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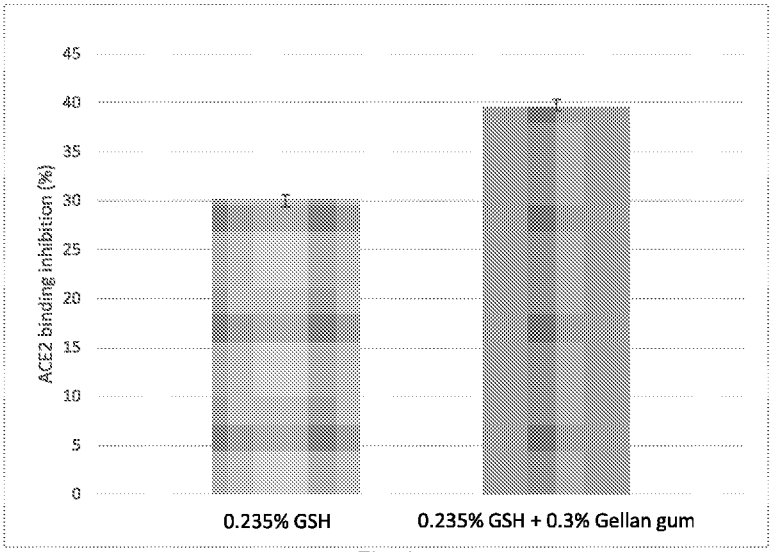

Fig. 1

(57) Abstract: A composition capable of prevention and therapy for respiratory viral diseases, especially for COVID-19 are provided. The composition for antiviral or oxidation preconditioning, comprising: at least one of L-Glutathione (GSH) and N-acetylcysteine, and gellan gum, wherein the composition is combined with a carrier for nose administration to a patient as spray in concentrations for antiviral or oxidation preconditioning effectively. The composition of this application could be combined with a suitable carrier to form a spray for nose administration to a patient, improving the therapy effect for respiratory viral diseases, especially for COVID-19.

WO 2024/104313 A1

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COMPOSITION FOR ANTIVIRAL OR OXIDATION PRETREATMENT, PREPARATION METHOD AND USAGE METHOD THEREOF

TECHNICAL FIELD

[0001] The present disclosure relates to the technical field of medicinal compositions, and particularly relates to compositions for antiviral or oxidation pretreatment, especially for prevention and therapy for COVID-19, preparation method and usage method thereof.

BACKGROUND

[0002] Viruses are incapable of free-living existence, even though they could infect cells and cause various diseases by invading cells and redirecting the synthetic machinery of mammalian cells toward the production of more virus particles. Viruses can enter cells via different mechanisms.

[0003] For respiratory viral diseases, viruses enter body usually via the epithelial cells of the respiratory tract. Usually, viruses enter the body through epithelial cells in the upper respiratory tract, for instance via nasal mucosa. This is especially the case if viruses are delivered by accident via hands to nasal mucosa.

[0004] When the virus reaches the surface of respiratory epithelium, it may enter the cell in order to propagate the disease.

[0005] First, the virus needs a specific cellular receptor on the cell membrane. Several specific receptors for different viruses are known. However, usually each virus has only one specific type of receptor on the target cell membrane. The receptors could be proteins, carbohydrate moieties or even membrane lipids. For influenza A, the virus specific receptor is alpha-2, 6-sialic acid. For SARS-Cov and SARS-Cov-2, the specific receptor is the ACE2 protein.

[0006] SARS-Cov-2 virus that induces human Covid-19 (Corona Virus Disease 2019) disease could either perform a so-called early entry or late entry into cellular cytoplasm. Coronaviruses are a family of viruses that could cause

illnesses such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

[0007] COVID-19 disorder is characterized by shortness of breath, increased mucus production, sore throat, cough, and fever. This may necessitate admission to a hospital, with subsequent admission to an intensive care unit for the respiratory support of the infected patient.

[0008] It is known that L-Glutathione (GSH) is a potent antioxidant. There are publications describing the oral/IV usage of GSH, such as US20180193404A1 in high dose oral form and focusing on the neutralizing power of GSH on ROS.

[0009] However, there is still a need for more forms of the drugs to prevent or reduce in spread of COVID-19, due to the worldwide pandemic of this infection.

SUMMARY

[0010] The first object of this invention is to provide a composition for antiviral or oxidation preconditioning, comprising: at least one of L-Glutathione and N-acetylcysteine, and gellan gum, wherein the composition is combined with a carrier for nose administration to a patient as spray in concentrations for antiviral or oxidation preconditioning effectively.

[0011] Optionally, the ratio of said at least one of L-Glutathione and N-acetylcysteine to gellan gum in mass is from 0.25 to 9, preferably from 0.25 to 1, further preferably from 0.3 to 0.8.

[0012] Optionally, the composition further comprises at least one member selected from the group consisting of a source of selenium, ascorbic acid or a derivative of ascorbic acid, preservative.

[0013] Optionally, the source of selenium comprises a member selected from the group consisting of elemental selenium, selenomethionine and selenocysteine.

[0014] Optionally, said gellan gum comprises low acyl gellan gum and

high acyl gellan gum with a mass ratio between 0.5:1 and 3:1, preferably between 1:1 and 2:1.

Preferably, said gellan gum is low acyl gellan gum.

[0015] Optionally, said at least one of L-Glutathione and N-acetylcysteine is present in an amount between 0.01% and 1%, preferably between 0.3% and 0.7% in mass based upon the mass of a combination of the composition and the carrier.

[0016] Optionally, said gellan gum is present in an amount between 0.05% and 1.5%, preferably between 0.15% and 1.5%, more preferably between 0. 5% and 1.2%, further preferably between 0.7% and 1% in mass based upon the mass of a combination of the composition and the carrier.

Preferably, said gellan gum is low acyl gellan gum.

[0017] Optionally, said source of selenium is present in an amount between 0.00001% and 0.002%, preferably between 0.000016% and 0.0016%, further preferably between 0.0001% and 0.0002% in mass based upon the mass of a combination of the composition and the carrier.

[0018] Optionally, said ascorbic acid or a derivative of ascorbic acid is present in an amount between 0.005% and 0.1%, preferably 0.01% in mass based upon the mass of a combination of the composition and the carrier.

[0019] Optionally, the preservative is selected form the group consisting of cetylpyridinium chloride, phenyl ethyl alcohol, benzoyl alcohol, polylysine and potassium sorbate.

[0020] Preferably, the preservative is present in an amount between 0.0005% and 1.5%, preferably between 0.01% and 1.5%, more preferably between 0.05% and 0.25% in mass based upon the mass of a combination of the composition and the carrier.

Preferably, the preservative is selected from the group consisting of polylysine and potassium sorbate.

Preferably, polylysine is present in an amount between 0.025% and 0.1%, more preferably between 0.03% and 0.07% in mass based upon the

mass of a combination of the composition and the carrier.

Preferably, potassium sorbate is present in an amount between 0.01% and 1%, more preferably between 0.05% and 0.2% in mass based upon the mass of a combination of the composition and the carrier.

Optionally, the composition further comprises hydroxyethylcellulose.

Preferably, hydroxyethylcellulose is present in an amount between 0.005% and 0.05%, preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier.

Optionally, the composition further comprises propanediol.

Preferably, propanediol is present in an amount between 2% and 10%, more preferably between 4% and 7% in mass based upon the mass of a combination of the composition and the carrier.

Optionally, the composition further comprises menthol and/or peppermint essential.

Preferably, menthol is present in an amount between 0.005% and 0.05%, more preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier.

Preferably, peppermint essential is present in an amount between 0.005% and 0.05%, more preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier.

[0021] Optionally, the carrier is water, preferably is distilled water.

[0022] Preferably, the pH of the spray is 5-6, preferably 5.

[0023] The second object of this invention is to provide a method for preparing the spray described the above, comprising steps of:

(1) mixing gellan gum with water and heating the mixture to 70-90°C;

(2) cooling the mixture to 40-60°C and adding glutathione for crosslinking for at least 2 minutes;

(3) adding the other ingredients except preservative and cooling the mixture to 20-30°C;

(4) adjusting the pH of the mixture to 5-6, and then adding the

preservative.

[0024] The third object of this invention is to provide a method for antiviral or oxidation preconditioning, especially for prevention and therapy for COVID-19 comprising nose administration to a patient with the spray which combines the composition according to the above and the carrier.

[0025] Optionally, the spray is introduced to the nasal cavity of a patient by use of a stream inhaler, nebulizer or vaporizer.

[0026] Optionally, the spray is applied for four times a day and once in each nostril, and each pump is giving 90-110 mg by weight.

BRIEF DESCRIPTION OF DRAWINGS

[0027] Fig. 1 is a bar chart showing cellular receptor (ACE2) binding inhibition of a spray comprising only L-Glutathione GSH in comparing with a spray comprising GSH and gellan gum.

[0028] Fig. 2 is a bar chart showing intracellular antioxidant GSH level in primary human nasal epithelial cells at 48 hours after being exposed to treatment with a spray comprising only gellan gum comparing with a spray comprising GSH and gellan gum.

[0029] Fig. 3 is a bar chart showing GSH level in the basal compartment of primary human nasal epithelial cellular models at 48 hours after being exposed to treatment with a spray comprising only gellan gum in comparing with a spray comprising GSH and gellan gum.

[0030] Fig. 4A is a line chart showing the percentage reduction of crosslinked GSH contents at different vitamin C solutions versus time with the spray having a pH of 5.0.

[0031] Fig. 4B is a line chart showing the percentage reduction of crosslinked GSH contents at different vitamin C solutions versus time with the spray having a pH of 6.0.

[0032] Fig. 5 is a bar chart showing the ACE2 binding inhibition at different concentrations of GSH in the spray.

[0033] Fig. 6 is a bar chart showing the binding inhibition percentages with different gellan gum concentrations crosslinked with 0.0156% GSH.

[0034] Fig. 7 showed the result of spray area test with various low acyl:high acyl (LA:HA) ratios.

Fig. 8 showed a picture showing the fragmentation of the resulting formulation when high acyl gemman gum was used with the preservatives.

DETAILED DESCRIPTION

[0035] The present invention will now be described in detail in conjunction with accompanying drawings and exemplary embodiments.

[0036] In some embodiments of this invention, a composition for antiviral or oxidation preconditioning is provided, which comprises: at least one of L-Glutathione and N-acetylcysteine, and gellan gum, wherein the composition is combined with a carrier for nose administration to a patient as spray in concentrations for antiviral or oxidation preconditioning effectively.

[0037] Oxidation preconditioning refers to an approach to boost the capacity of cells to resist oxidative stress.

[0038] L-Glutathione GSH is a potent intracellular antioxidant. A common denominator in all conditions associated with COVID-19 appears to be the impaired redox homeostasis responsible for reactive oxygen species (ROS) accumulation. Therefore, levels of GSH, the key antioxidant guardian in all tissues, may extinguish the exacerbated inflammation in COVID-19. Clinical trials on oral GSH are underway to alleviate the symptoms of COVID-19.

[0039] GSH could cause the mutation at the spike protein of SARS-CoV-2 and impaired their function. Further, GSH could physically block the interaction of the cellular receptor (ACE2) and SARS-CoV-2 surrogate virus and this invention has escalated the blocking by crosslinking with gellan gum. Based on the above, this invention provides a nasal spray with GSH as the major ingredients, aiming to perturb binding of SARS-CoV-2 virus to the

respiratory tract epithelium, whereas ACE2 is ubiquitous and the primary entry point of the virus. Since N-acetylcysteine NAC and GSH both contain sulphur group in their chemical structure, it is assumed that the crosslinking works on either NAC or GSH.

[0040] So far, only the oral or IV administration of GSH are known, such as that described in US20180193404A1, but nasal administration of GSH and/or NAC for example using nasal spray is not known. High dose of GSH is used in oral administration, without any co-factor, also not in crosslinked GSH form and likely directly diffusing into the cells. All of the known publications focused on the neutralizing power of GSH on reactive oxygen species (ROS), but none describing the physical interaction of GSH with virus cellular receptors.

[0041] The compositions of this invention could be combined with a suitable carrier to form a spray for nose administration to a patient. Under normal circumstances, external supplies of GSH would be transported into the cells shortly after it reaches the cell surface. To lengthen the time that the supplied GSH staying on the cell surface, gellan gum is added to the compositions of this invention. It was surprisingly found that gellan gum crosslinks with GSH and thickens the solution of the spray. Though the spray is gel-like, upon physical pressure, after passing through the nozzle, it becomes watery and sprayable. The hydrogel property also enables the solution to form a thin layer of gel once it reaches the respiratory tract and without dripping off the nose, thereby improving the therapy effect for respiratory viral diseases, especially for COVID-19.

[0042] In some preferred embodiments, the ratio of the at least one of L-Glutathione and NAC to gellan gum in mass is from 0.25 to 9, such as from 0.4 to 7.5, from 0.8-6.5, from 1.5-8, from 2 to 8, from 3 to 6, from 2.5 to 7.5, from 4 to 6, 1.5,3.5, 5, 6.5, 8 and so on. The above range of the ratio of the at least one of L-Glutathione and NAC to gellan gum in mass could achieve an effective anti-viral or oxidative preconditioning effect.

[0043] In order to achieve a better anti-viral or oxidative preconditioning effect, the ratio of the at least one of L-Glutathione and NAC to gellan gum in

mass is preferably from 0.25 to 1, further preferably from 0.3 to 0.8.

[0044] In some preferred embodiments, the compositions of this invention further comprise at least one member selected from the group consisting of a source of selenium, ascorbic acid or a derivative of ascorbic acid, preservative.

[0045] Selenium is a co-factor for GSH peroxidase, the enzyme that catalyzes the neutralization of ROS. Therefore, selenium in the compositions of this invention could facilitate the neutralization of ROS. Selenium is also an intracellular enzyme catalyzes oxidation of GSH, when converting free radical H_2O_2 to H_2O. The formulation contains selenium to enhance the efficiency in degrading free radical H_2O_2 after GSH enters the nasal epithelial cells. Ascorbic acid or a derivative thereof contained in the composition could stabilize the crosslinked GSH.

[0046] In some preferred embodiments, the source of selenium comprises a member selected from the group consisting of elemental selenium, selenomethionine and selenocysteine. L-selenomethionine is most preferred, which is a selenium analogue of the amino acid methionine, the most bioavailable form of selenium.

[0047] In some preferred embodiments, the gellan gum comprises low acyl gellan gum and high acyl gellan gum with a mass ratio between 0.5:1 and 3:1, preferably between 1:1 and 2:1. Low acyl gellan gum produces firm, non-elastic, brittle gel while high acyl gellan gum produce soft, elastic and non-brittle gel. The ratio was obtained under concerted considerations of nasal spray bottle compatibility (e.g. clogging the nozzle), spray area and spray evenness. The range of the above for the spray could produce the largest spray area.

[0048] Gellan gum is a microbial exopolysaccharide synthesized by Sphingomonas elodea (ATCC 31461). The repeating unit (RU) of the gellan gum polymer is a tetrasaccharide composed of two residues of D-glucose and one of each residues of L-rhamnose and D-glucuronic acid with the following

structure [→3)β-d-Glcp(1→4)-β-d-GlcAp(1→4)β-d-Glcp(1→4)-α-l-Rhap(1→]. The native polysaccharide is partially esterified; the 1,3-D-Glc residue can be linked to L-glycerate at C-2 and/or to acetate at C-6.

[0049] Gellan gum is an effective gelling and structuring agent. Gellan gum products are produced commercially in two forms; a high acyl (HA) form resembling the native form expressed by Sphingomonas elodea, with an average of 1 glycerate and 0.5 acetate substitutions per repeating unit; and a low acyl (LA) form in which the acyl substituents are completely removed by alkali treatment.

[0050] The acyl groups of gellan gum have profound influence on gel characteristics. HA gellan gum produces soft, elastic, non-brittle gels, whereas LA gellan gum produces firm, non-elastic, brittle gels.

While high acyl gellan gum would still provide the therapy effect for respiratory viral diseases, it is found that the high acyl gellan gum reacts with the preservatives, hardening the hydrogel and forming gel-fragments, which clots the spray bottle undesirably. A picture recording the fragmentation of the resulting formulation when high acyl gellan gum was used with the preservatives is shown in Fig. 8. It can be seen that the formation of fragments in resulting formulation was uneven and observable even with bare eyes. Therefore, preferably, said gellan gum is low acyl gellan gum.

[0051] In some preferred embodiments, the at least one of L-Glutathione and N-acetylcysteine is present in an amount between 0.01% and 1%, such as between 0. 2% and 0.9%, between 0.3% and 0.7%, between 0.1% and 0.6%, 0.05%, 0.15%, 0.4%, 0.55%, 0.75% and so on. The above amount range of the at least one of L-Glutathione and N-acetylcysteine in the composition could achieve effective antioxidant effect.

[0052] In order to achieve a better effective antioxidant effect, the at least one of L-Glutathione and N-acetylcysteine is present in an amount preferably between 0.3% and 0.7% in mass based upon the mass of a combination of the composition and the carrier.

[0053] In some preferred embodiments, the gellan gum is present in an amount between 0.05% and 1.5% (such as 0.1%-1.4%, 0.25%-1.25%, 0.2%-1%, 0.3%-0.0.9%, 0.4-0.8%, 0.2%,0.35%, 0.45%, 0.6%, 0.75%, 0.9%, 1.1%, 1.35% and so on), preferbaly between 0.15% and 1.5% in mass based upon the mass of a combination of the composition and the carrier. The above amount range of gellan gum in the composition can achieve effective crosslink with GSH. When high acyl gellan gum is not used due to undesirable properties described above, the concentration of low acyl gellan gum could be adjusted to maintain the crosslinking of L-Glutathione and gellan gum.

[0054] In order to achieve a better crosslink effect with GSH, the gellan gum is present in an amount preferably between 0.5% and 1.2%, further preferably between 0.7% and 1% in mass based upon the mass of a combination of the composition and the carrier and said gellan gum is preferably low acyl gellan gum.

[0055] In some preferred embodiments, the source of selenium is present in an amount between 0.00001% and 0.002% (such as between 0.00003% and 0.001%, between 0.0002% and 0.0009%, between 0.00009% and 0.0015%, 0.00008%, 0.0003%, 0.0009%,0.0012% and so on) in mass based upon the mass of a combination of the composition and the carrier. The above amount range of the source of selenium can effectively facilitate the neutralization of ROS.

[0056] In order to better facilitate the neutralization of ROS, the source of selenium is present in an amount preferably between 0.000016% and 0.0016%, further preferably between 0.0001% and 0.0002% in mass based upon the mass of a combination of the composition and the carrier.

[0057] In some preferred embodiments, the ascorbic acid or a derivative of ascorbic acid is present in an amount between 0.005% and 0.1% (such as between 0.01% and 0.08%, between 0.02% and 0.07%, between 0.04% and 0.09%, 0.009%, 0.025%, 0.05%, 0.075%, 0.095% and so on) in mass based upon the mass of a combination of the composition and the carrier. The

ascorbic acid is also referred to vitamin C. The above amount range of the ascorbic acid or a derivative thereof can stabilize the crosslinked GSH.

[0058] In order to better stabilize the crosslinked GSH, the ascorbic acid or a derivative of ascorbic acid is present in an amount preferably 0.01% in mass based upon the mass of a combination of the composition and the carrier.

[0059] In some preferred embodiments, the preservative is selected from the group consisting of cetylpyridinium chloride, phenyl ethyl alcohol, benzoyl alcohol, polylysine and potassium sorbate. For example, the preservative is cetylpyridinium chloride.

[0060] The preservative is present in an amount between 0.0005% and 1.5% (such as between 0.0008% and 1.4%, between 0.001 and 1.2%, 0.002% and 0.8%, between 0.04% and 0.7%, between 0.01% and 1.35%, 1%, 0.8%, 0.008%, 0.055%, 0.08%, 0.15%, 0.3%, 0.4%, and so on), preferably between 0.01% and 1.5%, more preferably between 0.05% and 0.25% in mass based upon the mass of a combination of the composition and the carrier.

In some preferred embodiments, the preservative is selected from the group consisting of polylysine and potassium sorbate. The preservatives system using cetylpyridinium chloride was not robust enough which failed the long term microbial test because cetylpyridinium chloride reacts with gellan gum and hardens the formulation with increasing concentration. Thus, this invention strengthens the preservatives by adding polylysine and/or potassium sorbate. Polylysine and potassium sorbate were chosen because they are a relatively safe and common preservative in nasal product.

In some preferred embodiments, in order to provide effective antibacterial effects, polylysine is present in an amount between 0.025% and 0.1% (such as between 0.03% and 0.1%, between 0.04% and 0.09%, between 0.04% and 0.07%, 0.025%, 0.05%, 0.065% and so on) in mass based upon the mass of a combination of the composition and the carrier.

In order to achieve better antibacterial effect, polylysine is present in an

amount between 0.03% and 0.07% in mass based upon the mass of a combination of the composition and the carrier.

In some preferred embodiments, in order to provide effective antibacterial effects, potassium sorbate is present in an amount between 0.01% and 1% (such as between 0.01% and 0.09%, between 0.02% and 0.08%, between 0.03% and 0.06%, 0.025%, 0.035%, 0.05%, 0.07% and so on) in mass based upon the mass of a combination of the composition and the carrier.

In order to achieve better antibacterial effect, potassium sorbate is present in an amount between 0.05% and 0.2% in mass based upon the mass of a combination of the composition and the carrier.

The combination use of polylysine and potassium sorbate with the above amount is shown to provide good antibacterial performance, which will be proved in the following experiments of antibacterial performance.

In some preferred embodiments, the composition further comprises hydroxyethylcellulose. Hydroxyethylcellulose was added to stabilize the hydrogel system. It acts as a stabilizer, maintaining the texture of the formulation.

In some preferred embodiments, in order to effectively stabilize the hydrogel system, hydroxyethylcellulose is present in an amount between 0.005% and 0.05% (such as between 0.005% and 0.04%, between 0.008% and 0.03%, between 0.015% and 0.35%, 0.0075%, 0.009%, 0.015%, 0.02%, 0.035% and so on) in mass based upon the mass of a combination of the composition and the carrier. When hydroxyethylcellulose is present in an amount between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier, it is found that the stabilizing effect is better.

In some preferred embodiments, the composition further comprises propanediol, which forms part of the preservative system and also may be used as a solvent for the optional menthol.

In some preferred embodiments, propanediol is present in an amount between 2% and 10% (such as between 2% and 9%, between 3% and 8%, between 5% and 7%, 2.5%, 4.5%, 6%, 7.5%, 8% and so on), more preferably between 4% and 7% in mass based upon the mass of a combination of the composition and the carrier.

In some preferred embodiments, the composition further comprises menthol and/or peppermint essential. As L-glutathione has a smell of 'sulphur', menthol and peppermint are added to dilute the smell and make the composition smell more pleasant.

In some preferred embodiments, menthol is present in an amount between 0.005% and 0.05% (such as between 0.005% and 0.04%, between 0.008% and 0.03%, between 0.015% and 0.35%, 0.0075%, 0.009%, 0.015%, 0.02%, 0.035% and so on), more preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier;

In some preferred embodiments, peppermint essential is present in an amount between 0.005% and 0.05% (such as between 0.005% and 0.04%, between 0.008% and 0.03%, between 0.015% and 0.35%, 0.0075%, 0.009%, 0.015%, 0.02%, 0.035% and so on), more preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier.

[0061] In some preferred embodiments, the carrier is water, preferably is distilled water.

[0062] To avoid irritation and prevent pathogenic bacteria growth, the pH of the spray is preferably 5-6, such as 5.15, 5.3, 5.45, 5.6, 5.75, 5.83, 5.95 and so on, most preferably 5. When the pH of the spray is 5, the ascorbic acid could retain the most GSH at the same time could avoid irritation and prevent pathogenic bacteria growth. The pH of the spray may be adjusted by for example adding NaOH, preferably in an amount between 0.002% and 0.028%, more preferably between 0.004% and 0.005% in mass based upon the mass

of a combination of the composition and the carrier.

[0063] According to another aspect of this invention, there is provided a method for preparing the spray comprising the composition and the carrier of this invention, comprising steps of:

(1) mixing gellan gum with water and heating the mixture to 70-90°C;

(2) cooling the mixture to 40-60°C and adding glutathione for crosslinking for at least 2 minutes;

(3) adding the other ingredients except preservative, including for example cetylpyridinium chloride, phenyl ethyl alcohol, benzoyl alcohol, polylysine and potassium sorbate, and cooling the mixture to 20-30°C.

(4) adjusting the pH of the mixture to 5-6, and then adding the preservative.

[0064] Preferably, the method comprises the following steps:

(1) mixing high acyl and low acyl gellan gum (or only low acyl gellan gum) with distilled water and heated up to 80°C;

(2) cooling the gel mixture down to 50°C, and adding GSH and crosslinking for several minutes for example 5 minutes;

(3) adding L-selenomethionine, L-ascorbic acid at an interval of 5 minutes;

(4) cooling the mixture to 25°C;

(5) adjusting the pH to 5 using NaOH;

(6) adding preservative e.g. propanediol or/and cetylpyridinium chloride or/and polylysine or/and potassium sorbate.

[0065] According to yet another aspect of this invention, there is provided a method for antiviral or oxidation preconditioning, especially for prevention and therapy for COVID-19 comprising nose administration to a patient with the spray which combines the composition and the carrier of this invention.

[0066] In some embodiments, the spray is introduced to the nasal cavity

of a patient by use of a stream inhaler, nebulizer or vaporizer.

[0067] In some embodiments, the spray is applied for four times a day and once in each nostril, and each pump is giving 90-110 mg by weight.

EXAMPLES

[0068] The amounts of the gradients below are referred to mass percentage.

Example 1

[0069]A nose spray comprises 0.235% of L-Glutathione, 0.3% of gellan gum. The mass ratio of low acyl gellan gum and high acyl gellan gum is 3:2.

Comparative example 1

[0070] A nose spray comprises only 0.235% of L-Glutathione.

Comparative example 2

[0071] A nose spray comprises only 0.3% of gellan gum.

[0072] The nose spray is prepared according to the method described in this invention and used distilled water as a carrier.

Physical protection against virus

[0073] Fig. 1 is a bar chart showing cellular receptor (ACE2) binding inhibition of a spray comprising only GSH comparing with a spray comprising GSH and gellan gum. The specific composition of the spray comprising only GSH is indicated as comparative example 1, and that of the spray comprising GSH and gellan gum is indicated as example 1.

[0074]The bar chart of Fig. 1 shows that crosslinked GSH with gellan gum was more effective in blocking the binding of SARS-CoV-2 spike protein to its cellular receptor than pure GSH. The binding inhibition experiment used a commercially available kit, Genscript® SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (Cat: L00847-RUO).

Oxidative preconditioning along respiratory tract

[0075] Fig. 2 is a bar chart showing intracellular antioxidant GSH level in primary human nasal epithelial cells at 48 hours after exposed to treatment with

a spray comprising only gellan gum comparing with a spray comprising GSH and gellan gum. The specific composition of the spray comprising only gellan gum is indicated as comparative example 2, and that of the spray comprising GSH and gellan gum is indicated as example 1.

[0076] The cells were pretreated with a spray comprising gellan gum without GSH in comparative example 2 and a spray comprising GSH and gellan gum in example 1 for 1 hour before exposing to mock or influenza virus. The mock refers to the same vector that carried the influenza but without any active virus. The result indicated that the spray comprising GSH and gellan gum in example 1 could significantly increase the intracellular GSH level.

[0077] The nasal spray of example 1 supplied additional potent antioxidant to the respiratory cells. The primary human nasal epithelial cells were pretreated with the nasal spray of example 1 and empty spray of the above comparative example 2 (comprising only 0.3% gellan gum). on apical side for 1 hour prior virus infection. Intracellular antioxidant GSH level 48 hour post infection was measured with LCMS/MS. The spray of example 1 increased intracellular GSH. The increment was even more significant upon virus infection ($p = 0.04$). This showed that the spray of example 1 could infiltrate into the cell and raise the bar neutralizing the oxidative stress when combating or before viral infection.

Oxidative preconditioning in local circulation

[0078] Fig. 3 is a bar chart showing GSH level in the basal compartment of primary human nasal epithelial cellular models at 48 hours after exposed to treatment with a spray comprising only gellan gum comparing with a spray comprising GSH and gellan gum. The specific composition of the spray comprising only gellan gum is indicated as comparative example 2, and that of the spray comprising GSH and gellan gum is indicated as example 1.

[0079] The cells were pretreated with the spray comprising gellan gum without GSH (i.e. the spray of comparative example 2) and the spray of example 1 for 1 hour before exposing to mock or influenza virus. The the

spray of example 1 could significantly increase the GSH level in the basal medium. By contrast, the GSH level was below detection when treated with gellan gum only.

[0080] When primary human nasal epithelial cells pretreated with the nasal spray of example 1 and empty spray of comparative example 2 on apical side for 1 hour prior virus infection. The GSH increment also was found in the basal compartment at 48 hour post infection. Effect of the nasal spray of example 1 could penetrate through the cell. It means application of spray not only increasing the intracellular GSH level, the GSH travels further to the basal side and out of the cells in the medium. This could imply that the active ingredient in nasal spray of this invention could enter the local circulation.

Stability of GSH

[0081] GSH is a potent antioxidant and prone to be oxidized in air. The percentage range of vitamin C in the spray to stabilize the crosslinked GSH has been found through experiments conducted in this invention.

[0082] Fig. 4A is a line chart showing the percentage reduction of crosslinked GSH contents at different vitamin C solutions versus time with the spray having a pH of 5.0. The sprays used in the test of figure 4A further comprise different amount of vitamin C in addition to those contained in the above example 1 and the spray has a pH of 5.0. The sprays were kept at room temperature. The amount of GSH was measured at periodically and compared to the amount at day 0.

[0083] It can be seen from Fig. 4A that the crosslinked GSH contents reduced slowly when the percentage range of vitamin C is from 0.01% to 0.1%, and the crosslinked GSH contents reduced the least when the percentage of vitamin C is 0.01%.

[0084] Therefore, the range of vitamin C in the spray was determined to be 0.01% to 0.1%, preferably 0.01% in mass based upon the mass of a combination of the composition and the carrier.

[0085]Further, Fig. 4B is a line chart showing the reduction of

crosslinked GSH contents at different vitamin C solutions versus time with the spray having a pH of 6.0. The sprays used in the test of figure 4B further comprise different amount of vitamin C in addition to those contained in the above example 1 and the spray has a pH of 6.0. The sprays were kept at room temperature. The amount of glutathione was measured at periodically and compared to the amount at day 0.

[0086]It can be seen from Fig. 4B that the crosslinked GSH contents reduced more when the spray has a pH of 6.0 compared with that the spray has a pH of 5.0.

[0087]The crosslinked GSH could be preserved at the pH of the spray of 5-6, best preserved at pH 5 together with vitamin C.

ACE2 inhibition percentages of different concentrations of Glutathione

[0088] Fig. 5 is a bar chart showing the ACE2 binding inhibition at different concentrations of GSH in the spray. The concentrations of GSH in the sprays are respectively 0.00156%, 0.0156%, 0.0312%, 0.2184%, 0.4875%, 0.975%.

[0089] The sprays used in Fig. 5 have different concentrations of GSH, but have the same concentrations for gellan gum (LA:HA= 3:2) of 0.3%.

[0090] Inhibition percentage below 30% was regarded as failure suggested by the manufacturer of the commercial kit.

[0091] It can be seen from Fig. 5 that ACE2 inhibition was success when the concentrations of GSH in the sprays are 0.0156%, 0.0312%, 0.2184%, 0.4875%, 0.975%.

[0092] Therefore, the effective amount of GSH in the spray was determined to be 0.01% to 1% according to our experiments, preferably 0.47%.

ACE2 inhibition percentages with different gellan gum

[0093]Fig. 6 is a bar chart showing the binding inhibition percentages with different gellan gum concentrations crosslinked with 0.0156% GSH.

[0094]It can be seen from Fig. 6 that

- addition of gellan gum increased ACE2 binding inhibition,
- the effective crosslinking amounts of gellan gum with GSH lies between 0.0.09% to 0.625% gellan gum,
- 0.588% has the highest ACE2 inhibition percentage.

[0095] Fig. 7 showed the result of spray area test with various LA:HA ratios.

Test method

[0096] 0.235% GSH, 0.01% ascorbic acid, 0.00016% selenium with various LA:HA ratios but a final weight of 0.588% gellan gum formula were filled into nasal spray bottles. Gel mixture was sprayed onto a 45° incline surface mimicking in incline of nasal cavity. Bottles were positioned at 3.5cm and 6.5cm from top of spray nozzle to spray surface. The spray area was photographed under three different conditions: right after spraying (T=0), dried on 0°C surface (T=17H) and dried on 45°C surface (T=17H). The area of spray was measured and calculated.

Result

[0097]Spray area of gel formulae at three different low acyl: high acyl gellan gum ratios composing final weight of 0.588%: sample 7 (LA: HA=9:1), sample 10 (LA:HA = 3:2), sample 12 (LA:HA = 1:1). All samples produced an ellipse pattern when sprayed onto a 45° incline surface. Spray surface areas of sample 7 are larger than samples 10 and 12 both at 3.5cm and 6.5cm distance. However, when sprayed at 6.5cm from the incline surface, sample 7 formed a hollow ellipse. Therefore, the spray area of sample 7 is presented with both the area of the outer ellipse and the inner hollow ellipse. At 3.5cm, surface area of sample 10 is slightly larger than sample 12, while at 6.5cm, surface areas of samples 10 and 12 are similar.

[0098]Based on spray evenness, by the data shown at Fig.7, ratio of LA:HA = 3:2 demonstrated the largest spray area and thus it is most desired LA:HA ratio.

Example 2

A nose spray comprises:

0.4605% of L-Glutathione,

0.3600% of low acyl gellan gum,

0.2400% of high acyl gellan gum,

0.0328% of L-selenomethionine (a natural food form of selenium, equivalent to selenium 0.5 wt%),

0.0100% of L (+)-Ascorbic acid,

0.0020% of cetylpyridinium chloride,

5.2647% of propanediol,

0.0200% of menthol, and

0.0225% of peppermint Essential Oil 0.902g/mL.

Example 3

A nose spray comprises:

0.4605% of L-Glutathione,

1.2000% of low acyl gellan gum,

0.0200% of natrosol™ 250 HHR hydroxyethylcellulose,

0.0328% of L-selenomethionine (a natural food form of selenium, equivalent to selenium 0.5 wt%),

0.0100% of L (+)-Ascorbic acid,

0.1000% of epolyly® ε-polylysine,

0.1000% of potassium sorbate,

0.0045% of NaOH,

5.2647% of propanediol,

0.0200% of menthol, and

0.0226% of peppermint Essential Oil 0.902g/mL.

Example 4

A nose spray comprises:

0.4605% of L-Glutathione,

0.9000% of low acyl gellan gum,

0.0200% of natrosol™ 250 HHR hydroxyethylcellulose,

0.0328% of L-selenomethionine (a natural food form of selenium, equivalent to selenium 0.5 wt%),

0.0100% of L (+)-Ascorbic acid,

0.0500% of epolyly® ε-polylysine,

0.1000% of potassium sorbate,

0.0045% of NaOH,

5.2647% of propanediol,

0.0200% of menthol, and

0.0226% of peppermint Essential Oil 0.902g/mL.

The above Examples 2-4 were subjected to viscosity test and microbial test.

The viscosity was measured by rotary viscometer.

For microbial test, bottled nasal sprays were sent to SGS for microbial test for Total Aerobic Microbial Count and Total Combined Yeast & Molds Count following guidelines from European Pharmacopoeia 10.0, Chapter 2.6.12 – Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests, and European Pharmacopoeia 10.0, Chapter 2.6.13 – Microbiological Examination of Nonsterile Products: Test for Specific Micro-organisms.

The test results are shown in the below tables.

Table 1

	Viscosity (cP)	Torque (%)
Example 2		
1	333.40	42.00
2	356.00	44.30
3	355.20	44.10
Average	348.20	43.47
CV%	3.68	2.93
Example 3		

1	344.00	68.80
2	341.00	68.20
3	344.00	68.90
Average	343.00	68.63
CV%	0.50	0.55
Difference (%) between Example 2 and Example*	-1.5	57.9
Example 4		
1	224.00	44.90
2	221.00	44.10
3	220.00	44.00
Average	221.67	44.33
CV%	0.94	1.11
Difference (%) between Example 2 and Example 4**	-36.3	2.0

* Calculation = (Average of Example 3 - Average of Example 2)/Average of Example 2*100%

** Calculation = (Average of Example 4 - Average of Example 2)/Average of Example 2*100%

Viscosity and Torque are the parameters measuring the texture of the spray. It can be seen from table 1 that at least one of the texture parameters only varied within 5% in Example 2 and Example 3, which indicated that the formations of Example 2 and Example 3 are stable and had long term antibacterial effect.

Table 2

	Total Aerobic Mecrobial Count	Total Combined Mould and Yeast Count	Excherichia Coli

Example 2	2.1×10^7	3.3×10^5	Not Detected
Example 3	$<1.0 \times 10^1$	$<1.0 \times 10^1$	Not Detected
Example 4	3.0×10^1	$<1.0 \times 10^1$	Not Detected

It can be seen from table 2 that the composition comprising epolyly® ε-polylysine and potassium sorbate could achieve excellent antibacterial performance, which could significantly prolong the preserved time of the nose spray.

[0099] It should be understood that the above embodiments are merely exemplary embodiments for the purpose of illustrating the principle of the disclosure, and the disclosure is not limited thereto. Various modifications and improvements can be made by a person having ordinary skill in the art without departing from the spirit and essence of the disclosure. Accordingly, all of the modifications and improvements also fall into the protection scope of the disclosure.

WHAT IS CLAIMED IS:

1. A composition for antiviral or oxidation preconditioning, comprising:

at least one of L-Glutathione and N-acetylcysteine, and

gellan gum,

wherein the composition is combined with a carrier for nose administration to a patient as spray in concentrations for antiviral or oxidation preconditioning effectively.

2. The composition of claim 1, wherein the ratio of said at least one of L-Glutathione and N-acetylcysteine to gellan gum in mass is from 0.25 to 9, preferably from 0.25 to 1, more preferably from 0.3 to 0.8.

3. The composition of claim 1, wherein the composition further comprises at least one member selected from the group consisting of a source of selenium, ascorbic acid or a derivative of ascorbic acid, preservative.

4. The composition of claim 3, wherein the source of selenium comprises a member selected from the group consisting of elemental selenium, selenomethionine and selenocysteine.

5. The composition of claim 1, wherein said gellan gum comprises low acyl gellan gum and high acyl gellan gum with a mass ratio between 0.5:1 and 3:1, preferably between 1:1 and 2:1,

preferably, said gellan gum is low acyl gellan gum.

6. The composition of any one of claims 1 to 5, wherein said at least one of L-Glutathione and N-acetylcysteine is present in an amount between 0.01% and 1%, preferably between 0.3% and 0.7% in mass based upon the mass of

a combination of the composition and the carrier.

7. The composition of any one of claims 1 to 5, wherein said gellan gum is present in an amount between 0.05% and 1.5%, preferably between 0.15% and 1.5%, more preferably between 0. 5% and 1.2%, further preferably between 0.7% and 1% in mass based upon the mass of a combination of the composition and the carrier,

preferably, said gellan gum is low acyl gellan gum.

8. The composition of claim 3 or 4, wherein said source of selenium is present in an amount between 0.00001% and 0.002%, preferably between 0.000016% and 0.0016%, further preferably between 0.0001% and 0.0002% in mass based upon the mass of a combination of the composition and the carrier.

9. The composition of claim 3 or 4, wherein said ascorbic acid or a derivative of ascorbic acid is present in an amount between 0.005% and 0.1%, preferably 0.01% in mass based upon the mass of a combination of the composition and the carrier.

10. The composition of claim 3 or 4, wherein the preservative is selected from the group consisting of cetylpyridinium chloride, phenyl ethyl alcohol, benzoyl alcohol, polylysine and potassium sorbate;

preferably, the preservative is present in an amount between 0.0005% and 1.5%, preferably between 0.01% and 1.5%, more preferably between 0.05% and 0.25% in mass based upon the mass of a combination of the composition and the carrier;

preferably, the preservative is selected from the group consisting of polylysine and potassium sorbate;

preferably, polylysine is present in an amount between 0.025% and

0.1%, more preferably between 0.03% and 0.07% in mass based upon the mass of a combination of the composition and the carrier;

preferably, potassium sorbate is present in an amount between 0.01% and 1%, more preferably between 0.05% and 0.2% in mass based upon the mass of a combination of the composition and the carrier.

11. The composition of any one of claims 1 to 10, wherein the composition further comprises hydroxyethylcellulose;

preferably, hydroxyethylcellulose is present in an amount between 0.005% and 0.05%, preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier.

12. The composition of any one of claims 1 to 11, wherein the composition further comprises propanediol;

preferably, propanediol is present in an amount between 2% and 10%, more preferably between 4% and 7% in mass based upon the mass of a combination of the composition and the carrier.

13. The composition of any one of claims 1 to 12, wherein the composition further comprises menthol and/or peppermint essential;

preferably, menthol is present in an amount between 0.005% and 0.05%, more preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier;

preferably, peppermint essential is present in an amount between 0.005% and 0.05%, more preferably between 0.01% and 0.03% in mass based upon the mass of a combination of the composition and the carrier.

14. The composition of any one of claims 1 to 13, wherein the carrier is water, preferably is distilled water;

preferably, the pH of the spray is 5-6, preferably 5. .

15. A method for preparing the spray of any one of claims 1 to 14, comprising steps of:

(1) mixing gellan gum with water and heating the mixture to 70-90°C;

(2) cooling the mixture to 40-60°C and adding glutathione for crosslinking for at least 2 minutes;

(3) adding the other ingredients except preservative and cooling the mixture to 20-30°C;

(4) adjusting the pH of the mixture to 5-6, and then adding the preservative.

16. A method for antiviral or oxidation preconditioning, especially for prevention and therapy for COVID-19 comprising nose administration to a patient with the spray which combines the composition according to any one of claims 1 to 14 and the carrier.

17. The method of claim 16, wherein the spray is introduced to the nasal cavity of a patient by use of a stream inhaler, nebulizer or vaporizer.

18. The method of claim 16, wherein the spray is applied for four times a day and once in each nostril, and each pump is giving 90-110 mg by weight.

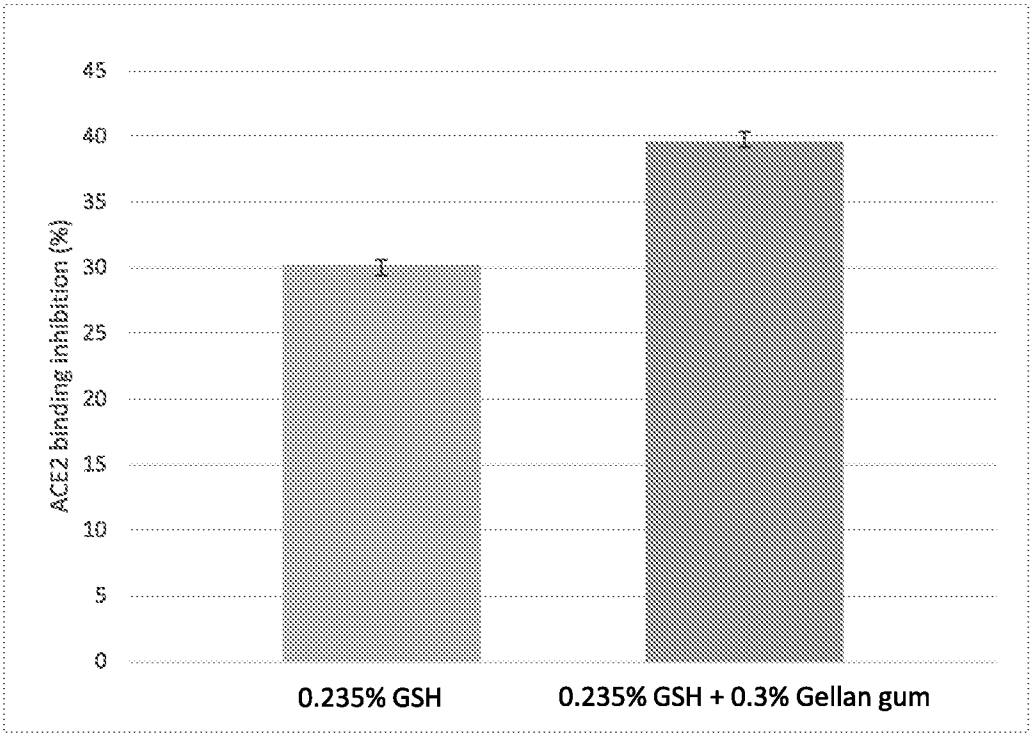
ACE2 binding inhibition (%)
45
40
35
30
25
20
15
10
5
0
0.235% GSH
0.235% GSH + 0.3% Gellan gum

Fig. 1

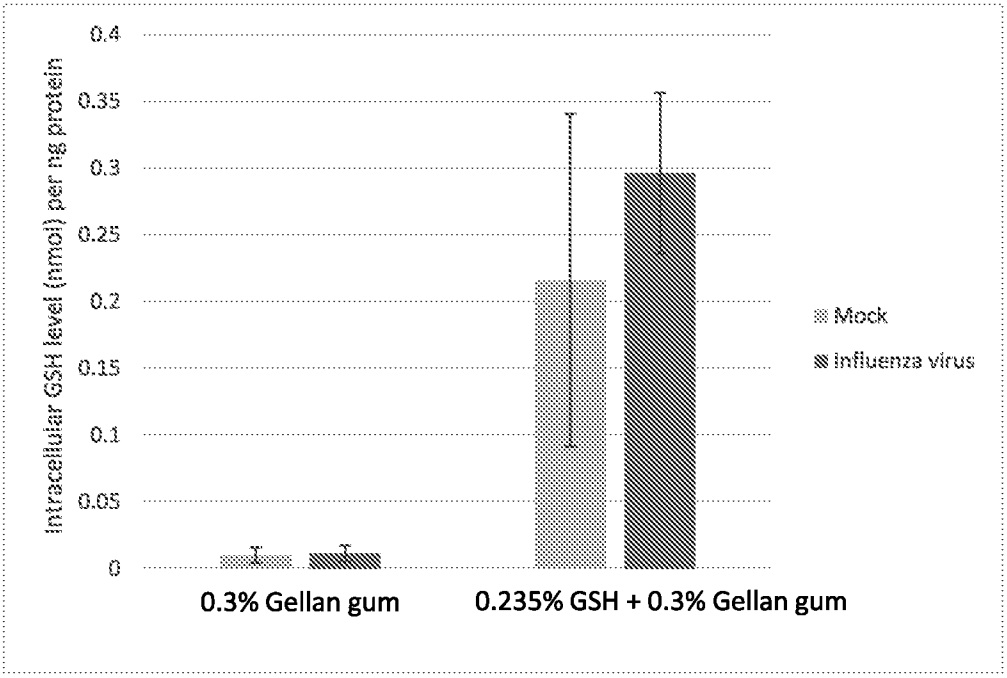
Intracellular GSH level (nmol) per mg protein
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Mock
Influenza virus
0.3% Gellan gum
0.235% GSH + 0.3% Gellan gum

Fig. 2

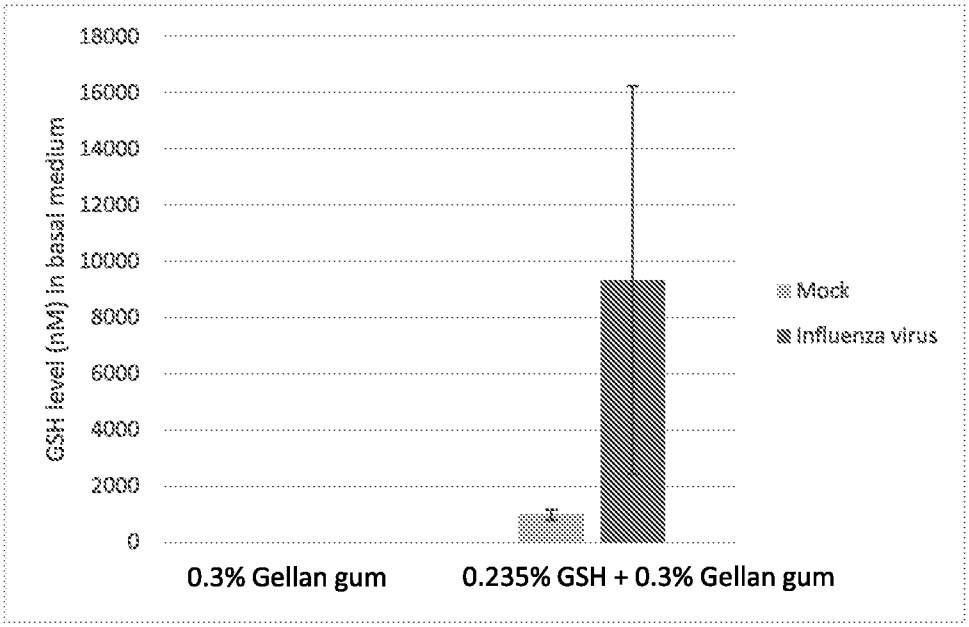
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
GSH level (nM) in basal medium
Mock
Influenza virus
0.3% Gellan gum
0.235% GSH + 0.3% Gellan gum

Fig. 3

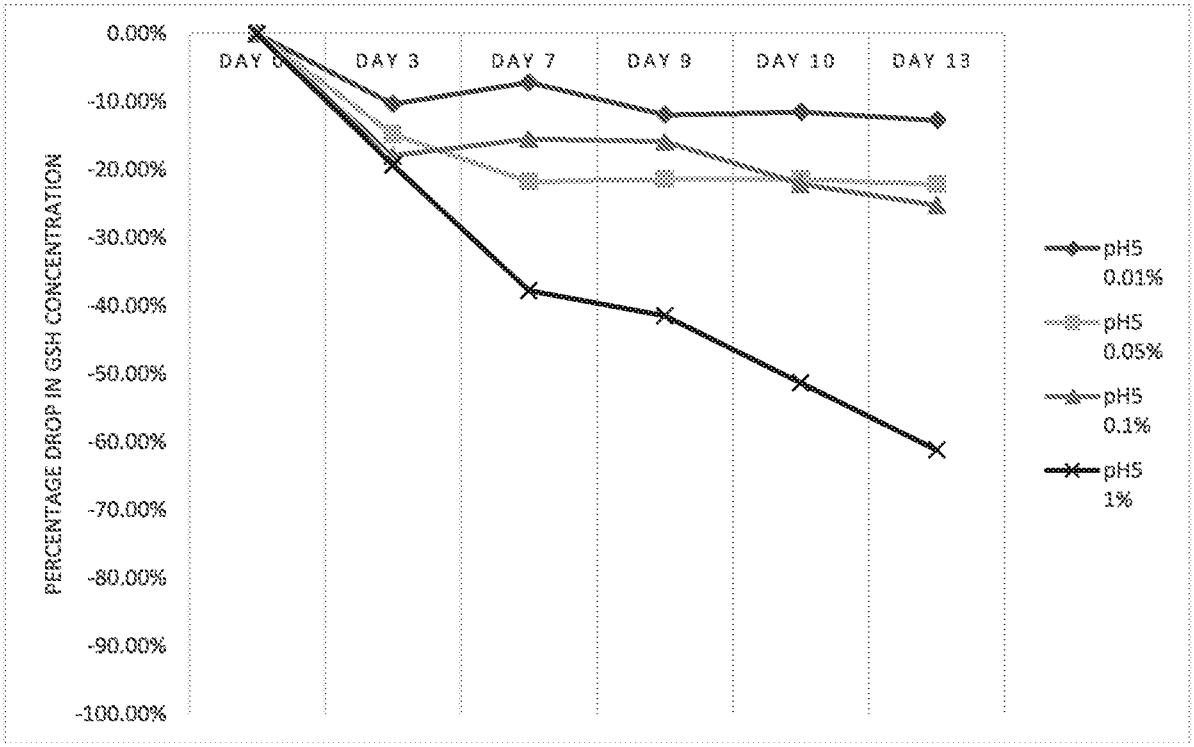
0.00%
-10.00%
-20.00%
-30.00%
-40.00%
-50.00%
-60.00%
-70.00%
-80.00%
-90.00%
-100.00%
PERCENTAGE DROP IN GSH CONCENTRATION
DAY 0
DAY 3
DAY 7
DAY 9
DAY 10
DAY 13
pHS 0.01%
pHS 0.05%
pHS 0.1%
pHS 1%

Fig. 4A

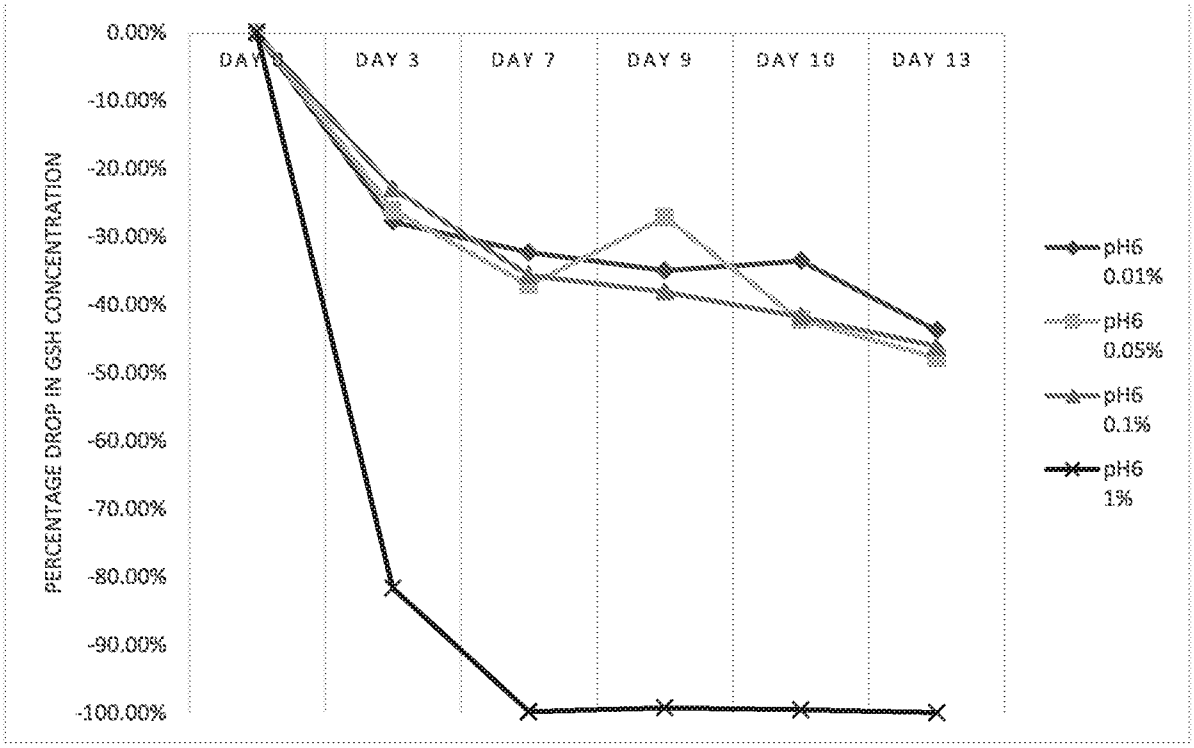
0.00%
-10.00%
-20.00%
-30.00%
-40.00%
-50.00%
-60.00%
-70.00%
-80.00%
-90.00%
-100.00%
PERCENTAGE DROP IN GSH CONCENTRATION
DAY 3
DAY 7
DAY 9
DAY 10
DAY 13
pH6 0.01%
pH6 0.05%
pH6 0.1%
pH6 1%

Fig. 4B

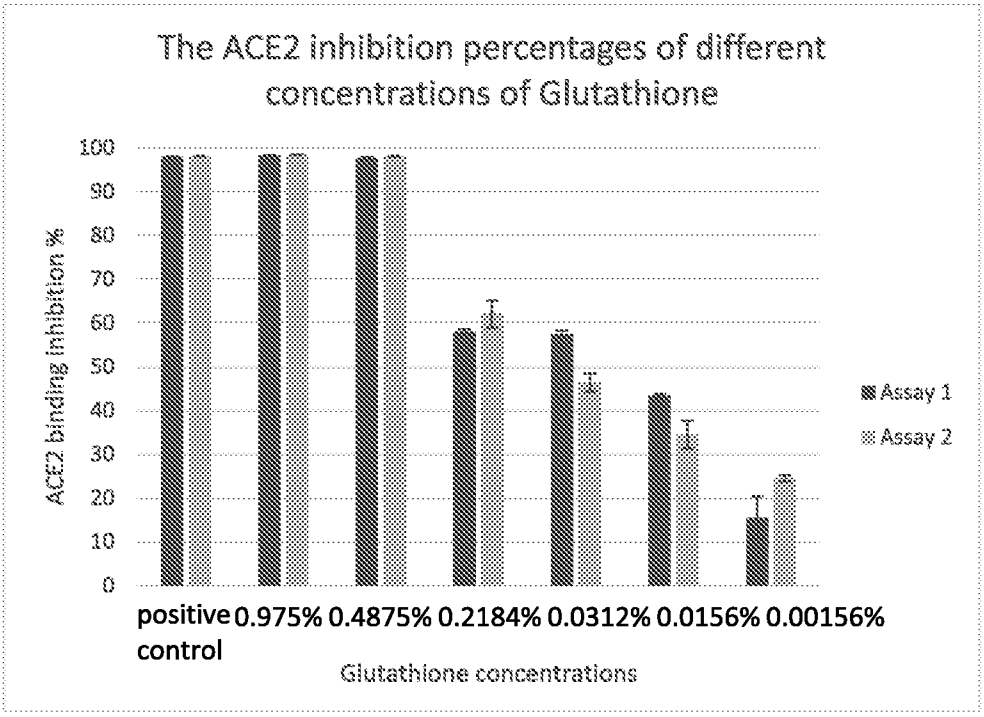
The ACE2 inhibition percentages of different concentrations of Glutathione
ACE2 binding inhibition %
100
90
80
70
60
50
40
30
20
10
0
Assay 1
Assay 2
positive control
0.975%
0.4875%
0.2184%
0.0312%
0.0156%
0.00156%
Glutathione concentrations

Fig. 5

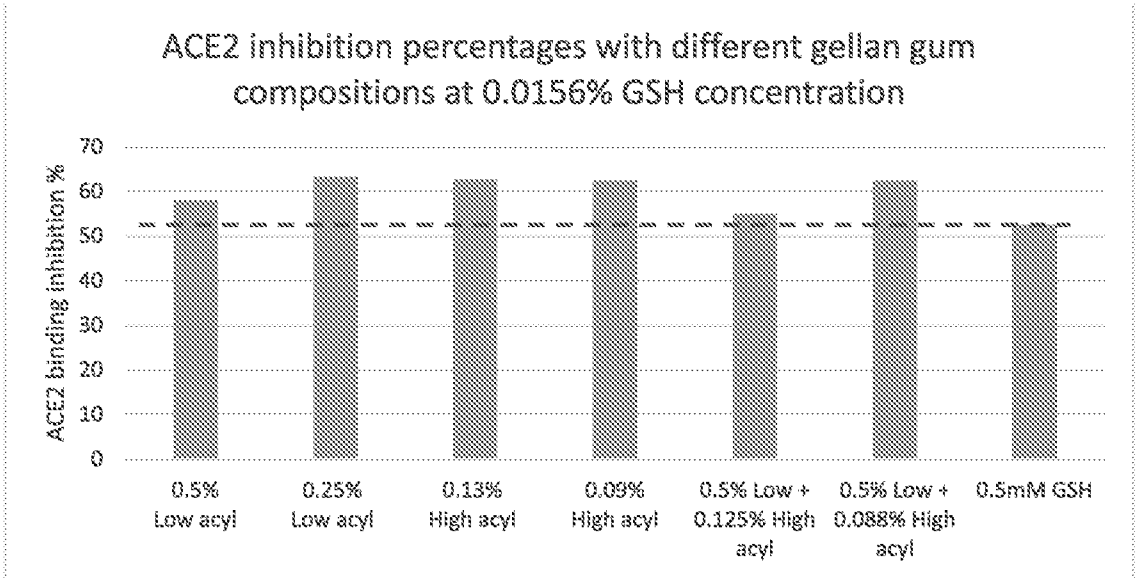

Fig. 6

Spray area (cm^2) A=(w+h)2*PI	sample 7 outer		sample 7 inner		sample 10		sample 12	
	3.5cm	6.5cm	3.5cm	6.5cm	3.5cm	6.5cm	3.5cm	6.5cm
Right after spraying	14.6	22.8	2.2	3.1	4.9	6.1	4.0	6.0
Dried on 0° surface	9.0	29.0	0.0	4.4	4.3	4.8	2.6	5.9
Dried on 45° incline	12.8	31.9	0.9	3.7	3.9	5.0	3.5	5.0

Fig. 7

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/131413

A. CLASSIFICATION OF SUBJECT MATTER

A61K38/06(2006.01)i; A61K31/198(2006.01)i; A61K47/36(2006.01)i; A61P31/12(2006.01)i; A61K9/12(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)

IPC: A61K A61P

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)

CJFD, CNTXT, DWPI, ENTXT, WPABS, WPABSC, ISI Web of Knowledge: GOVITA, GAO Vincent Chun Xin, WONG Siu Chong, glutathione, GSH, +acetylcysteine, gellan, nose, nasal, spray, antivirus, COVID-19, SARS, selenium, ascorbic, crosslink

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 113150180 A (CHANGZHOU UNIVERSITY) 23 July 2021 (2021-07-23) paragraphs 0013-0015, 0023-0031	1-2, 6-7, 14
Y	CN 113150180 A (CHANGZHOU UNIVERSITY) 23 July 2021 (2021-07-23) paragraphs 0013-0015, 0023-0031	1-14, 16-18
Y	WO 2022011305 A2 (BEYOND BARRIERS THERAPEUTICS, INC.) 13 January 2022 (2022-01-13) paragraphs 0007, 0016, 0032	1-14, 16-18
A	ZHOU, SHUWEN et al. "Liposome Loaded Ion/Temperature Dual Responsive Gellan Gum Hydrogel as Potential Nasal-To-Brain Delivery System" *Journal of Biomedical Nanotechnology*, Vol. 2, No. 18, 01 February 2022 (2022-02-01), pages 571-580	1-18
A	CN 101564374 A (BEIJING HERUNCHUANGXIN MEDICAL TECHNOLOGY DEVELOPMENT CO., LTD.) 28 October 2009 (2009-10-28) claims 1-4	1-18
A	CN 101683149 A (BAOLINGBAO BIOLOGY CO., LTD.) 31 March 2010 (2010-03-31) claims 1-6	1-18

☑ 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
"D" document cited by the applicant in the international application
"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
18 December 2023	**22 December 2023**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**HU,JingDong** Telephone No. **(+86) 010-53961914**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/131413

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2018193404 A1 (EMORY UNIVERSITY et al.) 12 July 2018 (2018-07-12) paragraphs 0066-0067	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/131413

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.: **16-18**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 16-18 direct to a method of treatment of the human/animal body, they do not meet the criteria set out in PCT Rules 39.1(iv). The search report has been carried out and based on the use of claimed composition in manufacturing medicaments for antivirus, oxidation precondition, or treating diseases.

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/CN2023/131413

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
CN 113150180 A	23 July 2021	None	
WO 2022011305 A2	13 January 2022	WO 2022011305 A3	10 February 2022
		US 2023263725 A1	24 August 2023
CN 101564374 A	28 October 2009	None	
CN 101683149 A	31 March 2010	None	
US 2018193404 A1	12 July 2018	WO 2017015481 A1	26 January 2017
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