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(71) Applicant (for all designated States except US): **N.V. NUTRICIA** [NL/NL]; Eerste Stationsstraat 186, NL-2712 HM Zoetermeer (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GRIMM, Marcus Otto Walter** [DE/DE]; Marienstrasse 9, 66424 Homburg (DE). **HARTMANN, Tobias** [DE/DE]; Eisenbacher Str. 15, 66909 Matzenbach (DE). **FRIEB-JAVORKOVÁ, Petra** [CZ/DE]; Kalkofenstraße 35, 66125 Saarbrücken (DE). **LAUFS, Ulrich** [DE/DE]; Warburging 37, 66424 Homburg (DE). **WEINGÄRTNER, Oliver** [DE/DE]; Vollhardstr. 1, 66424 Homburg (DE).

(74) Agent: **HATZMANN, M.J.**; Vereenigde, Johan de Wittlaan 7, NL-2517 JR Den Haag (NL).

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(54) Title: STIGMASTEROL FOR THE TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: The invention relates to the use of stigmasterol in the manufacture of a food composition, a nutraceutical composition, or a pharmaceutical composition for prophylactic or therapeutic treatment of amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal. Further, the invention relates to the use of stigmasterol in the manufacture of a food composition, a nutraceutical composition, or a pharmaceutical composition for prophylactic or therapeutic treatment of Alzheimer's disease.



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Title: Stigmasterol for the treatment of Alzheimer's Disease

The invention is directed to the use of stigmasterol for the treatment of a disorder of the nervous system, in particular an amyloidosis of the nervous system, *e.g.* Alzheimer's disease.

In medicine, amyloidosis refers to a variety of conditions in which amyloid proteins are abnormally deposited in organs and/or tissues. A protein or peptide is described as being amyloid if, due to an alteration in its secondary structure, it takes on a particular aggregated insoluble form similar to the beta-pleated sheet. Symptoms vary widely depending upon the site of amyloid deposition.

Cerebral amyloidosis is a significant aspect of Alzheimer's disease, for which there is currently no cure and that affects a considerable part of the human population, in particular of elderly people. Several publications have reported in general terms that subjects suffering from various age-related disorders may benefit from specific classes of compounds, *e.g.*, originating from plants.

For instance, the use of phytosterols in the treatment of cardiovascular diseases has been reported in WO 2007/124597. This publication relates to a composition comprising one or more free (unesterified) phytosterols and/or phytostanols which are substantially completely dissolved in one or more esterified phytosterols and/or phytostanols. In general terms, it is indicated that the compositions may be used for treatment of dementia. However, no experimental results are given, nor any possible explanation of how such treatment would be effective.

WO 06/121558 describes a composition allegedly suitable for treatment of a variety of age-related disorders, *e.g.* Alzheimer's disease. The composition comprises one or more of a variety of active components, including statins, bisphosphonates, polyphenolic compounds and omega-3 fatty acids. It is men-

tioned that the composition may also comprise phytosterols for inhibiting cholesterol absorption. The use of stigmasterol (or another specific phytosterol) specifically for treatment of amyloidosis of the nervous system is not shown.

WO 00/30666 relates to a composition comprising plant matter from a plant of the genus *Uncaria*. The composition may amongst others be used for a variety of brain stimulating uses, such as improving mental alertness, for reducing or preventing amyloid protein deposits or for promoting or supporting pancreatic function in a patient. The composition may contain a mixture of the plant sterols beta-sitosterol, stigmasterol and campesterol. The effectiveness of a specific phytosterol, in particular stigmasterol for treatment of amyloidosis of the nervous system is not shown.

Van Mierlo *et al.* (Abstracts/Chemistry and Physics of Lipids 154S (2008) S60) reported that dietary plant sterols, which are structurally very similar to cholesterol, can accumulate in the brain. It was found that beta-sitosterol, but not campesterol nor stigmasterol, induced a shift in the cleavage profile of beta-amyloid protein.

In general, the prior art provides little or no teaching that helps the skilled person to formulate dedicated preparations, comprising a specific active component, in particular a specific active phytosterol, for treatment of specific pathology.

The present inventors have found that specific phytosterols have different effects on a specific pathology, namely on pathologic aggregation of a peptide (A β), cleaved from Amyloid Precursor Protein (APP) via a cascade of beta-secretase activity and gamma-secretase activity. This is a pathology associated with Alzheimer's disease. In fact, as illustrated by the Example herein below, all but one phytosterols that were tested had an adverse affect on A β aggregation. Based on this research, the inventors have come to the conclusion that at least some phytosterols may in fact have an adverse effect on at least some forms of amyloidosis, in particular on amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal.

It is an object of the invention to provide a use of a specific compound, which may be present in a pharmaceutical composition, a nutraceutical composition or a food composition, in the manufacture of a composition for prophylactic or therapeutic treatment of pathologic aggregation of beta-amyloid peptide in the nervous system, in particular the cerebral system of a mammal.

It has been found that a specific phytosterol, unlike several other phytosterols, is suitable for such purpose. Accordingly, the present invention relates to the use of stigmasterol in the manufacture of a food composition, a nutraceutical composition, or a pharmaceutical composition for prophylactic or therapeutic treatment of amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal, in particular the central nervous system of a mammal, more in particular in the cerebral part of the nervous system of a mammal.

The invention further relates to the use of stigmasterol in the manufacture of a food composition, a nutraceutical composition, or a pharmaceutical composition for prophylactic or therapeutic treatment of Alzheimer's disease.

The invention further relates to stigmasterol for use as a gamma-secretase inhibitor and/or for use as a beta-secretase inhibitor. Such use may be non-medical (in an *in vitro* application) or medical, in which case the stigmasterol may in particular be for use as a gamma secretase inhibitor in the brain or another part of the nervous system of a mammal.

Phytosterols (also called plant sterols) are a group of steroid alcohols, phytochemicals naturally occurring in plants. Common phytosterols are stigmasterol, ergosterol, beta-sitosterol, campesterol and brassicasterol.

Amyloidosis is a group of diseases characterised by deposition of amyloids in the nervous system of a mammal. Amyloid is a generic term referring to a group of diverse, but specific extracellular protein deposits which all have common properties, staining characteristics, and x-ray diffraction spectra. Regardless of the nature of the amyloid protein deposited all amyloids

have the following characteristics: 1) an amorphous appearance at the light microscopic level and appear eosinophilic using hematoxylin and eosin stains; 2) typically stain with Congo red and demonstrate a red/green birefringence as viewed under polarized light. 3) typically contain a predominant beta-pleated sheet secondary structure, and 4) ultrastructurally amyloid usually consist of non-branching fibrils of indefinite length and with a diameter of 7-10 nm.

Forms of amyloidosis include the amyloid associated with Alzheimer's disease, Down's syndrome and Hereditary cerebral hemorrhage with amyloidosis of the Dutch type (wherein the specific amyloid is referred to as beta-amyloid protein or A β), the amyloid associated with chronic inflammation, various forms of malignancy and Familial Mediterranean Fever (wherein the specific amyloid is referred to as AA amyloid or inflammation-associated amyloidosis), the amyloid associated with multiple myeloma and other B-cell dyscrasias (wherein the specific amyloid is referred to as AL amyloid), the amyloid associated with type 11 diabetes (wherein the specific amyloid is referred to as amylin or islet amyloid), the amyloid associated with the prion diseases including Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru and animal scrapie (wherein the specific amyloid is referred to as PrP amyloid), the amyloid associated with long-term hemodialysis and carpal tunnel syndrome (wherein the specific amyloid is referred to as beta2-microglobulin amyloid), the amyloid associated with senile cardiac amyloid and Familial Amyloidotic Polyneuropathy (wherein the specific amyloid is referred to as prealbumin or transthyretin amyloid), and the amyloid associated with endocrine tumors such as medullary carcinoma of the thyroid (wherein the specific amyloid is referred to as variants of procalcitonin).

For a more detailed description of amyloid and amyloidosis reference is made to WO 00/30666, page 17-line 17- page 22 line 11, of which the contents are incorporated herein by reference.

As mentioned above, and illustrated by the example below, the inventors have found that of a group of tested phytosterols, only stigmasterol

was considered effective in reducing gamma-secretase activity. Other phytosterols (campesterol, beta-sitosterol and ergosterol), but also cholesterol (a sterol of animal origin) had an adverse effect.

Accordingly, it is preferred that the amount of such other phytosterols and optionally cholesterol is relatively low, or even that these other compounds are absent from any food composition, nutraceutical composition, or pharmaceutical composition for prophylactic or therapeutic treatment of amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal. Therefore, usually the concentration of stigmasterol in a composition of the invention as a weight percentage of the sum of phytosterols, in particular stigmasterol, ergosterol, beta-sitosterol, brassicasterol, and campesterol, and optionally also including cholesterol is 25-100 weight%, in particular 50 to 100 weight%, preferably 75 to 100 weight%, more preferably 90 to 100 weight%, in particular 95 to 100 weight%, more in particular 98 to 100 weight%.

In particular, it is preferred that the concentration of stigmasterol in a composition of the invention as a weight percentage of the sum of phytosterols, in particular stigmasterol, ergosterol, beta-sitosterol, brassicasterol and campesterol, and optionally also including cholesterol is 25-100 weight%, in particular 50 to 100 weight%, more in particular 75 to 100 weight%, 90 to 100 weight%, 95 to 100 weight%, or 98 to 100 weight%.

In a preferred embodiment, the stigmasterol is for treatment of a human, in particular an elderly person. In this respect, it is submitted that in the context of this application, an elderly person is a person of the age of 50 or more, in particular of the age of 55 or more, more in particular of the age of 60 or more, more in particular of the age of 65 or more. This rather broad definition takes into account the fact that the average age varies between different populations, on different continents, *etc.* Most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person (associated with the age at which one may begin to receive pension benefits), but like many westernized concepts, this does not adapt well to *e.g.*

the situation in Africa. At the moment, there is no United Nations (UN) standard numerical criterion, but the UN agreed cut-off is 60+ years to refer to the older population in Western world. The more traditional African definitions of an elder or 'elderly' person correlate with the chronological ages of 50 to 65 years, depending on the setting, the region and the country.

A composition of the present invention usually contains stigmasterol in an amount sufficient to administer to a subject (in particular a human adult (average weight about 70 kg)) a daily dosage of at least 0.5 mg/day, at least 5 mg/day, at least 25 mg/day, at least 50 mg/day, at least 100 mg/day, at least 200 mg/day, at least 400 mg/day, or at least 800 mg/day. The daily dosage may be 4000 mg/day or less, 2000 mg/day or less, 1000 mg/day or less, 500 mg/day or less, or 250 mg/day or less.

In particular in case of a nutraceutical composition, which may be a food or beverage, the amount of stigmasterol contained therein is suitably present in the composition in a quantity to provide the daily dosage in a single serving.

The term "serving" as used herein denotes an amount of food or beverage normally ingested by a human adult with a meal at a time and may range, e.g., from about 1 g (such as a nutritional shot) to about 500 g.

In one aspect, the present invention (a composition comprising) stigmasterol may be used as a nutritional supplement, e.g., as an additive to a multi-vitamin preparations comprising vitamins and minerals which are essential for the maintenance of normal metabolic function but are not synthesized in the body, especially for the treatment or prevention of age-related decline in brain neuronal function and/or cognitive functioning in a mammal.

The pharmaceutical composition, preferably for enteral application, may be solid or liquid galenical formulation. Examples of solid galenical formulations are tablets, capsules (e.g. hard or soft shell gelatine capsules), pills, sachets, powders, granules and the like which contain the active ingredient together with conventional galenical carriers. Any conventional carrier material

can be utilized. The carrier material can be organic or inorganic inert carrier material suitable for oral administration. Suitable carriers include water, gelatine, gum Arabic, lactose, starch, magnesium stearate, talc, vegetable oils, and the like. Additionally, additives such as flavouring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding. While the individual active ingredients are suitably administered in a single composition they may also be administered in individual dosage units.

If the composition is a pharmaceutical formulation, such formulation may contain the daily dosage in one or more dosage units. The dosage unit may be in a liquid form or in a solid form, wherein in the latter case the daily dosage may be provided by one or more solid dosage units, *e.g.* in one or more capsules or tablets.

A composition according to the invention, in particular a nutritional composition, such as a food or beverage or a supplement composition for a food or beverage, may comprise one or more further ingredients, such as, protein, fat, digestible carbohydrates, dietary fibres, such as indigestible carbohydrates, minerals, vitamins, organic acids, and flavouring agents. Examples of additional ingredients are, *e.g.* described in WO2003/041701 (N.V. Nutricia) and WO2007/073178 (N.V. Nutricia).

Advantageously, a nutritional composition according to the invention may comprise protein, preferably intact protein. Proteins enable the manufacturing of palatable products. Especially elderly and AD patients benefit from the protein as it strengthens their motor skills. Preferably, the nutritional composition according to the invention comprises milk protein. Preferably, the nutritional composition according to the invention comprises a protein selected from the group consisting of whey protein, casein or caseinate. Preferably, the nutritional composition according to the invention comprises caseinate, more preferably the nutritional composition according to the invention

comprises at least 70 weight%, more preferably at least 90 weight% casein and/or caseinate, based on total protein.

Preferably, the proteins are included in intact (unhydrolyzed) form, in order to have a palatable product. Such high molecular weight proteins increase the viscosity of the heat-treated liquid product, compared to the hydrolyzed forms. The present inventors were able to make an acceptable product, with good palatability and limited viscosity, by applying the measures according to the invention, still avoiding precipitation.

Preferably, the nutritional composition according to the invention comprises between 0.2 and 16 gram protein per 100 ml, preferably between 0.2 and 10 gram protein per 100 ml, more preferably between 1 and 6 grams protein per 100 ml, more preferably between 2 and 5 grams protein per 100 ml.

Advantageously, the nutritional composition according to the invention may comprise fat. With regard to the type of fat, a wide choice is possible, as long as the fat is of food quality. The fat may be a solid, a semi-solid or a liquid (oil) at room temperature (25 °C).

The fat may include medium chain triglycerides (MCT, mainly 8 to 10 carbon atoms long), long chain triglycerides (LCT, typically at least 12 carbon atoms long) or any combination of the two types.

MCTs are beneficial because they are easily absorbed and metabolized. Moreover, the use of MCTs will reduce the risk of nutrient malabsorption.

LCT sources, such as rapeseed oil, more in particular rapeseed oil low in erucic acid, sunflower oil, corn oil, palm kernel fat, coconut fat, palm oil, or mixtures thereof are preferred because they provide more energy per unit of fat.

In a specific embodiment the composition comprises one or more polyunsaturated fatty acids (PUFA's), in particular one or more PUFA's selected from docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA).

In a specific embodiment, the fat comprises 30 to 60 weight% of animal or algal fat, 40 to 70 weight% of vegetable fat and optionally 0 to 20 weight% of MCTs based on total fat of the nutritional composition according to the invention. The animal fat preferably comprises none or a low amount of milk fat, i.e. lower than 6 weight%, especially lower than 3 weight%. In particular, a mixture comprising one or more oils selected from the group of corn oil, egg oil, canola oil and marine oil may be present. Egg oils, fish oils and algal oils are a preferred source of non-vegetable fats. Marine oils containing DHA and/or EPA are preferably present in the nutritional composition according to the invention for obtaining a positive health effect, such as, for instance, the prevention of cardiovascular risks. For a desirable taste, the concentration preferably is 25 weight% or less, more preferably 15 weight% or less of the fat.

The amount of EPA ranges preferably between 4 weight% and 15 weight%, more preferably between 8 weight% and 13 weight% of the fat.

Preferably, the nutritional composition according to the invention comprises a phospholipid, preferably 0.1 to 50 weight% phospholipids, based on total weight of lipids, more preferably 0.5 to 20 weight%, more preferably between 1 and 5 weight%, based on total weight of lipids. Preferably, the nutritional composition according to the invention contains at least one selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol. The total amount of lipids is preferably between 10 and 30 weight% on dry matter, and/or between 2 and 6 g lipid per 100 ml for a liquid composition. Inclusion of phospholipids improve the stability of the nutritional composition according to the invention.

Advantageously, the nutritional composition according to the invention comprises one or more digestible carbohydrates. The digestible carbohydrates positively influence the operational skills of a subject, and add to the advantageous effect of the nutritional composition according to the invention. The total amount of digestible carbohydrates is preferably between 25 and 80 weight% on dry matter basis, preferably 40 to 80 weight. In case of a liquid

nutritional composition according to the invention, the composition preferably contains between 1 and 50 gram digestible carbohydrates per 100 ml of a liquid product, more preferably between 5 and 30 grams per 100 ml, more preferably 10 to 30 grams of digestible carbohydrates per 100 ml.

Examples of digestible carbohydrates are digestible pentoses, digestible hexoses and digestible oligosaccharides, e.g. digestible disaccharides and digestible trisaccharides. More specifically one or more digestible carbohydrates may be chosen selected from the group of galactose, mannose, ribose sucrose, trehalose, palatinose, lactose, maltodextrose, maltose and glucose.

Optionally, a nutritional composition according to the invention comprises one or more non-digestible carbohydrates (dietary fibres) such as oligosaccharides. As used herein, the term oligosaccharides in particular refers to saccharides comprising 3 to 25 monosaccharide units per molecule. The oligosaccharide(s) may in particular be selected from the group of fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), trans-galacto-oligosaccharides (TOS), xylo-oligosaccharides (XOS), soy oligosaccharides, and the like. Optionally, also higher molecular weight compounds such as inulin, resistant starch and the like may be incorporated in the composition according to the invention. In a further embodiment of the present invention, the composition according to the invention comprises a mixture of neutral and acid oligosaccharides, such as disclosed in WO 2005/039597 (N.V. Nutricia); compositions disclosed therein are incorporated herein by reference.

Further, one or more of the following components may in particular be present: taurine, cysteine, manganese, molybdenum, zinc, selenium, magnesium, chromium, iron, copper, vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B6, folic acid, vitamin B12, vitamin C, vitamin D, vitamin E and biotin.

Preferably, a liquid nutritional composition of the invention (food/nutraceutical) has an energy density of 80 to 450 kcal per 100 ml of the composition, more preferably between 90 and 250 kcal per ml of the liquid nu-

tritional composition. This is in particular considered advantageous because persons suffering from neuropathies or neurological problems often experience problems with eating. Their sensory capabilities and/or control of muscles generally have become imparted, as well as in some instances their ambition to apply proper eating habits. Part of these patients may experience a general loss in appetite and a relatively large part of this patient group became malnourished. A liquid nutritional composition is relatively easy to administer, and by having an energetic value in the specified range, such people can relatively easily obtain sufficient caloric intake.

Liquid nutritional products preferably have a long shelf life. However, increasing shelf life by heat treatments often results in destabilisation of the products and/or palatability, leading to a product which is undesirable. A nutritional composition according to the invention can be subjected to a heat treatment without major adverse effects on the palatability. Hence, the nutritional composition according to the invention is preferably heat-treated, more preferably the composition is subjected to a sterilization treatment. In a preferred embodiment, the nutritional composition according to the invention is subjected to an ultra-high temperature treatment (UHT-treatment). Such UHT-treatment is preferably applied in line, i.e. before the liquid final product is filled in the package of the unit.

Another embodiment, a food composition (for use) in accordance with the invention may in particular be selected from the group of spreads ; yoghurts, custards, ice-creams, butter, and other dairy products ; dairy-substitute products ; fruit drinks ; candy bars, and cookies.

The invention is further directed to a specific composition comprising stigmasterol, namely a food composition, a nutraceutical composition, or a pharmaceutical composition, comprising stigmasterol, wherein the stigmasterol concentration in the composition as a weight percentage of the sum of phytosterols, in particular stigmasterol, ergosterol, beta-sitosterol, brassicasterol, and campesterol, and optionally also including cholesterol is 25-100

weight%, in particular 50 to 100 weight%, preferably 75 to 100 weight%, more preferably 90 to 100 weight%, in particular 95 to 100 weight%, more in particular 98 to 100 weight%.

The stigmasterol concentration as percentage of the total dry weight can be chosen within wide limits. The concentration may be at least 0.05 weight%, at least 0.1 weight%, at least 0.25 weight%, at least 0.5 weight%, at least 1 weight% or at least 2.5 weight% based on the total dry weight of the composition. The concentration may be 90 weight% or less, 75 weight% or less, 50 weight% or less, 25 weight% or less, 10 weight% or less or 5 weight% or less, based on the total dry weight of the composition.

In a specific embodiment the composition is in a dosage unit form, *e.g.* in a packaging such as a bottle, a carton, a cup, in a strip (in case of a pharmaceutical or nutritional supplement), or the like.

In case the composition is in a dosage unit form, the dosage unit form may provide 0.5 to 2000 mg, in particular 5 to 1000 mg, more in particular 25 to 500 mg stigmasterol.

The invention is further directed to prophylactic or therapeutically treating amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal, the method comprising administering an effective dose of stigmasterol to the mammal.

The invention is further directed to prophylactic or therapeutically treating Alzheimer's disease, the method comprising administering an effective dose of stigmasterol to a mammal suffering from Alzheimer's disease or having a risk of developing Alzheimer's disease. With respect to 'having a risk', in general any mammal, in particular any human, is considered to have a risk. In particular mammals are considered to have a risk of developing Alzheimer's disease in case they have an increased genetic risk or in case they are elderly.

The administration may in particular be an enteral administration, although in principle any other form of administration may be used, depending upon the form in which the stigmasterol is to be administered. Alternative

forms of administration are known in the art and include injection, administration as a suppository, *etc.*

Effective dosages, specifics on the forms in which the stigmasterol may be administered are as described herein above.

The invention will now be illustrated by the following example.

EXAMPLE

General

Campesterol, ergosterol, beta-sitosterol, stigmasterol and cholesterol were obtained from SIGMA ALDRICH. For *in vitro* assays, stock solutions of
5 10 mM in ethanol were prepared and stored at -20°C under non oxidizing conditions.

Cell culture

Human neuroblastoma cell line SH-SY5Y-wt. grew in Dulbecco's
10 Modified Eagle's Medium (DEMEM)ALDRICH), supplemented with 10% of foetal calf serum (FCS) and 1x Non-essential Amino Acid Solution (MEM, SIGMA ALDRICH).

Before harvesting, 100% confluent cells were incubated in DMEM, containing 0.1% FCS + MEM for a period of 48h (2x24h).

15

In-vitro Assay for gamma-secretase activity

For preparation of total membranes, SH-SY5Y-wt cells (treated like shown above), were scraped and cracked in a buffer, containing 10 mM Tris-HCl pH 7.4. After separation of total membranes via ultracentrifugation, re-
20 suspended membranes were incubated with 100 µM of sterol and gamma-secretase activity was measured by detecting the fluorescence-generating

cleavage product of a specific gamma-secretase-substrate. Experiments were reproduced three times.

Results

5

Table 1: Effect of various (plant)-sterols on gamma-secretase-activity *in vitro*.

	Activity (% of control: ethanol)	p-value
Campesterol	115	0.008
Ergosterol	164	<0.001
Beta-Sitosterol	141	<0.001
Stigmasterol	82	0.001
Cholesterol	125	<0.001

As shown in Table 1, there is an effect on gamma-secretase-activity, caused by phytosterol incubation. Nearly all tested substances had an effect of increasing the activity of the enzyme in a span of 115% (campesterol) to 164% (ergosterol), compared to solvent control. The only plant sterol, lowering gamma-secretase-activity, was stigmasterol (82 %, compared to solvent control).

10

Discussion

Concerning Amyloid Precursor Protein -processing via gamma-secretase, most of the analyzed sterols (campesterol, beta-sitosterol, ergosterol, cholesterol) showed a clear increase in gamma-secretase activity. Only stigmasterol decreased the enzyme's activity to 82%. It is considered surprising that stigmasterol is effective as a gamma-secretase inhibitor and the other tested phytosterols are not, since there are great similarities in structure (identical steroid backbone and relatively small differences in the side chain).

Claims

1. Use of stigmasterol in the manufacture of a food composition, a nutraceutical composition, or a pharmaceutical composition for prophylactic or therapeutic treatment of amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal.
5
2. Use of stigmasterol in the manufacture of a food composition, a nutraceutical composition, or a pharmaceutical composition for prophylactic or therapeutic treatment of Alzheimer's disease.
3. Use according to any one of claim 1 and 2, wherein the stigmasterol is for use as a gamma-secretase inhibitor, for use as a beta-secretase inhibitor or for both of said uses.
10
4. Use according to any of the claims 1-3, wherein the stigmasterol concentration in the composition as a weight percentage of the sum of phytosterols, in particular stigmasterol, ergosterol, beta-sitosterol, brassicasterol, and campesterol, and optionally also including cholesterol is 25-100 weight%, preferably 50 to 100 weight%, more preferably 75 to 100 weight%, most preferably 90 to 100 weight%.
15
5. Use according to any of the claims 1-4, wherein the composition is for administration to a human.
6. Use according to claim 5, wherein the human is an elderly person.
20
7. Use according to any of the preceding claims, wherein the composition is to be administered to provide a daily dosage of 0.5 to 2000 mg, in particular of 5 to 1000 mg, more in particular 25 to 500 mg stigmasterol.
8. Use according to any of the preceding claims, wherein the composition comprises at least one component selected from the group of fats, proteins, carbohydrates and pharmaceutically acceptable carrier materials.
25
9. Use according to any of the preceding claims, wherein the

composition is in a dosage unit form.

10. Use according to any of the preceding claims, wherein the composition is a product selected from the group of spreads; yoghurts, custards, ice-creams, butter and other dairy products; dairy-substitute
5 products; fruit drinks; candy bars; and cookies.

11. Food composition, a nutraceutical composition, or a pharmaceutical composition, comprising stigmasterol, wherein the stigmasterol concentration in the composition as a weight percentage of the sum of phytosterols, in particular stigmasterol, ergosterol, beta-sitosterol, brassicasterol, and
10 campesterol, and optionally also including cholesterol is 25-100 weight%, preferably 50 to 100 weight%, more preferably 75 to 100 weight%, most preferably 90 to 100 weight%

12. Composition according to claim 11, wherein the stigmasterol concentration is 0.05 to 75 weight%, in particular 0.1 to 50 weight%, more in
15 particular 0.25 to 25 weight%, based on the total dry weight of the composition.

13. Composition according to claim 11 or 12, wherein the composition is in a dosage unit form, providing 0.5 to 2000 mg, in particular of 5 to 1000 mg, more in particular 25 to 500 mg stigmasterol.

20 14. Food composition according to any of the claims 11-13, selected from the group of spreads; yoghurts, custards, ice-creams and other dairy products; dairy-substitute products; fruit drinks; candy bars; and cookies.

15. Method for prophylactically or therapeutically treating amyloidosis of beta-amyloid peptide (A β) in the nervous system of a mammal, the method
25 comprising administering an effective dose of stigmasterol to the mammal.

INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2009/050315

A. CLASSIFICATION OF SUBJECT MATTER

INV. A23L1/30 A61K31/575

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)

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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, FSTA, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040.
Fax: (+31-70) 340-3016

Authorized officer

Fischer, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2009/050315

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