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(54) Title: NOVEL BLOOD PRESSURE LOWERING COMPOSITION

(57) Abstract: The present invention provides a composition comprising a peptide which is IPP and/or VPP; and at least one compound which can be extracted or purified from a natural source, this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape seed extract or isolate.

NOVEL BLOOD PRESSURE LOWERING COMPOSITION

Field of the invention

The present invention relates to a novel blood pressure lowering composition.

Background of the invention

Hypertension, commonly referred to as "high blood pressure" or HTN, is a medical condition in which the blood pressure is chronically elevated. While it is formally called arterial hypertension, the word "hypertension" without a qualifier usually refers to arterial hypertension. Hypertension can be classified as either essential (primary) or secondary. Essential hypertension indicates that no specific medical cause can be found to explain a patient's condition. Secondary hypertension indicates that the high blood pressure is a result of (i.e. secondary to) another condition, such as kidney disease or certain tumors (especially of the adrenal gland). Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated. (source: http://en.wikipedia.org/wiki/Hypertension).

Most textbooks mention that the cause of high blood pressure is not known for more than 90% of the persons in question. Genetics disposition is seen as relevant fact, but most of all high blood pressure is nowadays often linked to lifestyle and dietary factors

In lifestyle habits like coffee drinking, alcohol consumption, lack of exercise and stress may negatively influence blood pressure. Dietary factors like high saturated fat or high salt containing food and obesity play an important role as well.

Especially a change in lifestyle might be very helpful to decrease the blood pressure of most people. In that respect, nutraceuticals can be part of a healthy diet to decrease elevated blood pressure. For those people there exist nowadays many suitable compounds exist which are found to be helpful. There is a trend nowadays to use selected compounds that are sometimes already part of the regular diet. In general these selected compounds are consumed then at an increased dosage compared to the regular food intake.

On the other hand there is always a need to minimalize the necessary amounts of active compounds added to influence our physical conditions. Not only the production costs can be very high because of concentration and extraction costs, but also there is a feeling by the public that for example the amount of an active compound in a neutraceutical should be kept as low as possible. Synergetic compositions are able to meet this demand and therefor there is a need for synergetic combinations of active compounds in order to reduce this amount of active compounds.

Another observation made is that antihypertensives, compounds which are used to treat hypertension, will have a positive effect for only a certain percentage of people using the hypertensives. For example ACE (angiotensin converting enzyme) inhibiting peptides are found to be effective for about two third of people with high blood pressure, which amount corresponds with many prescription drugs.

In general a person in need of a blood pressure lowering effect will try one antihypertensive for about two months and only when after the two months there is no effect will try another antihypertensive. Sometimes in practice a lot of trial have to be done before a blood pressure lowering effect is found and in practice, many patients require therapy with multiple classes of blood pressure lowering pills before attaining a meaningful blood pressure lowering effect.

Therefore there is a need for blood pressure lowering compositions that will have an effect on higher numbers of people and at the same time comprising those compounds as effective ingredients, which are present in normal diets.

Description of the invention

The present invention discloses a novel blood pressure lowering composition which has an effect on at least four fifth of the people in need of such a composition.

The composition of the invention comprises:

- a peptide which has an ACE inhibiting effect; and
- at least one compound which can be extracted or purified from a natural source,this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape seed extract or isolate.

Prefered peptides are IPP (Ile-Pro-Pro) and VPP (Val-Pro-Pro). I or Ile is isoleucine. V or Val is Valine. P or Pro is proline.

It was surprisingly found that the combination of each of the above compounds with IPP and/ or VPP produced a synergistic blood pressure reducing effect, i.e. the combined effect was larger than the sum of the blood pressure reducing effects of each of the individual compounds. Moreover, it was surprisingly found that the composition of the invention has an effect on a larger group of people than on each of the effective ingredients.

The present invention also relates to a method of producing the composition of the invention by bringing together the peptide which is IPP and/or VPP and the at least one compound which can be extracted or purified from a natural source,this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape extract or isolate.

Furthermore the invention relates to the use of

- a peptide which has an ACE inhibiting effect; and
- at least one compound which can be extracted or purified from a natural source, this compound which can be extracted or purified from a natural source, this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape seed extract or isolate

in a food, feed, neutraceutical or dietary supplement or for the preparation of a food, feed, neutraceutical or dietary supplement.

In this use the peptide is preferably IPP or VPP. Moreover this use relates to ACE inhibition effect or for blood pressure lowering.

According to one aspect of the invention the peptide and the compound which can be extracted or purified from a natural source have together a synergetic effect on blood pressure lowering.

The present invention also relates to a method of treatment of a person in need of a blood pressure lowering effect which comprises administering to said person the composition of the invention.

The peptide having an ACE inhibiting effect may be produced according to any known process. It may be isolated from a protein source, it may be made by chemically or enzymatically hydrolyzing a protein or may be produced synthetically. Preferably the

peptide is produced by hydrolysing a suitable protein and is part of a hydrolysate. The hydrolysate may optionally be purified to increase the peptide content in the hydrolysate. Substrates for enzymatic hydrolysis include whole milk, skimmed milk, acid casein, rennet casein, acid whey products or cheese whey products. Other substrates for enzymatic hydrolysis are collagen based animal proteins such as gelatine as well as bones or fish-bones. Moreover, vegetable substrates like wheat gluten, milled barley and protein fractions obtained from, for example, soy, rice or corn are suitable substrates. Preferably milk or milk derived protein, such as casein or whey, is used.

The compound extracted from a natural source can be;

- Fish oil (EPA / DHA)

Several studies have reported a favorable effect of EPA/DHA on blood pressure. EPA and DHA may modulate the signaling intracellular Ca^{2+} ion, which leads vascular muscles to dilate. Other postulated mechanisms include shifting of the TxA_2 / TxA_3 balance in favor of TXA_3 and at the cost of the vasoconstrictive TxA_2; Altering prostaglandin synthesis; enhancing cell membrane fluidity, leading to altered ion channel activity.

- Green tea (ECGC)

For EGCG, some studies have reported favorable effects on blood pressure in rats, but no study has been found reporting effects in humans.

Mechanism of action

For green tea the primary mechanism of action underlying the putative blood pressure lowering responses would lie in the anti-oxidative action of the polyphenols. This antioxidant effect would improve the bioavailability of the endogenous vasodilator nitric oxide (NO). Some in vitro studies have suggested an ACE-inhibitory action of a number of polyphenols, but this effect has not been substantiated in humans.

- Gamma-amino-butyric acid (GABA)

GABA has been described to lower blood pressure in several papers (see refs). All four studies were of different design and used GABA derived from different sources. All 4 studies were conducted in Japan.

Since GABA administered at moderate doses does not cross the blood-brain barrier, its effects on blood pressure are considered to take place via peripheral mechanisms.

Based on studies in rats, the most likely mechanism appears to be attenuation of sympathetic neurotransmission through blockade of $GABA_B$ receptors at sympathetic nerve terminals or ganglionic sites. However, binding of GABA to peripheral benzodiazepine receptors has been described and may account for part of GABA's hypotensive effect as well.

1. Inoue K, Shirai T, Ochiai H, et al. Blood-pressure-lowering effect of a novel fermented milk containing gamma-aminobutyric acid (GABA) in mild hypertensives. EUR J CLIN NUTR 57 (3): 490-495 MAR 2003.

2. Kazami D, Ogura N, Fukuchi T, et al. Antihypertensive effect of Japanese taste seasoning containing gamma-amino butyric acid on mildly hypertensive and high-normal blood pressure subjects and normal subjects. J JPN SOC FOOD SCI 49 (6): 409-415 2002.

3. Watanabe et al. J. Jap. Food Sci. Technol. (2003) **50** 167-173:GABA-enriched *Agaricus blazei* mushrooms, mildly hypertensive subjects, placebo controlled double blind cross-over, 14 subjects, 1 week

4. Tsuchida T, et al. J Jpn Soc Nutr Food Sci (2003) **56** 97-102: GABA-rich Chlorella in 60 subjects with high-normal BP and hypertension.

- Grape seed extract (including Resveratrol)

An abstract in the Faseb Journal (The FASEB Journal. 2007;21:750.33) from the University of California at Davis has reported that blood pressure in subjects with pre-hypertension dropped by 8 / 6 mmHg for systolic and diastolic blood pressure after taking grape seed extract (300 mg).

Mechanism of action

For grape seed extract the primary mechanism of action underlying the putative blood pressure lowering responses would lie in the anti-oxidative action of the polyphenols. This antioxidant effect would improve the bioavailability of the endogenous vasodilator nitric oxide (NO). Some in vitro studies have suggested an ACE-inhibitory action of a number of polyphenols, but this effect has not been substantiated in humans.

- Tomato extract (lycopene)

Only one study has been published on blood pressure lowering properties of tomato extract in humans, but it appears to be a well-designed study with robust effects (~10 mmHg decrease in a placebo controlled study. Egelhard , Am Heart J. 2006).

Mechanism of action

For tomato extract the primary mechanism of action underlying the putative blood pressure lowering responses would lie in the anti-oxidative action of the polyphenols. This antioxidant effect would improve the bioavailability of the endogenous vasodilator nitric oxide (NO). Some in vitro studies have suggested an ACE-inhibitory action of a number of polyphenols, but this effect has not been substantiated in humans.

- Olive extract (hydroxytyrosol)

No effects reported in peer-reviewed literature. (Note that some evidence exists for Olive *leaf* extracts).

Mechanism of action

For olive extract the primary mechanism of action underlying the putative blood pressure lowering responses would lie in the anti-oxidative action of the polyphenols. This antioxidant effect would improve the bioavailability of the endogenous vasodilator nitric oxide (NO). Some in vitro studies have suggested an ACE-inhibitory action of a number of polyphenols, but this effect has not been substantiated in humans.

- Vitamin D

Seven human studies have been published on effects of vitamin D intervention (1 – 20 µg/day) on blood pressure (for a review, see Zitterman 2003; no more recent studies reported) with diffent results varying from without effect to having an effect.

Vitamin D improves Ca^{2+} metabolism and Ca^{2+} has been suggested to improve blood pressure. Alternatively, there are indications that vitamin D and its metabolites may inhibit ACE.

- B vitamins

Supplementing B vitamins to reduce blood pressure has led to mixed results. Some papers describe a lack of effect. A limited number of studies report minor beneficial effects (Aybak, 1995; Stehouwer, 2001; Mangoni, 2002) on blood pressure It should be noted that the subjects in one study (Mangoni) were all smokers and that only one study made a proper comparison with the placebo group.

- Hawthorne

Hawthorne has shown a trend towards blood pressure reduction in one study (Phytother Res. 2002 Feb;16(1):48-54.)

Mechanism of action

For hawthorne the primary mechanism of action underlying the putative blood pressure lowering responses would lie in the anti-oxidative action of the polyphenols. This antioxidant effect would improve the bioavailability of the endogenous vasodilator nitric oxide (NO). Some in vitro studies have suggested an ACE-inhibitory action of a number of polyphenols, but this effect has not been substantiated in humans.

- CoQ10 or Q10

A meta-analysis on the blood pressure lowering potential of co-enzyme Q10 has been performed in 2007 (*Journal of Human Hypertension* (2007) **21,** 297–306) addressing a number of clinical trials. It was concluded that coenzyme Q_{10} has the potential in hypertensive patients to lower systolic blood pressure without significant side effects.

As discussed above the outcome of studies done to the second component of the compostion of the invention is in most cases doubtful. Therefore it is rather surprising that these compounds show in the present composition such a positive effect. Especially CoQ10, grape seed extract, and polyphenols are preferred as second compound.

By protein hydrolysate, hydrolysate or hydrolysed protein is meant the product that is formed by enzymatic hydrolysis of the protein, an enriched hydrolysate being a fraction of the protein hydrolysate for example enriched in selected peptides or wherein peptides or polypeptides have been removed from the hydrolysate. So an enriched hydrolysate is preferably a mixture of peptides (or a peptide mixture). The peptide mixture of the invention is therefore a mixture of at least two, preferably at least three, more preferably at least four peptides. More preferably the mixture comprises a peptide population of which more than 50%, preferably even more than 60%, and most preferably more than 75% of the peptides present have a molecular weight below 500 Da. The protein hydrolysate used in the present invention has a DH of between 7 and 50, preferably a DH of between 10 and 40 and most preferably between 15 and 30.

A “peptide” or “oligopeptide” is defined herein as a chain of at least two amino acids that are linked through peptide bonds. The terms "peptide" and "oligopeptide" are

considered synonymous (as is commonly recognized) and each term can be used interchangeably as the context requires. A "polypeptide" is defined herein as a chain containing more than 30 amino acid residues. All (oligo)peptide and polypeptide formulas or sequences herein are written from left to right in the direction from amino-terminus to carboxy-terminus, in accordance with common practice. A protein is defined as used herein as the non-hydrolyzed protein. Moreover, especially when protein is discussed in general, protein can also mean the total of polypeptides, peptides and free amino acids.

“Free amino acids” are amino acids that are not joined to another amino acid by a peptide bound. “Amino acids” might be used on several occasions in this specification also meaning “free amino acids”. Preferably the amount of free amino acids in the composition of the invention is less than 5 wt% of the total protein.

The term nutraceutical as used herein denotes the usefulness in both the nutritional and pharmaceutical field of application. Thus, novel nutraceutical compositions comprising the composition of the invention can find use as supplement to food and beverages and as pharmaceutical formulations or medicaments for enteral or parenteral application which may be solid formulations such as capsules or tablets, or liquid formulations, such as solutions, suspensions or emulsions.

Examples of Foods for Special Nutritional Uses include the categories of sport foods, slimming foods, infant formula and clinical foods. The term dietary supplement as used herein denotes a product taken by mouth that contains a compound or mixture of compounds intended to supplement the diet. The compound or mixture of compounds in these products may include: vitamins, minerals, herbs or other botanicals and amino acids. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. The term nutraceutical as used herein denotes the usefulness in both the nutritional and pharmaceutical field of application. The nutraceutical compositions according to the present invention may be in any form that is suitable for administrating to the animal body including the human body, especially in any form that is conventional for oral administration, e.g. in solid form such as (additives/supplements for) food or feed, food or feed premix, tablets, pills, granules, dragées, capsules, and effervescent formulations such as powders and tablets, or in liquid form such as solutions, emulsions or suspensions as e.g. beverages, pastes and oily suspensions. Controled (delayed) release formulations incorporating the hydrolysates according to the invention also form

part of the invention. Furthermore, a multi-vitamin and mineral supplement may be added to the nutraceutical compositions of the present invention to obtain an adequate amount of an essential nutrient, which is missing in some diets. The multi-vitamin and mineral supplement may also be useful for disease prevention and protection against nutritional losses and deficiencies due to lifestyle patterns.

As stated above food or beverage are suitably used for administration of the present invention. Beverages which can be used for the supplementation of the composition of the invention can be in the form of beverage, such as sports drinks, energy drinks or other soft drinks, or any other suitable nutrient preparation.

A sports drink is a beverage which is supposed to rehydrate athletes, as well as restoring electrolytes, sugar, and other nutrients. Sports drinks are usually isotonic, meaning they contain the same proportions of nutrients as found in the human body. (Source: http://en.wikipedia.org/wiki/Sports_drink)

Energy drinks are beverages which contain (legal) stimulants, vitamins (especially B vitamins) and minerals with the intent to give the user a burst of energy. Common ingredients include caffeine, guarana (caffeine from the Guarana plant), taurine, various forms of ginseng, maltodextrin, inositol, carnitine, creatine, glucuronolactone and ginkgo biloba. Some may contain high levels of sugar, or glucose. Many such beverages are flavored and/or colored. (Source: http://en.wikipedia.org/wiki/Energy_drink)

A soft drink is a drink that does not contain alcohol, as opposed to hard drinks, that do. In general, the term is used only for cold beverages. Hot chocolate, tea, and coffee are not considered soft drinks. The term originally referred exclusively to carbonated drinks, and is still commonly used in this manner.(http://en.wikipedia.org/wiki/Soft_drink).

The one-letter and three-letter code of amino acids used herein is commonly known in the art and can be found in Sambrook, et al. (Molecular Cloning: A Laboratory Manual, 2nd,ed. Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

An endoprotease is defined herein as an enzyme that hydrolyses peptide bonds in a polypeptide in an endo-fasion and belongs to the group EC 3.4. The endoproteases are divided into sub-subclasses on the basis of catalytic mechanism. There are sub-subclasses of serine endoproteases (EC 3.4.21), cysteine endoproteases (EC 3.4.22), aspartic endoproteases (EC 3.4.23), metalloendoproteases (EC 3.4.24) and threonine endoproteases (EC 3.4.25). Exoproteases are defined herein as enzymes that hydrolyze peptide bonds adjacent to a terminal α-amino group (“aminopeptidases”), or a peptide

bond between the terminal carboxyl group and the penultimate amino acid ("carboxypeptidases").

In general the composition according to the invention has a bland or neutral taste and an improved solubility under acid conditions and can be used as basis for other beverages such as sport drinks or soft drinks or health drinks or fermented products. By the term bland taste of a composition or product of the invention is meant that the bitterness level of a 3 wt% protein in water sample, is similar to or lower than a level of 15 mg/litre of quinine sulphate dissolved in destilled water and tasted at a temperature of 14°C.

The quantity of enzyme required to achieve the desired degree of hydrolysis depends upon the enzyme used. However, the enzyme dosage and incubation conditions are optimised in such a way so that the majority of the casein protein fraction is dissolved in the aqueous phase of the reaction after incubation periods of typically 6 to 20 hours. By majority is meant that under pH 4, less than 20%, preferably less than 10%, more preferably less than 5% of the protein present in the casein fraction can be precipitated upon centrifugation for 10 minutes at 2000 g.

The enzyme inactivation step which can be used after the hydrolysis, can be a heat treatment which comprises heating to a temperature of at least 85°C for at least 10 minutes. If higher temperatures or more extreme pH values are used, shorter periods may be feasible. Such heat treatment is preferably carried out at an acidic pH value, preferably between 3 and 7. The enzyme inactivation treatment can be done for both fractions seperately or can be done after that the fractions are mixed to form the composition of the invention.

Optionally, to remove non solubilised material from the final product, decantation or low speed centrifugation at for example 2000-4000 g as can be carried out at industrial scale, is preferred. Optionally each hydrolysate or the mixture of both hydrolysates can be filtered using an ultrafilter, a microfilter, diatomaceous earth, fiberglass filters or using cross-flow filtration. Complete enzyme inactivation can be confirmed by a dye-gelatin test.

Optionally the filtered final hydrolysate(s) can be treated with activated charcoal or with nanofiltration, ion exchange or electro dialysis to remove a surplus of salts. The filtered hydrolysate(s) can be pasteurised or sterilised and, if required, further concentrated by drying techniques such as evaporation, nano filtration, spray drying,

fluidized bed drying or combinations thereof. Preferably the obtained product is in a granular form.

As such or preferably after centrifugation, the hydrolyzed casein protein containing fraction can be concentrated and dried. The dried product can be redissolved in the hydrolyzed whey protein containing fraction to obtain the desired protein concentration and protein ratio and then, if required, centrifuged or filtered and pasteurised or sterilised to obtain the product according to the invention.

Obviously the product can be subjected to additional enzyme treatments such as lactases or can be fermented with different types of starter cultures or can be combined with all kinds of ingredients such as oils, fats, emulsifyers, carbohydrates, fruit concentrates, flavours, colorants, alcohol, carbon dioxide, thickeners, acidulants, antioxidants, herbs or herb extracts, health promoting compounds like vitamins or provitamins or bioactive or tryptophane containing peptides or amino acids to formulate a product which is in line with the marketing needs.

Degree of Hydrolysis

The Degree of Hydrolysis (DH) as obtained during incubation with the various protolytic mixtures was monitored using a rapid OPA test (Nielsen, P.M.; Petersen, D.; Dambmann, C. Improved method for determining food protein degree of hydrolysis. *Journal of Food Science* **2001**, *66*, 642-646). The degree of hydrolysis is the extent to which peptide bonds are broken by the enzymatic hydrolysis reaction.

CLAIMS

1. A composition comprising
   - a peptide which is IPP and/or VPP; and
   - at least one compound which can be extracted or purified from a natural source, this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape seed extract or isolate.

2. A food, feed, neutraceutical or dietary supplement which comprises the composition of claim 1 or 2.

3. The composition of claim 1 for use as a nutraceutical preferably as a medicament.

4. A method of producing a composition according to any one of claims 1 to 3 by bringing together the peptide which is IPP and/or VPP and the at least one compound which can be extracted or purified from a natural source,this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape extract or isolate.

5. Use of
- a peptide which is IPP and/or VPP; and
- at least one compound which can be extracted or purified from a natural source,this compound is preferably selected from the group consisting of CoQ10, grape seed extract, resveratrol, EGCG, Vitamin D, Pufa, GABA, Lycopene, Hawthorne, hydroxytyrosol or is preferably selected on anti-oxidative action of the polyphenols present in grape extract or isolate

in a food, feed, nutraceutical or dietary supplement or for the preparation of a food, feed, neutraceutical or dietary supplement.

6. Use of claim 5 whereby the food, feed, nutraceutical or dietary supplement containig the peptide and compound which can be extracted or purified from a natural source is for ACE inhibition effect or for blood pressure lowering.

7. Use of any one of claims 5 to 6 whereby the peptide IPP and/or VPP and the compound which can be extracted or purified from a natural source have together a synergetic effect on blood pressure lowering.

8. Method of treatment of a person in need of a blood pressure lowering effect which comprises administering to said person a composition according to any one of claims 1 to 3.