mg/dl)	Triglycerides (mg/g)
HC	1,885 ± 315	180 ± 15.5
CM	1,420 ± 205	155 ± 12.7
TE	1,475 ± 195	139 ± 11.5
P	1,250 ± 145	142 ± 12.8
L	1,200 ± 180	135 ± 13.8
CM + TE	985 ± 85	115 ± 11.6
CM + L	780 ± 98	105 ± 11.6
P + TE	750 ± 64	110 ± 10.7
P + L	655 ± 90	90 ± 8.5

HC = hypercholesterolaemic controls
CM = carnitine mixture
TE = natural tomato carotenoid extract
P = propionyl L-carnitine
L = lycopene

Antiproliferative activity tests with evaluation of ornithine decarboxylase activity

As is known, like the phorbol myristates, teleocidin administered subcutaneously in the rat causes proliferative abnormalities in the skin of the animals thus treated which can even lead to the formation of tumour-type keratotic processes.

The proliferative abnormality is accompanied by an increase in ornithine decarboxylase enzyme and, as in all cases of pathological proliferative activation in general, the increase in ornithine decarboxylase activity is proportional to the severity of the lesion induced. In these tests, teleocidin dissolved in 0.2 cc of aqueous solution was injected subcutaneously into the depilated backs of mice at a dose of 5 μg/mouse. Over the seven days prior to this treatment, the test animals received oral administrations of either carnitine mixture alone (400 mg/kg) consisting in a combination of L-carnitine, acetyl L-carnitine, propionyl L-carnitine and isovaleryl L-carnitine in identical weight amounts to one another, or propionyl L-carnitine alone (400 mg/kg), or natural tomato carotenoid extract (100 mg/kg containing 5% lycopene) alone, or lycopene alone (5 mg/kg), or combinations of carnitine mixture with lycopene or lycopene-containing extracts, or of propionyl L-carnitine with lycopene or lycopene-containing extracts. In another set of tests, these products were applied to the skin of the mice half an hour prior to injection of teleocidin after suitable dispersion of the products first in dimethylsulphoxide and then in lanolin until a 200 mg/cc concentration of the carnitine mixture, or a 200 mg/cc concentration of the carotenoid extract containing 5% lycopene, or a 5 mg/cc concentration of lycopene were achieved.

The various preparations were applied at the dose of 0.3 cc on the skin area where teleocidin was injected and the area injected was protected with an occlusive bandage.

For the purposes of the ornithine decarboxylase assay in the skin areas injected with teleocidin, the procedure adopted five hours after injection consisted in the method described by O'Brien and Nakadate (O'Brien T.G., Cancer Res., 35, 1662, 1975; Nakadate T., Cancer Res., 42, 2841, 1982). The protein concentration of the epidermal extract was measured using the Lowry method (Lowry O.H., J: Biol. Chem., 193, 265, 1951). The results of these tests indicate that both the carnitine mixture and the carotenoids in the natural tomato extract, as well as propionyl L-carnitine alone and lycopene alone exert only a slight protective effect against the proliferative phenomena and against the increase in ornithine decarboxylase activity, but the protective effect, by contrast, proves surprisingly efficacious when these products are used in combination, thus demonstrating an unexpected and surprising synergistic effect.

Table 6

Ornithine decarboxylase activity

Treatment	Ornithine decarboxylase activity (nmol of CO_2/60 min/mg protein)	
	Oral administration	Cutaneous administration
Controls	0.05 ± 0.002	0.03 ± 0.001
Teleocidin	2.4 ± 0.3	2.6 ± 0.2
Carnitine mixture	1.92 ± 0.4	1.75 ± 0.3
Propionyl L-carnitine	1.90 ± 0.2	1.60 ± 0.1
Natural tomato extract	1.85 ± 0.3	1.80 ± 0.2
Lycopene	1.70 ± 0.1	1.65 ± 0.1
Carnitine mixture + natural tomato extract	0.35 ± 0.005	0.40 ± 0.06
Carnitine mixture + lycopene	0.30 ± 0.03	0.45 ± 0.05
Propionyl L-carnitine + natural tomato extract	0.36 ± 0.06	0.30 ± 0.04
Propionyl L-carnitine + lycopene	0.33 ± 0.05	0.31 ± 0.03

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

1)	Carnitine mixture (L-carnitine mg 125, acetyl L-carnitine mg125, propionyl L-carnitine mg 125, isovaleryl L-carnitine mg 125)	mg	500
	Natural extract of tomato (titled 5% in lycopene)	mg	100
2)	Carnitine mixture (L-carnitine mg 75, acetyl L-carnitine mg 75, propionyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	300
	Natural extract of tomato (titled 5% in lycopene)	mg	50
3)	Propionyl L-carnitine	mg	500
	Natural extract of tomato (titled 5% in lycopene)	mg	100
4)	Propionyl L-carnitine	mg	250
	Natural extract of tomato (titled 5% in lycopene)	mg	50
5)	Propionyl L-carnitine	mg	500
	Lycopene	mg	5
6)	Propionyl L-carnitine	mg	250
	Lycopene	mg	2.5
7)	Carnitine mixture (L-carnitine mg 75, acetyl L-carnitine mg 75, propionyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	300
	Lycopene	mg	5
8)	Carnitine mixture (L-carnitine mg 75, acetyl L-carnitine mg 75, propionyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	300
	Lycopene	mg	2.5
9)	Carnitine mixture (L-carnitine mg 75, acetyl L-carnitine mg 75, propionyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	300
	Carotenoids complex (Natural extracts from tomato, pink grapefruit, carrots, orange blossom)	mg	300
10)	Propionyl L-carnitine	mg	400
	Lycopene	mg	2.5
	β-carotene	mg	5
	α-carotene	mg	2
	Lutein	mg	5
	Zeaxanthin	mg	1

11)	Propionyl L-carnitine	mg	350
	Lycopene	mg	5
	Dwarf fan palm (*Serenoa repens*)	mg	50
	Exctract of *Pygeum africanum*	mg	50
12)	Carnitine mixture (L-carnitine mg 75, acetyl L-carnitine mg 75, propionyl L-carnitine mg 75, isovaleryl L-carnitine mg 75)	mg	300
	Natural extract of tomato (titled 5% in lycopene)	mg	100
	Exctract of dwarf fan palm (*Serenoa repens*)	mg	50
	Exctract of *Pygeum africanum*	mg	50
	Extract of cactus blossom (*Opuntia ficus indica*)	mg	50
	Zinc glycinate	mg	50
	Selenium (1-Selenium methionine)	µg	50
	Vit. E	mg	10
	CoQ_{10}	mg	10
13)	Carnitine mixture (L-carnitine mg 100, acetyl L-carnitine mg100, propionyl L-carnitine mg 100, isovaleryl L-carnitine mg 100)	mg	400
	Natural extract of tomato (titled 5% in lycopene)	mg	100
	Anthocyanins exctrated from cranberry	mg	50
	Polyphenols extracted from grapes	mg	10
	Vit. E	mg	10
	Selenium methionine	µg	50
14)	Propionyl L-carnitine	mg	300
	β-carotene	mg	5
	Lycopene	mg	5
	Lutein	mg	3
	Catechin	mg	5
	Lipoic acid	mg	5
	CoQ_{10}	mg	10
	Vit. C	mg	100
	Vit. PP	mg	25
	Vit. B_6	mg	25
	Vit. B_{12}	µg	250
	Taurine	mg	100

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.

The compositon according to the invention may also comprise vitamins, coenzymes, minerals substances and antioxidants.

Appropriate excipients to be used to prepare the compositions having regards to the specific route of administration, will be apparent to the pharmacy and food industry experts.

* C L M S *

CLAIMS

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

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 carotenoid is selected from the group comprising lycopene, α-carotene, β-carotene, zeaxanthin, cryptoxanthin, lutein or mixtures thereof.

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 claim 5, wherein said vegetal extract is the tomato (*Lycopersicon esculentum*) extract.

7. The composition of claim 6, wherein the tomato extract comprises from about 2 to 20% by weight of lycopene.

8. 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;

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sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

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

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

11. The composition of any of the preceding claims, which can be administered orally, parenterally, rectally, transdermally or by ocular instillation in the form of a medicament.

12. The dietary supplement of claim 10, for the prevention of diseases brought about by the presence of free radicals due to environmental pollution and by lipoperoxidation phenomena of atherosclerotic, vascular, cardiac or cerebral kind; proliferative alterations of tissues comprising prostatic, uterine, mammary or colon tissues; sight and retina alterations comprising cataract and macular degeneration of the retina.

13. The medicament of claim 11, for the therapeutic treatment of diseases brought about by the presence of free radicals due to environmental pollution and by lipoperoxidation phenomena of atherosclerotic, vascular, cardiac or cerebral kind; proliferative alterations of tissues comprising prostatic, uterine, mammary or colon tissues; sight and retina alterations comprising cataract and macular degeneration of the retina.

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

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

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

17. The medicament of claim 15, in the form of tablets, lozengens, pills, capsules, granulates, syrups, vials, collyria and eyewashes or drops.



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