**Title:** DIETETIC OR PHARMACEUTICAL COMPOSITIONS FOR THE RESTORATION OF ADENINE NUCLEOTIDE CELL CONTENT IN SKELETAL AND CARDIAC MUSCLES

**Abstract**

Dietetic or pharmaceutical compositions containing a (D)-ribose and magnesium (L)-aspartate mixture for use as nutritional integrators are herein described.
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Dietetic or pharmaceutical compositions for the restoration of adenine nucleotide cell content in skeletal and cardiac muscles

The present invention relates to dietetic or pharmaceutical compositions containing a mixture of (D)-ribose and magnesium (L)-aspartate in various ratios.

One of the most important problems in the skeletal and cardiac muscle physiopathology is to restore, or to maintain adenine nucleotide cell content within physiological limits during or after a prolonged and/or exhausting physical effort, by a necessary or advisable nutritional intervention. On the contrary, the balance between energy requirement and energy availability would be jeopardized. This unfavourable situation occurs when dephosphorylation of ATP into ADP, and subsequently into AMP, continues till adenosine, inosine and ipoxanthine production.

These products are released by the cell (R.M. Berne; Am. J. Physiol., 204,317,1963), and therefore are lost for the purpose of a possible restoration of adenine nucleotides.

Theoretically, the problem of adenine nucleotide degradation could be solved by means of some biochemical-nutritional possibilities, for example, administration of adenosine (K. Reibel and M.J. Rovetto; Am. J. Physiol., 237,247,1979) or inosine (V.T. Wiedmeier, R. Rubio and R.M. Berne; J. Mol. Cell. Card.; 4,445,1972), which however proved to be rather ineffective.
It has now been found that the administration of (D)-ribose surprisingly enhances adenine nucleotide synthesis, thus resulting in a higher availability of 5-phosphoribosyl-1-pyrophosphate, which is the limiting factor of adenine nucleotide biosynthesis. Accordingly, administration of (D)-ribose prevents and reduces adenine nucleotide decrease in muscles during strong stress conditions.

Therefore, dietetic or pharmaceutical compositions containing (D)-ribose, optionally combined with magnesium (L)-aspartate, are an object of the present invention.

In fact, it is well known that about 55% magnesium ions in the human body are located in the bones, while the remaining are in the soft tissues. A decrease in muscle Mg\(^{2+}\) has particularly been observed during magnesium deficiency and during intense physical exercises.

Magnesium ion mobilization, particularly the loss thereof from muscle cells during physical exercise, can be explained by the high activity of the Mg\(^{2+}\) dependent enzymes, which are involved in the energy metabolism (creatine phosphokinase, glycogen phosphorylase and myosin ATPase). The correlation between Mg\(^{2+}\) loss and exercise intensity can depend on: i) a reduced kidney concentrating capacity which is induced directly by the physical exercise or indirectly by the increase of the hormones inducing Mg\(^{2+}\) ion tubular reabsorption (aldosterone, antidiuretic hormone, thyroid hormones) whose hematic concentration can remain high up to 14 hours after the end of the physical exercise; ii)
acidosis, due to lactate accumulation, which can induce magnesiuria through a decrease in magnesium tubular reabsorption.

Accordingly, the (D)-ribose and magnesium (L)-aspartate combination assures a correct adenine nucleotide increase and, at the same time, allows to balance muscle Mg\(^{2+}\) concentration both in magnesium deficiencies and during physical exercises. Administration of the compositions of the present invention is also useful in pathologic conditions wherein a prompt restoration of weary muscles is necessary, for example in diabetes, alcoholism, cardiopathies, pregnancy.

The dietetic compositions of the present invention can contain from 200 to 2000 mg of (D)-ribose. When present in the composition, the magnesium (L)-aspartate unitary dose can range from 100 to 1000 mg. Weight ratios of (D)-ribose to magnesium (L)-aspartate are not critical and will generally range from 1:1 to 5:1.

The compositions of the present invention can further contain other active ingredients or integrators with adjuvant, complementary or useful activities.

Examples of said elements which are profitably used are:
- mineral salts and/or vitamins
- potassium aspartate.

The dietetic or pharmaceutical compositions of the invention can be prepared according to conventional techniques and excipients. Said compositions are prepared by admixing (D)-ribose and magnesium (L)-aspartate with physiologically acceptable excipients.
having pleasant appearance, smell and taste.

Examples of excipients known in the food industry are diluents, sweeteners, binders, flavoring aids, lubricants and non-sticking agents, natural and artificial food dyes.

Examples of diluents are: microcrystalline cellulose, glycine, lactose; maize, potatoes and rice starch; mannitol, sorbitol, sucrose, fructose; examples of sweeteners are: saccharin sodium, saccharin acid, aspartame, honey; examples of binders are: starch, polyvinylpyrrolidone, polyvinyl alcohol, hydroxyethylcellulose; examples of flavor aids are: citric acid and the salts thereof, tartaric acid and the salts thereof, sodium glutamate, sodium chloride, orthophosphoric acid and the salts thereof, menthol; examples of lubricants and non-sticking agents are: magnesium stearate, talc, 200 to 6000 PEGs (polyethylene glycols), glyceryl behenate, glycerin, mineral oil, silicone oils, levynite; examples of food dyes are: chlorophyll, bilberry anthocyanins; E104, E110; titanium dioxide, iron oxides; examples of dietetic compositions are: chewable, effervescent or swallowable tablets, syrups, fruit beverages, soluble granulate sachets, fruit jellies, candies.

The following examples further illustrate the invention.

**EXAMPLE 1**

**Chewable tablets**

1 Tablet contains

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D)-Ribose</td>
<td>200</td>
</tr>
<tr>
<td>Magnesium (L)-aspartate</td>
<td>200</td>
</tr>
</tbody>
</table>
Maize starch \( \text{mg} \) 50
Lactose \( \text{mg} \) 50
Magnesium stearate \( \text{mg} \) 5

**EXAMPLE 2**

5 Reflectable solution
250 ml of solution contain:

(D)‐Ribose \( \text{mg} \) 1000
Magnesium (L)‐aspartate \( \text{mg} \) 1000
Sorbitol \( \text{mg} \) 30

10 Citric acid \( \text{mg} \) 50
Sodium chloride \( \text{mg} \) 50
Methyl‐p‐hydroxybenzoate \( \text{mg} \) 45
Propyl‐p‐hydroxybenzoate \( \text{mg} \) 5
Purified water q.s. to \( \text{ml} \) 250

15 **EXAMPLE 3**

Granulate sachet
1 Sachet contains:

(D)‐Ribose \( \text{mg} \) 1000
Magnesium (L)‐aspartate \( \text{mg} \) 500

20 Lactose \( \text{mg} \) 200
Methylcellulose \( \text{mg} \) 10
Tartaric acid \( \text{mg} \) 5
Lemon flavor \( \text{mg} \) 25
Sorbitol q.s. to \( \text{g} \) 3

25 **EXAMPLE 4**

Chewable tablets
1 Tablet contains:

(D)‐Ribose \( \text{mg} \) 500
Magnesium (L)‐aspartate \( \text{mg} \) 500

30 Mannitol q.s. to \( \text{g} \) 1,5
Polyvinylpyrrolidone \( \text{mg} \) 50
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>mg 10</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>mg 3</td>
</tr>
<tr>
<td>Orange flavor</td>
<td>mg 20</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>mg 10</td>
</tr>
<tr>
<td>Talc</td>
<td>mg 8</td>
</tr>
</tbody>
</table>

**EXAMPLE 5**

**Chewable tablets**

1 Tablet contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D)-Ribose</td>
<td>mg 800</td>
</tr>
<tr>
<td>Mannitol q.s. to</td>
<td>g 1,5</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>mg 100</td>
</tr>
<tr>
<td>Citric acid</td>
<td>mg 10</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>mg 3</td>
</tr>
<tr>
<td>Orange flavor</td>
<td>mg 20</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>mg 10</td>
</tr>
<tr>
<td>Talc</td>
<td>mg 8</td>
</tr>
</tbody>
</table>

**EXAMPLE 6**

**Sugar pills**

1 Sugar pill contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D)-Ribose</td>
<td>mg 500</td>
</tr>
<tr>
<td>Magnesium (L)-aspartate</td>
<td>mg 100</td>
</tr>
<tr>
<td>Maize starch</td>
<td>mg 50</td>
</tr>
<tr>
<td>Talc</td>
<td>mg 30</td>
</tr>
<tr>
<td>Levylite</td>
<td>mg 25</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>mg 5</td>
</tr>
<tr>
<td>Sucrose</td>
<td>mg 150</td>
</tr>
<tr>
<td>E110</td>
<td>mg 0,025</td>
</tr>
<tr>
<td>Carnauba wax</td>
<td>mg 0,001</td>
</tr>
</tbody>
</table>
CLAIMS

1. Dietetic or pharmaceutical compositions containing (D)-ribose as active ingredient.

2. Dietetic or pharmaceutical compositions according to claim 1 further containing magnesium (L)-aspartate.

3. Dietetic or pharmaceutical compositions according to claim 1 or 2 containing from 200 to 2000 mg of (D)-ribose and from 100 to 1000 mg of magnesium (L)-aspartate.

4. Dietetic or pharmaceutical compositions according to anyone of the preceding claims, containing other active ingredients or integrators with adjuvant, complementary or anyway useful activities.

5. Dietetic or pharmaceutical compositions according to claim 4, further containing at least another active ingredient or integrator selected from the group consisting of mineral salts, vitamins and potassium aspartate.

6. Dietetic or pharmaceutical compositions according to anyone of the preceding claims, in the form of effervescent, chewable and swallowable tablets, syrups, fruit drinks, soluble granulate sachets, fruit jellies, candies.
INTERNATIONAL SEARCH REPORT
International Application No PCT/EP 92/00369

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/70; A23L1/304; A23L1/305; A23L1/09
A23L2/26; A23G3/00; A23L1/06;

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System Classification Symbols

Int.Cl. 5 A61K ; A23L

Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched 8

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

<table>
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<tr>
<th>Category</th>
<th>Citation of Document, 11 with indication, where appropriate, of the relevant passages 12</th>
<th>Relevant to Claim No.13</th>
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<tr>
<td>A</td>
<td>EP, A, 0 324 227 (RONCARI, RAYMOND A.) 19 July 1989 see abstract; claims 1-6</td>
<td>1, 6</td>
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<td>A</td>
<td>US, A, 4 824 660 (DEBRA A. ANGELO &amp; RICHARD A. WILSON) 25 April 1989 see abstract; claims 1, 2</td>
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<td>A</td>
<td>FR, A, 2 609 397 (LABORATOIRES SEROBIOLIOGIQUES) 15 July 1988 see abstract; claims 1, 2, 5</td>
<td>1-6</td>
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8 Special categories of cited documents: 10

"A" document defining the general state of the art which is not specially relevant to the claimed invention

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"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.

"Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

19 MAY 1992

Date of Mailing of this International Search Report

02. 06. 92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

LEHETTE C. F. M.
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9200369
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/05/92

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82