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(71) Applicant: **JIANGYIN USUN PHARMACEUTICAL CO., LTD.** [CN/CN]; B13, No. 2, Dongsheng West Road, Jiangyin, Jiangsu 214437 (CN).

(72) Inventors: **SAMUELSSON, Bengt I.**; Scheeles Vag 2, Scheelelaboratoriet, Hus A4, Plan 4, S-171 77 Stockholm (SE). **GU, Ming**; B13, No. 2, Dongsheng West Road, Jiangyin, Jiangsu 214437 (CN). **MENG, Nan**; B13, No. 2, Dongsheng West Road, Jiangyin, Jiangsu 214437 (CN).

(74) Agent: **WU, FENG & ZHANG**; 3 Fl, Building 2, Yard 3, Fengxiuzhonglu Road, Haidian District, Beijing 100094 (CN).

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(54) Title: ANTIVIRAL USE OF MUSSEL ADHESIVE PROTEINS

(57) Abstract: There is provided a mussel adhesive protein or a derivative thereof for use in the treatment of a viral infection and/or as an antiviral agent. Viruses that may be mentioned include herpes simplex, type 1 virus, herpes simplex, type 2 virus, human papillomavirus, influenza virus and parainfluenza virus.

ANTIVIRAL USE OF MUSSEL ADHESIVE PROTEINS

Field of the Invention

This invention relates to the new use of known compounds.

Background and Prior Art

A virus is a very small organism comprising genetic material (DNA or RNA) that is capable of infecting a biological organism. A virus invades and attaches itself to a living cell, after which it multiplies to produce more virus particles (virions), which attach to and enter susceptible cells.

A virus may either kill a cell or alter its functions, the by-products of which leads to the infection of other cells. This will then generally lead to what is termed as viral diseases (or viral infections).

In general, viruses only infect one type of cell, but can be transmitted in various ways, including contact with infected individuals or their bodily secretions, animals (such as arthropods), or inanimate objects. Viruses can also be transmitted by inhalation or swallowing.

Following viral infection, an organism's immune defence system is triggered. Lymphocytes and monocytes attempt to attack and destroy the invasive virus. This is referred to as the body's innate or natural immunity. The innate immune response can often lead a patient feeling unwell or fatigued. If a patient's immune system is compromised, or not effective enough to prevent the spread of a virus, this can lead to severe illness and, in some instances, morbidity and/or death.

Antiviral medicines typically act by interfering with viral replication, for example slowing replication rate to increase the likelihood of the innate immune respose intervening. There is a clear clinical need for medicines that exhibit better and/or different antiviral properties.

Mussel adhesive protein, also known as *Mytilus edulis* foot protein (mefp), is a protein secreted by marine shellfish species, such as *Mytilus edulis*, *Mytilus coruscus* and *Perna viridis*. The adhesive protein is secreted by mussels from the byssus gland where it is produced and stored. When secreted on a surface of a solid, such as a rock, but also other solid objects, such as metals, wood, glass, etc., a water-proof bond is formed which fixes the mussel to the solid object. Mussels are typically attached, in groups, to coastal reefs or to the bottoms of ships. The bond is incredibly strong, having the ability to resist wave impacts in coastal waters.

Studies on *Mytilus edulis*, *Mytilus galloprovincialis*, *Mytilus californias* and *Perna viridis* have thus far identified eleven separate adhesive protein subtypes derived from mussel byssus: mfp-1 (sometimes referred to as “mefp-1”, hereinafter used interchangeably), mfp-2/mefp-2, mfp-3/mefp-3, mfp-4/mefp-4, mfp-5/mefp-5, mfp-6/mefp-6, collagen, pre-COL-P, pre-COL-D, pre-COL-NG, PTMP (proximal thread matrix protein), and DTMP (distal proximal thread matrix protein). See, for example, Zhu *et al*, *Advances in Marine Science*, **32**, 560 (2014) and Gao *et al*, *Journal of Anhui Agr. Sci.*, **39**, 19860 (2011).

All mussel adhesive proteins, including sub-types thereof, have two structural characteristics, in that they comprise: (1) lysine, such that the protein carries a high positive charge loading (due to the NH_2 termini); (2) 3,4-dihydroxyphenylalanine (DOPA, dopamine), the catechol part of which is responsible for the formation of strong covalent bonds and consequently the ability of mussel adhesive proteins to bind to solid surfaces.

Products based on mussel adhesive protein products are presently used in a limited number of fields (including micro-cellular bonding, as tissue bonding agents and the treatment of wounds and burns). Commercial products are either directly used as a solution of mussel adhesive protein or are stored as a freeze-dried powder for dissolution prior to use.

To the applicant’s knowledge, the use of a mussel adhesive protein as an antiviral agent with a view to preventing the onset, or the spread, of viral diseases is not specifically disclosed in the prior art.

Disclosure of the Invention

According to the invention, there is provided at least one mussel adhesive protein or a derivative, such as a pharmaceutically-acceptable derivative, thereof for use in the treatment of a viral infection.

In the context of the present invention, the term “a mussel adhesive protein” includes any adhesive protein that may be derived (isolated or extracted) from the byssus of mussel species, including those mentioned herein and preferably *Mytilus edulis* (blue mussel).

The term thus include full length proteins, including all sub-types, that are or may be derived from mussels, such as the collagens pre-COL-P, pre-COL-D and pre-COL-NG, the mussel feet matrix proteins PTMP and DTMP, and, more preferably, mfps or mefps, such as mefp-2, mefp-3, mefp-4, mefp-5, mefp-6 and especially mefp-1, and includes mixtures or combinations of any of these proteins, such as mefps. Although mixtures/combinations of the aforementioned MAP sub-types may be provided as the MAP “component” in accordance with the invention, we prefer that the purity of the principal MAP sub-type (e.g. mefp-1) is at least 25% by weight of the total amount of any such mixture.

Thus, the at least one mussel adhesive protein that is an essential element of the invention is hereinafter referred to the at least one “MAP”. Mussel adhesive proteins are referred to together hereinafter, collectively or separately, as “MAPs”.

Known methods of extracting, preparing, separating and purifying naturally-occurring MAPs may be employed, for example mixed adsorption chromatography (see Chinese Patent No. ZL200710179491.0), carboxymethyl ion exchange chromatography (see Chinese Patent No. ZL200710179492.5), and/or salting out and dialysis (Chinese Patent No. ZL200910087567.6). Commericial sources of MAPs include USUN Bio Co. (China; sold as MAP Medical Device®), BD Biosciences (USA), Kollodis (South Korea) and Biopolymer (Sweden). MAPs may alternatively be produced using known recombinant DNA methods.

Derivatives of MAPs include pharmaceutically-acceptable derivatives, such as isolated lower molecular weight products (for example with a molecular weight in the range of about 500 Da to about 2,000 (e.g. about 1,200, such as about 800) Da, which may allow for easier permeation through biological membranes, such as the skin barrier or a mucosal surface. Such derivatives may also include other compounds that comprise amino acid sequences that are the same as, or are (e.g. minor) variants of, sequences that have been identified in naturally-occurring MAPs, and which may be synthesized by chemical and/or biological processes (e.g. chemical modifications of naturally-occurring MAPs, or direct synthesis). By "(e.g. minor) variants of amino acid sequences identified in naturally-occurring MAPs", we mean variations in those sequences that do not negatively affect the requisite properties of the relevant naturally-occuring MAP to a measurable degree.

Derivatives of MAPs include "MAP Peptide" and salts (e.g. cationic salts) thereof, which is a decapeptide of the sequence: Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys (see Waite, *Int. J. Adhesion and Adhesives*, **7**, 9 (1987)). MAP Peptide may derived and/or isolated as a low molecular weight derivative of naturally-occurring MAPs, or may be synthesized, for example as described by Yamamoto in *J. Chem. Soc., Perkin Trans. 1*, 613 (1987). See also Dalsin *et al*, *J. Am. Chem. Soc.*, **125**, 4253 (2003). Other derivatives include a peptide of the sequence Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys, a regioisomer, a stereoisomer, or a salt, thereof, which may be made by analogous techniques (see, for example Kanyalkar *et al* in *Biomaterials*, 389 (2002) and Belli *et al* in *Dental Materials*, **26**, e125 (2010)).

Such derivatives of MAPs may be employed in accordance with the invention alone, or in combination with one or more other such derivatives, and/or one or more of the aforementioned full length MAPs.

As described below, the applicant has surprisingly found that MAPs and derivatives thereof possess antiviral properties that may allow for the treatment of a viral infection *per se*, that is treatment of a viral infection, or a viral disease, by interfering with the replication of the virus within a host, as opposed to the

treatment of any symptoms of any viral infection or disease, such as pain and/or inflammation. Such antiviral properties may also allow for the the prevention of the onset of such an infection or disease, the protection of cells in a host from (e.g. further) viral infection, prevention or arrest of the spread of viral infection or disease (within a single host, or from one host to a new host), or for the prevention of reactivation of a virus after latency in a host.

According to a further aspect of the invention there is provided a method of treatment of a viral infection, which method comprises the administration of at least one MAP or a derivative thereof to a patient in need of such treatment.

“Patients” include reptilian and, preferably, mammalian (particularly human) patients.

Viral infections that may be mentioned include those caused by viruses in the following families: adenoviridae (e.g. adenovirus), papillomaviridae (e.g. human papillomavirus), polyomaviridae (e.g. BK virus; JC virus), herpesviridae (e.g. herpes simplex, type 1; herpes simplex, type 2; varicella-zoster virus; Epstein–Barr virus; human cytomegalovirus; human herpes virus, type 8), poxviridae (e.g. smallpox), hepadnaviridae (e.g. hepatitis B virus), parvoviridae (e.g. parvovirus B19), astroviridae (e.g. human astrovirus), caliciviridae (e.g. norovirus; Norwalk virus), picornaviridae (e.g. coxsackievirus, hepatitis A virus; poliovirus; rhinovirus), coronoviridae (e.g. severe acute respiratory syndrome virus), flaviviridae (e.g. hepatitis C virus; yellow fever virus; dengue virus; West Nile virus; tick-borne encephalitis virus), retroviridae (e.g. human immunodeficiency virus; HIV), togaviridae (e.g. rubella virus), arenaviridae (e.g. Lassa virus), bunyaviridae (e.g. hantavirus; Crimean-Congo hemorrhagic fever virus; Hantaan virus), filoviridae (e.g. Ebola virus; Marburg virus; Ravn virus), orthomyxoviridae (e.g. influenza viruses, including influenza A virus (e.g. H1N1 and H3N2 viruses), influenza B virus or influenza C virus), paramyxoviridae (e.g. measles virus; mumps virus; parainfluenza virus, respiratory syncytial virus), rhabdoviridae (e.g. rabies virus), hepeviridae (e.g. hepatitis E virus), reoviridae (e.g. rotavirus; orbivirus; coltivirus; Banna virus), as well as viruses not assigned to families, such as hepatitis D virus.

Viruses that may be more specifically mentioned include herpes simplex, type 1 and herpes simplex, type 2 viruses, human papillomavirus, influenza virus and parainfluenza virus.

In accordance with the invention, MAPs/derivatives may be administered locally or systemically, for example orally, intravenously or intraarterially (including by intravascular and other perivascular devices/dosage forms (e.g. stents)), intramuscularly, cutaneously, subcutaneously, transmucosally (e.g. sublingually or buccally), rectally, intravaginally, transdermally, nasally, pulmonarily (e.g. tracheally or bronchially), topically, or by any other parenteral route, in the form of a pharmaceutical preparation comprising the compound(s) in pharmaceutically acceptable dosage form(s). Topical forms of administration may be enhanced by creating a spray comprising active ingredients, e.g. by using a powder aerosol or by way of an aqueous mist using an appropriate atomisation technique or apparatus, such as a nebulizer.

Preferred modes of delivery of MAPs and derivatives thereof include topically (e.g. to the skin or a mucosal surface, including the lung, or preferably the nasal or the vaginal mucosa) in an appropriate (e.g. pharmaceutically-acceptable) vehicle and/or a commercially-available formulation, but may also include oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, or intraperitoneal delivery.

MAP/derivative will generally be administered in the form of one or more (e.g. pharmaceutical) formulations in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical or other (e.g. cosmetic) practice. Acceptable carriers may be chemically inert to the active compounds and may have no detrimental side effects or toxicity under the conditions of use. Such carriers may also impart an immediate, or a modified, release of active ingredient.

Suitable pharmaceutical formulations may be commercially available or otherwise prepared according to techniques that are described in the literature, for example, Remington *The Science and Practice of Pharmacy*, 22nd edition, Pharmaceutical

Press (2012) and *Martindale – The Complete Drug Reference,* 38th Edition, Pharmaceutical Press (2014) and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations including MAPs and derivatives thereof may be achieved non-inventively by the skilled person using routine techniques.

MAPs (for example Mefp-1) and derivatives thereof, may be in the form of an aqueous formulation such as an emulsion, a suspension and/or a solution (e.g. an (optionally) buffered aqueous formulation (e.g. solution), such as a physiological saline-containing formulation (e.g. solution), a phosphate-containing formulation (e.g. solution), an acetate-containing formulation (e.g. solution) or a borate-containing formulation (e.g. solution)), or a freeze-dried powder.

Active ingredients may in the alternative be combined with appropriate excipents to prepare:

- gel formulations (for which suitable gel matrix materials include cellulose derivatives, carbomer and alginates, gummi tragacanthae, gelatin, pectin, carrageenan, gellan gum, starch, Xanthan gum, cationic guar gum, agar, noncellulosic polysaccharides, vinyl polymers, acrylic resins, polyvinyl alcohol, carboxyvinyl polymer and, particularly, hyaluronic acid);
- lotions (condensates; for which suitable matrix materials include cellulose derivatives, glycerin, noncellulosic polysaccharides, polyethylene glycols of different molecular weights and propanediol);
- pastes or ointments (for which suitable paste matrix materials include glycerin, vaseline, paraffin, polyethylene glycols of different molecular weights, etc.);
- creams or foams (for which suitable excipients (e.g. foaming agents) include hydroxypropyl methyl cellulose, gelatin, polyethylene glycols of different molecular weights, sodium dodecyl sulfate, sodium fatty alcohol polyoxyethylene ether sulfonate, corn gluten powder and acrylamide);
- powder aerosols (for which suitable excipients include mannitol, glycine, dextrin, dextrose, sucrose, lactose, sorbitol and polysorbates); and/or
- liquid (aerosol) sprays for oral use or for inhalation (for which suitable excipients include viscosity modifiers, such as hyaluronic acid,

emulsifiers, buffering agents, alcohols, water, preservatives, sweeteners, flavours, etc.).

Moisturizing agents, such as glycerol, glycerin, polyethylene glycol, trehalose, glycerol, petrolatum, paraffin oil, hyaluronic acid and salts (e.g sodium and potassium salts) thereof, octanoic/capyic triglyceride, and the like; and/or antioxidants, such as vitamins and glutathione; and/or pH modifiers, such as acids, bases and pH buffers, may also be included in such formulations, as appropriate. Furthermore, surfactants/emulsifiers, such as hexadecanol (cetyl alcohol), fatty acids (e.g. stearic acid), sodium dodecyl sulfate (sodium lauryl sulfate), sorbitan esters (e.g. sorbitan stearate, sorbitan oleate, etc.), monoacyl glycerides (such as glyceryl monostearate) polyethoxylated alcohols, polyvinyl alcohols, polyol esters, polyoxyethylene alkyl ethers (e.g. polyoxyethylene sorbitan monooleate), polyoxyethylene castor oil derivatives, ethoxylated fatty acid esters, polyoxylglycerides, lauryl dimethyl amine oxide, bile salts (e.g. sodium deoxycholate, sodium cholate), phospholipids, N,N-dimethyldodecylamine-N-oxide, hexadecyltrimethyl-ammonium bromide, poloxamers, lecithin, sterols (e.g. cholesterol), sugar esters, polysorbates, and the like; preservatives, such as phenoxyethanol, ethylhexy glycerin, and the like; and thickeners, such as acryloyldimethyltaurate/ VP copolymer may be included. In particular stearic acid, glyceryl monostearate, hexadecanol, sorbitan stearate, cetyl alcohol, octanoic/capric glyceride etc. may be included, particularly in cream formulations.

MAPs (for example Mefp-1) and derivatives thereof, and (e.g. pharmaceutical) formulations (e.g. aqueous solutions, gels, creams, ointments condensates/lotions, pastes and/or foams as described above) including them, may further be combined with an appropriate matrix material to prepare a dressing or a therapeutic patch for application on a biological surface, such as the skin or a mucosal surface. Such formulations may thus be employed to impregnate a matrix material, such as gauze, non-woven cloth or silk paper. The therapeutic patch may alternatively be, for example, a band-aid, a facial mask, an eye mask, a hand mask, a foot mask, etc.

Vaseline may be employed for use in applying such dressings to wounds, but we have also found that the PEG-based ointments may be combined with matrix materials to prepare dressings without the need to use vaseline.

MAPs and derivatives thereof may also be combined in treatment with one or more growth factors selected from platelet-type growth factors (including platelet-derived growth factors, PDGFs); osteosarcoma-derived growth factors (ODGF), epidermal growth factors (EGFs), transforming growth factors (TGFα and TGFβ), fibroblast growth factors (αFGF, βFGF), insulin-like growth factors (IGF-Ⅰ, IGF-Ⅱ), nerve growth factors (NGF), interleukin-type growth factors (IL-1, IL-1, IL-3), erythropoietin (EPO), and colony stimulating factor (CSF).

Administration of active ingredients may be continuous or intermittent. The mode of administration may also be determined by the timing and frequency of administration, but is also dependent, in the case of antiviral treatment, on the (e.g. potential) severity of the condition.

Depending on the disorder, and the patient, to be treated, as well as the route of administration, active ingredients may be administered at varying therapeutically effective doses to a patient in need thereof.

Similarly, the amount of active ingredients in a formulation will depend on the (e.g. potential) severity of the condition, and on the patient, to be treated, but may be determined by the skilled person.

In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient, depending on the (e.g. potential) severity of the condition and route of administration. The dosages mentioned herein are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Doses may be administered between once and four times daily.

Appropriate concentrations of MAPs and derivatives thereof in an aqueous solution product may be may be about 0.01 (e.g. about 0.1) to about 15.0 (e.g. about 1.5) mg/mL, and appropriate pH values are in the range of about 1.0 to about 7.0 (for example about 3.0 to about 6.5), irrespective of whether the formulation employed is a combined preparation or a kit of parts as hereinbefore described. Suitable commercial sources of such aqueous solutions include USUN Bio Co., Jiangyin, Jiangsu Province, China.

Appropriate topical doses of MAPs and derivatives thereof are in the range of about 0.1 to about 50 μg/cm^2 of treated area, such as about 0.5 to about 20 μg/cm^2 of treated area, including about 1 to about 10 μg/cm^2 of treated area, for example about 2 to about 8 μg/cm^2 of treated area, such as about 5 μg/cm^2 of treated area.

In any event, the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect an appropriate therapeutic response in the patient over a reasonable timeframe (as described hereinbefore). One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by *inter alia* the pharmacological properties of the formulation, the nature and (e.g. potential) severity of the condition being treated, and the physical condition and mental acuity of the recipient, as well as the age, condition, body weight, sex and response of the patient to be treated, and the stage and/or potential severity of any disease, as well as genetic differences between patients.

In the uses and methods described herein, MAPs and derivatives thereof may also be combined with one or more active ingredients that possess antiviral properties. Such patients may thus also (and/or already) be receiving therapy based upon administration of one or more of such other active ingredients, by which we mean receiving a prescribed dose of one or more of those active ingredients mentioned herein, prior to, in addition to, and/or following, treatment with MAP/derivative.

Such antiviral agents that may be used in combination with MAPs/derivatives thereof in the treatment of viral infections include standard vaccines that may be

employed against the viral infection in question, as well as known and/or appropriate antiviral drugs, such as abacavir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, balavir, cidofovir, combivir, dolutegravir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, ecoliever, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, a fusion inhibitor, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, an integrase inhibitor, interferon, interferon type I, interferon type II, interferon type III, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, nitazoxanide, a nucleoside analogues, novir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, a protease inhibitor, pyramidine, raltegravir, a reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, saquinavir, sofosbuvir, stavudine, a synergistic enhancer (antiretroviral), telaprevir, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir and zidovudine. Antiviral drugs that may be mentioned specifically include acyclovir.

Other antiviral agents that may be used in combination include enzymes, such as trypsin, which may be combined with a MAP or a MAP derivative, especially either Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys or a salt thereof, or Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys or a salt thereof.

When MAPs/derivatives are “combined” with other antiviral agents in this way, the active ingredients may be administered together in the same formulation, or administered separately (simultaneously or sequentially) in different formulations.

Such combination products provide for the administration of MAPs and derivatives thereof in conjunction with the other antiviral agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a MAP/derivative, and at least one comprises the other antiviral agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including MAP/derivative and the other antiviral agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including at least one MAP or a derivative thereof; another antiviral agent; and a pharmaceutically-acceptable adjuvant, diluent or carrier (which formulation is hereinafter referred to as a "combined preparation"); and

(2) a kit of parts comprising components:

(A) a pharmaceutical formulation including at least one MAP or a derivative thereof in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(B) a pharmaceutical formulation including another antiviral agent in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

According to a further aspect of the invention, there is provided a method of making a kit of parts as defined above, which method comprises bringing component (A), as defined above, into association with a component (B), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components "into association with" each other, we include that components (A) and (B) of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

(I) one of components (A) and (B) as defined herein; together with

(II) instructions to use that component in conjunction with the other of the two components.

Wherever the word “about” is employed herein, for example in the context of amounts, such as concentrations and/or doses of active ingredients, molecular weights or pHs, it will be appreciated that such variables are approximate and as such may vary by ± 10%, for example ± 5% and preferably ± 2% (e.g. ± 1%) from the numbers specified herein. In this respect, the term “about 10%” means e.g. ±10% about the number 10, i.e. between 9% and 11%.

The methods described herein may also have the advantage that, in the treatment of the conditions mentioned hereinbefore, they may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it/they may have other useful pharmacological properties over, similar methods (treatments) known in the prior art for use in the treatment of viral diseases or infections or otherwise.

The invention is illustrated by the following examples.

Examples

Example 1

Effect of MAP on The Activity of Human Herpes Simplex Virus, Type-II (HSV-2).

A serum free 1640 medium (RPMI1640 culture medium; GIBCO/BRL; Thermo Fisher Scientific China, Nanjing, China) was prepared using standard methods. It was formulated as a complete medium containing 10% serum by adding neonatal bovine serum (Zhejiang Tianhang Biotechnology Co., Ltd. Luoshe, China) before use, or was formulated as a maintenance solution by adding 2% of the same serum.

MAP lyophilized powder was prepared by freeze-drying of a MAP solution (USUN Bio Co., Ltd.), with a purity of MAP of 87.04% and a pH of the original solution of 4.5. The lyophilized powder (6.02 mg) was dissolved in 301 μL of aqueous sodium chloride (in aqua pro injection, Jiangsu Hengrui Medicine Co., Ltd, Jiangsu Province, China) to prepare a 20 μg/μL stock solution.

0.05 mL of the stock solution was added to 1.95 mL of the complete medium to formulate a 500 μg/mL drug solution (maintenance solution was used instead of the complete medium in antivirus tests Nos. 3 and 4 below). Then, working solutions with concentrations of 250, 125, 62.5, 31.25, 15.625, 7.8125, 3.9063, 1.9531 and 0.9766 μg/mL were prepared by double dilution.

20.34 mg of sodium laurylsulfonate (SDS; manufactured by AMRESCO LLC, Solon, OH, USA and packed by Biosharp Company, Hefei, China; purity: 99%) was dissolved in 10.17 mL of the culture medium (again, maintenance solution was used instead of the medium in the antivirus tests) to produce a 2000 μg/mL stock solution. Then working solutions with concentrations as above were prepared by double dilution.

2.25 mg of acyclovir (ACV; Zhiyuan Pharmaceutical Co., Ltd, Wuxi City, China; purity: 99.3%) was dissolved in 2.25 mL of the culture medium (again, maintenance solution was used instead of the medium in the antivirus tests) to form a 1000 g/mL stock solution. Then, 0.8 mL of the stock solution was double diluted to provide concentrations of 500, 250 and 125 μg/mL. 0.2 mL of the stock solution was added to 1.95 mL of the culture medium to provide a concentration of 100 μg/mL, which was then diluted to concentrations of 50, 25 and 12.5 μg/mL.

1. HSV-2 Viral Toxicity Test

0.5 mL of a suspension of human herpes simplex virus type-II (HSV-2; SAV strain; Shanghai Institute of Cell Biology) was inoculated into the monolayer culture of Vero cells (Shanghai Institute of Cell Biology) and removed after 1 hour of adsorption.

The maintenance solution was replaced and cultured at 37°C (under 5% CO_2) until more than 95% of the cells showed obvious pathological changes under a microscope (Nikon ECLIPSE TS100 inverted phase control microscope (with imaging system)). The cells were harvested and repeatedly frozen and thawed, and centrifuged at 3000 rpm for 10 minutes in a Model 400C Medical Low Speed Centrifuge (Beijing Baiyang Centrifuge Co., Ltd.). The supernatant was collected as viral solution.

The Vero cell suspension with a density of 2 × 105 was inoculated into a 96 well culture plate (Costar, Corning Inc., Oneonta, NY, USA) at 0.1 mL/well, cultured at 37ºC (under 5% CO_2, Thermo Scientific CO_2 incubator) for 18 hours until a monolayer was visible under a microscope. The virus collected above was inoculated into monolayer Vero cells in a 10-fold dilution with the maintenance solution at 0.1 mL/well. The maintenance solution was replenished and cultured at 37ºC (under 5% CO_2). Pathological changes of the cells were observed under a microscope after culturing for 24 hours. Each dilution was repeated in 3 wells. Normal cells were used as a control in the experiment. The virus virulence test was repeated 3 times.

Three visual fields were observed for each well. The average percentage of pathological cells (P) in the field of vision was determined.

The median infectious dose ($TCID_{50}$) of the virus was calculated according to Reed and Muench conventional methods, that is $TCID_{50}$, which is the logarithm of the next dilution above 50% of pathological changes + proportionate distance (PD) × logarithm of the dilution coefficient. PD is (the percentage of pathological changes above 50% minus 50%) divided by (the percentage of pathological changes above 50% minus the percentage of pathological changes below 50%). The 3 tests gave measured $TCID_{50}$ values were 4.89, 4.06 and 4.55, respectively.

2. Cytotoxicity of MAP and Control Drugs

Vero cells were inoculated on the 96-well culture plate and grew into monolayers. 0.2 mL of MAP or control drugs per well with different concentrations (as above) were added. This was repeated in 3 wells for each concentration. The solvent and normal cell cultures were used as a negative control. Cells were cultured at 37ºC (5% CO_2) and growth and morphological changes of the cells were observed under the microscope for 2 days. Three visual fields were selected for each well, the percentage of pathological cells was counted, and the average values were calculated. The time point of the test was set as 24 hours and the median toxic concentration (TC_{50}) and maximum non-toxic concentration (TC_0) were calculated. The experiment was repeated 3 times.

Cells were inoculated as described above. The solvent and normal cell cultures were used as negative controls. 24 hours after adding MAP and the control drugs, 5 mg/mL of 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide; MTT; Sigma-Aldrich (China), Shanghai, China) in PBS (diluted from a 10 x stock solution, Sigma-Aldrich (China)) was introduced (20 µL/well), and cultivation continued for 4 hours. Then, the supernatant in each well was discarded and 150 µL of dimethyl sulfoxide (DMSO; Sigma-Aldrich (China)) was added, followed by 10 minutes of shaking in the dark at room temperature.

The optical absorption value (OD_{550}) at 550 nm was measured by an enzyme-linked immunosorbent meter (MULTISKAN SPECTRUM; Thermo Scientific, Shanghai, China).

Results from the three parallel tests conducted by cell morphology observations under the microscope revealed that MAP had a TC_{50} of >125 µg/mL and $TC_{0\ of}$ ≤62.5 µg/mL; SDS had a TC_{50} of >62.5 µg/mL and a $TC_{0\ of}$ ≤62.5 µg/mL, and ACV had a TC_{50} of >1000 µg/mL and a TC_0 of ≤250 µg/mL.

The results from the MTT method showed that MAP had no cytotoxicity on Vero cells in the range of 500 down to 15.625 g/mL. SDS showed no cytotoxicity at 62.5 g/mL and below on Vero cells. The maximum concentration of ACV to show significant cytotoxicity on Vero cell was 100 g/mL.

3. Effect of MAP and SDS on the Cytopathic Effect of Viruses After Directly Acting on HSV-2

HSV-2 virus, preserved at -80°C (in a Haier DW-86L486 ultra-low temperature freezer) with $TCID_{50}$ determined was diluted to 200 $TCID_{50}$ at the determined titer. The 200 $TCID_{50}$ solutions were mixed with an equal volume of MAP or SDS liquid at which the viral titer was 100 $TCID_{50}$. The mixed solution was incubated in a water bath (DK-8B constant temperature electrothermal water bath; Shanghai Jinghong Biotech Co., Ltd.) at 37ºC for 1 hour, and then inoculated into the 96-well culture plate containing monolayer Vero cells. To each well was added 0.1 mL.

The supernatant containing virus and drugs was discarded after 1 hour of adsorption. Then the monolayer Vero cells were washed twice with the maintenance liquid. Finally, the maintenance liquid was added (0.2 mL/well). The resultant mixture was continuously cultured at 37ºC (5% CO_2) until the cytopathic rate of the drug free culture reached 95% under the microscope. The evaluating time point of the test was set as 24 hours.

Beside the experimental groups, three control groups were tested in parallel, (solvent, no drug control (virus control), and normal cell control). Each group was made up of 3 wells and the experiment was repeated 4 times.

The virus was diluted to 0.1, 1, 10, 100 and 1000 $TCID_{50}$ and inoculated into a monolayer cell culture. Each dilution was conducted in triplicate. The cytopathic rates were observed for each well (there should no cytopathic effects at 0.1 $TCID_{50}$, whereas a cytopathic effect should be seen at 100 $TCID_{50}$; otherwise the neutralization tests were not established).

The evaluation indices were the same as that of the virus toxicity test. Three visual fields were observed for each well. The average percentage of pathological cells (P) in the field of vision was determined. The median infective dose ($TCID_{50}$) of the virus was calculated according to Reed and Muencl conventional methods (as above).

Toxicity of drugs to the cells was determined by the cell morphology method, while antiviral tests were carried out at non-toxic concentrations. After incubating with different concentrations of MAP and SDS for 1 hour, 100 $TCID_{50}$ HSV-2 (SAV strain) was inoculated into monolayer Vero cell culture. The cytopathic effect of the cells caused by viral infection was inhibited in varying degrees suggested that MAP had an inhibitory effect on HSV-2.

Using 250 g/mL as the stock solution, the neutralization titers of MAP determined by these four tests were 1:4.6 (54.88 μg/mL), 1:2.8 (88.39 μg/mL), 1:2.6 (96.39 μg/mL) and 1:4.4 (56.61 μg/mL).

The contrast drug SDS also showed inhibitory effect on HSV-2. Using 125 g/mL as the stock solution, the neutralization titers of SDS were 1:5.7 (22.10 μg/mL), 1:5.7 (21.93 μg/mL), 1:5.8 (21.46 μg/mL) and 1:6.0 (20.86 μg/mL).

4. Effect of MAP and ACV on HSV-2 (Direct Method)

The virus was diluted to 100 $TCID_{50}$ and inoculated into monolayer Vero cells culture at 0.1 mL in each well. The supernatant was discarded after 1 hour of adsorption and washed 2 times with the maintenance solution. Then, different concentrations of MAP or control drug ACV were added at 0.2 mL/well. The culture was continuously cultivated at 37ºC (5% CO_2). Each concentration was repeated in triplicate and solvent, virus without drug treatment (virus control) and normal cell culture (cell control) were set as controls.

During the culture period, the pathological changes were observed under a microscope and the tests were terminated when the cytopathic rate of the virus control reached >95%. The evaluation time point of the test was 24 hours and the experiment was repeated 3 times.

The judgment index was the same as that of virus toxicity test, i.e. selected three field at each well for microscopic examination, determine the percentage of diseased cells (P) in the field of vision, take the average of three horizons.

The linear regression equation was calculated according to percentage of cytopathic effect of each reagent concentration group toward drug concentration. The IC_{50} value was calculated and the significance test of correlation coefficient was also calculated.

The antiviral tests were carried out at non-toxic concentrations. When HSV-2 infected Vero cells was treated with different concentrations of MAP or ACV, MAP showed a degree of inhibition on cytopathic effects of Vero cell caused by infection with 100 $TCID_{50}$ HSV-2 with an IC_{50} of >125 μg/mL. The contrast drug ACV showed IC50 values of 6.38 μg/mL, 2.20 μg/mL and 5.36 μg/mL.

The results showed that the MAP powder has an influence on the activity of HSV-2 and could protect 50% cells from pathological changes in the range of 54.88 μg/mL to 96.39 μg/mL.

Example 2

Effect of MAP on The Activity of Human Herpes Simplex Virus, Type-I (HSV-1)

A serum free 1640 medium was prepared using RPMI1640 powder (1000 mL dosage; Thermo Fisher Scientific China), L-glutamine (0.29 g; Sinopharm Chemical Reagent Co. Ltd, Shanghai, China), sodium bicarbonate (2.2 g; Sinopharm Chemical Reagent Co.), HEPEs (2.39 g; Thermo Fisher Scientific China) and deionized water (1000 mL).

The agents were mixed, dissolved and filtered to sterilize. This mixture was formulated as a complete medium containing 10% serum by adding neonatal bovine serum before use, or was formulated as a maintenance solution by adding 2% of the same serum.

MAP stock solution was prepared by diluting an MAP solution with a concentration of 4.0 mg/mL with sodium chloride to prepare a 20 μg/μL stock solution.

Thereafter, essentially the same tests as described in Example 1 above using human herpes simplex virus type-I (HSV-1; SAV strain; Shanghai Institute of Cell Biology) were carried out.

In the HSV-1 viral toxicity test, the 3 tests gave measured $TCID_{50}$ values were 4.09, 4.13 and 4.26, respectively.

The cytotoxicity of MAP and control drugs test gave essentially the same results as reported in Example 1 above.

The results of direct assay showed that the MAP solution has an influence on the activity of HSV-1 and could protect 50% cells from pathological changes in the range of 44.64 μg/mL to 58.14 μg/mL (the neutralization titers of MAP determined

by the four tests were 1:5.6 (44.64 μg/mL), 1:4.9 (51.02 μg/mL), 1:4.3 (58.14 μg/mL) and 1:5.2 (48.08 μg/mL).

The results of indirect assay showed that MAP solution has inhibition on cytopathic effects of Vero cell caused by infection with HSV-1 with an values of 50.3 μg/mL.

Example 3

Effect of MAP on the Activity of Human Influenza A Virus H1N1

The challenge virus is human influenza A virus (H1N1) (Wuxi Center for Disease Control, Wuxi, China).

MDCK cells (ATCC CCL-34; Wuxi Center for Disease Control, Wuxi, China) are cultivated in DEME medium (DEME high glucose culture medium with L-glutamine; Thermo Fisher Scientific China), plus 10% FBS (Fetal Bovine Serum, Thermo Fisher Scientific China). The culture medium is prepared by adding 50 mL of FBS and 5 mL penicillin and streptomycin stock solution (containing 10000 U/mL penicillin G and 10000 g/mL streptomycin sulfate) to 1.445 mL of DEME solution. The resultant is sterilized by filtration.

Virus growth medium is prepared by adding 1 μg/mL TPCK [6-(1-tosylamido-2-phenyl) ethyl chloromethyl ketone] treated trypsin (Thermo Fisher Scientific China) to the DEME medium containing 1% HEPES (1M stock solution) and 1% glutamine.

6.4 mg of lyophilized MAP powder (prepared as described in Example 1 above) is dissolved in 1000 μL of aqueous sodium chloride to prepare a 6.4 μg/μL stock solution. 0.1 mL of the stock solution is added to 0.9 mL of the complete medium to formulate a 640 μg/mL drug solution. Then, working solutions with concentrations of 320, 160, 80, 40, 20, 10, 5, 2.5 and 1.25 μg/mL are prepared by double dilution.

MDCK cells are inoculated on the 96-well culture plate and grow into monolayers. 0.2 mL of MAP per well with different concentrations (as above) is added. This is

repeated in 3 wells for each concentration. The solvent and normal cell cultures are used as a negative control. Cells are cultured at 35ºC (5% CO2) and growth and morphological changes of the cells are observed under the microscope for 2 days. Three visual fields are selected for each well, the percentage of pathological cells is counted, and the average values are calculated. The time point of the test is set as 24 hours and the median toxic concentration (TC50) and maximum non-toxic concentration (TC0) are calculated. The experiment is repeated 3 times.

Results from the three parallel tests conduct by cell morphology observations under the microscope reveals that MAP has a TC50 of >80 μg/mL and TC0 of ≤40 μg/mL. The results of direct assay show that the MAP solution has an influence on the activity of H1N1 and can protect 50% cells from pathological changes in the range of 38.54 μg/mL to 31.14 μg/mL.

Example 4

MAP Hydrogel for Vaginal HPV Infection Treatment

100 g of a MAP hydrogel is prepared consisting of MAP (0.1 g; USUN Bio Co., Ltd.), methyl cellulose (2.5 g), propanediol (11 g), glycerol (11 g), acetic acid (pH regulator) 0 to 0.5 g (all (Sinopharm Chemical Reagent Co. Ltd.), made up with water for injection.

Subjects with HPV infection but without cytopathic changes are enrolled. MAP hydrogel is used once a day for 30 days. The hands and the perineum are cleaned before use. The gel is placed in the tank of an Ollery Medical Compress Atomizer (Guangzhou Demi Medical Equipment Co. Ltd., China) and a spray nozzle is connected to the catheter of the atomizer.

Then the catheter is inserted deep into the vagina and the atomizer employed until all of the gel is atomized.

During this period, 4 follow-up visits are required at 0, 2, 3 and 4 weeks of the treatment. At each follow-up visit, the vagina and cervix are cleaned with a normal saline cotton ball, and cervical mucus and vaginal secretions are cleaned

with dry cotton balls. Dry cotton balls are also used to smear an appropriate amount of the hydrogel on the surface of cervix and cervical canal.

After 30 days of trial, vaginal endoscopy, leucorrhea examination and cervical smear examination are performed to evaluate HPV inhibition.

Claims

1. A mussel adhesive protein or a derivative thereof for use in the treatment of a viral infection.

2. A mussel adhesive protein or a derivative thereof for use as an antiviral agent.

3. The use of a mussel adhesive protein or a derivative thereof for the manufacture of a medicament for the treatment of a viral infection.

4. The use of a mussel adhesive protein or a derivative thereof for the manufacture of an antiviral medicament.

5. A method of treatment of a viral infection in a host, with method comprises administration of at least one mussel adhesive protein or a derivative thereof to that host.

6. A compound for use as defined in Claim 1, a use as defined in Claim 3, or a method as defined in Claim 5, wherein the treatment comprises prevention of the onset of a viral infection or disease, the protection of cells in a host from viral infection, the prevention of the spread of a viral infection (intra-host or inter-host), and/or the prevention of reactivation of a virus after latency in a host.

7. A compound for use as defined in any one of Claims 1, 2 or 6, a use as defined in any one of Claims 3, 4 or 6, or a method as defined in any one of Claims 5 or 6, wherein the at least one mussel adhesive protein is selected from the group: mefp-1 mefp-2, mefp-3, mefp-4, mefp-5, mefp-6 and combinations thereof.

8. A compound for use, use or method as defined in Claim 7 wherein the at least one mussel adhesive protein comprises mefp-1.

9. A compound for use as defined in any one of Claims 1, 2 or 6, a use as defined in any one of Claims 3, 4 or 6, or a method as defined in any one of Claims 5 or 6, comprising a derivative of a mussel adhesive protein, which is a

peptide of the sequence Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-DOPA-Lys or a salt thereof.

10. A compound for use as defined in any one of Claims 1, 2 or 6, a use as defined in any one of Claims 3, 4 or 6, or a method as defined in any one of Claims 5 or 6, comprising a derivative of a mussel adhesive protein, which is a peptide of the sequence Ala-Lys-Pro-Ser-Tyr-Hyp-Hyp-Thr-Tyr-Lys or a salt thereof.

11. A compound for use, use or method as defined in any one of Claims 1 to 10 wherein the virus is selected from herpes simplex, type 1 virus, herpes simplex, type 2 virus, human papillomavirus, an influenza virus and a parainfluenza virus.

12. A compound for use, use or method as defined in any one of Claims 1 to 11 wherein the compound is administered topically to the skin.

13. A compound for use, use or method as defined in any one of Claims 1 to 11 wherein the compound is administered topically to a mucosal surface.

14. A compound for use, use or method as defined Claim 13 wherein the mucosal surface is in the lung, or is the nasal or the vaginal mucosa.

15. A compound for use, use or method as defined in Claim 14 wherein the topical administration is by way of a powder aerosol spray comprising the active ingredient.

16. A compound for use, use or method as defined in Claim 14 wherein the topical administration is by way of an aqueous mist comprising the active ingredient.

17. A compound for use, use or method as defined in Claim 16 wherein the aqueous mist is formed by way of a nebulizer or the like.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2018/095367

A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/17(2006.01)i; A61K 38/08(2006.01)i; A61K 35/618(2015.01)i; A61P 31/20(2006.01)i; A61P 31/22(2006.01)i; A61P 31/16(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K38; A61K35; A61P31

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

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

DWPI,SIPOABS,CNABS, CNKI, PubMed, ISI web of Knowledge: mussel adhesive protein, mytilus edulis foot protein,MAP, mefp,viral infection,herpes,influenza virus,AKPSYPPTYK,DOPA, JIANGYIN BENGT I.SAMUELSSON INSTITUTE OF LIFE SCIENCE,GU Ming,MENG Nan,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017011982 A1 (BENGT I. SAMUELSSON INST. OF LIFE SCIENCE RES.) 26 January 2017 (2017-01-26) claims 1-2, 4, 6, description, page 4, lines 27-29, examples 7-8	1-8, 11-17
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☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 September 2018	**19 September 2018**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**MAO,Ying**
Facsimile No. **(86-10)62019451**	Telephone No. **86-(10)-53961979**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2018/095367

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2018/095367

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

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

1. ☑ Claims Nos.: **5-17**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 5 relates to a method of treatment of viral infection in a host. Therefore claim 5 and dependent claims 6-17 do not warrant an international search according to the criteria set out in PCT Rule 39.1(iv). An international search is still carried out on the basis of the mussel adhesive protein or its derivative in the manufacture of a medicament for treating a viral infection in a host.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2018/095367

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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