OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Demande-Application**

(21) (A1) **2,296,540**
(86) 1998/07/10
(87) 1999/01/28

(72) CAVAZZA, CLAUDIO, IT
(71) SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A., IT

(51) Int.Cl.[7] A23L 1/302, A23L 1/305, A23L 1/30
(30) 1997/07/16 (RM97A000435) IT

(54) **COMPOSITION NOURRISSANTE POUR SUJET EN ETAT DE STRESS**

(54) **NUTRITIONAL COMPOSITION FOR SUBJECTS UNDER STRESS**

(57) L'invention concerne une composition nourrissante (aliment fonctionnel) pour sujets se trouvant dans un état d'affaiblissement consécutif au stress. Ladite composition comprend une combinaison: (a) de L-carnitine ou de L-carnitine d'alcanoyle ou d'un de leurs sels pharmacologiquement acceptables; (b) d'un mélange d'extraits végétaux naturels (ex: yohimbine et guarana); (c) de lécithine de soja; et (d) d'acide malique.

(57) A nutritional composition (medical food) for subjects in a debilitated state as a result of stress is disclosed, which comprises a combination of: (a) L-carnitine or an alkanoyl L-carnitine or one of their pharmacologically acceptable salts; (b) a mixture of natural plant extracts (e.g. yohimbine and guarana); (c) lecithin of soya; and (d) malic acid.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A23L 1/302, 1/305, 1/30	A1	(11) International Publication Number: WO 99/03364
		(43) International Publication Date: 28 January 1999 (28.01.99)

(21) International Application Number: PCT/IB98/01056

(22) International Filing Date: 10 July 1998 (10.07.98)

(30) Priority Data:
RM97A000435 16 July 1997 (16.07.97) IT

(71) Applicant *(for all designated States except US)*: SIGMA–TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A. [IT/IT]; Viale Shakespeare, 47, I–00144 Roma (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CAVAZZA, Claudio [IT/IT]; Piazza Campitelli, 2, I–00186 Roma (IT).

(74) Agent: FASSI, Aldo; Con Lor S.p.A., Via Renato Fucini, 5, I–20133 Milano (IT).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NUTRITIONAL COMPOSITION FOR SUBJECTS UNDER STRESS

(57) Abstract

A nutritional composition (medical food) for subjects in a debilitated state as a result of stress is disclosed, which comprises a combination of: (a) L–carnitine or an alkanoyl L–carnitine or one of their pharmacologically acceptable salts; (b) a mixture of natural plant extracts (e.g. yohimbine and guarana); (c) lecithin of soya; and (d) malic acid.

NUTRITIONAL COMPOSITION FOR SUBJECTS UNDER STRESS

DESCRIPTION

The present invention relates to a nutritional composition or medical food for subjects in a debilitated state as a result of stress.

In the developed countries, stress syndrome afflicts a substantial number of people. The causes of the stress are multiple and attributable mainly to living conditions in large and overcrowded urban areas and to the problems these give rise to such as traffic, noise and pollution. Another important cause consists in problems associated with working activity or economic worries.

This syndrome afflicts all social classes, but mainly affects people involved in the production cycle, who often, as a result, are subject to greater competitive stress stimuli both in the work environment and in the conduct of their social relations.

Generally speaking, stress syndrome is not a debilitating "disease" to the extent that it makes people bed-ridden, but it is certainly a frequent cause of people taking days off work. Since it afflicts a substantial number of individuals, it causes a considerable burden of economic damage to the entire community during the working year. Stress syndrome, which in the past was improperly called "*nervous breakdown*", is characterised, in the absence of active disease, by concomitant states of malaise, such as a lack of strength, debilitation, states of mental and physical fatigue, lack of concentration and attention, and lack of sexual vigour and libido.

There are no specific drugs for the treatment of stress. Temporary detachment from the causes of the stress, for instance by spending a holiday in a pleasant locality and in a relaxing

environment, would certainly have a positive effect, facilitating recovery of mental and physical well-being with an improvement in physical performance and an increase in sexual vigour and libido.

This, however, is not always possible for various reasons such as, for example, work commitments, family demands and economic difficulties.

A number of patients suffering from stress are treated with benzodiazepines or with drugs which are active in mood disorders. Benzodiazepines are used to alleviate symptoms such as anxiety or irritability, but present the drawback of causing addiction as well as further depressing libido and sexual vigour, thus triggering a mechanism in male subjects of reproductive age which itself proves to be a cause of additional malaise.

A number of substances which are useful for the treatment of sexual impotence of psychogenic or other origin are already well known. Equally well known are substances endowed with stimulant activity. For example, L-carnitine, when used for the treatment of patients undergoing regular dialysis treatment, also induces recovery of normal sexual function in such patients (De Felice SL, Lyons P, Gaffar MC, Sheridan MJ, *Dial-Transplant*, 1996, vol/iss/pg. 25/6 368-373).

Popular medicine (and belief) in oriental and South American countries (China, Brazil) have, since time immemorial, accredited the extracts of the roots, bark and leaves of various "exotic" plants with multiple therapeutic and stimulant effects. Ginseng has been used in Chinese medicine for more than 2000 years for the treatment of sexual impotence and for other diseases. Also well known is the activity of yohimbine in improving sexual function; see, for example, "Clinical Studies in Impotence": K Reid et al., Lancet 2, 421-423 (1987). Guarana is used by Brazilian indigenous

populations for the preparation of a stimulating beverage (Pharmacognosy, Edward P Claus, Varro E Tyler, Lynn R Brady, 6th edition pp. 292-293). Damiana has also long been known to be endowed, according to popular belief, with stimulant activity (J Psychoactive Drugs 16 (3): 267-268, 1984).

The purpose of the present invention is now to provide a therapeutic medical food suitable for alleviating and treating states of malaise caused by stress and for promoting sexual vigour. The therapeutic medical food of the invention comprises the following compounds in combination:

1) L-carnitine or an alkanoyl L-carnitine in which the linear or branched-chain alkanoyl has 2-8, and preferably 2-6, carbon atoms, or one of their pharnacologically acceptable salts;
2) ginseng (natural extract of *Panax ginseng*);
3) yohimbine (natural extract of *Corynanthe yohimbe*);
4) guarana (natural extract of *Paullinia cupana*);
5) damiana (natural extract of *Turnera diffusa, var. aphrodisiaca*);
6) lecithin of soya, and
7) malic acid.

The alkanoyl L-carnitine should preferably be chosen from among the group comprising acetyl, propionyl, butyryl, valeryl and isovaleryl L-carnitine or one of its pharmacologically acceptable salts.

What is meant by pharmacologically acceptable salt of L-carnitine or of an alkanoyl L-carnitine is any salt of these with an acid which does not give rise to unwanted toxic or side effects. Such acids are well known to pharmacologists and experts in pharmacy.

Non-limiting examples of pharmacologically acceptable salts of L-carnitine or of the alkanoyl L-carnitines are chloride, bromide, orotate, acid aspartate, acid citrate, acid phosphate, fumarate and

acid fumarate, lactate, maleate and acid maleate, acid oxalate, acid sulphate, glucose phosphate, tartrate and acid tartrate.

The components of the combination according to the invention, once combined, exhibit an unexpected potent synergistic effect which brings about an improvement in physical performance and in the mental and physical condition of patients suffering from stress syndrome. Very important and surprising is the synergistic effect shown by the combination of ginseng, yohimbine and L-carnitine in restoring sexual vigour and libido.

The effect of the combination is, in fact, distinctly superior to the sum of the effects of the individual components.

Of particular interest is the interaction between malic acid and L-carnitine. The complementary effect exerted by these two compounds on energy production via two different metabolic pathways - malic acid via the Krebs cycle, and L-carnitine via β-oxidation - stimulates the body to produce a large amount of energy, which is useful in enabling the individual to emerge from the state of fatigue, debilitation or asthenia caused by stress.

The interaction between guarana and damiana also results in an intense stimulatory effect, enabling most subjects presenting a state of torpor or lack of interest to emerge from these conditions.

L-carnitine and lecithin of soya favour the metabolisation of fatty acids, exerting a hypolipaemic effect on the body, which, though having no direct repercussions in terms of improving stress syndrome, is aimed at enhancing the individual's general state of health.

The weight-to-weight ratio of L-carnitine or of an alkanoyl L-carnitine to ginseng, yohimbine, guarana and damiana may vary over a broad range, This ratio should preferably range from

1:0.1:0.0025:0.1:0.1 to 1:10:0.25:100:100. One preferred ratio is 1:1:0.025:1:1.

By way of non-limiting examples a number of sachet formulations according to the invention are given containing the following components in combination:

Composition 1

L-carnitine HCl	200 mg
Ginseng	200 mg
Lecithin of soya	400 mg
Aspartame	20 mg
Sucrose	1500 mg
Tangerine flavouring	100 mg
Yohimbine	5 mg
Malic acid	50 mg
Granular mannitol q.s. to	3000 mg

Composition 2

L-carnitine HCl	200 mg
Ginseng	200 mg
Lecithin of soya	200 mg
Aspartame	20 mg
Sucrose	1000 mg
Tangerine flavouring	100 mg
Yohimbine	5 mg
Guarana	200 mg
Damiana	200 mg
Malic acid	50 mg
Granular mannitol q.s. to	3000 mg

Composition 3

L-carnitine HCl	200 mg
Ginseng	200 mg
Lecithin of soya	200 mg
Aspartame	20 mg
Sucrose	1000 mg
Tangerine flavouring	100 mg
Yohimbine	5 mg
Guarana	500 mg
Damiana	500 mg
Malic acid	50 mg
Granular mannitol q.s. to	3000 mg

The composition according to the invention may additionally contain vitamins, metals, coenzymes, inorganic or organic antioxidants or their precursors.

CLAIMS

1. A medical food composition suitable for alleviating and treating states of malaise caused by stress, comprising the following in combination:

   (a) L-carnitine or an alkanoyl L-carnitine in which the linear or branched-chain alkanoyl group has 2-8, and preferably 2-6 carbon atoms, or one of their pharmacologically acceptable salts;

   (b) a mixture of natural plant extracts;

   (c) lecithin of soya;

   (d) malic acid.

2. The composition of claim 1, wherein the alkanoyl L-carnitine is selected from the group comprising acetyl, propionyl, butyryl, valeryl and isovaleryl L-carnitine or one of its pharmacologically acceptable salts.

3. The composition of claim 1, wherein the natural plant extracts are selected from the group comprising the natural extract of *Corynanthe yohimbe* or yohimbine, the natural extract of *Panax ginseng* or ginseng, the natural extract of *Paullinia cupana* or guarana, and the natural extract of *Turnera diffusa* or damiana.

4. The composition of claim 3, wherein the weight-to-weight ratio of L-carnitine or of an alkanoyl L-carnitine to ginseng, yohimbine, guarana and damiana ranges from 1:0.1:0.0025:0.1:0.1 to 1:10:0.25:100:100.

5. The composition of claim 4, wherein said ratio is 1:1:0.025;1:1.

6. The composition of the preceding claims, further comprising vitamins, metals, coenzymes, inorganic or organic antioxidants or their precursors.

7. The composition of any of the preceding claims for the treatment of stress-induced or psychogenic sexual impotence.

8. The composition of any of the preceding claims for the treatment of states of fatigue, lack of strength or asthenia caused by stress.

9. The composition of any of the preceding claims, which presents itself in the form of a solid, semisolid, liquid, semiliquid, powder, grains, tablets, capsules, granules, or powder for oral use.