CHOLESTEROL LOWERING SUPPLEMENT

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(54) CHOLESTEROL LOWERING SUPPLEMENT

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(57) ABSTRACT

The invention provides a composition and a method for lowering blood serum cholesterol levels or for preventing elevated blood serum cholesterol levels, as well as a suitable composition comprising (a) one or more phytosterols and/or phytostanols capable of reducing cholesterol absorption in the intestine and/or one or more soluble fibres capable of inhibiting ileal bile acid absorption, (b) a composition capable of inhibiting cholesterol biosynthesis, and (c) a composition capable of increasing cholesterol metabolism, wherein at least one of compositions (b) and (c) is preferably derived from plants.
CHOLESTEROL LOWERING SUPPLEMENT

BACKGROUND OF THE INVENTION

[0001] Cardiovascular diseases (CVD) are the major cause of death and disability in industrialised countries, despite recent declines in CVD mortality rates. They account for more deaths annually than any other disease, including all forms of cancer combined. In the USA more than 1 million heart attacks occur each year and more than half a million people still die as a result. This enormous toll has focused attention on the possible prevention of CVD by various means, especially through lowering of plasma cholesterol levels. It is well established now that elevated cholesterol, and in particular low-density lipoprotein (LDL) cholesterol, in plasma plays an important role in the development of atherosclerosis. Clinical trials have demonstrated clearly that decreasing cholesterol concentrations in plasma can contribute to primary and secondary prevention of coronary events and mortality. Some studies have estimated a 2% reduction in risk of a coronary artery event by a 1% reduction of total serum cholesterol. 

[0002] Serum cholesterol levels can for example be lowered by a daily intake of some components similar to cholesterol. The components similar to cholesterol reduce the absorption of cholesterol from the intestines into the bloodstream.

[0003] U.S. Pat. No. 5,958,913 discloses a substance comprising a saturated sterol fatty acid ester capable of lowering LDL cholesterol levels in serum and which is fat soluble. The substance can be taken orally as a food additive, food substitute or supplement. A daily consumption of saturated sterol fatty acid ester in an amount between about 0.2 and about 20 g/day has been shown to reduce the absorption of endogenic cholesterol.

[0004] Dietary fibres have been described to lower serum cholesterol levels. Dietary fibres can be classified into two major groups depending on their solubility in water. Structural fibres like lignin and cellulose are insoluble, whereas natural gel-forming fibres like peas, and gums and psyllium are soluble. Soluble fibres play an important role in lowering serum cholesterol. There are different mechanisms by which soluble fibres lower blood cholesterol, e.g. by increasing faecal bile acid excretion.

[0005] Soluble fibres increase faecal bile acid excretion by several mechanisms: 1) binding bile acids, 2) forming gels or highly viscous solutions in the intestine and interfering with micelle formation (3). Soluble fibres are able to interact with bile acids, which results in an increased faecal excretion of bile acids. Bile acids are derived from cholesterol, and are normally effectively recycled by reabsorption from the ileum and resecretion by the liver as bile salts. To the extent that bile acids are lost with the faeces, the liver must replace the lost bile salts using cholesterol. The viscosity and gelling properties of soluble fibres may have important effects on the hydrolysis and absorption of cholesterol and the absorption of bile acids in the small intestine. Fibres that increase the viscosity of the intestinal contents may decrease intestinal motility, thereby decreasing the mixing of nutrients, digestive enzymes, and other intestinal components which will result in decreased micelle formation and absorption.

[0006] Alternatively, compositions that inhibit the cholesterol biosynthesis, for example by inhibiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), an enzyme involved in the cholesterol biosynthesis, can lower blood serum cholesterol by slowing down the production of cholesterol. It is believed that inhibition of HMG-CoA reductase results in a reduction in hepatic cholesterol synthesis and intracellular cholesterol stores, a compensatory increase in low-density lipoprotein (LDL) receptors, and a subsequent enhanced removal of LDL-cholesterol from plasma. Potent inhibitors of HMG-CoA reductase include for example the compounds referred to as statins, which family comprises for example lovastatin, pravastatin and fluvastatin.


[0008] An enzyme involved in the cholesterol metabolism (conversion of cholesterol into other components) is cholesterol 7a-hydroxylase. Hepatic cholesterol 7a-hydroxylase catalyses the conversion of cholesterol into 7a-cholesterol, which is believed to be the rate-limiting step in conversion of cholesterol into bile acids. It has been suggested that the increase of cholesterol 7a-hydroxylase activity results in the decrease of blood serum cholesterol and thus is an important pathway of elimination of cholesterol from the body. Methods for treatment of blood serum cholesterol related disorders by inhibition of cholesterol 7a-hydroxylase are known in the art.

[0009] WO 91/15213 discloses a method for treatment of cholesterol gallstones employing side-chain hydroxylated cholesterol derivative. In particular the method for treatment of cholesterol gallstones involves the administration of 25- or 26-hydroxycholesterol, which enhance the activity of cholesterol 7a-hydroxylase, thereby inhibiting for example cholesterol precipitation. Additionally, Wang et al. showed...
that several herbal preparations are capable of increasing cholesterol 7α-hydroxylase activity.


[0010] According to Raichet et al.48, feeding cholesterol to rats increased cholesterol absorption from 1.2 to 70 mg/day and inhibited its synthesis in the liver and enhanced conversion of cholesterol to bile acids from 13.7 to 27.3 mg/day. Furthermore, when given cholesterol to the rats, HMG-CoA reductase activity was inhibited 80%. With beta-sitosterol, cholesterol absorption was inhibited but cholesterol synthesis was increased from 20.0 to 28.8 mg/day.

[0011] The majority of cholesterol lowering compositions currently known in the art include ingredients which either lower cholesterol absorption within the intestines or inhibit cholesterol biosynthesis, e.g. by inhibition of HMG-CoA reductase. As Raichet et al.49 demonstrated, the inhibition of cholesterol absorption in the intestine (using β-sitosterol) lowers cholesterol absorption, however, the inhibition of cholesterol absorption in the intestines is followed by an increase in HMC-CoA reductase activity. Increase of the HMG-CoA reductase activity is likely to increase cholesterol biosynthesis and thereby reduce the net effect of cholesterol absorption inhibitors. It is therefore desirable to decrease serum cholesterol levels using combination compositions, which reduce cholesterol absorption within the intestine and additionally inhibit cholesterol biosynthesis, e.g. by inhibiting HMG-CoA reductase activity.

[0012] Methods of reducing plasma cholesterol levels comprising administering a combination of an effective amount of cholesterol biosynthesis inhibitor and an effective amount of cholesterol absorption inhibitor are disclosed in U.S. Pat. No. 5,661,145. The administered combination includes a beta-lactam cholesterol absorption inhibitor and a HMG-CoA reductase inhibitor, which can for example be a statin, for example lovastatin or pravastatin. Other pharmaceutical compositions including certain cholesterol absorption inhibitors and cholesterol synthesis inhibitors useful for the treatment of hypercholesterolemia and atherosclerosis are described in U.S. Pat. No. 5,807,834.

[0013] WO 98/01759 describes a method of determining in an animal the ratio of serum campesterol to the level of β-sitosterol comprising several steps. Additionally, a combination composition for enhancing in an animal the inhibitory effect of phytosterols on cholesterol enterocyte absorption, which comprises one or more phytosterols which inhibit predominantly one or both of cholesterol and beta sitosterol and one or more compounds which limit cholesterol synthesis, e.g. compounds selected from HMG-CoA reductase inhibitors, for example lovastatin, is described. Further described is the main disadvantage of the above composition i.e. the use of statins, and the critical side effects related with the use of statins.

[0014] WO 00/15201 discloses a composition for preventing and treating CVD containing phytosterols or phytostanols as agents inhibiting cholesterol absorption and tocotrienols as agents suppressing cholesterol biosynthesis.

[0015] WO 00/38725 provides combinations of cardiovascular therapeutic compounds for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesterol ester transport protein inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others.

[0016] U.S. Pat. No. 5,958,417 describes a herbal combination comprising Crataegus, Ho Shou Wu, Cassia Seed, Chrysanthemum, Lotus Leaf, Alisma, Hu-Zhang, and Rhubarb wherein the herbs are present in specific weight percentages. However, the herbal combination lacks a potent cholesterol absorption-inhibiting component.

[0017] Notwithstanding these disclosures, there remains a need in the art for compositions for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels. Combination compositions including cholesterol absorption inhibitors and cholesterol synthesis inhibitors useful for reduction of blood serum cholesterol levels known in the art are mostly chemically manufactured compositions and the known compositions are therefore undesirable for many people, not natural and costly.

[0018] Additionally, the combination compositions known in the art cannot be used frequently for a longer period since negative side effects will occur. Recent studies have indicated that drugs like statins, often used as HMG-CoA reductase inhibitors in combination compositions, and fibrates can be carcinogenic or cause other undesirable side effects. Newman et al.43 reported that all members of the classes statins and fibrates cause cancer in rodents. Furthermore, two hyperlipidemic patients treated with simvastatin a potent inhibitor of HMG-CoA reductase, experienced cholestasis after beginning treatment. The rash resolved after discontinuation of medication and subsequent treatment with topical moisturisers and topical corticosteroids (Mehregan et al.44). Khoda et al.45 alerts clinicians to the possible adverse effect of simvastatin and other statins by reporting a case of a 79-year-old man who had onset of fatigue, myalgia, and pleuritic chest pain 3 months after initiation of therapy with simvastatin. Lovastatin was reported to cause liver failure (Tolman46).

[0019] Furthermore, combination compositions known in the art to date only comprise effective amounts of at most two of the blood serum cholesterol reducing activities, selected from reduction of cholesterol absorption in the intestine, inhibition of cholesterol biosynthesis and increase of cholesterol metabolism.
SUMMARY OF THE INVENTION

[0020] The present invention overcomes the above problems and provides combination compositions for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels comprising one or more phytosterols and phytostanols capable of reducing cholesterol absorption in the intestine, and/or soluble fibres and mixtures thereof, capable of inhibiting ileal bile acid absorption, and an effective amount of a plant derived composition capable of inhibiting cholesterol biosynthesis and an effective amount of a plant derived composition capable of increasing cholesterol metabolism.

[0021] The combination composition disclosed here fulfills the need for cholesterol-reducing compositions having plant-derived active components. The composition according to the invention can therefore be administered for a longer period, thus making it suitable for use in compositions for reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels. The invention provides a balanced composition for use in reducing blood serum cholesterol levels or preventing elevated blood cholesterol levels. These combination compositions avoid the potential side effects or compensatory effects associated with the administration of relatively high levels of components alone directed at reducing cholesterol absorption in the intestine or at inhibiting cholesterol synthesis or at increasing cholesterol metabolism, or at only two of those three mechanisms.

[0022] The present invention provides a composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels comprising:

[0023] a. one or more compounds capable of reducing cholesterol absorption in the intestine and/or inhibiting ileal bile acid absorption, selected from phytosterols and phytostanols and soluble fibres and mixtures thereof,

[0024] b. an effective amount of a composition capable of inhibiting cholesterol biosynthesis,

[0025] c. an effective amount of a composition capable of increasing cholesterol metabolism.

[0026] Advantageously, at least one of compositions (b) and (c) is derived from plants, i.e., obtained by extraction of plants, using water, water/alcohol mixtures, alcohols, hydrocarbons or halogenated hydrocarbons as extracting liquids. Preferably, both composition (b) and composition (c) are derived from plants, most preferably from different plants or different combinations of plants.

[0027] A further object of the present invention is to provide a method of reducing serum cholesterol levels or preventing elevated blood serum cholesterol levels comprising, administering to a person a composition comprising one or more phytosterols and/or phytostanols and/or soluble fibres, capable of reducing cholesterol absorption in the intestine and/or capable of inhibiting ileal bile acid absorption, an effective amount of a plant derived composition capable of inhibiting cholesterol biosynthesis and an effective amount of a plant derived composition capable of increasing cholesterol metabolism.

DESCRIPTION OF THE INVENTION

[0028] The term cholesterol biosynthesis is well-known in the art and generally refers to the biochemical pathways of cholesterol synthesis within the animal (e.g. human) body. The term cholesterol metabolism is also well-known in the art and generally refers to the biochemical pathways involved in the removal of cholesterol from the body.

[0029] The phytosterol and/or phytostanol or mixtures thereof capable of reducing cholesterol absorption in the intestine can be any composition of phytosterol and/or phytostanol or mixtures thereof known in the art and having a cholesterol absorption reducing effect. Phytosterols are steroids derived from plants, yeasts or fungi, which have a hydroxyl group at C-3 and no other functional groups and differ from animal sterols, in particular cholesterol, in that the side chain at position 17 contains a double bond and/or an additional methyl, ethyl or ethyldiene group, in particular at position 24. The term phytosterol and/or phytostanol according to the invention, comprises all such analogues, which may further have a double bond at the 5-position in the cyclic unit as in most natural phytosterols, or one or more double bonds at other positions (e.g. 6, 7, 8(9), 8(14), 14, 5/7, or no double bonds in the cyclic unit as in the stanols, or even additional methyl groups as e.g. in α-cis-stanol, the term includes natural phytosterols and derivatives thereof.

[0030] According to a preferred embodiment the phytosterol and/or phytostanols or mixtures thereof are obtained from vegetable oil or wood pulp. More in particular, α-, β-, γ-sitosterol, stigmasterol, ergosterol, campesterol, avenasterol, brassicasterol, desmosterol, cholestanol, portferasterol, chimonasterol, sitostanol, stigmasterol, campestanol or a mixture of one or more of the above phytosterols and phytostanols is used. According to an even more preferred embodiment, sitosterol or mixtures including a sitosterol are used. The concentration of phytosterols and/or phytostanols in composition (a) is at least 10%, preferably at least 25%, more preferably at least 50%, most preferably at least 80% by dry weight of composition (a).

[0031] The soluble fibre capable of inhibiting ileal bile acid absorption can bind ileal bile acids in the intestine, thereby preventing or reducing the re-absorption of bile acids. The term soluble fibre refers to fibres which are not digested by the acids or enzymes in the digestive tract, but are fermented by the intestinal bacteria and are soluble in water. The soluble fibre of the present invention is preferably selected from the group consisting of pectin, citrus pectin, β-glucan, such as β-1,6-glucan, especially β-1,3-glucan, soluble fibre from psyllium husk (hereafter referred to as psyllium), xanthan gum, guar gum, locust bean gum, gum arabic, soy fibre and mixtures thereof, more preferably from the group consisting of psyllium, pectin, β-glucan and mixtures thereof, even more preferably the soluble fibre is β-glucan. The β-glucan soluble fibre is preferably obtained from oat, and even more preferably is part of a whole oat soluble fibre composition. Derivatives and modifications of the soluble fibres, especially hydrolysates, can also suitably be used in the compositions of the invention. Preferably, the polysaccharides of the fibres or their hydrolysates have an average chain length of at least 20, preferably at least 100 monosaccharide units. In a particular embodiment, the fibre comprises β-glucan together with at least one member selected from pectin, xanthan gum, guar gum, locust bean gum and gum arabic, preferably in a ratio between 9:1 and 1:9.

[0032] Preferably, the soluble fibre is administered in an amount between 0.2 g and 100 g soluble fibre per day, more preferably between 0.5 and 50 g, even more preferably between 1 and 25 grams, most preferably between 2 and 10 grams per day. The β-glucan is preferably administered in an
amount between 0.5 and 30 gram, more preferably in an amount between 0.6 and 10 gram, even more preferably in an amount between 0.7 and 8 gram.

[0033] Table 1 gives the preferred and the most preferred daily amounts for the soluble fibres when each soluble fibre preparation is administered as the sole soluble fibre source. The quantities of these fibres may be reduced when combinations of soluble fibres are administered.

<table>
<thead>
<tr>
<th>Soluble fibre</th>
<th>Preferred range (g/day)</th>
<th>Most preferred range (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pectin</td>
<td>0.5–20</td>
<td>1–15</td>
</tr>
<tr>
<td>chitosan</td>
<td>0.4–25</td>
<td>1–20</td>
</tr>
<tr>
<td>β-glucan</td>
<td>0.5–20</td>
<td>0.7–8</td>
</tr>
<tr>
<td>whole oat soluble fibre</td>
<td>0.5–30</td>
<td>0.7–8</td>
</tr>
<tr>
<td>psyllium</td>
<td>0.5–30</td>
<td>1.6–30</td>
</tr>
<tr>
<td>xanthan gum</td>
<td>0.75–35</td>
<td>1–30</td>
</tr>
<tr>
<td>soy fibre</td>
<td>1–40</td>
<td>3–30</td>
</tr>
<tr>
<td>locust bean gum</td>
<td>0.5–40</td>
<td>1–35</td>
</tr>
<tr>
<td>gum Arabic</td>
<td>1–50</td>
<td>2–40</td>
</tr>
<tr>
<td>guar gum</td>
<td>1–40</td>
<td>2–25</td>
</tr>
</tbody>
</table>

[0034] The soluble fibre may be mixed with the composition capable of inhibiting cholesterol biosynthesis and the composition capable of increasing cholesterol metabolism prior to administration. The fibre including serum cholesterol lowering mixture may also contain phystostigmine, phystostigmine or mixtures thereof. Alternatively, and preferably, the soluble fibre is administered separately from the composition comprising a composition capable of increasing cholesterol metabolism and a composition capable of inhibiting cholesterol biosynthesis. Thus, the composition according to the invention can be a single mixture, or it can be a combination of two or more physically separated mixtures.

[0035] Preferably, the composition comprising a composition capable of increasing cholesterol metabolism and a composition capable of inhibiting cholesterol biosynthesis is provided in the form of a pill, capsule or tablet and the soluble fibre composition is provided as a powder, emulsion, suspension, syrup or elixir. The pill, capsule or tablet preferably has a weight between 0.1 and 5 g, more preferably between 0.2 and 4 g, especially between 0.5 and 2.5 g. The powder, emulsion, suspension, syrup or elixir preferably has a weight of between 200 mg and 100 g, preferably between 1 and 15 g, dry weight. The amounts given for the pills, capsules, powders etc., may be provided in a single daily dose unit, or be divided over multiple (e.g. 2-4) daily dose units.

[0036] The plant-derived composition capable of inhibiting cholesterol biosynthesis according to the invention preferably comprises a composition capable of inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase inhibitor) and/or inhibiting squaene synthase (squalene synthase inhibitor). HMG-CoA reductase inhibitors can decrease the activity of HMG-CoA reductase, thus inhibiting the conversion of HMG-CoA to mevalonate. The HMG-CoA reductase inhibitors can act on the HMG-CoA reductase directly or indirectly by decreasing the activity of one or more enzymes (e.g. HMG-CoA reductase phosphatase) or cofactors involved in the activation of HMG-CoA reductase or increasing the activity of one or more enzymes (e.g. HMG-CoA reductase kinase) or cofactors involved in the down regulation of HMG-CoA reductase or by decreasing the HMG-CoA reductase gene transcription or of HMG-CoA reductase RNA translation.

[0037] Squalene synthase inhibitors can decrease the activity of squalene synthase, thus inhibiting the conversion of farnesyl pyrophosphate into squalene. Squalene synthase inhibitors can act on the squalene synthase directly, or indirectly by decreasing the activity of one or more enzymes or cofactors involved in the activation of squalene synthase; or increasing the activity of one or more enzymes or cofactors involved in the down regulation of squalene synthase; or decreasing the squalene synthase gene transcription or squalene synthase RNA translation. According to a preferred embodiment the composition capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors.

[0038] The composition capable of inhibiting cholesterol biosynthesis is preferably obtained from whole plants or from one or more parts thereof, for example stems, stalks, roots, shoots, rhizomes, tubers, fruits, foliage, kernels, husks, hulls or mixtures thereof. Preferably, the composition is an extract from whole plants or plant parts. Such extracts can be obtained by harvesting the plants, optionally composting the plants and/or separating certain parts of the plants, drying, extracting the plants or plant parts using liquid extraction, and optionally concentrating the extract. Drying of the plants is usually necessary to avoid degradation of labile components or microbial contamination upon storage, transport or processing, and results in lowering the water content from e.g. 50-90% to e.g. less than 25%, preferably less than 20%, most preferably between 5 and 15%. Drying is performed under mild conditions i.e. at temperatures between 0 and 80° C, in particular between 10 and 60° C, or by freeze-drying. Before or after drying, the plants or plant parts may be reduced in particle size to coarse fragments or even to fine powder by processes such as grinding, flaking or mincing. Grinding using a hammer mill or equivalent machine is preferred. Extraction according to the invention refers to separating the desired plant material by physical or chemical means, preferably with the aid of a solvent. Suitable solvents include water, water-alcohol mixtures, alcohols, ethers, hydrocarbons or other organic solvents or mixtures thereof. Water and water-based solvent mixtures are preferred. Extraction can be performed by maceration, i.e. soaking for a time between e.g. one minute and several hours, optionally using agitation, followed by filtration. For larger scale operations, counter-current extraction can be used. The resulting solutions can be concentrated to liquid or solid extracts using e.g. thin layer evaporators, freeze-drying or spray-drying techniques. Spray-drying resulting in concentrated to dry powders is preferred. Suitable plant extracts containing inhibitors of cholesterol biosynthesis are commercially available.

[0039] Preferred sources for the composition capable of inhibiting cholesterol biosynthesis include *Alisma orientale* (pharmaceutical name Rhizoma alismatis); *Typha*, spp., for example *Typha angustifolia* or *Typha orientalis* (pharmaceutical name Polien Typha); *Salvia miltiorrhiza* (pharmaceutical name Radix salviae miltiorrhiza); *Polygonum multiflorum* (pharmaceutical name Radix Polygoni multiflorae); *Cimicifuga racemosa* spp., for example, *C. ledigii*, *C. racemosa*, *C. racemosa* subsp. *acuminata*, *C. wenyuian* or *C. aromaticum*, (pharmaceutical name Radix curcumae or Rhizoma curcumae); *Ligusticum* spp., for example *L. wallichii*, (pharmaceutical name Rhizoma Ligustici); *Polygonatum* spp., for example *P. kingianum*, *P. sibiricum* or *P. cyrtogenum* (pharmaceutical name Rhizoma polygonati); *Polygonum cuspidatum* (pharmaceutical name Rhizoma polygoni cuspidati); *Corydalis* spp. (pharmaceutical name Rhizoma Corydalis); *Chrysanthemum morifolium* (pharmaceutical name Flos Chrysanthemi);
Arthmisia capillaris (pharmaceutical name Herba Artimisiae capillaris); Crataegus pinnatifida or its variations or subspecies (pharmaceutical name Fructus Crataegi pinnatifidi); Elsholtzia ciliata (pharmaceutical name Radix Elsholtzia ciliata); Astragalus membranaceus (pharmaceutical name Radix Astragali). According to a particularly preferred embodiment, *Polygonum multiflorum* is used as a source for the composition capable of inhibiting cholesterol biosynthesis, more preferably an aqueous extract of *Polygonum multiflorum*.

Preferably, the composition capable of increasing cholesterol metabolism increases the conversion of cholesterol into bile acids and/or inhibits the esterification of cholesterol. According to an even more preferred embodiment, the composition capable of increasing cholesterol metabolism enhances the activity of cholesterol 7α-hydroxylase (cholesterol-7α-hydroxylase activator) and/or inhibits the activity of Acyl-CoA acyl transferase (Acyl-CoA acyl transferase inhibitor).

A cholesterol 7α-hydroxylase activator can enhance the activity of cholesterol 7α-hydroxylase, thus enhance the conversion of cholesterol into 7α-cholesterol. Cholesterol 7α-hydroxylase activators can act on the cholesterol 7α-hydroxylase directly or indirectly by increasing the activity of enzymes and cofactors involved in the activation of cholesterol 7α-hydroxylase or decrease the activity of enzymes or cofactors involved in the down-regulation of cholesterol 7α-hydroxylase (e.g. by effecting enzymes involved in the phosphorylation and dephosphorylation of cholesterol 7α-hydroxylase) or increasing the cholesterol 7α-hydroxylase gene transcription or cholesterol 7α-hydroxylase RNA translation.

Acyl-CoA acyl transferase inhibitors can inhibit the conversion of cholesterol into cholesteryl oleate. Acyl-CoA acyl transferase inhibitors can act on the Acyl-CoA acyl transferase directly, or indirectly by decreasing the activity of one or more enzymes or cofactors involved in the activation of Acyl-CoA acyl transferase or increasing the activity of one or more enzymes or cofactors involved in the down-regulation of Acyl-CoA acyl transferase or decreasing the Acyl-CoA acyl transferase gene transcription or Acyl-CoA acyl transferase RNA translation. According to a preferred embodiment, the composition capable of increasing cholesterol metabolism comprises one or more cholesterol 7α-hydroxylase activators, which act systemically.

The composition capable of enhancing cholesterol metabolism is preferably obtained from whole plants or from one or more parts thereof, for example stems, stalks, roots, shoots, rhizomes, tubers, fruits, foliage, kernels, husks, hulls or mixtures thereof. The whole plants or plant parts providing enhancing of cholesterol metabolism may be subjected to extraction as described above for plants providing inhibitors of cholesterol biosynthesis. Suitable extracts containing the plant-derived metabolic enhancers are commercially available.

Preferred sources for obtaining the compositions capable of increasing cholesterol metabolism include *Polygonum multiflorum* (pharmaceutical name Radix Polygonyi multiflorae): *Cassia* spp., for example *C. kwangsiensis*, *C. longa*, *C. phaseoloides*, *C. wenyuiana* or *C. aromaticca*, (pharmaceutical name Radix Cassiae or Rhizoma Cassiae); *Ligusticum* spp., for example *L. schizanthum*, pharmaceutical name Rhizoma Ligustici; *Polygonatum* spp., for example *P. kingianum*, *P. sibericum* or *P. cyrtomum* (pharmaceutical name Rhizoma polygonati); *Polygonum cuspidatum* (pharmaceutical name Rhizoma polygoni cuspidati); *Corydalis* spp. (pharmaceutical name Rhizoma Corydali); *Chrysanthemum morifolium* (pharmaceutical name Flos Chrysanthemi); *Arthmisia capillaris* (pharmaceutical name Herba Artimisiae capillaris); *Acanthopanax senticosus* (pharmaceutical name Radix Acanthopann). According to a particularly preferred embodiment, *Chrysanthemum morifolium* is used as a source for the composition capable of increasing cholesterol metabolism, more preferably an aqueous extract of *Chrysanthemum morifolium*.

The dry weight ratio between composition (a) and the combination of compositions (b) and (c) is preferably between 10:1 and 1:10, more preferably between 4:1 and 1:4, if (a) does not contain soluble fibre; if (a) contains soluble fibre, the dry weight ratio between (a) and (b) + (c) is preferably between 100:1 and 1:5, more preferably between 30:1 and 1:1. The dry weight ratio between compositions (b) and (c) is preferably between 10:1 and 1:10, more preferably between 3:1 and 1:3. If composition (a) contains both (a1) phytosterols and/or phytostanols and (a2) soluble fibre, the weight ratio between the (a1) and (a2) is preferably between 1:100 and 5:1, more preferably between 1:50 and 1:2.

Elevated serum cholesterol levels are often closely related to a reduced vascular health. It is therefore advantageous to include in the composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels, an effective amount of a composition for the prevention and/or treatment of vascular disorders. Preferably one or more compounds selected from the group of polyunsaturated fatty acids, antioxidants, phospholipids, folio acid, vitamin B12, vitamin B6, magnesium, coenzyme Q10 and zinc are included in the composition according to the invention. These compositions may serve as additives or potentiators, thus increasing the cholesterol lowering effect of phytosterols and/or phytostanols, and/or for treatment and prevention of vascular disorders. Preferred polyunsaturated fatty acids are omega-6-fatty acids or omega-3-fatty acids or mixtures thereof, for example eicosapentaenoic acid, docosahexaenoic acid or linoleic acid. As a preferred antioxidant, a tocopherol, for example vitamin E, is used. As a preferred phospholipid, lecithin is used.

According to an even further preferred embodiment, long chain polyunsaturated fatty acids, phospholipids and a compound selected from the group of folio acid, vitamin B12, Vitamin B6, magnesium, zinc are included in composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels.

The composition according to the invention is preferably administered orally. The composition can for example be added to food or feed products such as beverages or products with a substantial oil content or ingested as nutritional supplement in the form of for example tablet, capsules, microbead, emulsion, powder, granule, suspension, syrup, elixir, chewing gums and the like.

Preferred daily intake amounts of the components according to the invention greatly depend on the concentration of available and/or active component present in the composition. This is especially applicable for the plant-derived material capable of inhibiting cholesterol biosynthesis and the composition capable of increasing cholesterol metabolism. According to a preferred embodiment, the daily dose of the composition according to the invention includes about 0.01 to 5 gram phytosterol and/or phytostanol or
mixtures thereof, more preferably about 0.1 to 1 gram most preferred about 0.2 to 0.6 gram. The composition capable of inhibiting cholesterol biosynthesis preferably comprises per daily dose about 0.01 to about 30 gram, depending on the type of herbal preparation used. For example, when using crude preparations of Polygonum multiflorum, e.g. unprocessed root, the daily intake is preferably between about 0.5 gram and about 15 gram. When processed Polygonum multiflorum is used (the process for preparation of processed Polygonum multiflorum is well known in the art and reduces LD50 value of Polygonum multiflorum compared to crude Polygonum multiflorum), the daily intake is preferably between about 0.5 gram and about 30 gram. According to a preferred embodiment of this invention concentrated extract of one or more of the plant sources are used. According to a further preferred embodiment, a concentrated extract of Polygonum multiflorum is used, corresponding to about 0.5 to about 30 gram crude Polygonum multiflorum, preferably about 3-10 gram crude Polygonum multiflorum. Thus when using an aqueous extract having a concentration ratio of 16:1 (16 times concentrated), the daily intake is preferably about 0.05 gram to about 2 grams, even more preferably about 0.1 gram to about 0.7 gram of the extract.

The composition capable of increasing cholesterol metabolism preferably comprises per daily dose about 0.01 to about 30 gram depending on the type of herbal preparation used. For example, when using crude preparations of Chrysanthemum morifolium, e.g. unprocessed flower, the daily intake is preferably about 1 gram to about 15 gram. According to a preferred embodiment, a concentrated extract of Chrysanthemum morifolium is used corresponding to about 1-15 gram crude Chrysanthemum morifolium, preferably about 3-10 gram crude Chrysanthemum morifolium. Thus when using an aqueous extract of Chrysanthemum morifolium having a concentration ratio of about 10:1 (10 times concentrated), the daily intake is preferably about 0.01 gram to about 3 grams, even more preferably about 0.1 gram to about 0.7 gram of the extract.

EXAMPLE 1

[0051] Capsule Composition I

[0052] A capsule comprising:

[0053] 500 mg phytosterol mixture; including about brassicasterol (6%), campesterol (30%), stigmasterol (22%), sitosterol (58%).


[0056] Three capsules per day is the recommended treatment.

EXAMPLE 2

[0057] Capsule Composition II

[0058] A capsule comprising:

[0059] 500 mg phytosterol mixture, including about brassicasterol (6%), campesterol (30%), stigmasterol (22%), sitosterol (58%).

[0060] 250 mg Radix Polygoni multiflora extract

[0061] 200 mg Flos Chrysanthemi extract

[0062] 400 mg lecithin

[0063] 60 mg cicosapentaenoic acid

[0064] 60 mg docosahexaenoic acid.

[0065] Three capsules per day is the recommended treatment.

EXAMPLE 3

Capsule Composition III

[0066] The capsule described in example 1, further comprising:

[0067] 1000 mg soybean oil

[0068] 150 mg lauric acid and monooctin.

[0069] Three capsules per day is the recommended treatment.

EXAMPLE 4

Capsule Composition IV

[0070] The capsule described in example 2, further comprising:

[0071] 400 IU vitamin E.

EXAMPLE 5

Treatment and Prevention of High Cholesterol Levels

[0072] Administering to a subject showing a high risk of elevated serum cholesterol

[0073] a capsule containing 250 mg Radix Polygoni multiflora extract and 200 mg Flos chrysanthemi extract and

[0074] a sachet containing water and soluble fibre mixture providing

<table>
<thead>
<tr>
<th>645 mg</th>
<th>Pectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1888 mg</td>
<td>Guar Gum</td>
</tr>
<tr>
<td>991 mg</td>
<td>Gum Arabic</td>
</tr>
<tr>
<td>921 mg</td>
<td>Locust Bean Gum</td>
</tr>
<tr>
<td>80 mg</td>
<td>Beta-glucan</td>
</tr>
<tr>
<td>537 mg</td>
<td>Oat Fibre</td>
</tr>
</tbody>
</table>

[0075] Two capsules and one sachet per day is the recommended treatment.

EXAMPLE 6

Capsule Composition V

[0076] A capsule comprising

[0077] 250 mg Radix polygoni multiflora extract

[0078] 200 mg Flos Chrysanthemi extract

[0079] 750 mg oat β-glucan. Three capsules per day is the recommended treatment.

19. (canceled)

20. A composition comprising:

(a) one or more soluble fibres capable of inhibiting ileal bile acid absorption;

(b) a composition capable of inhibiting cholesterol biosynthesis;
(b) a composition capable of inhibiting cholesterol biosynthesis;

(c) a composition capable of increasing cholesterol metabolism;

wherein at least one of compositions (b) and (c) is obtained from plants.

21. A composition according to claim 20, wherein at least one of compositions (b) and (c) is an extract from a plant or plant parts.

22. A composition according to claim 21, wherein compositions (b) and (c) are extracts from different plant or parts thereof.

23. A composition according to claim 20, wherein composition (b) capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors and/or squalene synthase inhibitors, preferably one or more HMG-CoA reductase inhibitors.

24. A composition according to claim 23, wherein the composition (b) is derived from a plant or plant part selected from Alisma orientale, Typha spp., Salvia miltiorrhiza, Polygonum multiflorum, Carcuma spp., Ligusticum spp., Polygonatum spp., Polygonum cuspidatum, Corydalis spp., Chrysanthemum morifolium, Arthemisia capillaries; Cra-taeus pinnatifida, Eleutherococcus senticosus, Astragalus membranaceus and subspecies and varieties thereof, the composition especially comprising an extract of Polygonum multiflorum.

25. A composition according to claim 24, wherein composition (c) capable of increasing cholesterol metabolism is derived from a plant or plant part selected from Polygonum multiflorum, Carcuma spp., Ligusticum spp., Polygonatum spp., Polygonum cuspidatum, Corydalis spp., Chrysanthemum morifolium, Arthemisia capillaries and Acanthopanax senticosus; wherein compositions (b) and (c) are extracts from different plants or parts thereof.

26. A composition according to claim 20, wherein composition (a) comprises between 200 mg and 100 g, per daily dosage unit, of one or more soluble fibres selected from pectin, chitosan, β-glucan, psyllium, xanthan gum, guar gum, locust bean gum, gum Arabic, soy fibre and mixtures thereof, preferably comprising pectin and/or β-glucan.

27. A composition according to claim 20, wherein the weight ratio between the fibres of composition (a) and the combination of compositions (b) and (c) is between 1:5 and 100:1.

28. A composition according to claim 20, wherein composition (a) further contains at least 10% by dry weight of phytosterols and/or phytostanols capable of reducing cholesterol absorption in the intestine.

29. A composition according to claim 28, wherein the phytosterol and/or phytostanol or mixture thereof comprises a plant sterol obtained from vegetable oil or wood pulp.

30. A composition according to claim 28, comprising a phytosterol selected from sitosterol, stigmasterol, ergosterol, campsterol, avenasterol, brassicasterol, desmosterol, chal- nosterol, poriferasterol, elionasterol, sitostanol, stigmasterol and campestanol.

31. A composition according to claim 30, wherein the phytosterol comprises a sitosterol.

32. A composition according to claim 20, wherein composition (c) capable of increasing cholesterol metabolism comprises an effective amount of a composition capable of increasing conversion of cholesterol into bile acids and/or inhibiting the esterification of cholesterol.

33. A composition according to claim 22, wherein composition (c) comprises one or more cholesterol 7α-hydroxylase activators and/or one or more Acryl-CoA acyl transferase inhibitors.

34. A composition according to claim 33, wherein the composition capable of increasing cholesterol metabolism is derived from a plant or plant part selected from Polygonum multiflorum, Polygonum cuspidatum, Carcuma spp., Ligusticum spp., Polygonatum spp., Corydalis spp., Chrysanthemum morifolium, Arthemisia capillaries and Acanthopanax senticosus, the composition especially comprising an extract of Chrysanthemum morifolium.

35. A composition according to claim 20, further comprising an effective amount of a component for the prevention and/or treatment of vascular disorders.

36. A composition according to claim 35, wherein the component for the prevention and/or treatment of vascular disorders is selected from a polyunsaturated fatty acid preferably comprising an omega-6-fatty acid and/or an omega-3-fatty acid, antioxidants preferably comprising vitamin E and/or another tocopherol, a phospholipid preferably comprising lecithin, folic acid, vitamin B12, vitamin B6, magnesium, coenzyme Q10 and zinc.

37. A food or beverage product comprising a composition according to claim 20.

38. A nutritional supplement comprising a composition according to claim 20.

39. A tablet, capsule, microbead, emulsion, powder, granule, suspension, syrup, elixir or chewing gum comprising a composition according to claim 20.

40. A method of reducing serum cholesterol levels or preventing elevated blood serum cholesterol levels comprising administering to a person in need thereof an effective amount of:

(d) at least 10 mg per day of one or more phytosterols and/or phytostanols capable of reducing cholesterol absorption in the intestine, and/or at least 200 mg per day of one or more soluble fibres capable of inhibiting ileal bile acid absorption;

(e) a plant-derived composition capable of inhibiting cholesterol biosynthesis; and a plant-derived composition capable of increasing cholesterol metabolism.

* * * * *