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(54) Title: MULTI NUTRIENT SUPPLEMENTATION

(57) Abstract: Various embodiments of the invention relate to compositions comprising vitamins, minerals and trace elements, anti-oxidants, amino acids, probiotics, and other components and methods for using such compositions to treat or prevent diseases associated with oxidative stress, including cardiovascular disease.



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MultiNutrient Supplementation

I. Secondary prevention.

Summary

Nutrients like amino acids, fatty acids, vitamins, trace elements, minerals and antioxidants as well as food extracts and nutritional and life-style interventions have been found to diminish risk factors for cardiovascular disease (CVD).

In two consecutive studies, a broad spectrum of nutrients was given to 125 patients with abnormal values for CVD risk factors as analysed by Arteriograph. Significantly improved values were obtained after two months for arterial stiffness of the aorta, endothelial function of small arteries, brachial and central blood pressure.

It is concluded that studies on nutritional supplementation preferably should be performed using not single but rather multi components.

Introduction

Health care has more and more understood the need for more active prevention. A large number of published studies have showed positive effects by dealing with such risk factors as stress, smoking, bad diets and sedentary life-style. Many studies have also demonstrated positive effects on health by vitamins, trace elements, mineral, fatty acids and amino acids as supplements

or dietary ingredients. Unfortunately, Health care has so far not understood the potential value of dietary supplements.

With the advent of new evaluation methods, such as aortic arterial stiffness and endothelial function, it has become easier to evaluate the potential impact of specific interventions like broad-spectrum nutrients upon cardiovascular disease (CVD).

Methods

Patient selection.

All patients had been thoroughly examined and diagnosed in the ordinary medical system. After analysis by Arteriograph, patients with abnormal values were offered treatment with MultiNutrient supplementation as described in ref.1. Smokers and cancer patients were not included.

Reasons to use nutrient supplements.

A typical western diet contains energy-rich, but nutrient-poor food with a high level of sugar and fat. Production methods have been directed more at volume than nutritional value. Many persons, therefore, get less of essential nutrients and more of calories than recommendable. Other factors may increase the risk, e.g. malabsorption, genetic polymorphism, increased demand by stress and disease, loss of appetite. Biochemical differences exist between individuals and may mean increased need, not satisfied by RDI-doses. Statistically, if the need among the population is according to a normal curve, it is clear that 2.5% lies outside each end of the curve. For 40 essential nutrients this means that the probability that a certain person, who gets RDI of all the nutrients, gets enough of all 40 nutrients, is only 36%. To this comes the above mentioned factors, that will diminish the probability even further (2). This reasoning would be an argument both for better diet and supplements.

Subclinical deficiencies. The importance of subclinical deficiencies of essential nutrients in the population is much discussed. The Swedish National Nutrition Board states that deficiencies are uncommon and warns against taking supplements, since they may increase morbidity and mortality (3). Bruce Ames, well known for his test, on the contrary, states that the best policy for the health of the population would be to give everybody supplements. He gives proof that subclinical deficiencies are common and gives rise to an increased risk for chronic diseases (4-5). To me, this gave a motive for including RDI-doses of essential vitamins, trace elements and minerals.

Interactions. High doses of single minerals or trace elements may cause imbalance of other elements, as illustrated for zink and copper (6). To me this was another reason to include RDI-doses of elements, without respect to whether they have been shown to influence arterial function (Zn, Ca, Mg, 7-9) or whether they have not.

Vitamins. A large number of studies have shown or failed to show an influence of some vitamins, e.g. C, D, E, K, on the risk for CVD (10-14).

Trace elements, minerals. Similar comments can be made for e.g. selenium and magnesium (8, 15).

Amino acids. A large number of papers have dealt with the importance of L-arginin and nitric oxide, NO (16).

Fatty acids. Like the situation for most essential nutrients there is no clear consensus about the influence of EPA and DHA on the risk for CVD (17). Mostly, however, it is agreed that eating fat fish, rich in EPA and DHA, is good for cardio-vascular health (3).

Probiotics. When I started treatment, probiotics was added, although there were no studies demonstrating an effect on CVD. A recent study has now found a diminished risk of stroke by probiotics (18).

Liver function. The liver has an important function for the excretion of endo- and exogenous toxins. When its capacity is insufficient, free radicals increase CVD-risk. N-acetyl-cystein improves the detoxification capacity and has thereby a potential influence on CVD-risk (19).

My way of thinking.

In research most studies deal with only one single component. However, CVD-risk is influenced by many different elements. This should motivate that more often studies are made with a mixture of several nutrients, multi-nutrient studies, more close to studies of diets. Of course, double-blinding is then more difficult, but this should not prevent relevant conclusions. This fact has been understood by researchers on antioxidant treatment (20). A recent illustration to my reasoning is a study, demonstrating a clear effect on CVD-mortality by selenium and Q-10 given together (21). It was long ago stated that antioxidant-rich food, but not single antioxidants in supplements, decreased CVD-risk. This is to me proof that supplement therapies should be multinutrient, not mono- or oligonutrient. Many studies draw irrelevant conclusions, e.g. in JAMA 2012 (22), in a study of only three vitamins it is concluded that multivitamin supplements do not lead to a diminished CVD-risk in men. This would be a seriously illogical conclusion, since the authors did not study many nutrients. E.g. vitamin D was not included, although a linear inverse relation has been demonstrated between circulating 25(OH)vitamin D and CVD-risk (23). Other studies have found that deficiency of B-vitamins and of antioxidants leads to increased risk of mild cognitive damage and Alzheimer's disease (24).

It would be time to be more strict in the interpretation of mono- and oligonutrient double-blind studies. Is it really good science to state "Multivitamin supplements do not decrease CVD-risk" as a conclusion from treatment by only three vitamins of the known twelve? Maybe, there are also good reasons to consider the fact that vitamins work in cooperation with other cofactors, such as trace elements and minerals, in a very large number of essential enzyme reactions, not to mention other nutrients, e.g. fatty acids and amino acids, that might be of influence.

Treatment.

The first 85 patients were given all essential vitamins, trace elements and minerals, several antioxidants, fish oil, l-arginin, N-acetyl-cystein and probiotics in doses as described in ref.1.

Results.

According to the above described way of thinking a multi-nutrient therapy was devised for 85 patients with unexpectedly clear results already after two months.

TABLE 1.

Pulse wave velocity (PWVao), augmentation index (AIXbrach), brachial and central (cSBP) blood pressure before and after 2 months of treatment by MultiNutrient Supplementation in 85 patients.

PWVao:Elasticity of the aortic wall and cardio-vascular risk.

AIXbrach:Function of peripheral arteries and cardio-vascular risk.

cSBP: Puts a load on the heart, if higher than SBPbrach.

	<u>Before</u>	<u>After</u>	<u>p-value</u>
PWV,m/s*	12.0	10.0	<0.001
PWV, biol.age*/**	92.9	63.2	<0.001
AIX*	+5.2	-14.1	<0.001
SBP,mmHg	161.4	133.0	<0.001
DBP,mmHg	89.6	75.2	<0.001
cSBP,mmHg	150.0	122.6	<0.001

*From ref.1.

**Calculated according to ref.25.

In order to make treatment simpler and less expensive, cysteine, which is supplement-registered in Sweden, was used instead of acetyl-cystein, which is drug-registered in Sweden. In the study in ref.1 tablets or capsules were given from eight different bottles. Later, the contents in six different bottles was put into one single bottle. Fish oil and the probiotic were kept separately as before. Using this simpler, but still the same treatment, similar results have been obtained.

TABLE 2.

Pulse wave velocity (PWVao), augmentation index (AIXbrach), brachial and central blood pressure and Diastolic Area Index (DAI) before and after two months of treatment by MultiNutrient Supplementation In 40 patients.

	<u>Before</u>	<u>After</u>	<u>p-value</u>
PWV,m/s	11.9	10.0	<0.001
PWV,biol.age*	89.5	62.6	<0.001
AIX	+27.4	+4.1	<0.001
SBP,mmHg	161.8	144.2	<0.001
DBP,mmHg	93.5	86.2	<0.001
cSBP,mmHg	166.7	147.3	<0.001
DAI, % **	45.7	50.6	<0.001

*Calculated according to ref.25.

**DAI: Indicates perfusion of the coronary arteries.

Discussion.

Analysis of arterial stiffness and function gives information on several hidden risk factors, that may lay behind many cases of sudden and unexpected CVD-events. Thus, a warning can be obtained, leading to treatment and follow-up. Of course, also research on mechanisms is made possible.

The results presented may indicate a possibility to diminish several risk factors for CVD. This motivates several questions.

1. Does diminishing of the risk factors by multi-nutrient supplementation also influence morbidity and mortality? There does exist proof that the risk for CVD increases with the value measured for factors here discussed.
2. What supplementation is needed to maintain low values? In my experience this varies between individuals and can best be decided by repeated analyses.
3. Can similar or better results be obtained by life-style modification and/or drugs? More research is needed.
4. Can the supplementation treatment be simplified by lower doses and/or fewer components? This remains to be studied.
5. Can even better results be obtained by adding further components, e.g. such as Q-10 and nitrate-containing extracts of food?

It is to be hoped that more consideration shall be given to the multi-nutrient philosophy in future research. If such research gives support, this will lead to practical application in health policy. Then laws, rules and paradigm must be changed to make it easier for physicians and other categories to apply multi-nutrient therapy as a complement to drugs, surgery and life-style modification.

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II. Primary prevention.

Summary

Nutrients like amino acids, fatty acids, vitamins, trace elements, minerals and antioxidants as well as food extracts and nutritional and life-style interventions have been found to diminish risk factors for cardiovascular disease (CVD).

A broad spectrum of 33 different nutrients was given to 60 patients with abnormal values for CVD risk factors as analysed by Arteriograph but without any other known risk factor for CVD. Significantly improved values were obtained after two months for arterial stiffness of the aorta, endothelial function of small arteries, brachial and central blood pressure. This gives some support to the possibility for using multinutrients not only for secondary but also for primary prevention.

It is concluded that studies on nutritional supplementation preferably should be performed using not single or oligo but rather multi components.

Introduction

Health care has more and more understood the need for more active prevention. A large number of published studies have showed positive effects by dealing with such risk factors as stress, smoking, bad diets and sedentary life-style. Many studies have also demonstrated positive effects on health by vitamins, trace elements, mineral, fatty acids and amino acids as supplement or dietary ingredients. Unfortunately, Health care has so far not understood the potential value of dietary supplements.

With the advent of new evaluation methods, such as aortic arterial stiffness and endothelial function, it has become easier to evaluate the potential impact of specific interventions like broad-spectrum nutrients upon cardiovascular disease (CVD).

Methods

Patient selection.

All patients had been thoroughly examined and diagnosed in the ordinary medical system. After analysis by Arteriograph, patients with abnormal values were offered treatment with MultiNutrient supplementation as described in ref.1. Smokers and cancer patients were not included. Patients with any other known risk factor for CVD, such as high blood pressure, high lipids, gross overweight, diabetes, rheumatoid arthritis, were also excluded.

Reasons to use nutrient supplements.

A typical western diet contains energy-rich, but nutrient-poor food with a high level of sugar and fat. Production methods have been directed more at volume than nutritional value. Many persons, therefore, get less of essential nutrients and more of calories than recommendable. Other factors may increase the risk, e.g. malabsorption, genetic polymorphism, increased demand by stress and disease, loss of appetite. Biochemical differences exist between individuals and may mean increased need, not satisfied by RDI-doses. Statistically, if the need among the population is according to a normal curve, it is clear that 2.5% lies outside each end of the curve. For 40 essential nutrients this means that the

probability that a certain person, who gets RDI of all the nutrients, gets enough of all 40 nutrients, is only 36%. To this comes the above mentioned factors, that will diminish the probability even further (2). This reasoning would be an argument both for better diet and supplements.

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Interactions. High doses of single minerals or trace elements may cause imbalance of other elements, as illustrated for zinc and copper (6). To me this was another reason to include RDI-doses of elements, without respect to whether they have been shown to influence arterial function (Zn, Ca, Mg, 7-9) or whether they have not.

Vitamins. A large number of studies have shown or failed to show an influence of some vitamins, e.g. C, D, E, K, on the risk for CVD (10-14).

Trace elements, minerals. Similar comments can be made for e.g. selenium and magnesium (8, 15).

Amino acids. A large number of papers have dealt with the importance of L-arginine and nitric oxide, NO (16).

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My way of thinking.

In research most studies deal with only one single component. However, CVD-risk is influenced by many different elements. This should motivate that studies are more often made with a mixture of several nutrients, multi-nutrient studies, more close to studies of diets. Of course, double-blinding is then more difficult, but this should not prevent relevant conclusions. This fact has been understood by researchers on antioxidant treatment (20). A recent illustration to my reasoning is a study, demonstrating a clear effect on CVD-mortality by selenium and Q-10 given together (21). It was long ago stated that antioxidant-rich food, but not single antioxidants in supplements, decreased CVD-risk. This is to me proof that supplement therapies should be multinutrient, not mono- or oligonutrient. Many studies draw irrelevant conclusions, e.g. in JAMA 2012 (22), in a study of only three vitamins it is concluded that multivitamin supplements do not lead to a diminished CVD-risk in men. This would be a seriously illogical conclusion, since the authors did not study many nutrients. E.g. vitamin D was not included, although a linear inverse relation has been demonstrated between circulating 25(OH)vitamin D and CVD-risk (23). Other studies have found that deficiency of B-vitamins and of antioxidants leads to increased risk of mild cognitive damage and Alzheimer's disease (24).

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essential enzyme reactions, not to mention other nutrients, e.g. fatty acids and amino acids, that might be of influence.

Results.

According to the above described way of thinking a multi-nutrient therapy was devised for 60 patients with unexpectedly clear results already after two months. In order to make treatment simpler and less expensive, cysteine, which is supplement-registered in Sweden, was used instead of acetyl-cystein, which is drug-registered in Sweden. In the study in ref.1 tablets or capsules were given from eight different bottles. Later, the contents in six different bottles was put into one single bottle. Fish oil and the probiotic were kept separately as before.

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PWVao: Elasticity of the aortic wall and cardio-vascular risk.

AIXbrach: Function of peripheral arteries and cardio-vascular risk.

cSBP: Puts a load on the heart, if higher than SBPbrach.

	<u>Before</u>	<u>After</u>	<u>p-value</u>
PWV,m/s	11.6	9.4	<0.001
PWV, biol.age*	86.8	53.7	<0.001
AIX	+17.8	-8.3	<0.001
SBP,mmHg	154.1	136.9	<0.001
DBP,mmHg	89.4	82.3	<0.001
cSBP,mmHg	161.0	136.2	<0.001
DAI**	46.7	50.8	<0.01

*Calculated according to ref.25. **Indicates perfusion of coronary arteries.

Discussion.

Analysis of arterial stiffness and function gives information on several hidden risk factors, that may lay behind many cases of sudden and unexpected CVD-events. Thus, a warning can be obtained, leading to treatment and follow-up. Of course, also research on mechanisms is made possible.

The results presented may indicate a possibility to diminish several risk factors for CVD. This motivates several questions.

1. Does diminishing of the risk factors by multi-nutrient supplementation also influence morbidity and mortality? There does exist proof that the risk for CVD increases with the value measured for factors here discussed (26).
2. What supplementation is needed to maintain low values? In my experience this varies between individuals and can best be decided by repeated analyses.
3. Can similar or better results be obtained by life-style modification and/or drugs? More research is needed.
4. Can the supplementation treatment be simplified by lower doses and/or fewer components? This remains to be studied in more detail.
5. Can even better results be obtained by adding further components, e.g. such as Q-10 and nitrate-containing extracts of food?

It is to be hoped that more consideration shall be given to the multi-nutrient philosophy in future research. If such research gives support, this will lead to practical application in health policy. Then laws, rules and paradigm must be changed to make it easier for physicians and

other categories to apply multi-nutrient therapy as a complement to drugs, surgery and life-style modification.

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III. Long-term effect.

Summary

In earlier studies treatment for two months with 33 different nutrients was shown to diminish such risk factors for cardio-vascular disease (CVD) as assayed by the Arteriograph . This was demonstrated both as secondary and as primary prevention. 23 patients have now been treated for up to 36 months, using full dose for the two first months and later varying, but lower doses. By making repeated analyses and giving individual, lower doses as needed the good effect shown after two months could be maintained and even improved further.

It is concluded that nutritional supplementation such as given in the first two papers in this series can be continued at lower individual dose as controlled by Arteriograph assay.

2.

Introduction

In three earlier studies (1-3) it was demonstrated that nutritional supplementation using a broad spectrum of nutrients significantly diminished such risk factors for cardio-vascular disease (CVD) as measured by the Arteriograph (4). In the present study it was asked whether a lower dose could maintain the improved values or even further diminish these risk factors.

Methods

Patient selection.

All patients had been thoroughly examined and diagnosed in the ordinary medical system. After analysis by Arteriograph, patients with abnormal values were offered treatment with MultiNutrient supplementation as described in ref.1. Smokers and cancer patients were not included. All patients in this study are included I ref. 1-3.

Results.

The patients could maintain and further improve the values for aortic stiffness and and biological age of the aorta as compared to the short-term studies in ref. 1-3. (Table 1-2). All other values were maintained at the diminished value obtained after two months.

TABLE 1.

Pulse wave velocity (PWVao), augmentation index (AIXbrach), brachial and central (cSBP) blood pressure before and after 6-36 months (Mean value 20 months) of treatment by MultiNutrient Supplementation in 23 patients.

PWVao (Pulse wave velocity, aorta): Elasticity of the aortic wall and cardio-vascular risk.

AIXbrach (Augmentation index, brachial): Function of peripheral arteries and cardio-vascular risk.

cSBP (Central systolic blood pressure): Puts a load on the heart, if higher than SBPbrach.

	<u>Before</u>	<u>After</u>	<u>p-value</u>
PWV,m/s	12.1	9.6	<0.001
PWV, biol.age*	93.3	57.0	<0.001
AIX	+11.5	-10.1	<0.001
SBP,mmHg	157.2	139.0	<0.001
DBP,mmHg	91.2	80.7	<0.001
cSBP,mmHg	160.5	137.1	<0.001
DAI**	49.5	52.0	<0.05

*Calculated according to ref.5. **Indicates perfusion of coronary arteries.

TABLE 2.

Comparison between the decrease in values for aortic stiffness as measured by pulse wave velocity (PWV) and biological age of the aorta in ref. 1-3 and in the present study.

	Ref.1	Ref.2	Ref.3	Present study.
PWV m/s	2.0	2.0	2.2	2.5
PWV, biol.age, years	29.7	29.7	33.3	36.3

Discussion.

Analysis of arterial stiffness and function gives information on several hidden risk factors, that may lay behind many cases of sudden and unexpected CVD-events. Thus, a warning can be obtained, leading to treatment and follow-up. Of course, also research on mechanisms is made possible.

The results presented may indicate a possibility to diminish several risk factors for CVD and to maintain or even improve further this effect by using lower dose for up to three years.

References.

1. Öckerman PA. Improvement of Arterial Stiffness by Multi-Nutrient Supplementation. *J Orthomol Med.* 2011;26(4):159-162.
2. Öckerman PA. Diminishing Risk Factors:MultiNutrient Supplementation as a Complement to Life-style Modification and Drugs. I.Secondary Prevention. In manuscript.
3. Ibidem: II. Primary prevention.
4. Kahan T. *et al.* Aortic stiffness measured by a novel oscillometric method independently predicts cardiovascular morbidity and mortality:A study of 4146 subjects. 23rd European Meeting on Hypertension & Cardiovascular Protection; Milan, June 14-17, 2013.
5. Illyés M *et al.* Budapest, Hungary.

SUMMARY.

Using a method, Arteriography, considered by European cardiologists to be “Golden Standard” for assay of several risk factors for heart infarct and stroke, patients with increased risk have been identified and treated by a unique combination of vitamins, minerals, trace elements, amino acids, antioxidants, omega-3 fatty acids and probiotics. Highly significant improvement has been demonstrated after treatment for two months and two years for patients with a history of earlier cardiovascular disease (secondary prevention) as well as for patients with no earlier disease, but with increased risk at arteriography assay (primary prevention).

Documentation is presented in unpublished manuscripts. It is stressed that giving 33 different nutrients at high doses is of paramount importance to explain why much better results were obtained than in other studies using “multivitamins”. Also, treatment studies of patients with increased risk factors at assay with Arteriography by multinutrients have not earlier been published by other scientists.

CLAIMS

What is claimed is:

1. A method for treating or prevent a disease and/or condition associated with oxidative stress comprising administering to a human subject a therapeutically effective amount of a composition comprising vitamin A, vitamin B₁, vitamin B₂, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E, vitamin K, folic acid, calcium source, potassium source, magnesium source, phosphate source, iodine, copper source, chromium source, manganese source, molybdenum source, selenium source, zinc source, one or more tocopherols or salts thereof, lycopene, one or more carotenoids, one or more flavonoids, biotin, inositol, choline, one or more amino acids, a probiotic composition comprising the powder of one or more dried fruits and pollen extract, and fish oil.
2. The method of claim 1, wherein the treating comprises preventing the progression of a disease and/or condition associated with oxidative stress.
3. The method of claim 1, wherein the disease and/or condition associated with oxidative stress is selected from the group consisting of cardiovascular disease, cancer, type-2 diabetes mellitus, atherosclerosis, chronic inflammatory conditions, ischemia/reperfusion injury, sepsis, neurodegenerative diseases, Parkinson's disease, Alzheimer's disease, heart failure, myocardial infarction, schizophrenia, bipolar disorder, fragile X syndrome, sickle cell disease, lichen planus, vitiligo, autism, chronic fatigue syndrome, and combinations thereof.
4. The method of claim 3, wherein the disease and/or condition associated with oxidative stress is cardiovascular disease.
5. The method of claim 4, wherein the cardiovascular disease is at least one of atherosclerosis, heart infarct, and stroke.

6. The method of claim 1, wherein the composition comprises vitamin A (0.01-10 mg), vitamin B₁ (1-50 mg), vitamin B₂ (1-50 mg), vitamin B₃ (1-100 mg), vitamin B₅ (1-100 mg), vitamin B₆ (0.5-50 mg), vitamin B₁₂ (0.0001-2 mg), vitamin C (0.1-1000mg), vitamin D (0.0001-1 mg), vitamin E (1-500 mg), vitamin K (0.001-5 mg), folic acid (0.0001-5 mg), calcium source (0.1-1000 mg), potassium source (0.1-1000 mg), magnesium source (0.1-1000 mg), phosphate source (1-500 mg), iodine source (0.0001-5 mg), copper source (0.0001-10 mg), chromium source (0.0001-10 mg), manganese source (0.0001-50 mg), molybdenum source (0.0001-10 mg), selenium source (0.0001-10 mg), zinc source (0.001-50 mg), lycopene (0.0001-20 mg), one or more carotenoids (0.0001-20 mg), one or more flavonoids (1-500 mg), biotin (0.0001-20 mg), inositol (0.001-100 mg), choline (0.0001-500 mg), one or more amino acids (0.0001-100 g), a probiotic composition (1-10 mL) comprising the powder of one or more dried fruits (0.0001-2000 mg) and pollen extract (1-10,000 mg), and fish oil (0.0001-20 g).
7. The method of claim 6, wherein the composition comprises an additional amount of vitamin D such that the total amount of vitamin D is 0.0004-4 mg vitamin D.
8. The composition of claim 6, wherein the composition comprises an additional amount of at least one of vitamin C, a potassium source, a magnesium source, and a calcium source.
9. The method of claim 1, wherein the probiotic composition comprises *Lactococcus lactus*, *Lactobacillus rhamnosus*, inulin, and dried powder of blueberries.
10. The method of claim 1, wherein the composition comprises vitamin A, vitamin B₁, vitamin B₂, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E, vitamin K, folic acid, potassium chloride, magnesium oxide, dicalcium phosphate, iodine, copper gluconate, chromium sulfate, manganese gluconate, potassium molybdate, selenomethionine, zinc lactate, d-alpha-tocopherol acetate, lycopene, beta-carotene, citrus flavonoids, L-cysteine or N-acetyl cysteine, L-

arginine, a probiotic composition comprising dried powder of blueberries and pollen extract, d-biotin, inositol, choline-L-bitartarate, and fish oil.

11. A method of delaying or preventing the onset of a disease and/or condition associated with oxidative stress comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising vitamin A, vitamin B₁, vitamin B₂, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E, vitamin K, folic acid, calcium source, potassium source, magnesium source, phosphate source, iodine, copper source, chromium source, manganese source, molybdenum source, selenium source, zinc source, -lycopene, one or more carotenoids, one or more flavonoids, biotin, inositol, choline, one or more amino acids, a probiotic composition comprising the powder of one or more dried fruits and pollen extract, and fish oil.

12. A composition comprising:

- (i) vitamin A, vitamin B₁, vitamin B₂, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E, vitamin K, folic acid, calcium source, potassium source, magnesium source, phosphate source, iodine, copper source, chromium source, manganese source, molybdenum source, selenium source, zinc source, -lycopene, one or more carotenoids, one or more flavonoids, biotin, inositol, choline, one or more amino acids,
- (ii) a probiotic composition comprising the powder of one or more dried fruits and pollen extract,
- (iii) fish oil, and
- (iv) one or more pharmaceutically acceptable excipients.

13. The composition of claim 12, wherein the composition is in the form of a tablet, powder, liquid, capsule or combinations thereof.

14. The composition of claim 12, wherein components (i) and (iv) are comprised in the same dosage unit, separate from the probiotic composition and the fish oil.

15. The composition of claim 12, wherein the dosage unit is one or more tablets, caplets, capsules, tablet-within-a-tablet, tablet/caplet/capsule-within-a-capsule, liquid caps or sachets.
16. The composition of claim 12, wherein the composition comprises vitamin A (0.01-10 mg), vitamin B₁ (1-50 mg), vitamin B₂ (1-50 mg), vitamin B₃ (1-100 mg), vitamin B₅ (1-100 mg), vitamin B₆ (0.5-50 mg), vitamin B₁₂ (0.0001-2 mg), vitamin C (0.1-1000mg), vitamin D (0.0001-1 mg), vitamin E (1-500 mg), vitamin K (0.001-5 mg), folic acid (0.0001-5 mg), calcium source (0.1-1000 mg), potassium source (0.1-1000 mg), magnesium source (0.1-1000 mg), phosphate source (1-500 mg), iodine source (0.0001-5 mg), copper source (0.0001-10 mg), chromium source (0.0001-10 mg), manganese source (0.0001-50 mg), molybdenum source (0.0001-10 mg), selenium source (0.0001-10 mg), zinc source (0.001-50 mg), lycopene (0.0001-20 mg), one or more carotenoids (0.0001-20 mg), one or more flavonoids (1-500 mg), biotin (0.0001-20 mg), inositol (0.001-100 mg), choline (0.0001-500 mg), one or more amino acids (0.0001-100 g), a probiotic composition (1-10 mL) comprising the powder of one or more dried fruits (0.0001-2000 mg) and pollen extract (1-10,000 mg), and fish oil (0.0001-20 g).
17. The composition of claim 12, wherein the composition comprises an additional amount of vitamin D such that the total amount of vitamin D is 0.0004-4 mg vitamin D.
18. The composition of claim 12, wherein the composition comprises an additional amount of at least one of vitamin C, a potassium source, a magnesium source, and a calcium source.
19. The composition of claim 12, wherein the probiotic composition comprises *Lactococcus lactus*, *Lactobacillus rhamnosus*, inulin, and dried powder of blueberries.
20. The composition of claim 12, wherein the composition comprises vitamin A, vitamin B₁, vitamin B₂, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D,

vitamin E, vitamin K, folic acid, potassium chloride, magnesium oxide, dicalcium phosphate, iodine, copper gluconate, chromium sulfate, manganese gluconate, potassium molybdate, selenomethionine, zinc lactate, lycopene, beta-carotene, citrus flavonoids, L-cysteine or N-acetyl cysteine, L-arginine, a probiotic composition comprising dried powder of blueberries and pollen extract, d-biotin, inositol, choline-L-bitartrate, and fish oil.

21. A kit comprising the composition of claim 12 in a suitable container.
22. The kit of claim 21, wherein the composition is comprised in a dosage unit.
23. The kit of claim 22, wherein the dosage unit is one or more tablets, caplets, capsules, tablet-within-a-tablet, tablet/caplet/capsule-within-a-capsule, liquid caps or sachets.
24. The kit of claim 21, wherein the composition comprises vitamin A, vitamin B₁, vitamin B₂, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E, vitamin K, folic acid, potassium chloride, magnesium oxide, dicalcium phosphate, iodine, copper gluconate, chromium sulfate, manganese gluconate, potassium molybdate, selenomethionine, zinc lactate, lycopene, beta-carotene, citrus flavonoids, L-cysteine or N-acetyl cysteine, L-arginine, a probiotic composition comprising dried powder of blueberries and pollen extract, d-biotin, inositol, choline-L-bitartrate, and fish oil in amounts sufficient to treat or prevent diseases associated with oxidative stress.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2013/000186

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, BIOSIS, COMPENDEX, EMBASE, MEDLINE, PUBCHEM

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Öckerman, Per-Arne "Improvement of arterial stiffness by Multi-nutrient supplementation" Journal of Orthomolecular Medicine (2011), vol 26, no 4, pages 83-86; whole document --	1-24
X	US 20130224281 A1 (MONTESINOS CARLOS A ET AL), 29 August 2013 (2013-08-29); paragraphs [0006]-[0007]; claims 1-13, 20; table 7 --	1-7, 11-17, 21-24
A	EP 2374452 A1 (AJINOMOTO KK), 12 October 2011 (2011-10-12); abstract; examples 1-3 --	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

“&” document member of the same patent family

Date of the actual completion of the international search

29-09-2014

Date of mailing of the international search report

29-09-2014

Name and mailing address of the ISA/SE

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2013/000186

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5776887 A1 (WIBERT GREGORY J ET AL), 7 July 1998 (1998-07-07); column 3, line 60 - column 4, line 27; column 5, line 19 - column 5, line 29; example 8 --	1-24
A	US 20130095204 A1 (JOUNI ZEINA ET AL), 18 April 2013 (2013-04-18); abstract; paragraphs [0135], [0138], [0140]; tables 1-16 --	1-24
A	US 20060127505 A1 (HAINES DAVID ET AL), 15 June 2006 (2006-06-15); abstract; table A -- -----	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2013/000186

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-7 and 9-11
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-7 and 9-11 relate to a method for treatment of the human or animal body by therapy, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of: second sheet**International Patent Classification (IPC)**

A61K 31/07 (2006.01)
A61K 31/01 (2006.01)
A61K 31/015 (2006.01)
A61K 31/095 (2006.01)
A61K 31/122 (2006.01)
A61K 31/145 (2006.01)
A61K 31/155 (2006.01)
A61K 31/197 (2006.01)
A61K 31/30 (2006.01)
A61K 31/315 (2006.01)
A61K 31/355 (2006.01)
A61K 31/375 (2006.01)
A61K 31/4188 (2006.01)
A61K 31/455 (2006.01)
A61K 31/51 (2006.01)
A61K 31/519 (2006.01)
A61K 31/555 (2006.01)
A61K 31/59 (2006.01)
A61K 31/675 (2006.01)
A61K 31/714 (2006.01)
A61K 33/08 (2006.01)
A61K 33/14 (2006.01)
A61K 33/18 (2006.01)
A61K 33/24 (2006.01)
A61K 33/42 (2006.01)
A61K 35/60 (2006.01)
A61K 35/74 (2006.01)
A61K 36/752 (2006.01)
A61P 9/00 (2006.01)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE2013/000186

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