(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 August 2004 (19.08.2004)

PCT

(10) International Publication Number
WO 2004/069262 A1

(51) International Patent Classification[7]: A61K 35/78, A61P 9/10

(21) International Application Number: PCT/IB2004/000284

(22) International Filing Date: 5 February 2004 (05.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
112/MAS/2003 7 February 2003 (07.02.2003) IN

(71) Applicant *(for all designated States except US)*: **ORCHID CHEMICALS & PHARMACEUTICALS LTD** [IN/IN]; Orchid Towers, 313, Valluvar Kottam High Road, Ngambakkam, 600 034 Chennai (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JINDAL, Kour, Chand** [IN/IN]; House no. 78, Sector - 9, Panchkula, 134113 Haryana (IN). **RAO, Canakapalli, Bhaktavastala** [IN/IN]; Orchid Towers, 313, Valluvar Kottam High Road, Nungambakkam, 600 034 Chennai (IN). **RAMANATHAN, Muthiah** [IN/IN]; 40-A, Main Road, Marakkadai, Lakshmangudi P.O, 614102 Tanjore (IN). **SURESH, Bhojaraj** [IN/IN]; Principal Quarters, JSS Collge of Pharmacy, 643 001 Ootacamund (IN).

(74) Common Representative: **ORCHID CHEMICALS & PHARMACEUTICALS LTD**; Orchid Towers, 313, Valluvar Kottam High Road, Ngambakkam, 600 034 Chennai (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HERBAL COMPOSITION COMPRISING COMMIPHORA MUKUL, ALLIUM SATIVUM AND CURCUMA LONGA

(57) Abstract: The present invention relates to a herbal composition for use in the treatment and / or prophylaxis of hypercholesterolemia, atherosclerosis, hyperlipidemia and hypertension in mammals. The composition comprises a synergistic mixture of extracts of three herbs selected from a group of *Commiphora mukul, Allium sativum and Curcuma longa.*

WO 2004/069262 A1

HERBAL COMPOSITION COMPRISING COMMIPHORA MUKUL, ALLIUM SATIVUM AND CURCUMA LONGA

Filed of the invention

The present invention relates to a herbal composition for use in the treatment and / or prophylaxis of hypercholesterolemia, atherosclerosis, hyperlipidemia and hypertension in mammals. The composition comprises a synergistic mixture of extracts of three herbs selected from a group of *Commiphora mukul, Allium sativum* and *Curcuma longa.*

Background of the invention

Babu *et. al* Mol. Cell. Biochem. 1997, 166(1-2) 169-175 describes hypolipidemic action of *Curcuma longa* in streptozocin induced diabetic rats.

Dixit *et. al* Ind. Jour. of Pharmacol. 1988, 32(4) 299-304 describes hypolipidemic effects of *Curcuma longa* and *Nardostachys jatamansi* in triton induced hyperlipidemic rats.

Berthold *et. al* Jour. of American Med. Assoc. 1998, 279(17) 1900-1902 describes effect of garlic oil preparation in serum lipoproteins and cholesterol metabolism in randomized controlled trial in humans.

Yeh *et. al* Lipids 1994, 29(3) 189-193 describes reduction of plasma lipids using garlic.

Singh *et. al* Cardiovascular Drug Ther. 1994, 8(4) 659-664 describes hypolipidemic effect of *Commiphora mukul* as an adjunct to dietary therapy in patients with hypercholesterolemia.

Although the use of various herbs have been described in related areas, the synergistic combination of *Commiphora mukul, Allium sativum* and *Curcuma longa* for use as agents for the control of hypercholesterolemia, hyperlipidemia and hypertension in mammals has never previously been described.

US patent No. 6,162,438 discloses an edible herbal composition for use as agents for controlling hypercholesterolemia, atherosclerosis, hyperlipidemia and

hypertension in mammals. The edible composition is a mixture or at least six, preferably at least three herbs selected from the group consisting of *Terminalia arjuna, Cynara scolymus, Zingibar officinale, Allium sativum, Crataegus oxycantha, Curcuma longa, Boerhaavia diffusa* and *Trigonella foenumgraecum.* The composition preferably contains the herbs in approximately equal amounts.

WO 94/1894 and U.S. Pat. No. 5,707,631 are directed to a therapeutic herbal composition including *Trigonella foenumgraecum* seed, *Syzygium aromataticum* fruit, *Allium sativum* bulb, *Cinnamomum zeylanicum* bark, *Saussurea costus* root and *Euphorbia lathyris* bud; the U.S. patent discloses the foregoing herbs in combination with sodium chloride (preferably sea salt).

US patent No. 5,900,240 discloses an edible composition comprising a mixture of at least two herbs selected from the group consisting of *Syzygium cumini, Gymnema sylvestre, Momordica charantia* and *Solanum melongena.* The herbal mixtures are useful as dietary supplements and are especially useful for lowering the blood glucose level in mammals, particularly humans suffering from diabetes mellitus.

Currently there exists a great need for non-synthetic, holistic therapeutic compositions for the control of hypercholesterolemia (high cholesterol levels), hyperlipidemia (high triglyceride levels) and hypertension in mammals. It has been found that the herbal composition of the present invention are synergistic in their effect and daily ingestion of such composition is an effective therapeutic method of achieving such control without the troublesome side effects on the liver, digestive system and kidneys associated with synthetic drugs.

Objective of the invention

The main objective of the present invention is to provide a herbal composition for use in the treatment and / or prophylaxis of hypercholesterolemia, atherosclerosis, hyperlipidemia and hypertension in mammals.

Yet another objective of the present invention is to provide a herbal composition, which produces no adverse effects and may be taken in multiple daily doses over prolonged period of time.

Summary of the invention

Accordingly, the present invention relates to a herbal composition comprising a synergistic mixture of extracts of three herbs selected from a group of *Commiphora mukul (guggul), Allium sativum* (garlic) and *Curcuma longa (turmeric).*

In another embodiment of the present invention, the herbal composition contains pharmaceutically acceptable ingredients.

In another embodiment of the present invention, the herbal composition is useful in the treatment and/or prophylaxis of hypercholesterolemia, atherosclerosis, hyperlipidemia and hypertension in mammals.

Detailed description of the invention

In an embodiment of the present invention, there is provided a synthetic pharmaceutical composition comprising curcumin, allin and guggulosterone and other pharmaceutically acceptable ingredients.

In an embodiment of the present invention, the curcuma extract contains 80 to 95% curcumin, garlic extract contains 2 to 4% allin and guggul extract contains 3 to 10% guggulosterone, as the active constituents.

In an embodiment of the present invention, the pharmaceutically acceptable excipients are selected from diluents, disintegrants, lubricants, binders, glidants and preservatives.

In an embodiment of the present invention, the diluents used are selected from dicalcium phosphate (DCP), microcrystalline cellulose (MCC), starch, magnesium oxide and the like or mixtures thereof.

In an embodiment of the present invention, the disintegrant used is selected from sodium starch glycollate (SSG), cross-carmellose sodium (CCS) and the like or mixtures thereof.

In an embodiment of the present invention, the binders used are selected from povidone, hydroxypropyl methylcellulose (HPMC) and the like or mixtures thereof.

In an embodiment of the present invention, the lubricants used are selected from magnesium stearate, talc, hydrogenated vegetable oils and the like or mixtures thereof.

In an embodiment of the present invention, the glidants used are selected from colloidal silicon dioxide (aerosil), talc and the like or mixtures thereof.

In an embodiment of the present invention, the preservatives used are selected from parabens such as methylparaben, ethylparaben, propylparaben; sodium benzoate, sorbic acid and the like; or mixtures thereof.

In an embodiment of the present invention, the total amount of herbal extract in the composition may be present in the range of 20 to 80 % based on the weight of the composition, with the balance being the other pharmaceutically acceptable ingredients.

In an embodiment of the present invention, the individual extracts in the herbal composition may be present in therapeutically acceptable ratio, preferable ratios are 3:3:2, 2:3:2, 3:2:2, 2:2:3, 1:1:1, 1:2:2, 1:3:3, 1:2:3 or 1:3:2.

The extract of garlic appears in light brown colour with characteristic odour, which is freely soluble in water. The extract of guggul appears in light to dark brown colour, sticky to touch, which is insoluble in water. Curcuma longa extract appears in orange yellow colour with characteristic odour, which is insoluble in water.

The herbal composition of the present invention may be used in the form of tablet, capsule, syrup, suspension, dry powders etc.

In an embodiment of the present invention, there is provided a process for the preparation of tablets or capsules containing herbal composition comprising the steps of :

i) mixing garlic, curcuma extracts and diluents,

ii) adding to the mixture obtained in step (i) a solution of guggul extract and preservatives dissolved in isopropyl alcohol,

iii) granulating the mixture obtained in step (ii) using conventional granulator

iv) drying the granules using conventional drier,

v) sifting the granules

vi) drying the granules,

vii) adding disintegrants, glidants, lubricants and blending the mixture and

viii) compressing into tablets or filling into capsules.

The tablets may be administered as such or as coated tablet. The coating may be done using conventional coating techniques such as film coating, enteric coating, sugar coating etc.

The dosage of the herbal compositions of the invention to be ingested will vary, depending on factors such as severity of the hypertension, hypercholesterolemia and hyperlipidemia, age, diet, physical condition and body weight of the patient, etc. As a general guide, it is expected that patients with a body weight in the range of 60-90 kg would ingest about 100-1,000 mg/day of the herbal compositions. It is to be understood that these dosage levels are only general guides and the proper dosage level for individual patients may vary considerably depending on the factors indicated above.

The following non-limiting examples shall serve to illustrate the invention. Unless otherwise indicated, all amounts and parts are on a weight basis.

Example 1

Garlic (150 g), curcuma extract (100 g), microcrystalline cellulose (91.8 g) and starch (350 g) were sifted through ASTM # 40 and mixed. To this mixture, a solution of guggul extract (150 g), methylparaben (2 g), propylparaben (0.2 g), sorbic acid (1 g) dissolved in 50 ml of IPA was added and granulated the mixture using rapid mixer granulator. The granules were dried at 60 °C in fluidized bed dried, sifted through ASTM # 20, milled through multimill and sifted through ASTM # 20. To the dried granules, sodium starch glycollate (35 g) and cross- carmellose sodium (70 g), colloidal silicon dioxide (20 g) and magnesium stearate (5 g) were added followed by blending and then compressed the blend using conventional tabletting machine to obtain tablets.

Example 2

Garlic (100 g), curcuma extract (150 g), microcrystalline cellulose (91.8 g) and starch (350 g) were sifted through ASTM # 40 and mixed. To this mixture, a solution of guggul extract (100 g), methylparaben (2 g), propylparaben (0.2 g), sorbic acid (1 g) dissolved in 50 ml of IPA was added and granulated the mixture using rapid mixer granulator. The granules were dried at 60 °C in fluidized bed dried, sifted through ASTM # 20, milled through multimill and sifted through ASTM # 20. To the dried granules, sodium starch glycollate (35 g) and cross- carmellose sodium (70 g), colloidal silicon dioxide (20 g) and magnesium stearate (5 g) were added followed by blending and then compressed the blend using conventional tabletting machine to obtain tablets.

The herbal composition of the present invention lowered random triglyceride, cholesterol and increased HDL. This was demonstrated by *in vivo* animal experiments.

Triton induced hyperlipidemia

The systemic administration of the surfactant triton to rats resulted in elevation of cholesterol and triglyceride. Wistar rats weighing 180 to 200 g were starved for 18 hrs and then injected intraperitoneally 200 mg/kg of triton. The test drugs were administered simultaneously along with triton. The blood samples were collected at the time intervals of 24h and 48h after the administration of the herbal composition and the blood cholesterol, triglyceride and HDL levels were calculated using the conventional formulae. The results are shown in table 1.

Table 1 :

Plasma lipid profile in Triton induced hyperlipidemic Wistar rats

S. No.	Triglycerides ↓		HDL ↑	
	24	48 h	24 h	48 h
Example 2	33.3	84.5	77.3	234.0
Example 1	62.4	87.7	87.5	165.3
Guggul (43 mg/kg)		--		27.6
Garlic (43 mg/kg)		26		91.2
Tturmeric (75 mg/kg		0.7		75.7

Plasma lipid profile in diet induced atherosclerotic rats

Male Wistar albino rats weighing between 100 to 125 g were used for this study. Cholesterol rich diet was fed for 5 weeks, then the drug was administered once daily for 7 days with free access to regular food and water. The plasma samples were collected and cholesterol, triglyceride, VLDL, LDL and HDL levels were calculated using the conventional formulae. The results are shown in table 2.

Table 2 :

S. No.	Cholesterol ↓	Triglyceride ↓	VLDL ↓	LDL ↓	HDL ↑
Example 2	60	36	36	87	-
Example 1	61.2	38	38	93	10

Plasma lipid profile in diet induced hypercholesterolemia in Rabbits

White New Zealand rabbits were supplemented with 2% of cholesterol and continued at this regiment for a period of 10 weeks. Drugs were administered as a fine suspension on 0.3% CMC and administered orally using oral catheter tube, once daily during the last four weeks of the study. The blood was withdrawn from the ear marginal vein before and after treatment and the plasma was separated to estimate the blood lipid profile. The results are shown in table 3.

Table 3 :

S. No.	Cholesterol ↓	Triglyceride ↓	VLDL ↓	LDL ↓	HDL ↑
Example 1	35	71	71	41	12

Claims :

1. A herbal composition comprising a synergistic mixture of extracts of three herbs selected from a group of *Commiphora mukul (guggul), Allium sativum* (garlic) and *Curcuma longa (turmeric).*

2. The herbal composition as claimed in claim 1, contains pharmaceutically acceptable ingredients selected from diluents, disintegrants, lubricants, binders, glidants and preservatives.

3. The herbal composition as claimed in claim 2, wherein the diluent used is selected from dicalcium phosphate (DCP), microcrystalline cellulose (MCC), starch, magnesium oxide or mixtures thereof.

4. The herbal composition as claimed in claim 2, wherein the disintegrant used is selected from sodium starch glycollate (SSG), cross-carmellose sodium (CCS) or mixtures thereof.

5. The herbal composition as claimed in claim 2, wherein the binder used is selected from povidone, hydroxypropyl methyl cellulose (HPMC) or mixtures thereof.

6. The herbal composition as claimed in claim 2, wherein the lubricant used is selected from magnesium stearate, talc, hydrogenated vegetable oils or mixtures thereof.

7. The herbal composition as claimed in claim 2, wherein the glidant used is selected from colloidal silicon dioxide (aerosil), talc or mixtures thereof.

8. The herbal composition as claimed in claim 2, wherein the preservative used is selected from parabens such as methylparaben, ethylparaben, propylparaben; sodium benzoate, sorbic acid or mixtures thereof.

9. The herbal composition as claimed in claim 1, wherein the total amount of herbal extract in the composition present in the range of 20 to 80 % based on the weight of the composition.

10. The herbal composition as claimed in claim 1, in the form of tablet, capsule, syrup, suspension, dry powder.

11. A pharmaceutical composition comprising curcumin, allin, guggulosterone and other pharmaceutically acceptable ingredients.

12. The pharmaceutical composition as claimed in claim 11, wherein the curcumin is extracted from curcuma extract, allin is extracted from garlic extract and guggulosterone is extracted from guggul extract.

13. The pharmaceutical composition as claimed in claim 12, wherein the curcumin in curcuma extract is about 80 to 95%, allin in garlic extract is about 2 to 4%, guggulosterone in guggul extract is 3 to 10%.

14. A process for the preparation of tablets or capsules containing herbal composition comprising the steps of :

i) mixing garlic, curcuma extracts and diluents,

ii) adding to the mixture obtained in step (i) a solution of guggul extract and preservatives dissolved in isopropyl alcohol,

iii) granulating the mixture obtained in step (ii) using conventional granulator

iv) drying the granules using conventional drier,

v) sifting the granules

vi) drying the granules,

vii) adding disintegrants, glidants, lubricants and blending the mixture and

viii) compressing into tablets or filling into capsules.

15. A method for the treatment and / or prophylaxis of hypercholesterolemia, atherosclerosis, hyperlipidemia and hypertension in mammals comprising administering the herbal composition as claimed in claim 1 to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P9/10

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

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)

EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE NAPRALERT 'Online! GODHWANI J L ET AL: "MODIFICATION OF IMMUNOLOGICAL RESPONSE BY GARLIC , GUGGAL AND TURMERIC:AN EXPERIMENTAL STUDY IN ANIMALS" XP002283789 retrieved from STN Database accession no. 92:85456 abstract & ABSTR 13TH ANNU CONF INDIAN PHARMACOL SOC JAMMU-TAWI INDIA SEPT 30-OCT 2 1980 P. B2-.., 1980, ----- -/--	1,2,11, 12

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

[ ] 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2004	23/06/2004

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	Escolar Blasco, P

1

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE NAPRALERT 'Online! GODHWANI J D ET AL: "MODIFICATION OF IMMUNOLOGICAL RESPONSE BY GARLIC , GUGGAL AND TUMERIC:AN EXPERIMENTAL STUDY IN ALBINO RATS" XP002283790 retrieved from STN Database accession no. 92:83942 abstract & PROC INDIAN PHARMACOL SOC 1980 P. ABSTR-I-2., 1980, -----	1,2,11, 12
X	DATABASE NAPRALERT 'Online! GODHWANI J L ET AL: "MODIFICATION OF INNUMOLOGICAL PESPONSE BY GARLIC , GUGGAL AND TURMERIC:AN EXPERIMENTAL STUDY IN ANIMALS" XP002283791 retrieved from STN Database accession no. 92:82694 abstract & ABSTR 13TH ANNU CONF INDIAN PHARMACOL SOC,JAMMU-TAWI,INDIA,SEPT 30-OCT 2,1980. P. ABSTR-12., 1980, -----	1,2,11, 12
Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1984, SRIVASTAVA M ET AL: "EFFECT OF HYPOCHOLESTEROLEMIC AGENTS OF PLANT ORIGIN ON CATECHOLAMINE BIOSYNTHESIS IN NORMAL AND CHOLESTEROL FED RABBITS" XP002283792 Database accession no. PREV198580097863 abstract & JOURNAL OF BIOSCIENCES (BANGALORE), vol. 6, no. 3, 1984, pages 277-282, ISSN: 0250-5991 -----	1-15
Y	ARORA R B ET AL: "LIPOTAB A POLYPHARMACEUTICAL PLANT DRUG COMBINATION IN HYPERLIPIDEMIA AND HYPERCHOLESTREMIA" INDIAN JOURNAL OF PHARMACOLOGY, XX, XX, vol. 16, no. 1, 28 December 1983 (1983-12-28), page 22, XP009029469 ISSN: 0253-7613 abstract -----	1-15
	-/--	

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARNES J: "(4) hyperlipidaemia" PHARMACEUTICAL JOURNAL 10 AUG 2002 UNITED KINGDOM, vol. 269, no. 7210, 10 August 2002 (2002-08-10), pages 193-195, XP001181754 ISSN: 0031-6873 page 193, left-hand column, paragraph 1	1-15