In the international patent application WO-A-95/15766 peptide derivatives with antiviral activity are disclosed, which consist of seven amino acids, including the following sequence: Arg-Arg-Trp-Trp-Cys-Arg-X, where X is an amino acid or an amino acid derivative that contains a chiral center.

In the international patent application WO-A-98/04707 some antiviral agents are disclosed showing a mechanism based on preventing the association between two viral proteins required for the DNA replication of HSV virus. Several peptide sequences are disclosed, corresponding to a portion of the protein UL8 of HSV-1 virus, for example, IELVFTGVLAGVWGEGGKFV.

In the international patent application WO-A-01/57072 some peptides with the capacity of crossing lipid membranes are disclosed, which exhibit antiviral activity against herpes simplex virus. Several sequences that show such activity are cited, for example, NH2-RRKKAAVALLPAVLLALLAP-COOH.

In the international patent application WO-A-2006/018431 it is disclosed that the peptide designated as Hervip, which consists in the amino acid sequence 112-147 of human β-hemoglobin, has activity against herpes simplex virus. This peptide corresponds to the following sequence of 35 amino acids: NH_2-VCVLAHHFGKEFTPPVQAAYQKWAGVANALAHKYH-COOH.

In view of the wide variety of solutions described in the prior art regarding the use of peptides in the prevention and/or treatment of the infections caused by herpesviruses, it appears that a satisfactory solution has not yet been found.

Thus, there remains a need to develop new compositions and methods for treating herpesvirus infections which are effective and practical, and that are also safe, so that they involve a minimal risk of side effects.

Object of the invention

The object of the present invention is the use of a casein hydrolysate as antiherpetic.

It is also a part of the object of the invention a pharmaceutical composition for topical administration comprising such hydrolysate.

Detailed description of the invention

The object of the present invention is the use of a casein hydrolysate for the preparation of a medicament for the prevention and/or treatment of infections caused by herpesvirus, wherein the hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

That is, the object of the invention is a casein hydrolysate for use in the prevention and/or treatment of infections caused by herpesvirus, wherein the hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

The authors of the present invention have observed that, surprisingly, the casein hydrolysate of the invention is extremely effective for achieving a rapid remission of the outbreaks by reactivation of the herpes virus infections, as well as for preventing or minimizing the appearance of new manifestations of the infection.

Casein hydrolysate

The name casein includes a group of phosphoproteins present in the milk, which represents approximately a 3% of the bovine milk. The main components of casein are alpha-, beta-, gamma- and kappa-caseins, among which beta casein is the major fraction of bovine milk.

The casein used as substrate for the hydrolysis is preferably casein from bovine milk, more preferably beta-casein from bovine milk.

The casein hydrolysate used as antiherpetic according to the use of the present invention, is a hydrolysate whose composition is determined by the use of a proline specific endoprotease in the hydrolysis of the casein, so that the hydrolysate has a composition characterized by a high content of peptides with a proline at the carboxy-terminal end.

In the use of the invention, the molar fraction of the peptides in such hydrolysate carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate hydrolysate.

The characteristics of this hydrolysate and of the proline specific endopeptidase used in its preparation are described in the international patent application WO-A-02/45524. In that document it is also disclosed the method for determining the molar fraction of the peptides carrying a carboxy terminal proline, expressed in %, as well as the method for determining the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

In this patent application it is disclosed the preparation of protein hydrolysates with a high ratio of proline residues in the carboxyl-terminal position, in the context of the preparation of dietetic protein supplements, especially for sport drinks, with the advantage that such composition has an improved taste, free from the characteristic bitter taste that usually exhibit many of these hydrolysates.

The authors of the present invention have found that, surprisingly, this casein hydrolysate exhibits an excellent therapeutic activity against herpesvirus infections.

Preferably, the molar fraction of the peptides of this hydrolysate carrying a carboxy terminal proline, expressed in %, is at least three times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

Preferably, in the casein hydrolysate according to the use of the present invention, the average length of the peptides in the hydrolysate is comprised between 3 and 9 amino acids.

Preferably, the molar fraction of peptides carrying a carboxy terminal proline in the casein hydrolysate is at least 25%, and still more preferably it ranges between 30% and 70%.

Within the context of the present invention, when discussing the molar fraction of peptides, peptides are understood to be those whose molecular mass ranges between 400 and 2000 Dalton, which can be determined, for example, using the liquid chromatography/mass

spectrometry (LC/MS) method described in the Materials and Methods section of the international patent application WO-A-02/45524 cited above.

In general, the casein hydrolysate according to the use of the present invention is a hydrolysate where at least the 50% of the casein substrate is hydrolysed. Preferably at least a 10% of the casein substrate is converted into peptides with a molecular mass between 400 and 2000 Dalton, more preferably, between 20% and 90%, and still more preferably between 30% and 80% of the casein substrate is converted into such peptides.

In a preferred embodiment the casein hydrolysate has the following amino acid composition: between 54-64 of lysine, between 22-30 of methionine, between 25-33 of threonine, between 18-26 of histidine, between 26-34 of arginine, between 46-56 of valine, between 34-42 of isoleucine, between 70-80 of leucine, between 33-41 of phenylalanine, between 45-55 of the sum of aspartic acid plus asparagine, between 160-180 of the sum of glutamine plus glutamic acid, between 20-26 of alanine, between 80-90 of proline, between 40-48 of tyrosine, between 37-45 of serine, between 11-17 of glycine, between 0.8-1.2 of cysteine, and between 6-10 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

In a more preferred embodiment the casein hydrolysate has the following amino acid composition: between 57-61 of lysine, between 24-28 of methionine, between 27-31 of threonine, between 20-24 of histidine, between 28-32 of arginine, between 49-53 of valine, between 36-40 of isoleucine, between 73-77 of leucine, between 35-39 of phenylalanine, between 48-52 of the sum of aspartic acid plu asparagine, between 166-176 of the sum of glutamine plus glutamic acid, between 21-25 of alanine, between 82-88 of proline, between 42-46 of tyrosine, between 39-43 of serine, between 13-15 of glycine, between 0.8-1.2 of cysteine and between 7-9 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

In a particularly preferred embodiment the casein hydrolysate has approximately the following amino acid composition: 59 of lysine, 26 of methionine, 29 of threonine, 22 of histidine, 30 of arginine, 51 of valine, 38 of isoleucine, 75 of leucine, 37 of phenylalanine, 50 of the sum of aspartic acid plus asparagine, 171 of the sum of glutamine plus glutamic acid, 23 of alanine, 85 of proline, 44 of tyrosine, 41 of serine, 14 of glycine, 1 of cysteine, and 8 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

A casein hydrolysate according to the specified characteristics is available under the trademark PeptoPro® (DSM). According to its data sheet, this product has applications in food and beverages to enrich their protein content.

Use of the casein hydrolysate

The authors of the present invention have noticed that the casein hydrolysate according to the characteristics specified above shows excellent antiherpetic properties, being effective for the prevention and/or treatment of infections caused by herpesviruses.

The infections caused by herpesviruses, according to the use of the present invention, relate to the infections caused by any type of herpesvirus, in particular those caused by herpesviruses selected from the group consisting of herpes simplex type 1, herpes simplex type 2, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, herpesvirus type 6, herpesvirus type 7, and Kaposi's Sarcoma herpesvirus; preferably herpes simplex type 1, herpes simplex type 2 and varicella zoster virus.

In a preferred embodiment, the use according to the present invention relates to the prevention and/or treatment of herpesvirus infections selected from the group consisting of herpes labialis, genital herpes, and herpes zoster.

Within the context of the present invention the term "treatment" refers to the administration of the product with a curative purpose, once some symptoms or external manifestations of the infection have been observed, such as pain, burning, inflammation or itching in the affected area, as well as the appearance of pustules, vesicles, blisters, or rash, for example, or other symptoms or specific manifestations for each type of particular pathology. The curative purpose of such treatment is understood as being directed to the elimination, alleviation, improvement, or lessening of the severity of the external manifestations of the infection. Habitually it is not strictly a cure meaning the eradication of the virus, as the herpesviruses usually remain in an asymptomatic latent state in the infected individuals throughout their lives, alternating with periods of reactivation. The curative purpose in this sense means the cure of the disease outbreaks which have appeared, in order to achieve their remission and the return of the infection to an asymptomatic latent state.

Within the context of the present invention the term "prevention" refers to the administration of the product when there are no symptoms or external manifestations of the infection, but it is administered with a prophylactic purpose with the intention of preventing or delaying the appearance of new outbreaks of the infection, i.e., keeping it in an asymptomatic latent state.

In Examples 3, 4 and 5 some efficacy trials performed with the casein hydrolysate are shown. In those examples the casein hydrolysate was administered to patients suffering from various types of herpes, and they all showed a great efficacy in the relief of symptoms (treatment) as well as in the disappearance or diminution of the reactivation phases (prevention).

As the product used in the present invention is completely harmless, derived from the hydrolysis of casein from bovine milk and commonly used as a dietetic supplement, the use according to the present invention has the advantage that it is possible to maintain a long preventive treatment, without the risk of experiencing undesirable side effects, as usually happens with other antiviral treatments, so that the patients taking preventative doses are able to remain without any outbreak of the disease for very long periods, as shown in these examples.

In a preferred embodiment, the use of the casein hydrolysate according to the invention is characterized in that the hydrolysate is administered orally.

In a more preferred embodiment, the casein hydrolysate is administered according to a daily oral dose comprised between 4 and 40 g. In a still more preferred embodiment, a unit oral dose comprised between 4 and 8 g of the casein hydrolysate is used, and more preferably comprised between 5.5 and 6.5 g, which is administered from 1 to 5 times daily, and more preferably from 1 to 3 times daily.

Generally within a period of one week, the symptoms of herpes remit completely. In the case of herpes labialis, usually, preferably within 2 to 3 days, and in the case of genital herpes and herpes zoster preferably within 4 to 6 days.

The casein hydrolysate can also be used preventively after the remission of the symptoms by taking a daily unit oral dose of between 4 and 8 g for a period ranging from 12 to 24 months.

In another preferred embodiment, the use of the casein hydrolysate according to the present invention is characterized in that the hydrolysate is administered topically, so that it is locally applied on the area affected by the lesion.

Preparations with the casein hydrolysate

The casein hydrolysate according to the use of the present invention typically comes in powder solid form and can be administered either directly or in combination with at least one pharmaceutically acceptable excipient and/or carrier, in the form of a pharmaceutical composition.

It is also part of the object of the present invention, the use of a casein hydrolysate for the preparation of a medicament for the prevention and/or treatment of infections caused by herpesvirus, characterised in that the casein hydrolysate is administered in the form of a pharmaceutical composition comprising a pharmacologically effective amount of this hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, wherein this hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

I.e., it is also part of the object of invention a casein hydrolysate for use in the prevention and/or treatment of infections caused by herpesvirus, characterized in that the hydrolysate is administered in the form of a pharmaceutical composition comprising this casein hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, wherein this hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

The pharmaceutical composition can be prepared using methods that are well known to the skilled in the art such as those contained in handbooks of pharmaceutical technology, such as the book *Remington The Science and Practice of Pharmacy*, 20th edition, Lippincott, Williams & Wilkins, Philadelphia, 2000 [ISBN: 0-683-306472].

The pharmaceutical compositions suitable for the use according to the present invention are all those appropriate for being administered either orally or topically.

In one embodiment of the invention, the pharmaceutical composition is a composition suitable for oral administration. Any pharmaceutical form suitable for oral administration is included within the use according to the object of the present invention, preferably solid compositions in powder or granulate form, or either liquid, in solution, suspension or syrup form, for example.

Preferably, the pharmaceutical composition for oral administration is in powder or granulate form. More preferably, it is in powder form.

In another embodiment of the invention, the pharmaceutical composition is a composition appropriate for topical administration. Any pharmaceutical form suitable for topical administration is included within the use according to the object of the present invention, either in a solid, liquid or semisolid form. Solid compositions for topical administration are generally in powder form, and may include a suitable carrier, such as talc, silica or microcrystalline cellulose, among others. The liquid compositions suitable for topical administration can be prepared by dissolving or dispersing the casein hydrolysate in a suitable carrier such as, for example, water, alcohols, glycols, or mixtures thereof, and are, for example, lotions, liniments, or tinctures; or else this liquid composition can be used to impregnate a support in the form of dressing or bandage that is applied to the affected area, or alternatively the liquid composition can be sprayed onto the affected area using pump sprayers or aerosols. Other forms of topical administration are semisolid compositions such as creams, gels, ointments or pastes.

Preferably, the pharmaceutical composition for topical administration is in the form of a cream, gel, ointment or paste.

The pharmaceutically acceptable excipients that can be used for preparing pharmaceutical compositions in solid form are well known to those skilled in the art and include, for example, diluents such as calcium carbonate, sodium carbonate, magnesium carbonate, magnesium oxide, calcium sulfate, calcium phosphate, sodium chloride, microcrystalline or powdered cellulose, cellulose acetate, ethyl cellulose, dextrates, dextrins, dextrose, lactose, lactitol, fructose, sorbitol, sucrose, maltodextrins, maltose, glyceryl palmitostearate, kaolin, polymethacrylates, pregelatinized starch or starch, among others, and mixtures thereof; lubricants, such as calcium stearate, magnesium stearate, talc, stearic acid, glyceryl behenate, glyceryl palmitostearate, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, or hydrogenated castor oil, among others, and mixtures thereof; disintegrants such as alginic acid,

derivatives, or emulsifying wax, among others, and mixtures thereof; suspending agents such as xanthan gum, guar gum, alginic acid, bentonite, carbomers, sodium or calcium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl alginate, microcrystalline or powdered cellulose, anhydrous colloidal silica, dextrins, gelatins, kaolin, magnesium aluminum silicate, maltitol, povidone, sorbitan esters, or tragacanth, among others, and mixtures thereof; flocculating agents such as sodium acetate, sodium phosphate, sodium citrate, sodium lauryl sulfate, starch, alginates, tragacanth, or carbomers, among others, and mixtures thereof; wetting agents as benzalkonium chloride, sodium docusate, sodium lauryl sulfate, sorbitan esters, polyoxyethylene stearates or polyoxyethylene sorbitan fatty acid esters, among others, and mixtures thereof; preservatives such as benzalkonium chloride, benzyl alcohol, bronopol, parabens, sodium benzoate, sodium propionate, sorbic acid or thimerosal, among others, and mixtures thereof; flavoring agents as maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, tartaric acid, peppermint, artificial or natural fruit aromas, among others, and mixtures thereof; sweetening agents such as sorbitol, maltitol, mannitol, dextrose, maltose, xylitol, saccharin, sucrose, sucralose, aspartame, acesulfame potassium or trehalose, among others, and mixtures thereof; coloring agents such as curcumin, lactoflavin, iron oxides (red, yellow or black), caramel, lactoflavin phosphate, cochineal red, titanium dioxide, or carotenes, among others, and mixtures thereof; or mixtures thereof.

The semisolid topical formulations in the form of creams, gels, ointments or pastes comprise a pharmaceutically acceptable carrier in which the casein hydrolysate is dissolved, emulsified, dispersed or suspended. This carrier is selected from water, a non-aqueous water miscible carrier, such as for example ethanol or isopropanol, and a non-aqueous water-immiscible carrier, such as for example paraffin oil. Optionally, such semisolid compositions for topical administration contain a pharmaceutically acceptable excipient such as, for example, surfactant and emulsifier agents, lipidic and emollient compounds, consistency factors and thickening agents, stabilizers, hydrotropes, preservative agents, essences, coloring agents, silicone compounds, fats, waxes, lecithins, phospholipids, UV sun protection factors, or mixtures thereof.

The excipients suitable to be used in the pharmaceutical compositions of the present invention are well known to those skilled in pharmaceutical technology and are described, for example, in the book R.C. Rowe, P.J. Sheskey and P.J. Weller, *Handbook of Pharmaceutical Excipients*, Fourth Edition, Pharmaceutical Press, 2003.

In a preferred embodiment, the pharmaceutical composition is in the form of powder or granulate for oral use. The powder is usually prepared by mixing the casein hydrolysate in powder form with at least one pharmaceutically acceptable excipient. The granulate consists of powder particles that have been aggregated to form larger particles, and it is prepared according to procedures which are well known to those skilled in the art, such as dry granulation or wet granulation.

The compositions in the form of powder or granulate are usually taken after dissolution or dispersion in water or another liquid.

In one embodiment of the invention, the powder or granulate composition is presented in a bulk container as, for example, in a glass container with a wide opening, so that the required dose for each administration is taken as needed, preferably with the help of a measurement device or dispenser to measure the dose to be administered.

In another embodiment of the invention, the powder or granulate composition is presented in the form of monodose sachets, containing the unit dose suitable for oral administration. Those sachets can be made of paper or either of aluminium or plastic laminates. Preferably, the oral unit dose comprises between 4 and 8 g of the casein hydrolysate, more preferably between 5 and 7 g, and still more preferably about 6 g of the hydrolysate.

In a particularly preferred embodiment of the invention, the composition for oral use is in powder form. More preferably, the composition in powder form comprises the casein hydrolysate, and a pharmaceutically acceptable excipient which is selected from sweeteners, flavouring agents and coloring agents, or mixtures thereof.

Preferably, the composition in powder form contains a quantity of the casein hydrolysate ranging between 70% and 99%, and more preferably ranging between 80% and 95%, expressed as weight ratio relative to the total weight of the composition.

In another preferred embodiment of the invention, the pharmaceutical composition according to the use of the present invention is a composition for topical administration, preferably in the form of cream, gel, ointment or paste. Preferably, this composition for topical administration comprises an amount of the casein hydrolysate ranging between 5% and 25%, and more preferably ranging between 7% and 15%.

It is also a part of the object of the present invention a pharmaceutical composition comprising a casein hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, characterized in that the composition is in the form of cream, gel, ointment or paste for topical administration, wherein this casein hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate. Preferably, this composition for topical administration contains an amount of the casein hydrolysate ranging between 5% and 25%, and more preferably ranging between 7% and 15%, expressed in weight.

Creams, as it is well known to those skilled in pharmaceutical technology are semisolid emulsions, which can be of the oil-in-water (o/w) type or water-in-oil (w/o) type, formulated from an oil phase, an aqueous phase and an emulsifying agent. The oil phase consists of a carrier which can be, for example, liquid paraffin or a vegetable oil such as, for example, castor oil, almond oil, peanut oil, sesame oil, cottonseed oil or corn oil.

Gels are obtained from a liquid that is gelled by adding a rheological agent or a gelling agent. Some of the gelling agents suitable to be used in the present invention are, for example, carrageenan, guar gum, tragacanth gum, locust bean gum, pectin, agar, alginic acid, carbomers, carboxymethylcellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and polyethylene glycol, among others.

Ointments are semisolid fat preparations, which contain the active ingredient dissolved or in dispersed form. Ointments can be formulated with various vehicles such as paraffin, plastibases (a mixture of polyethylene with a series of hydrocarbons), vegetable oils, such as peanut oil, sesame oil, olive oil, cottonseed oil, almond oil, corn oil, silicones or polyethylene glycols, among others, or with a mixture thereof.

Pastes are prepared analogously to the ointments, and they show a more solid consistency since they contain greater amounts of insoluble solids.

Next, some examples are provided with the purpose of illustrating the invention, but not limiting it.

CLAIMS

1.- Use of a casein hydrolysate for the preparation of a medicament for the prevention and/or treatment of infections caused by herpesvirus, wherein the hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

2.- Use according to claim 1, characterized in that the molar fraction of the peptides in the hydrolysate carrying a carboxy terminal proline, expressed in %, is at least three times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

3.- Use according to claims 1 or 2, characterized in that the average length of the peptides in the casein hydrolysate is comprised between 3 and 9 amino acids.

4.- Use according to claim 1, characterized in that the molar fraction of peptides carrying a carboxy terminal proline in the casein hydrolysate is at least 25%.

5.- Use according to claim 4, characterized in that the molar fraction of peptides carrying a carboxy terminal proline in the casein hydrolysate is between 30% and 70%.

6.- Use according to any of claims 1 to 5, characterized in that the casein hydrolysate has the following amino acid composition: between 54-64 of lysine, between 22-30 of methionine, between 25-33 of threonine, between 18-26 of histidine, between 26-34 of arginine, between 46-56 of valine, between 34-42 of isoleucine, between 70-80 of leucine, between 33-41 of phenylalanine, between 45-55 of the sum of aspartic acid plus asparagine, between 160-180 of the sum of glutamine plus glutamic acid, between 20-26 of alanine, between 80-90 of proline, between 40-48 of tyrosine, between 37-45 of serine, between 11-17 of glycine, between 0.8-1.2 of cysteine, and between 6-10 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

7.- Use according to any of claims 1 to 6, characterized in that the infections are caused by herpesviruses selected from the group consisting of herpes simplex type 1, herpes simplex type 2, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, herpesvirus type 6, herpesvirus type 7, and Kaposi's Sarcoma herpesvirus.

8.- Use according to claim 7, characterized in that the herpesvirus is selected from the group consisting of herpes simplex type 1, herpes simplex type 2 and varicella zoster virus.

9.- Use according to any of claims 1 to 6, characterized in that the herpesvirus infection is selected from the group consisting of herpes labialis, genital herpes, and herpes zoster.

10.- Use according to any of claims 1 to 9, characterized in that the casein hydrolysate is administered orally.

11.- Use according to claim 10, characterized in that the casein hydrolysate is administered according to a daily dose comprised between 4 and 40 g.

12.- Use according to claim 10, characterized in that a unit oral dose of between 4 and 8 g of the casein hydrolysate is used, which is administered from 1 to 5 times daily.

13.- Use according to any of claims 1 to 9, characterized in that the hydrolysate is administered topically.

14.- Use according to any of claims 1 to 9, characterized in that the casein hydrolysate is administered in the form of a pharmaceutical composition comprising a pharmacologically effective amount of the hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier.

15.- Use according to claim 14, characterized in that the pharmaceutical composition is a composition suitable for oral administration.

16.- Use according to claim 15, characterized in that the pharmaceutical composition is in powder or granulate form.

17.- Use according to claim 16, characterized in that the composition is dosed in monodose sachets containing between 4 and 8 g of the casein hydrolysate.

18.- Use according to claim 14, characterized in that the pharmaceutical composition is a composition suitable for topical administration.

19.- Use according to claim 18, characterized in that the pharmaceutical composition is in the form of cream, gel, ointment or paste.

20.- A pharmaceutical composition comprising a casein hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, characterized in that the composition is in the form of cream, gel, ointment or paste for topical administration, wherein the casein hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

21.- Composition according to claim 20, characterized in that it comprises an amount of the casein hydrolysate comprised between 5% and 25%, expressed in weight.

In the international patent application WO-A-95/15766 peptide derivatives with antiviral activity are disclosed, which consist of seven amino acids, including the following sequence: Arg-Arg-Trp-Trp-Cys-Arg-X, where X is an amino acid or an amino acid derivative that contains a chiral center.

In the international patent application WO-A-98/04707 some antiviral agents are disclosed showing a mechanism based on preventing the association between two viral proteins required for the DNA replication of HSV virus. Several peptide sequences are disclosed, corresponding to a portion of the protein UL8 of HSV-1 virus, for example, IELVFTGVLAGVWGEGGKFV.

In the international patent application WO-A-01/57072 some peptides with the capacity of crossing lipid membranes are disclosed, which exhibit antiviral activity against herpes simplex virus. Several sequences that show such activity are cited, for example, NH2-RRKKAAVALLPAVLLALLAP-COOH.

In the international patent application WO-A-2006/018431 it is disclosed that the peptide designated as Hervip, which consists in the amino acid sequence 112-147 of human β-hemoglobin, has activity against herpes simplex virus. This peptide corresponds to the following sequence of 35 amino acids: NH_2-VCVLAHHFGKEFTPPVQAAYQKWAGVANALAHKYH-COOH.

In view of the wide variety of solutions described in the prior art regarding the use of peptides in the prevention and/or treatment of the infections caused by herpesviruses, it appears that a satisfactory solution has not yet been found.

Thus, there remains a need to develop new compositions and methods for treating herpesvirus infections which are effective and practical, and that are also safe, so that they involve a minimal risk of side effects.

Summary

The invention is defined in the independent claim. Some optional features of the invention are defined in the dependent claims.

Disclosed herein is the use of a casein hydrolysate as antiherpetic.

Also disclosed is a pharmaceutical composition for topical administration comprising such hydrolysate.

Detailed description of the invention

There is disclosed herein is the use of a casein hydrolysate for the preparation of a medicament for the prevention and/or treatment of infections caused by herpesvirus, wherein the hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

That is, a casein hydrolysate is disclosed for use in the prevention and/or treatment of infections caused by herpesvirus, wherein the hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

The inventors have observed that, surprisingly, the disclosed casein hydrolysate is extremely effective for achieving a rapid remission of the outbreaks by reactivation of the herpes virus infections, as well as for preventing or minimizing the appearance of new manifestations of the infection.

Casein hydrolysate

The name casein includes a group of phosphoproteins present in the milk, which represents approximately a 3% of the bovine milk. The main components of casein are alpha-, beta-, gamma- and kappa-caseins, among which beta casein is the major fraction of bovine milk.

The casein used as substrate for the hydrolysis is preferably casein from bovine milk, more preferably beta-casein from bovine milk.

The casein hydrolysate used as antiherpetic, is a hydrolysate whose composition is determined by the use of a proline specific endoprotease in the hydrolysis of the casein, so that the hydrolysate has a composition characterized by a high content of peptides with a proline at the carboxy-terminal end.

In the use described here, the molar fraction of the peptides in such hydrolysate carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate hydrolysate.

The characteristics of this hydrolysate and of the proline specific endopeptidase used in its preparation are described in the international patent application WO-A-02/45524. In that document it is also disclosed the method for determining the molar fraction of the peptides carrying a carboxy terminal proline, expressed in %, as well as the method for determining the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

In this patent application it is disclosed the preparation of protein hydrolysates with a high ratio of proline residues in the carboxyl-terminal position, in the context of the preparation of dietetic protein supplements, especially for sport drinks, with the advantage that such composition has an improved taste, free from the characteristic bitter taste that usually exhibit many of these hydrolysates.

The inventors have found that, surprisingly, this casein hydrolysate exhibits an excellent therapeutic activity against herpesvirus infections.

Preferably, the molar fraction of the peptides of this hydrolysate carrying a carboxy terminal proline, expressed in %, is at least three times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

Preferably, in the casein hydrolysate according to the use described here, the average length of the peptides in the hydrolysate is comprised between 3 and 9 amino acids.

Preferably, the molar fraction of peptides carrying a carboxy terminal proline in the casein hydrolysate is at least 25%, and still more preferably it ranges between 30% and 70%.

Within the present context, when discussing the molar fraction of peptides, peptides are understood to be those whose molecular mass ranges between 400 and 2000 Dalton, which can be determined, for example, using the liquid chromatography/mass

spectrometry (LC/MS) method described in the Materials and Methods section of the international patent application WO-A-02/45524 cited above.

In general, the casein hydrolysate according to the use described here is a hydrolysate where at least the 50% of the casein substrate is hydrolysed. Preferably at least a 10% of the casein substrate is converted into peptides with a molecular mass between 400 and 2000 Dalton, more preferably, between 20% and 90%, and still more preferably between 30% and 80% of the casein substrate is converted into such peptides.

In a preferred embodiment the casein hydrolysate has the following amino acid composition: between 54-64 of lysine, between 22-30 of methionine, between 25-33 of threonine, between 18-26 of histidine, between 26-34 of arginine, between 46-56 of valine, between 34-42 of isoleucine, between 70-80 of leucine, between 33-41 of phenylalanine, between 45-55 of the sum of aspartic acid plus asparagine, between 160-180 of the sum of glutamine plus glutamic acid, between 20-26 of alanine, between 80-90 of proline, between 40-48 of tyrosine, between 37-45 of serine, between 11-17 of glycine, between 0.8-1.2 of cysteine, and between 6-10 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

In a more preferred embodiment the casein hydrolysate has the following amino acid composition: between 57-61 of lysine, between 24-28 of methionine, between 27-31 of threonine, between 20-24 of histidine, between 28-32 of arginine, between 49-53 of valine, between 36-40 of isoleucine, between 73-77 of leucine, between 35-39 of phenylalanine, between 48-52 of the sum of aspartic acid plu asparagine, between 166-176 of the sum of glutamine plus glutamic acid, between 21-25 of alanine, between 82-88 of proline, between 42-46 of tyrosine, between 39-43 of serine, between 13-15 of glycine, between 0.8-1.2 of cysteine and between 7-9 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

In a particularly preferred embodiment the casein hydrolysate has approximately the following amino acid composition: 59 of lysine, 26 of methionine, 29 of threonine, 22 of histidine, 30 of arginine, 51 of valine, 38 of isoleucine, 75 of leucine, 37 of phenylalanine, 50 of the sum of aspartic acid plus asparagine, 171 of the sum of glutamine plus glutamic acid, 23 of alanine, 85 of proline, 44 of tyrosine, 41 of serine, 14 of glycine, 1 of cysteine, and 8 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

A casein hydrolysate according to the specified characteristics is available under the trademark PeptoPro® (DSM). According to its data sheet, this product has applications in food and beverages to enrich their protein content.

Use of the casein hydrolysate

The inventors have noticed that the casein hydrolysate according to the characteristics specified above shows excellent antiherpetic properties, being effective for the prevention and/or treatment of infections caused by herpesviruses.

The infections caused by herpesviruses, according to the use described here, relate to the infections caused by any type of herpesvirus, in particular those caused by herpesviruses selected from the group consisting of herpes simplex type 1, herpes simplex type 2, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, herpesvirus type 6, herpesvirus type 7, and Kaposi's Sarcoma herpesvirus; preferably herpes simplex type 1, herpes simplex type 2 and varicella zoster virus.

In a preferred embodiment, the use as described here relates to the prevention and/or treatment of herpesvirus infections selected from the group consisting of herpes labialis, genital herpes, and herpes zoster.

Within the present context the term "treatment" refers to the administration of the product with a curative purpose, once some symptoms or external manifestations of the infection have been observed, such as pain, burning, inflammation or itching in the affected area, as well as the appearance of pustules, vesicles, blisters, or rash, for example, or other symptoms or specific manifestations for each type of particular pathology. The curative purpose of such treatment is understood as being directed to the elimination, alleviation, improvement, or lessening of the severity of the external manifestations of the infection. Habitually it is not strictly a cure meaning the eradication of the virus, as the herpesviruses usually remain in an asymptomatic latent state in the infected individuals throughout their lives, alternating with periods of reactivation. The curative purpose in this sense means the cure of the disease outbreaks which have appeared, in order to achieve their remission and the return of the infection to an asymptomatic latent state.

Within the present context the term "prevention" refers to the administration of the product when there are no symptoms or external manifestations of the infection, but it is administered with a prophylactic purpose with the intention of preventing or delaying the appearance of new outbreaks of the infection, i.e., keeping it in an asymptomatic latent state.

In Examples 3, 4 and 5 some efficacy trials performed with the casein hydrolysate are shown. In those examples the casein hydrolysate was administered to patients suffering from various types of herpes, and they all showed a great efficacy in the relief of symptoms (treatment) as well as in the disappearance or diminution of the reactivation phases (prevention).

As the product used is completely harmless, derived from the hydrolysis of casein from bovine milk and commonly used as a dietetic supplement, the use as described here has the advantage that it is possible to maintain a long preventive treatment, without the risk of experiencing undesirable side effects, as usually happens with other antiviral treatments, so that the patients taking preventative doses are able to remain without any outbreak of the disease for very long periods, as shown in these examples.

In a preferred embodiment, the use of the casein hydrolysate described here is characterized in that the hydrolysate is administered orally.

In a more preferred embodiment, the casein hydrolysate is administered according to a daily oral dose comprised between 4 and 40 g. In a still more preferred embodiment, a unit oral dose comprised between 4 and 8 g of the casein hydrolysate is used, and more preferably comprised between 5.5 and 6.5 g, which is administered from 1 to 5 times daily, and more preferably from 1 to 3 times daily.

Generally within a period of one week, the symptoms of herpes remit completely. In the case of herpes labialis, usually, preferably within 2 to 3 days, and in the case of genital herpes and herpes zoster preferably within 4 to 6 days.

The casein hydrolysate can also be used preventively after the remission of the symptoms by taking a daily unit oral dose of between 4 and 8 g for a period ranging from 12 to 24 months.

In another preferred embodiment, the use of the casein hydrolysate described here is characterized in that the hydrolysate is administered topically, so that it is locally applied on the area affected by the lesion.

Preparations with the casein hydrolysate

The casein hydrolysate according to the described use typically comes in powder solid form and can be administered either directly or in combination with at least one pharmaceutically acceptable excipient and/or carrier, in the form of a pharmaceutical composition.

The use of a casein hydrolysate for the preparation of a medicament for the prevention and/or treatment of infections caused by herpesvirus, may be characterised in that the casein hydrolysate is administered in the form of a pharmaceutical composition comprising a pharmacologically effective amount of this hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, wherein this hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

A casein hydrolysate for use in the prevention and/or treatment of infections caused by herpesvirus, may be characterized in that the hydrolysate is administered in the form of a pharmaceutical composition comprising this casein hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, wherein this hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

The pharmaceutical composition can be prepared using methods that are well known to the skilled in the art such as those contained in handbooks of pharmaceutical technology, such as the book *Remington The Science and Practice of Pharmacy*, 20th edition, Lippincott, Williams & Wilkins, Philadelphia, 2000 [ISBN: 0-683-306472].

The pharmaceutical compositions suitable for the described use are all those appropriate for being administered either orally or topically.

In one described embodiment, the pharmaceutical composition is a composition suitable for oral administration. Any pharmaceutical form suitable for oral administration is included within the described use, preferably solid compositions in powder or granulate form, or either liquid, in solution, suspension or syrup form, for example.

Preferably, the pharmaceutical composition for oral administration is in powder or granulate form. More preferably, it is in powder form.

The pharmaceutical composition may be a composition appropriate for topical administration. Any pharmaceutical form suitable for topical administration is included within the described use, either in a solid, liquid or semisolid form. Solid compositions for topical administration are generally in powder form, and may include a suitable carrier, such as talc, silica or microcrystalline cellulose, among others. The liquid compositions suitable for topical administration can be prepared by dissolving or dispersing the casein hydrolysate in a suitable carrier such as, for example, water, alcohols, glycols, or mixtures thereof, and are, for example, lotions, liniments, or tinctures; or else this liquid composition can be used to impregnate a support in the form of dressing or bandage that is applied to the affected area, or alternatively the liquid composition can be sprayed onto the affected area using pump sprayers or aerosols. Other forms of topical administration are semisolid compositions such as creams, gels, ointments or pastes.

Preferably, the pharmaceutical composition for topical administration is in the form of a cream, gel, ointment or paste.

The pharmaceutically acceptable excipients that can be used for preparing pharmaceutical compositions in solid form are well known to those skilled in the art and include, for example, diluents such as calcium carbonate, sodium carbonate, magnesium carbonate, magnesium oxide, calcium sulfate, calcium phosphate, sodium chloride, microcrystalline or powdered cellulose, cellulose acetate, ethyl cellulose, dextrates, dextrins, dextrose, lactose, lactitol, fructose, sorbitol, sucrose, maltodextrins, maltose, glyceryl palmitostearate, kaolin, polymethacrylates, pregelatinized starch or starch, among others, and mixtures thereof; lubricants, such as calcium stearate, magnesium stearate, talc, stearic acid, glyceryl behenate, glyceryl palmitostearate, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, or hydrogenated castor oil, among others, and mixtures thereof; disintegrants such as alginic acid,

derivatives, or emulsifying wax, among others, and mixtures thereof; suspending agents such as xanthan gum, guar gum, alginic acid, bentonite, carbomers, sodium or calcium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl alginate, microcrystalline or powdered cellulose, anhydrous colloidal silica, dextrins, gelatins, kaolin, magnesium aluminum silicate, maltitol, povidone, sorbitan esters, or tragacanth, among others, and mixtures thereof; flocculating agents such as sodium acetate, sodium phosphate, sodium citrate, sodium lauryl sulfate, starch, alginates, tragacanth, or carbomers, among others, and mixtures thereof; wetting agents as benzalkonium chloride, sodium docusate, sodium lauryl sulfate, sorbitan esters, polyoxyethylene stearates or polyoxyethylene sorbitan fatty acid esters, among others, and mixtures thereof; preservatives such as benzalkonium chloride, benzyl alcohol, bronopol, parabens, sodium benzoate, sodium propionate, sorbic acid or thimerosal, among others, and mixtures thereof; flavoring agents as maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, tartaric acid, peppermint, artificial or natural fruit aromas, among others, and mixtures thereof; sweetening agents such as sorbitol, maltitol, mannitol, dextrose, maltose, xylitol, saccharin, sucrose, sucralose, aspartame, acesulfame potassium or trehalose, among others, and mixtures thereof; coloring agents such as curcumin, lactoflavin, iron oxides (red, yellow or black), caramel, lactoflavin phosphate, cochineal red, titanium dioxide, or carotenes, among others, and mixtures thereof; or mixtures thereof.

The semisolid topical formulations in the form of creams, gels, ointments or pastes comprise a pharmaceutically acceptable carrier in which the casein hydrolysate is dissolved, emulsified, dispersed or suspended. This carrier is selected from water, a non-aqueous water miscible carrier, such as for example ethanol or isopropanol, and a non-aqueous water-immiscible carrier, such as for example paraffin oil. Optionally, such semisolid compositions for topical administration contain a pharmaceutically acceptable excipient such as, for example, surfactant and emulsifier agents, lipidic and emollient compounds, consistency factors and thickening agents, stabilizers, hydrotropes, preservative agents, essences, coloring agents, silicone compounds, fats, waxes, lecithins, phospholipids, UV sun protection factors, or mixtures thereof.

The excipients suitable to be used in the pharmaceutical compositions are well known to those skilled in pharmaceutical technology and are described, for example, in the book R.C. Rowe, P.J. Sheskey and P.J. Weller, *Handbook of Pharmaceutical Excipients*, Fourth Edition, Pharmaceutical Press, 2003.

In a preferred embodiment, the pharmaceutical composition is in the form of powder or granulate for oral use. The powder is usually prepared by mixing the casein hydrolysate in powder form with at least one pharmaceutically acceptable excipient. The granulate consists of powder particles that have been aggregated to form larger particles, and it is prepared according to procedures which are well known to those skilled in the art, such as dry granulation or wet granulation.

The compositions in the form of powder or granulate are usually taken after dissolution or dispersion in water or another liquid.

The powder or granulate composition may be presented in a bulk container as, for example, in a glass container with a wide opening, so that the required dose for each administration is taken as needed, preferably with the help of a measurement device or dispenser to measure the dose to be administered.

The powder or granulate composition may be presented in the form of monodose sachets, containing the unit dose suitable for oral administration. Those sachets can be made of paper or either of aluminium or plastic laminates. Preferably, the oral unit dose comprises between 4 and 8 g of the casein hydrolysate, more preferably between 5 and 7 g, and still more preferably about 6 g of the hydrolysate.

In a particularly preferred arrangement, the composition for oral use is in powder form. More preferably, the composition in powder form comprises the casein hydrolysate, and a pharmaceutically acceptable excipient which is selected from sweeteners, flavouring agents and coloring agents, or mixtures thereof.

Preferably, the composition in powder form contains a quantity of the casein hydrolysate ranging between 70% and 99%, and more preferably ranging between 80% and 95%, expressed as weight ratio relative to the total weight of the composition.

In another preferred arrangement, the pharmaceutical composition according to the use of the present invention is a composition for topical administration, preferably in the form of cream, gel, ointment or paste. Preferably, this composition for topical administration comprises an amount of the casein hydrolysate ranging between 5% and 25%, and more preferably ranging between 7% and 15%.

A pharmaceutical composition comprising a casein hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier, may be characterized in that the composition is in the form of cream, gel, ointment or paste for topical administration, wherein this casein hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate. Preferably, this composition for topical administration contains an amount of the casein hydrolysate ranging between 5% and 25%, and more preferably ranging between 7% and 15%, expressed in weight.

Creams, as it is well known to those skilled in pharmaceutical technology are semisolid emulsions, which can be of the oil-in-water (o/w) type or water-in-oil (w/o) type, formulated from an oil phase, an aqueous phase and an emulsifying agent. The oil phase consists of a carrier which can be, for example, liquid paraffin or a vegetable oil such as, for example, castor oil, almond oil, peanut oil, sesame oil, cottonseed oil or corn oil.

Gels are obtained from a liquid that is gelled by adding a rheological agent or a gelling agent. Some of the gelling agents suitable to be used are, for example, carrageenan, guar gum, tragacanth gum, locust bean gum, pectin, agar, alginic acid, carbomers, carboxymethylcellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and polyethylene glycol, among others.

Ointments are semisolid fat preparations, which contain the active ingredient dissolved or in dispersed form. Ointments can be formulated with various vehicles such as paraffin, plastibases (a mixture of polyethylene with a series of hydrocarbons), vegetable oils, such as peanut oil, sesame oil, olive oil, cottonseed oil, almond oil, corn oil, silicones or polyethylene glycols, among others, or with a mixture thereof.

Pastes are prepared analogously to the ointments, and they show a more solid consistency since they contain greater amounts of insoluble solids.

Next, some examples are provided with the purpose of illustrating the invention, but not limiting it.

CLAIMS

1.- Use of a casein hydrolysate for the preparation of a medicament for the prevention and/or treatment of infections caused by herpesvirus, wherein the hydrolysate comprises peptides wherein the molar fraction of peptides carrying a carboxy terminal proline, expressed in %, is more than two times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

2.- Use according to claim 1, characterized in that the molar fraction of the peptides in the hydrolysate carrying a carboxy terminal proline, expressed in %, is at least three times the molar fraction of proline, expressed in %, in the casein substrate used to generate the hydrolysate.

3.- Use according to claims 1 or 2, characterized in that the average length of the peptides in the casein hydrolysate is comprised between 3 and 9 amino acids.

4.- Use according to claim 1, characterized in that the molar fraction of peptides carrying a carboxy terminal proline in the casein hydrolysate is at least 25%.

5.- Use according to claim 4, characterized in that the molar fraction of peptides carrying a carboxy terminal proline in the casein hydrolysate is between 30% and 70%.

6.- Use according to any of claims 1 to 5, characterized in that the casein hydrolysate has the following amino acid composition: between 54-64 of lysine, between 22-30 of methionine, between 25-33 of threonine, between 18-26 of histidine, between 26-34 of arginine, between 46-56 of valine, between 34-42 of isoleucine, between 70-80 of leucine, between 33-41 of phenylalanine, between 45-55 of the sum of aspartic acid plus asparagine, between 160-180 of the sum of glutamine plus glutamic acid, between 20-26 of alanine, between 80-90 of proline, between 40-48 of tyrosine, between 37-45 of serine, between 11-17 of glycine, between 0.8-1.2 of cysteine, and between 6-10 of tryptophan; wherein the amounts are expressed in grams of each amino acid per kilogram of hydrolysate.

7.- Use according to any of claims 1 to 6, characterized in that the infections are caused by herpesviruses selected from the group consisting of herpes simplex type 1, herpes simplex type 2, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, herpesvirus type 6, herpesvirus type 7, and Kaposi's Sarcoma herpesvirus.

8.- Use according to claim 7, characterized in that the herpesvirus is selected from the group consisting of herpes simplex type 1, herpes simplex type 2 and varicella zoster virus.

9.- Use according to any of claims 1 to 6, characterized in that the herpesvirus infection is selected from the group consisting of herpes labialis, genital herpes, and herpes zoster.

10.- Use according to any of claims 1 to 9, characterized in that the casein hydrolysate is administered orally.

11.- Use according to claim 10, characterized in that the casein hydrolysate is administered according to a daily dose comprised between 4 and 40 g.

12.- Use according to claim 10, characterized in that a unit oral dose of between 4 and 8 g of the casein hydrolysate is used, which is administered from 1 to 5 times daily.

13.- Use according to any of claims 1 to 9, characterized in that the hydrolysate is administered topically.

14.- Use according to any of claims 1 to 9, characterized in that the casein hydrolysate is administered in the form of a pharmaceutical composition comprising a pharmacologically effective amount of the hydrolysate and at least one pharmaceutically acceptable excipient and/or carrier.

15.- Use according to claim 14, characterized in that the pharmaceutical composition is a composition suitable for oral administration.

16.- Use according to claim 15, characterized in that the pharmaceutical composition is in powder or granulate form.

17.- Use according to claim 16, characterized in that the composition is dosed in monodose sachets containing between 4 and 8 g of the casein hydrolysate.

18.- Use according to claim 14, characterized in that the pharmaceutical composition is a composition suitable for topical administration.

19.- Use according to claim 18, characterized in that the pharmaceutical composition is in the form of cream, gel, ointment or paste.