Title: PHARMACEUTICAL OR NUTRACEUTICAL COMPOSITIONS CONTAINING CHROMIUM OR IRON COMPLEXES OF ALPHA-LIPOIC ACID

Abstract: Compositions to be incorporated in products with hypoglycemicizing, anti-oxidant, vasoprotective and anti-hyperlipemic activity, or in products recommended for the treatment of anemias and states or iron deficiency, the compositions being based on chromium (III) or iron (III) salts or complexes with α-lipoic acid or with the corresponding klydroliopico acid (chromium lipoate and iron lipoate), which make chromium and iron easily absorbable and improve their bioavailability. The invention also concerns the use of one or more chromium (III) or iron (III) salts or complexes with α-lipoic acid or with the corresponding dihydrolloico acid for the production of nutraceutical, pharmaceutical or veterinary preparations.
PHARMACEUTICAL OR NUTRACEUTICAL COMPOSITIONS CONTAINING CHROMIUM OR IRON COMPLEXES OF ALPHA-LIPOIC ACID

DESCRIPTION

The present invention concerns pharmaceutical or nutraceutical preparations containing chromium or iron salts or complexes with $\alpha$-lipoic acid and their applications. More specifically, the invention concerns compositions to be incorporated in products of a mainly hypoglycemicizing, antioxidant, vaso-protective and anti-hyperlipemic activity, or in products recommended for the treatment of anaemia and iron-deficiency conditions that are based on chromium (III) or iron (III) salts of complexes with $\alpha$-lipoic acid or with the corresponding dihydrolipoic acid.

As is well-known, chromium is a micronutrient essential from a nutritional standpoint. One of its biological roles is to enhance insulin action, thus influencing the metabolism of carbohydrates, lipids and proteins. Indeed, experimental chromium deficiencies induced in animals cause an intolerance to carbohydrates similar to diabetes mellitus, with growth disorders and high cholesterol levels in the blood. In man, although it has been ascertained that diabetes is not a pathology caused by chromium deficiency, there are known cases of chromium deficiency during total parenteral nutrition which are characterised by, amongst other symptoms, states of serious intolerance to glucose that are resistant to insulin. One state of reduced chromium-sensitive tolerance to carbohydrates was also found in malnourished children and, in some cases, in diabetics. Moreover, a chromium deficiency was also associated with hypercholesterolemy and, in some cases it was hypothesised that such a deficiency could also be involved in the atherosclerotic process.

Although it may be found in oxidation states ranging from 2+ to 6+, more commonly 3+ and 6+, in food chromium is present mostly as Cr3+, the more stable oxidation state and probably the most important biological form. Unlike hexavalent chromium, trivalent chromium is toxic only if ingested in
Unlike hexavalent chromium, trivalent chromium is toxic only if ingested in large quantities. The daily requirement for an adult ranges from 50 to 200 μg/day, since its intestinal absorption is very low.

The highest levels of chromium concentration have been found in hazelnuts and peanuts, in egg yolks, in some meats and in vegetables and cheeses. In Italy, green vegetables, cereals and their derivatives provide the most chromium in the diet. It is also known that the percentage of inorganic 3+ chromium absorbed by foods is low, and it is even lower as the quantity of ingested chromium increases.

In any case, the best form of chromium supplementation is the organic form contained in beer yeast, which is absorbed in the range of 10-25%, while inorganic chromium, usually chromium chloride (CrCl₃ x 6H₂O) is absorbed in the range of 1-3%. Chromium absorption is greater the lower the gastric acidity, which at high levels totally blocks this absorption. Endogenous chromium is excreted mainly with urine (90-95%), while faeces mainly contain unabsorbable chromium.

Once absorbed, chromium is carried by transferrin and albumin, the latter supposedly intervening when transferrin is no longer available. At the blood level, chromium competes with iron for protein conveyance since the saturation of transferrin with iron reduces chromium transportation and retention. Chromium then partly passes to the liver, where it is incorporated in a complex molecule that constitutes its biologically active form, called "glucose tolerance factor" (GTF), probably made up of two nicotinic acid molecules and three amino acids (glycine, L-cysteine and L-glutamic acid). This factor seems to form a ternary complex with insulin and the insulin receptors, enhancing the action of insulin itself at the tissue level.

More generally, it has been hypothesised that chromium facilitates insulin action by either regulating the number of membrane receptors or by favouring receptor-insulin interaction, or even both. Moreover, it may also regulate the synthesis of molecules enhancing insulin action, by acting at the gene-expression level.

Chromium thus does not have any hypoglycaemic action per se, but is
essential for proper insulin function. With chromium deficiency, insulin and the oral hypoglycemizing compounds lose their properties, which return once the metal is again supplemented in the diet.

It has been reported that chromium supplementation can lead to a reduction of glycaemia in the region of 36%, and may also favourably affect triglyceride and cholesterol levels. A specific indication is thus senile diabetes, in which chromium supplementations are intended to enhance insulin activity, thereby reducing its organic need. This decrease of insulin levels may lead to a lipogenesis reduction. A chromoim deficiency may lead to a reduced tolerance for glucose, thus also leading to risks of necrosis and hepatic degeneration. Glucose is more easily stored as glycogen during chromium supplementation.

Ingesting a load of glucose considerably increases – after 90 minutes – the urinary excretion of chromium, perhaps because greater quantities of GTF are put into circulation. Continuous high doses of glucose do not lead to the same result, evidently owing to the total depletion of the organic reserves of the metal.

In view of the above, it may well be understood that prolonged administration of chromium can lead both a diabetic subject and a normal subject to improving his tolerance to glucides and lowering the insulinenic curve.

Among the other positive effects that have been attributed to chromium supplementation in one's diet, there is to be considered an effect of reducing the cholesterol levels in the blood, which some experimental studies have reported, as well as the existence of a direct relationship between the absence of coronary lesions and high tissue and seric levels of chromium, reported in other studies. In the ophthalmic field, chromium, in association with selenium, protects the retinal vessels damaged by hyperglycaemia, and a diet that is particularly poor in chromium can lead to corneal opacity, congestion of iris vessels and cataract.

Finally, it must be noted that chromium is also important for the reproductive sphere, where a deficiency of this metal seems to reduce fertility and spermatozoa production in males (while it does not affect female fertility), and
seems to affect foetus growth. A serious chromium depletion in the mother can lead to serious eye damage in the newborn. In this regard, it has been confirmed that chromium gradually increases during the embryo’s life, and pregnancy considerably depletes the women’s reserves (by around one third), which are then further depleted through breast-feeding.

Another element whose presence in the body is extremely important is iron. A deficiency of this metal leads to sideropenic anaemia – a very widespread disorder in Europe (affecting about 20-30% of women of child-bearing age and adolescents) – which is caused by the depletion of iron reserves. An iron deficiency has negative repercussions also on other biological systems and mechanisms, such as the immune system, the brain neurotransmission systems and heat regulation. Clinically, anaemia due to iron deficiency presents itself with asthenia, paleness, tachypnea and tachycardia. However, certain signs, such as difficulties in concentrating and fatigue at work, can be found already in the stages prior to the deficiency and these must be identified by measuring haematic parameters.

Iron is present in food in two forms: associated with the heme in red meats (the easiest form of absorption) and associated with other food components (absorbable after cooking the food). Certain foods, although rich in iron, are not a good source of this metal. For example, the iron contained in spinach cannot be absorbed because it is chelated by oxalates. As with other nutrients or pharmaceuticals that are permanently dissociated in the gastrointestinal tract, iron has a low oral bioavailability, it being absorbed in the range of 10% on average. In the presence of vitamin C and in acidic conditions, it forms a liposoluble iron-vitamin C adduct which can be absorbed as it is, which improves its oral bioavailability.

Iron ions face modifications of their oxidation state during digestion and absorption. In the acidic pH conditions of the stomach or in the presence of reducing agents such as vitamin C, the Fe(III) ion is reduced to Fe(II): this facilitates iron dissociation from the ligands. In alkaline pH conditions of the duodenum, the heme is absorbed by the cells of the mucosa, and inside the cells the iron is dissociated from the heme and is oxidised to Fe(III).
The absorption of iron and of other mineral nutrients is also hindered by a diet rich in food fibre. The fibre binds the mineral nutrients favouring their faecal elimination; in situations of mineral deficiencies, the fibre reduces mineral absorption also because of the increased intestinal peristalsis.

Going back to diabetic pathologies, another widely used compound in this field is α-lipoic acid, also known as thiocyclic acid or 1,2-dithiolan-3-pentanoic or 1,2-dithiolan-3-valeric acid. This is a relatively small molecule made up of a chain of eight carbon atoms and two sulphur atoms located at the end, and corresponds to the following structure formula:

![Structure formula of α-lipoic acid]

In the reduced form, also known as dihydrolipoic acid, the sulphur atoms are present as free thiols (-SH), while in the oxidised form, thanks to the generation of a disulphur bond (-S-S-), they give rise to a ring-shaped end structure. Given its particular molecular structure, α-lipoic acid can participate in both oxidoreduction reactions and can act as a carrier of electrons or of acetyl groups (or other acyl groups).

α-lipoic acid is present in a large variety of natural substances since it is an essential factor of the metabolism and is active in extremely low quantities. As well as being a powerful antioxidant, it acts as a co-factor for many enzymes taking part in the process of converting glucose, fatty acids and other energy sources into adenosin-triphosphate (ATP). The availability of lipoic acid at cell level increases the performance of the Krebs cycle and thus the efficiency of the entire process. Actually, the complete system for the oxidative decarboxylation of pyruvic acid and α-ketoglutaric acid requires, besides thiamin, other coenzymes including lipoic acid.

Besides reducing the levels of glycaemia, lactic acid and pyruvate in diabetics, α-lipoic acid reduces both lipid peroxidation and glycosylation of
proteins, and prevents diabetic neuropathies of vascular origin. During physical exercise, it can favour the entry of glucose in the skeletal muscle.

α-lipoic acid is not only able to increase the efficiency of insulin, but it can also improve the conveyance of glucose inside cells by using independent routes than those of insulin itself. All this, along with a better efficiency of using glucose through normal metabolic processes, contributes to normalising the glucose level in the blood. Moreover, the likelihood that dangerous compounds of a free radical character may form, the advanced glycation end-products (AGE), is considerably reduced. These products can be generated starting from cell proteins following the accumulation of high levels of glucose in the blood. Glycosylation reactions and AGE formation are known to contribute to cell ageing and degeneration.

Numerous studies carried out on animals show that the administration of α-lipoic acid can lower the risk of a cataract. This pathology is very often related to high levels of glucose in the blood and to overexposure to sunlight. These factors contribute to the formation of free radicals which can then cause damage to the proteins of the lens and favour AGE generation.

The most significant properties of lipoic acid may be summarised as follows:

- high absorption: being a relatively small molecule, lipoic acid can be readily absorbed and carried through cell membranes where it can then exert its action;
- versatility: α-lipoic acid maintains its activity both in aqueous cell compartments (cytoplasm) and in lipid ones (cell membrane);
- maintenance of its antioxidant power in both forms: although the reduced form (dihydrolipoic acid) is more active, there are appreciable antioxidant properties associated with the oxidised form as well;
- broad range of action: dihydrolipoic acid is active against many radical species;
- the ability to strengthen and complete the defensive network of other antioxidant molecules: α-lipoic acid in its reduced form can give up its electron to the
oxidised — and thus no longer active — forms of glutathione (glutathione disulphate) and of vitamin C (dehydroascorbic acid), regenerating them to a reduced glutathione and to ascorbic acid; after giving up an electron, dihydrolipoic acid returns to the oxidised form of lipoic acid.

α-lipoic acid is usually present in greater quantity in tissues that are richer in mitochondria. Particular rich sources are potatoes, broccoli and spinach, even though the greatest source of lipoic acid is red meat and some innards (particularly the heart). Although lipoic acid does not, in itself, represent a constituent definable as essential, since our body is able to synthesise it, it is still found in small quantities in the human body. The lipoic acid contained in food is not quite bioavailable, because it is present in a hardly absorbable complex form.

The normally recommended dose for general preventive purposes against degenerations caused by free radicals for healthy subjects is 50 mg/day. To reduce intolerance to glucose, from 100 to 300 mg/day is recommended. With diabetics, on the other hand, 600 mg/day is the recommended amount, to be taken under the strict supervision of a doctor. In these cases, the administration of high doses of α-lipoic acid can reduce the need for other pharmaceuticals which can lower glucose levels in the blood.

As regards toxicity, a daily intake of 50 mg of α-lipoic acid has so far not been linked to any side effect. Some studies, with dosages from 100 to 600 mg/day for periods ranging from three to six months, have shown a low toxicity in man. On the other hand, hypoglycaemia and allergic reactions of the skin have been sporadically reported with higher doses. Other studies have documented the absence of mutagenous, teratogenous or cancerogenous powers.

Both chromium and iron are supplied in many dietary preparations and supplements in order to treat states of organic deficiency or to improve certain functions of the body; the former particularly in the treatment of conditions linked to diabetes, to reduce insulin-resistance and control hypercholes-terolemia, while the latter in treatments against anaemia states. For the first
series of indications, there is a very widespread use of chromium and $\alpha$-lipoic acid combinations, often together with other ingredients, that are marketed as oral hypoglycemic agents. In this case, as already noted, chromium as an inorganic or organic salt is combined with $\alpha$-lipoic acid to enhance the latter's hypoglycemic effect.

Most of these preparations contain — in a mix with $\alpha$-lipoic acid — organic chromium compounds such as picolinate (chromium pyridine-2-carboxylate), tripicolinate (wherein all the three Cr3+ valences are neutralised with an equal number of picolinate ions), nicotinate (chromium pyridine-3-carboxylate), polynicotinate or trinicotinate. As an example, the international patent application published with No. WO 03/079819 (Anglo-French Drugs and Industries Ltd.) describes a dietary supplement for the treatment of patients with diabetic neuropathy that contains a combination of $\alpha$-lipoic acid, inositol and elemental chromium, wherein the latter is added to the composition in the form of chromium picolinate. Furthermore, US patent 6733793 (MetalProteomics LLC) concerns a composition of dietary supplement with a capacity for insulin-like activity and which contains, besides vanadyl sulphate and taurine, $\alpha$-lipoic acid and chromium — the latter in the form of the relative carnitine salt.

A further example of a similar preparation, wherein the active ingredients are only lipoic acid and the chromium-based compound, is described in US patent application 2002/0098247 (Komorowski et al.), concerning a composition to improve the insulin-sensitivity as well as to reduce hyperglycaemia and hypercholesterolemia, which includes a pharmaceutically effective dosage of $\alpha$-lipoic acid associated with at least one chromium salt or complex selected from the group consisting of picolinate, nicotinate, tripicolinate, polynicotinate, chloride, chromium histidinate and chromium-containing yeasts.

Over and beyond the fact that some laboratory studies have shown a potential toxicity of chromium picolinate, all the known formulations feature two ingredients, chromium and lipoic acid, as two separate components. In view of the foregoing, an object of the present invention is instead to provide a
nutraceutical non-toxic complex or organic salt enclosing in a single compound a double hypoglycemizing effect, thus combining in a single ingredient the functions of two different nutrients, more specifically that of α-lipoic acid and of chromium.

Another object of the present invention is to provide a preparation in which the conveyed metal (be it chromium or iron) results more easily absorbed, thus offering a greater bioavailability than the one obtained with other already used salts and compounds, respectively for the oral supplementation of chromium and iron. Moreover, the proposed preparations according to the present invention must be based on compounds that are natural and endogenous for man, in order to present lower toxicity risks with respect to other similar commercially available products.

To this end, the present invention proposes the complete or partial salification of trivalent chromium, or trivalent iron, with α-lipoic acid (racemate or active enantiomer), in order to obtain Cr(III) or Fe(III) salts or complexes with α-lipoic acid, so that both the functions of lipoic acid and of the metal concerned can be enclosed within a single compound. In practice, as regards salification with chromium by using α-lipoic acid, the present invention enables obtaining a hypoglycemizing compound which is also an antioxidant, and which has vasoprotective properties in diabetes.

The compounds representing the product of the salification reaction of α-lipoic acid with Cr(III) or with Fe(III), in which one, two or three of the valences of the trivalent metal ion are neutralised with one, two or three anions (carboxy ion) of lipoic acid (in oxidised form) or of dihydrolipoic acid (in reduced form), are compounds known per se, as shown, for example, by US patent No. 6462202 (Degussa AG). This concerns an α-lipoic acid purification method that can also start from an α-lipoic acid salt wherein the cations forming the salt can also be complex cations with central metal atoms like Fe(III) and Cr(III). Nowhere, though, is there any description found on the use of these complex cations in nutraceutical or pharmaceutical preparations in which the body must be supplemented with chromium or iron in an easily
absorbed form that is directly bioavailable.

Therefore, the present invention specifically provides a nutraceutical, pharmaceutical or veterinary composition comprising one or more salts or complexes of Cr(III) or Fe(III) with α-lipoic acid or with the corresponding dihydrolipoic acid, respectively of the following formulas:

\[ \left[ CH_2-CH_2-CH-(CH_2)_4-COO^- \right]_n \text{Me}^{3+} \left[ (3-n)/a \ A^{\beta} \right] \]  
\[ \text{S} \quad \text{S} \]  
\[ \left[ CH_2-CH_2-CH-(CH_2)_4-COO^- \right]_n \text{Me}^{3+} \left[ (3-n)/a \ A^{\beta} \right] \]  
\[ \text{SH} \quad \text{SH} \]  

wherein \( n \) is an integer between 1 and 3, \( \text{Me} \) can be either chromium or iron and \( A^{\beta} \) is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2.

More specifically, the said α-lipoic acid may be in the form of an optically pure isomer or the corresponding racemate, and more particularly it may be in the form of the corresponding R-(+)-enantiomer, that has turned out to be the optical isomer with a mainly anti-inflammatory activity, or in the form of the corresponding S-(−)-enantiomer, which is reported as having a more markedly analgesic activity.

According to some specific embodiments of the present invention, the \( A^{\beta} \) anion shown in formulas (1) and (2) is an inorganic anion selected from chloride, i.e. \( \text{Cl}^- \), and sulphate, i.e. \( \text{SO}_4^{2-} \), but other anions that in chemical synthesis make possible the precipitation of the required salt and give rise to a pharmaceutically acceptable product can be selected according to the normal practice of pharmaceutical chemistry.

Considering the specific case of chromium, the present invention envisages various forms of chromium lipoate that can all be synthesised in the two following formulas:

\[ \left[ CH_2-CH_2-CH-(CH_2)_4-COO^- \right]_n \text{Cr}^{2+} \left[ (3-n)/a \ A^{\beta} \right] \]
wherein n is an integer between 1 and 3, and $A^{n-}$ is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2. More in particular, in the case where the anion $A^{n-}$ is a chloride, the possible chromium lipoate variants proposed for the nutraceutical and pharmaceutical preparations according to the present invention are the following:

$$[\text{CH}_2-\text{CH}_2-\text{CH}-(\text{CH}_2)_4-\text{COO}^-]_n \text{Cr}^{3+} [(3-n)/a \text{ A}^{n-}]$$

In the specific case of iron, the present invention envisages various forms of iron lipoate that can all be synthesised in the following two formulas:

$$[\text{CH}_2-\text{CH}_2-\text{CH}-(\text{CH}_2)_4-\text{COO}^-]_n \text{Fe}^{3+} [(3-n)/a \text{ A}^{n-}]$$
wherein n is an integer between 1 and 3, and \( A^{\alpha} \) is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2. In this case, too, the anion \( A^{\alpha} \) can advantageously be a chloride.

According to a further aspect thereof, the present invention envisages the use of one or more salts or complexes of Cr(III) or of Fe(III) with \( \alpha \)-lipoic acid or with the corresponding dihydrolipoic acid, respectively of the formulas:

\[
[\text{CH}_2\text{-CH}_2\text{-CH-(CH}_2)_4\text{-COO}']_n \text{Fe}^{3+}[(3-n)/a \text{ A}^{\alpha}]
\]  

\[
[\text{CH}_2\text{-CH}_2\text{-CH-(CH}_2)_4\text{-COO}']_n \text{M}^{3+}[(3-n)/a \text{ A}^{\alpha}]
\]

wherein n is an integer between 1 and 3, Me can be either chromium or iron and \( A^{\alpha} \) is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2, for the preparation of nutraceutical or pharmaceutical compositions. Where the trivalent metal is chromium, these compositions are advantageously products having a hypoglycemizing, anti-oxidising, vasoprotective, anti-hyperlipemic, slimming, anti-cellulitic and/or anti-inflammatory activity, and are more specifically preparations for the treatment and/or prophylaxis of hyperglycaemia, for the improvement of glucidic tolerance and/or the reduction of insulin resistance.

In the case where the metal carried by the lipoate is iron, the compositions according to the present invention are recommended for the treatment and/or prophylaxis of a anaemias, such as sideropenic anaemias, iron-deficient hypochromic anaemias, anaemias due to pregnancy or following a haemorrhage, and in general for the treatment and/or prophylaxis of states of iron deficiency.

The compounds according to the present invention can be synthesised by reacting solutions of suitably salified lipoic acid (or dihydrolipoic acid)
with dosed quantities of a chromium or iron salt whose anion is the aforesaid $\text{A}^{5+}$ - the latter too preventively dissolved in an aqueous solution. Depending on the proportions between lipoic acid (or dihydrolipoic acid) and the chromium or iron salt, the salification reaction (or complex forming reaction) will give rise to a complex containing one, two or three lipoate ions coordinated by the Cr$^{3+}$ or Fe$^{3+}$ ion, while the remaining valences of the metal are saturated with the same number of equivalents of the starting $\text{A}^{5+}$ anion.

More specifically, the synthesis of the compound of formula (1aa) (chromium lipoate with three lipoate groups in the molecule) can be carried out according to the following procedure:

- solution A: dissolving 3 moles of $\alpha$-lipoic acid with 3 moles of sodium hydroxide, in an aqueous phase;
- solution B: dissolving 1 mole of chromium chloride in an aqueous phase;
- mixing solution A with solution B and stirring with a magnetic stirrer;
- separating the precipitate from the supernatant by centrifugation;
- washing the precipitate several times in water;
- adding 95% ethanol to the precipitate and drying at room temperature.

The synthesis of a compound similar to the one above in which the metal-forming the complex is Fe(III) may be carried out according to the same procedure illustrated above, by using 1 mole of iron chloride instead of chromium chloride.

With specific reference to the chromium complexes according to the present invention, the molecular weights and other parameters of the various compounds synthesised are reported below.
<table>
<thead>
<tr>
<th>Compound of the formula:</th>
<th>Molecular weight (anhydrous)</th>
<th>Chromium concn. (on the anhydrous product)</th>
<th>Lipoic acid concn. (reduced or not) (on the anhydrous product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1aa</td>
<td>667.97</td>
<td>7.78%</td>
<td>92.22%</td>
</tr>
<tr>
<td>2aa</td>
<td>674.02</td>
<td>7.71%</td>
<td>92.29%</td>
</tr>
<tr>
<td>1ab</td>
<td>498.10</td>
<td>10.43%</td>
<td></td>
</tr>
<tr>
<td>2ab</td>
<td>502.13</td>
<td>10.36%</td>
<td></td>
</tr>
<tr>
<td>1ac</td>
<td>328.23</td>
<td>15.08%</td>
<td></td>
</tr>
<tr>
<td>2ac</td>
<td>330.25</td>
<td>15.74%</td>
<td></td>
</tr>
</tbody>
</table>

As regards the dosages of the chromium complexes according to the present invention to be used in the proposed preparations with hypoglycemicizing and antioxidant activity, the following schemes indicate the correspondence with required dosages of chromium metal (with reference to complexes with actual α-lipoic acid, in oxidised form):

**Compound of formula (1aa):**
- 50 µg of Cr → 642.7 µg of Cr lipoate;
- 100 µg of Cr → 1285.3 µg of Cr lipoate;
- 200 µg of Cr → 2570.7 µg of Cr lipoate.

**Compound of formula (1ab):**
- 50 µg of Cr → 479.4 µg of Cr lipoate;
- 100 µg of Cr → 958.8 µg of Cr lipoate;
- 200 µg of Cr → 1917.6 µg of Cr lipoate.

**Compound of formula (1ac):**
- 50 µg of Cr → 316.4 µg of Cr lipoate;
- 100 µg of Cr → 632.8 µg of Cr lipoate;
- 200 µg of Cr → 1265.6 µg of Cr lipoate.

The chromium(III) or iron(III) salts or complexes with α-lipoic acid (or dihydrolipoic acid) proposed according to the present invention can be formulated in nutraceutical or pharmaceutical products on the basis of well-known procedures in pharmaceutical technology, in particular, but not exclusively, to
be presented in the form of tablets, rigid capsules, soft gelatine capsules, granular preparations, drinkable solutions and the like. Further suitable active and/or coadjuvant ingredients can be added, as well as appropriate excipients for the formulation of products for oral administration, such as sweetening and aromatising agents, and, where necessary, one or more lubricant or anti-adherent agents in order to facilitate production.

Some embodiments of the preparations according to the present invention, as well as some experimental data concerning their performance and their comparison with products of the prior art, are reported merely for exemplification purposes in the following reports:

Chromium: increase of the absorbed amount via oral supplementation

10 male volunteers were given 50 µg of Cr in the form of chromium chloride, via oral supplementation, and the increase in chromium in the blood was assessed one hour after administration.

After seven days of wash-out, the same group of subjects received 50 µg of Cr in the form of chromium picolinate, after which their haematic levels of chromium were assessed in the same way as in the preceding trial.

After a further seven-day wash-out period, the same 10 volunteers were given 50 µg of Cr in the form of chromium lipoate (compound of formula (1aa), i.e. 642.7 µg of Cr lipoate) and the increase in haematic chromium was again assessed using the same method as above.

The findings can be summarised as follows, in terms of the average percentage increase in haematic chromium over and above base levels:

- chromium chloride + 2% (p<0.05)
- chromium picolinate + 10% (p<0.05)
- chromium lipoate + 15% (p<0.05)

Chromium: reduction of post-prandial glycaemia

10 male volunteers were given 50 µg of Cr in the form of chromium chloride, via oral supplementation, and, after 60 minutes, they received a glucose load consisting of 70 g of maltodestrin. The glycemic increase was then measured one hour after glucose administration and the average per-
ccentage reduction of the glycemic increase was reported with respect to controls.

After seven days of wash-out, the same group of subjects received 50 μg of Cr in the form of chromium picolinate, after which the glucose load was administered and then their glycaemia levels were measured one hour after glucose administration.

After a further seven-day wash-out period, the same trial was repeated with the same subjects, by administering 50 μg of Cr in the form of chromium lipoate (compound of formula (1aa), i.e. 642.7 μg of Cr lipoate).

The findings can be summarised as follows, in terms of the average percentage reduction of the glycemic increase with respect to controls:

- chromium chloride: - 5% (p<0.05)
- chromium picolinate: - 20% (p<0.05)
- chromium lipoate: - 25% (p<0.05)

**Chromium: antioxidant power**

In this case, 10 male volunteers were given 50 μg of Cr in the form of chromium chloride, via oral supplementation, and the percentage reduction of malondialdehyde (MDA) was assessed with respect to base levels one hour after administering the chromium compound. Measurement was carried out by using the TBA method (thio-barbituric acid).

After seven days of wash-out, the same group of subjects received 50 μg of Cr in the form of chromium picolinate, after which the percentage reduction of MDA was measured as in the preceding case.

After a further seven-day wash-out period, the same trial was repeated with the same subjects, by administering 50 μg of Cr in the form of chromium lipoate (compound of formula (1aa), i.e. 642.7 μg of Cr lipoate).

The findings can be summarised as follows, in terms of the average percentage reduction of plasmatic MDA with respect to base levels:

- chromium chloride: - 2.5% (p<0.05)
- chromium picolinate: - 5.5% (p<0.05)
- chromium lipoate: - 15.0 (p<0.05)
**Iron: oral absorption**

A group of 10 male volunteers ingested 100 mg of iron from iron sulphate. Their sideremia was determined at time 0 and then every hour thereafter until 6 hours after administration of the iron load.

After a week of wash-out, the same subjects ingested 100 mg of iron from the iron lipoate complex (compound of formula (1aa), i.e. 1285.3 µg of Cr lipoate); the sideremia was determined at time 0 and then every hour thereafter until six hours after administration of the iron load.

The absorption values were then quantified in terms of AUC \(0\rightarrow6\) (µg h/dl) as follows:

- iron sulphate: 412
- iron lipoate: 478

In view of the above, it appears that the area below the curve for the first six hours with iron lipoate is 16% more than what is obtained with iron sulphate.

The present invention has been disclosed with particular reference to some specific embodiments thereof, but it should be understood that modifications and changes may be made by the persons skilled in the art without departing from the scope of the invention as defined in the appended claims.
CLAIMS

1. A nutraceutical, pharmaceutical or veterinary composition comprising one or more chromium(III) or iron(III) salts or complexes with α-lipoic acid or with the corresponding dihydrolipoic acid, respectively of the following formulas:

\[
\begin{align*}
[&CH_2-CH_2-CH-(CH_2)_4-COO']_n \text{Me}^{3+} [(3-n)/a \ A^{a-}] \\
S & \text{----} \text{S} \\
& \text{SH} & \text{SH}
\end{align*}
\]

wherein \( n \) is an integer between 1 and 3, Me can be either chromium or iron and \( A^{a-} \) is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2.

2. A composition according to claim 1, wherein the said α-lipoic acid is in the form of an optically pure isomer or of the corresponding to racemate.

3. A composition according to claim 2, wherein the said α-lipoic acid is in the form of the corresponding R-(+) enantiomer or in the form of the corresponding S-(−) enantiomer.

4. A composition according to any one of claims 1-3, wherein the said \( A^{a-} \) anion is an inorganic anion selected from the group consisting of: chloride, i.e. \( \text{Cl}^- \), and sulphate, i.e. \( \text{SO}_4^{2-} \).

5. A nutraceutical, pharmaceutical or veterinary composition according to claims 1 or 2, comprising one or more chromium(III) salts or complexes, respectively of the following formulas:

\[
\begin{align*}
&[CH_2-CH_2-CH-(CH_2)_4-COO']_n \text{Cr}^{3+} [(3-n)/a \ A^{a-}] \\
S & \text{----} \text{S} \\
& \text{SH} & \text{SH}
\end{align*}
\]
wherein n is an integer between 1 and 3, and $A^{n-}$ is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2.

6. A composition according to claim 5, wherein $A^{n-}$ is a Cl$^{-}$ ion.

7. A composition according to claim 6, comprising one or more chromium(III) salts or complexes selected from among the following:

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_3\text{Cr}^{3+}$$

(1aa)

$$\text{S} \quad \text{S}$$

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_3\text{Cr}^{3+}$$

(2aa)

$$\text{SH} \quad \text{SH}$$

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_2\text{Cr}^{3+}\text{Cl}^-$$

(1ab)

$$\text{S} \quad \text{S}$$

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_2\text{Cr}^{3+}\text{Cl}^-$$

(2ab)

$$\text{SH} \quad \text{SH}$$

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_2\text{Cr}^{3+}[2\text{Cl}^-]$$

(1ac)

$$\text{S} \quad \text{S}$$

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_2\text{Cr}^{3+}[2\text{Cl}^-]$$

(2ac)

$$\text{SH} \quad \text{SH}$$

8. A nutraceutical, pharmaceutical or veterinary composition according to claims 1 or 2, comprising one or more iron(III) salts or complexes, respectively of the following formulas:

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_n\text{Fe}^{3+}[(3-n)/a\text{ A}^{n-}]$$

(1b)

$$\text{S} \quad \text{S}$$

$$[\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}^-]_n\text{Fe}^{3+}[(3-n)/a\text{ A}^{n-}]$$

(2b)

$$\text{SH} \quad \text{SH}$$

wherein n is an integer between 1 and 3, and $A^{n-}$ is a physiologically accept-
able organic or inorganic anion with a valence of 1 or 2.

9. A composition according to claim 8, wherein A\(^{a-}\) is a Cl\(^{-}\) ion.

10. Use of one or more chromium(III) or iron(III) salts or complexes with \(\alpha\)-lipoic acid or the corresponding dihydrolipoic acid, respectively of the following formulas:

\[
[\text{CH}_2\text{CH}_2\text{CH}-(\text{CH}_2)_4\text{COO}]_n \text{Me}^{3+} [(3\text{-}n)/a \text{ A}^{a-}] \quad (1)
\]

\[
[\text{CH}_2\text{CH}_2\text{CH}-(\text{CH}_2)_4\text{COO}]_n \text{Me}^{3+} [(3\text{-}n)/a \text{ A}^{a-}] \quad (2)
\]

\[
\text{S} \quad \text{S}
\]

\[
\text{SH} \quad \text{SH}
\]

wherein n is an integer between 1 and 3, Me can be chromium or iron and A\(^{a-}\) is a physiologically acceptable organic or inorganic anion with a valence of 1 or 2, for the preparation of nutraceutical, pharmaceutical or veterinary compositions.

11. Use according to claim 10, wherein Me is chromium(III), for the preparation of compositions having a hypoglycemizing, anti-oxidant, vasoprotective, anti-hyperlipemic, slimming, anti-cellulitic and/or anti-inflammatory activity.

12. Use according to claim 11 for the preparation of compositions for the treatment and/or prophylaxis of hyperglycaemia, the improvement of glucose tolerance and/or the reduction of insulin resistance.

13. Use according to claim 10, wherein Me is iron(III), for the preparation of compositions for the treatment and/or prophylaxis of anaemias and states of iron deficiency.