Title: KIT OF PARTS COMPRISING L-GLUTAMINE AND EGCG

Abstract: The invention relates to a kit of parts for maintaining or improving the state of health, consisting of L-Glutamine, optionally as component of a dipeptide, and the green tea extract (-)-epigallocatechin gallate (EGCG). L-Glutamine and EGCG are particularly packed together in a double sachet. The invention also relates to the application of such a kit of parts for the purpose of enhancing sporting performance and as means of preventing or reducing the risk of developing a physical disorder. The kit of parts is applied in particularly advantageous manner for the purpose of increasing the activity of the immune system and in the case of cardiovascular diseases, diabetes mellitus, in particular type-2, high blood pressure, obesity and overweight, neurological mucous membrane disorders, hair cell disorders, cardiac disorders and peripheral nerve disorders, bacterial and viral infections, rheumatic inflammations and burns.
KIT OF PARTS COMPRISING L-GLUTAMINE AND EGCG

The invention relates to a kit of parts for maintaining or improving the state of health, and the application of such a kit. The invention further relates to a method for preparing such a kit of parts.

There continues to be a great need for substances which favourably affect the state of health. There is particular interest in nutritional supplements generally deemed safe to be administered and used. Two important groups of nutritional supplements are formed by on the one hand amino acids and on the other antioxidants, such as for instance polyphenols. A group of polyphenols with strong antioxidant properties is formed by the catechins which occur in green tea, such as for instance (-)-epicatechin (EC), (-)-epigallocatechin gallate (EGCG), epigallocatechin (EGC) and epicatechin gallate (ECG).

Both prospective, placebo-controlled, randomized clinical comparative research and animal experiment research and *in vitro* research making use of the culture of specific cell lines show that natural amino acids and the antioxidant polyphenols which completely differ therefrom both have an effect in a number of health areas important for maintaining or improving the state of health.

The first health area relates to the favourable effect of natural amino acids and antioxidant polyphenols in reducing the risk of developing cardiovascular diseases, in particular arteriosclerosis and diabetes mellitus, in particular type-2. A dyslipidemia manifesting itself in an increased cholesterol, increase in the LDL cholesterol and decrease in the HDL cholesterol with increase in the triglycerides, diabetes mellitus type-2 (DMT2), hypertension and overweight are, in addition to smoking and a lack of daily physical exercise, the most important risk factors for the development of cardiovascular disease due to arteriosclerosis. In the case of diabetes mellitus type-2 insulin resistance and a reduced insulin secretion by the β-cells in the pancreas are the key pathogenic factors.

In respect of amino acids:

- There are clinical trials which show that the parenteral supplementation of the amino acid L-glutamine in the form of a dipeptide increases the glucose tolerance by:
1- reducing the insulin resistance (1), whereby the glucose ingestion by the body improves (2) and
2- increasing the insulin plasma level (3).

This latter probably progresses on the one hand due to a relatively weak stimulation of the insulin secretion by β-cells via stimulation of the gamma-glutamyl cycle-mediated glutathione production and of the production of ATP by mitochondrial oxidation. The natural amino acid glutamine probably has a signal-transmitting role (4, 48) in this stimulation of the insulin secretion.

- On the other hand, orally administered L-Glutamine also enhances, via incretin-dependent mechanisms, the secretion of GLP-1 (glucagon-like peptide 1) by the L-cells of the intestinal wall, which increases the secretion of insulin in lean and obese patients with type-2 diabetic mellitus (5).

In respect of antioxidant polyphenols:
- these have a regulating effect on the insulin secretion by β-cells in the pancreas through an allosteric inhibition of the glutamate dehydrogenase (GDH). EGCG has a positive effect on the glucose tolerance / diabetes type-2, of rodents (7) and probably on the diabetic retinopathy in humans (8);
- they improve the glucose tolerance by reducing the insulin resistance in humans and increase the fat oxidation during moderately intensive physical exertion (9);
- in animal models they have in addition, probably as antioxidant, a favourable effect on the development of arteriosclerosis, blood pressure, obesity/overweight (10). The polyphenol EGCG also reduces cholesterol in humans (11) and counters postprandial increase of the triglycerides (12). A favourable result in preventing diabetes mellitus type 2 in adults has also been described (13).

The daily ingestion of the antioxidant polyphenol catechins for 12 weeks reduced body fat/overweight and the content of the oxidized LDL (14).

The second health area relates to the favourable effect of natural amino acids and antioxidant polyphenols on bacterial inflammations and on autoimmune-mediated inflammations, such as for instance rheumatoid inflammations.

In respect of natural amino acids: the natural amino acid L-Glutamine forms a fuel and nutrient for rapidly proliferating gut epithelial cells and immune cells around the gut and bronchial tree (15, 16, 17, 18) and hereby supports the mucosal and immune
barrier against attacking micro-organisms. In the case of inflammations it also reduces the endogenous inflammation reaction by preventing the release of pro-inflammatory mediators (IL-8, IL-6, TNF-α) from granulocytes and the production of metalloproteinase in for instance the postischemic gut (19) and enhancing the production of anti-inflammatory factors (IL-10) by T-lymphocytes (20, 21, 22) as well as the cysteiny1-leukotriene generation (23, 24). The L-Glutamine affects the inflammation reaction by attenuating the NFk-B activation (25). The natural amino acid L-Glutamine also enhances the production of the glutathione involved in relief of oxidative stress (26) and of the heat shock proteins (27, 28, 29), and activation occurs of peroxisome proliferator activated receptor gamma, an anti-inflammatory transcription factor which protects the gut from damage by cytokines released during ischemia (52). In respect of antioxidant polyphenols: The antioxidant polyphenol catechin, such as EGCG, has a local bactericidal, fungicidal and antiviral effect, such as in the gut, making use of its oxidative action in high local concentrations and has a systemic inhibiting effect on the activation of the pro-inflammatory infection cascade, inter alia by inhibiting the NFkB and HMGB1, countering TNF-α and IL-1β induced toxicity. In the case of severe inflammations the antioxidant polyphenol catechin acts not only as antioxidant (30, 31) but also inhibits the metalloproteinase-2 activity induced by IL-1β and made possible by chemokines. Evaluation of the signal transmission paths showed that EGCG preferentially blocked the phosphorylation of PKCdelta and inhibited the activation and translocation to the cell nucleus of the NF-kappa β in synovial fibroblasts treated with IL-1β in rheumatoid arthritis patients (32). The antioxidant polyphenol EGCG in vitro also counters the autoantigen expression in normal human cellular components (33).

The third health area relates to the favourable effect of natural amino acids and antioxidant polyphenols on mucositis and peripheral polyneuropathy induced by chemotherapy and radiotherapy.

In respect of natural amino acids: L-Glutamine forms an important fuel and nutrient for the epithelial and immune cells of the intestinal wall (GALT) and for those of the bronchial tree (16). A number of clinical studies are known which indicate that L-Glutamine can reduce the peripheral neurological side-effects of chemotherapy and radiotherapy (34, 35, 36 and 37), L-Glutamine has a favourable effect on the occurrence
of the mucositis often associated with chemotherapy and radiotherapy (38). A possible favourable effect in combating multiple sclerosis has also been reported (49).

In respect of antioxidant polyphenols: these nutritional supplements can also reduce the side-effects of chemotherapy and radiotherapy (39).

The fourth health area relates to the favourable effect of natural amino acids and antioxidant polyphenols for maintaining or improving fitness and sporting performance.

In respect of natural amino acids: there are many publications about supplementing the normal level of natural amino acids for the above stated indications. Exertion initially induces an increase in the plasma glutamine level, but with continued exertion the plasma glutamine falls below the normal lower limit value. This fall in the glutamine level is however seen as a potential cause of exertion-induced immune incompetence which is linked to an observed increased susceptibility to infection among athletes (40, 51). After prolonged exertion, hunger and physical stress the body has an increased need for glutamine, which justifies oral use thereof at that moment. The administration of L-Glutamine compensates the increased use by the body, and in particular the increased absorption by the kidney, in an attempt to keep the acid base balance in equilibrium, and provides for the increased use of glutamine by liver and gastrointestinal tract for the gluconeogenesis. A possible favourable effect of glutamine in combatting Duchenne muscular dystrophy has also been reported (50).

In respect of antioxidant polyphenols: by stimulating fat-burning the use hereof is favourable in improving stamina. The effect of EGCG on fat-burning is dosage-dependent in laboratory animals and is associated with a lower respiration quotient and a higher fatty acid β-oxidation in the skeletal muscles. The plasma lactate levels were lower in these animals after exertion. This is associated with an increase in the free fatty acid concentration. This indicates an increased use of lipids as energy source in the case of humans (41) and mice (42) fed with polyphenol EGCG.

The fifth health area relates to the favourable effect of natural amino acids and antioxidant polyphenols on virus infections, such as infection with influenza, HIV, HIV/AIDS, HCV, HBV, HSV and HPV.

In respect of natural amino acids: there are publications which indicate that oral use of natural amino acid L-Glutamine is effective in the treatment of Influenza A (53) and in the treatment of chronic diarrhoea and/or "wasting" in the case of HIV/AIDS.
patients, as with Cryptosporidium diarrhoea, resulting not only in a reduction of the symptoms but also in an improved resorption of the antiviral therapy (HAART) (43). Use of the oral amino acid L-Glutamine is also expressed in enhanced lymphocyte proliferation, this being significant because a number of CD4+ lymphocytes above 200/mm$^3$ has been found to be clinically significant in reducing the risk of opportunistic infections.

In respect of antioxidant polyphenols: the antioxidant polyphenol EGCG is likewise effective in the case of Influenza A (54, 55) and in the case of HIV infection mitigates the neurotoxicity of the IFN-gamma-reinforced damage caused by HIV-I glycoprotein gpl20 and Tat, both in vitro and in vivo (46). There is clear evidence of a very strong binding of EGCG to the CD4 molecule which impedes the binding of gpl20 to the CD4+ T-cells in humans (47). EGCG binds to the CD4+ T-cells in a manner such that the calculated binding of gpl20 to the CD4-EGCG complex is negligible (48). The favourable binding of EGCG to the CD4 can thus effectively block the gpl20-CD4. EGCG has a protective effect in respect of HIV-induced dementia (56) and the infection itself (57).

The US patent application 2008/0131525 describes a solution of the natural amino acid glutamine and a number of specific antioxidants such as selenium, zinc, vitamin C, vitamin E. and β-carotene to be delivered parenterally to a critically ill patient. A formulation of an extract of green tea with a large number of other ingredients such as vitamins, minerals and amino acids and components which in solution provide an effervescent effect is described in the international application WO 01/00038. The European patent EP 1572175B, which patent corresponds to the Canadian patent application CA 2499006, describes a formulation comprising an extract of green tea comprising an extract of green tea including the polyphenol (−)-epigallocatechin gallate (EGCG) and a nitrogen oxide donor such as amino acids such as glutamine, specifically for the preoperative gastrointestinal administration of an agent which reduces the risk of postoperative complications. Compositions with nutritional supplements comprising many ingredients are also described in a large number of other publications, such as in

- German patent application DE 102006038224: in addition to glutamine and EGCG the compositions also comprise at least Tyrosine and Taurine, and these
compositions are suitable for treating neuroendocrine health problems,
- US patent 5,904,924: this patent describes a nutritional composition which is a mixture of about 60 natural products and herbs,
- US patent application US 2004/007 1681: described herein is a lolly which comprises, in addition to an extract of green tea and glutamine, at least six other ingredients,
- International patent application WO 2007/135766: describes an ointment for leukoplakia or oral cancer comprising a green tea extract and alginic acid,
- European patent application EP 2025248: a large number of compositions are described for the treatment of cachexia and/or anorexia, such as for instance a composition comprising eicosapentaenoic acid, a phytochemical compound such as green tea and glutamine,
- International patent application WO 2006/020131: described herein are a large number of compositions, for instance comprising antioxidants, wherein many are mentioned, such as for instance tea extract and amino acids with branched carbon chains, many of which are mentioned, such as for instance glutamine,
- US patent application 2009/001 1048: a large number of dietary supplements are described for removing heavy metals from the body, wherein a composition comprises, in addition to about 20 other ingredients, an extract of green tea and glutamine,
- European patent application EP 2095727 corresponding to WO 2008/082582: described herein are packed beverages comprising a large number of possible catechins, amino acids and also sweeteners.

In view of the abundance of described possible beneficial compositions, wherein different fields of application are indicated in each case, there is a demand for one simple composition with multiple activity. There is a great need for one safe nutritional supplement which reduces the risk of developing a disease and/or complications thereof, such as by reducing the risk of arteriosclerosis and diabetes mellitus type-2, increasing the activity of the immune system against oxidative stress or by improving the muscle condition of people with a poor nutritional level.

The present invention has for its object to provide a composition which is very effective in respect of improving the state of health and in maintaining the state of
health in many areas.

In order to achieve the stated object, the invention provides a kit of parts of the type stated in the preamble, substantially comprising a) L-Glutamine and b) \((-\)\)-epigallocatechin gallate (EGCG), preferably consisting only of a) L-Glutamine and b) EGCG. a) L-Glutamine and b) EGCG are preferably packed together in a double sachet, both a) L-Glutamine and b) EGCG more are preferably present independently of each other in the form chosen from the group of powder and capsule. Both components will generally be used in this form, although the ingestion of at least one of the components in dissolved form also forms part of the invention. The kit of parts according to the invention preferably comprises about 1 - 60 g active L-Glutamine, more preferably about 5 - 30 g active L-Glutamine, in particular about 9 g active L-Glutamine and about 50 - 1500 mg EGCG, more preferably about 100 - 400 mg EGCG, in particular about 150 mg EGCG. Generally recommended as daily dosage is a dosage no higher than 3 x the content of the double sachet according to the invention.

The kit of parts according to the invention is preferably applied in oral manner, although all other known and suitable administering methods, such as for instance parenteral, subcutaneous, intramuscular or intravenous, also form part of the invention.

According to another aspect of the invention, an application of such a kit of parts is provided for the purpose of enhancing sporting performance.

According to yet another aspect of the invention, an application of such a kit of parts is provided as means of preventing or reducing the risk of developing a physical disorder. The application of such a kit of parts serves particularly to increase the activity of the immune system.

The application of a kit of parts particularly prevents or reduces the risk of developing one or more of the following physical disorders:

- cardiovascular disease, more particularly on the basis of arteriosclerosis
- diabetes mellitus, in particular type-2
- high blood pressure
- obesity / overweight
- neurological mucous membrane disorders, hair cell disorders, cardiac disorders and peripheral nerve disorders, also as side-effects of chemotherapy and radiotherapy,
bacterial and viral infections
- rheumatic inflammations
- burns
- Duchenne muscular dystrophy.

In these cases increased oxidative stress plays an important pathogenetic role which is targeted by the application.

The kit of parts according to the invention is applied particularly effectively in the case of

- one or more of the infections with a virus from the group consisting of influenza, HIV, HIV/AIDS, HCV, HBV, HSV and HPV
- one or more neurological disorders as caused by one or more of the diseases of the group consisting of those of Alzheimer, Parkinson and Huntington and multiple sclerosis or
- a salivary/lacrimal and mucous membrane disorder as caused by Sjogren's disease.

The application of substantially a) L-Glutamine and b) EGCG together for the above described indications within an appropriate period of time also forms part of the present invention.

Finally, the present invention provides a method for preparing a kit of parts, characterized in that a) L-Glutamine and b) EGCG are packaged together in a kit, preferably in the form of a double sachet, in particular chosen independently of each other from the group of powder and capsule. Desired adjuvants are co-packaged in a manner known to the skilled person.

The invention will be further elucidated hereinbelow. Combining the action of two products as the result of a consciously chosen selection of that of the conditionally essential natural amino acid a) L-Glutamine and, as exogenous antioxidant, the most active component of the natural product green tea: b) (-)-epigallocatechin gallate (EGCG), belonging to the group of anti-oxidant polyphenols, has a greater efficacy than may be anticipated from merely bringing together two random nutritional supplements.

The part of the kit a) L-Glutamine is understood in this patent document to mean L-Glutamine or a derivative thereof, as well as L-Glutamine as part of a dipeptide. As derivative it is possible to envisage glutamate, as dipeptides it is possible to envisage the
two dipeptides Alanine-Glutamine and Glycine-Glutamine, Ala-Gln and Gly-Gln respectively. A weight of active L-Glutamine is understood to mean a weight of derivative corresponding in number of MoI to the weight of L-Glutamine per se. The term 'substantially' indicates that, in addition to the stated active ingredients, other ingredients can be present which are not active, or hardly so, such as adjuvants, without this detracting from the scope of protection of the invention.

Particularly favourable is the application of a kit of parts with both products packed in a double sachet specifically referred to as 2-Prepare For Optimal Care®. However, the use of the separate components a) L-Glutamine and EGCG together within an appropriate period of time of preferably no longer than one to two hours must also be deemed as forming part of the invention.

The naturally occurring amino acid L-Glutamine is commercially available. EGCG can be extracted from green tea, for instance as described in the European patent EP 1767097, and is also commercially available from for instance DSM Nutritional Products AG as Teavigo®, 200 mg in a gelatin-free capsule.

The EGCG component of the kit is understood to mean a composition with an EGCG content of at least 90%, generally of at least about 95%. Since this compound is extracted from green tea, this purity is obtained here.

Both active parts of the kit are particularly used as powder or capsule as preferably applied in the double sachet. The formulation of the capsule has the advantage that the bitter taste of EGCG is eliminated. Other formulations such as pills, tablets, effervescent tablets, film tablets, which can also be packed in a double sachet, will of course also fall within the scope of protection of the invention. Adjuvants known to the skilled person can also be present in all formulations in addition to the active ingredients. Both active components are otherwise generally separated from each other in the double sachet, particularly by means of a closure. Separate packaging has the advantage that EGCG, which in high concentration acts locally as an oxidative substance, does not adversely affect (the action of) L-glutamine.

There is a great need for safe nutritional supplements or combinations thereof which reduce the risk of developing a disease, as is also apparent from the number of articles and patent documents appearing in this field. The present invention provides such a combination, with the combination of a) L-Glutamine, a conditionally essential
amino acid, as first component, which amino acid increases the activity of the immune system and improves the muscle condition of persons with a poor nutritional level, in the case of burns and prior to and during heavy muscular exertion as in endurance sports. The second component, the component of green tea extract EGCG, is a caffeine-free antioxidant which appears to mitigate complications from infections/inflammations, reduces cholesterol content, triglycerides and blood sugar, slows down the development and progression of Alzheimer and Parkinson disease and, by shifting the ratio of carbohydrate/fat burning in favour fat burning, improves stamina during great physical exertion by postponing excessive lactic acid production (acidification).

The action of the two reliable nutritional supplements, i.e. the natural amino acid a) L-Glutamine and the antioxidant polyphenol b) EGCG, each forming part of a group of compounds with a different mechanism of action, support each other advantageously in a great number of areas, in particular those stated above.

Although the invention is elucidated above on the basis of a large number of different applications of the kit of parts, it will be apparent that the invention is by no means limited thereto. On the contrary, many variations are still possible within the scope of the invention for a person with ordinary skill in the art.

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Claims

1. Kit of parts for maintaining or improving the state of health, substantially comprising a) L-Glutamine and b) (-)-epigallocatechin gallate (EGCG).

2. Kit of parts for maintaining or improving the state of health as claimed in claim 1, consisting only of a) L-Glutamine and b) (-)-epigallocatechin gallate (EGCG).

3. Kit of parts as claimed in one or more of the claims 1 or 2, wherein a) L-Glutamine and b) EGCG are packed together in a double sachet.

4. Kit of parts as claimed in one or more of the claims 1-3, wherein both a) L-Glutamine and b) EGCG are present independently of each other in the form chosen from the group of powder and capsule.

5. Kit of parts as claimed in one or more of the claims 1-4, comprising 1-60 g active a) L-Glutamine, preferably about 9 g, and 50-1500 mg active b) EGCG, preferably about 150 mg.

6. Application of a kit of parts as specified in one or more of the claims 1-5 in oral manner.

7. Application of a kit of parts as specified in one or more of the claims 1-6 for the purpose of enhancing sporting performance.

8. Application of a kit of parts as specified in one or more of the claims 1-6 as means of preventing or reducing the risk of developing a physical disorder.

9. Application of a kit of parts as claimed in claim 7 for the purpose of increasing the activity of the immune system.
10. Application of a kit of parts as claimed in claim 8 or 9, wherein the physical disorder is one or more of the following:
   - cardiovascular disease, particularly on the basis of arteriosclerosis
   - diabetes mellitus, in particular type-2
   - high blood pressure
   - obesity / overweight
   - neurological mucous membrane disorders, hair cell disorders, cardiac disorders and peripheral nerve disorders, also as side-effects of chemotherapy and radiotherapy,
   - bacterial and viral infections
   - rheumatic inflammations
   - burns
   - Duchenne muscular dystrophy.

11. Application of a kit of parts as claimed in claim 10, wherein the virus infection relates to one or more of the infections with a virus from the group consisting of influenza, HIV, HIV/AIDS, HCV, HBV, HSV and HPV.

12. Application of a kit of parts as claimed in claim 10, wherein the neurological disorder relates to one or more of the diseases of the group consisting of those of Alzheimer, Parkinson and Huntington and multiple sclerosis.

13. Application of a kit of parts as claimed in claim 10, wherein the mucous membrane disorder relates to Sjogren’s disease.

14. Application of substantially a) L-Glutamine and b) EGCG together within an appropriate period of time for the indications described in one or more of the claims 7-13.

15. Method for preparing a kit of parts as specified in one or more of the claims 1-5, characterized in that a) L-Glutamine and b) EGCG are packaged together in a kit.
## INTERNATIONAL SEARCH REPORT

**INTERNATIONAL APPLICATION**  
International application No  
PCT/NL2010/000050

### A. CLASSIFICATION OF SUBJECT MATTER

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#### ADJ.

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

### 0. FIELDS SEARCHED

**Minimum documentation searched** (classification system followed by classification symbols)

A23L  A61K

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

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>US 5 904 924 A (6AYNOR MITCHELL L [US] ET AL) 18 May 1999 (1999-05-18) claim column 4, line 5 - column 5, line 15 column 3, line 34 - line 50</td>
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**X** Further documents are listed in the continuation of Box C.  
**X** See patent family annex.

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**Date of the actual completion of the international search:**  
16 June 2010

**Date of mailing of the international search report:**  
22/06/2010

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Neys, Patricia
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<td>claims 1, 6, 7, 10, 11, 13, 14 page 3, line 10 - page 4, line 5 page 4, line 29 - line 32 page 5, line 29 - page 6, line 3 page 8, line 17 - page 10, line 3</td>
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