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(54) Title: PREPARATIONS CONTAINING BERRY EXTRACTS FOR USE IN THE PROPHYLAXIS AND/OR TREATMENT OF VIRAL INFECTIONS CAUSED BY PNEUMOVIRIDAE

(57) Abstract: The present invention is related to compositions for use in treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family and wherein the composition comprises an extract of black currants and bilberries.



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Preparations containing berry extracts for use in the prophylaxis and/or treatment of viral infections caused by Pneumoviridae

The present invention is related to preparations containing one or more berry extracts for use in
5 treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family and wherein the composition comprises an extract of black currants and bilberries.

Anthocyanins are water-soluble vacuolar pigments that may appear red, purple or blue, depending on the surrounding pH-value. Anthocyanins belong to the class of flavonoids, which are
10 synthesized via the phenylpropanoid pathway. They occur in all tissues of higher plants, mostly in flowers and fruits and are derived from anthocyanidins by addition of sugars. Anthocyanins are glycosides of flavylum salts. Each anthocyanin thus comprises three component parts: the hydroxylated core (the aglycone); the saccharide unit; and the counterion. Anthocyanins are naturally occurring pigments present in many flowers and fruit and individual anthocyanins are
15 available commercially as the chloride salts, e.g. from Polyphenols Laboratories AS, Sandnes, Norway. The most frequently occurring anthocyanins in nature are the glycosides of cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin.

It is known that anthocyanins, especially resulting from fruit intake, have a wide range of biological
20 activities, including antioxidant, anti-inflammatory, antimicrobial and anti-carcinogenic activities, improvement of vision, induction of apoptosis, and neuroprotective effects. Particularly suitable fruit sources for the anthocyanins are cherries, bilberries, blueberries, black currants, red currants, grapes, cranberries, strawberries, and apples and vegetables such as red cabbage. Bilberries, in particular *Vaccinium myrtillus*, and black currants, in particular *Ribes nigrum*, are especially
25 suitable.

Bilberries contain diverse anthocyanins, including delphinidin and cyanidin glycosides and include several closely related species of the genus *Vaccinium*, including *Vaccinium myrtillus* (bilberry), *Vaccinium uliginosum* (bog bilberry, bog blueberry, bog whortleberry, bog huckleberry, northern
30 bilberry, ground harts), *Vaccinium caespitosum* (dwarf bilberry), *Vaccinium deliciosum* (Cascade bilberry), *Vaccinium membranaceum* (mountain bilberry, black mountain huckleberry, black huckleberry, twin-leaved huckleberry), *Vaccinium ovalifolium* (oval-leaved blueberry, oval-leaved bilberry, mountain blueberry, high-bush blueberry).

Dry bilberry fruits of *V. myrtillus* contain up to 10% of catechin-type tannins, proanthocyanidins, and anthocyanins. The anthocyanins are mainly glucosides, galactosides, or arabinosides of delphinidin, cyanidin, and – to a lesser extent – malvidin, peonidin, and petunidin (cyanidin-3-O-glucoside (C3G), delphinidin-3-O-glucoside (D3G), malvidin-3-O-glucoside (M3G), peonidin-3-O-glucoside and petunidin-3-O-glucoside). Flavonols include quercetin- and kaempferol-glucosides.
40 The fruits also contain other phenolic compounds (e.g., chlorogenic acid, caffeic acid, o-, m-, and p-coumaric acids, and ferulic acid), citric and malic acids, and volatile compounds.

Black currant fruits (*R. nigrum*) contain high levels of polyphenols, especially anthocyanins, phenolic acid derivatives (both hydroxybenzoic and hydroxycinnamic acids), flavonols (glycosides of myricetin, quercetin, kaempferol, and isorhamnetin), and proanthocyanidins (between 120 and 166 mg/100 g fresh berries). The main anthocyanins are delphinidin-3-O-rutinoside (D3R) and cyanidin-3-O-rutinoside (C3R), but delphinidin- and cyanidin-3-O-glucoside are also found (Gafner, Bilberry – Laboratory Guidance Document 2015, Botanical Adulterants Program).

EP 1443948 A1 relates to a process for preparing a nutritional supplement (nutraceutical) comprising a mixture of anthocyanins from an extract of black currants and bilberries. Anthocyanins were extracted from cakes of fruit skin produced as the waste product in fruit juice pressing from *V. myrtillus* and *R. nigrum*. It could be shown that the beneficial effects of individual anthocyanins are enhanced if instead of an individual anthocyanin, a combination of different anthocyanins is administered orally, in particular a combination comprising both mono and disaccharide anthocyanins. It is thought that the synergistic effect arises at least in part from the different solubilities and different uptake profiles of the different anthocyanins.

Pneumoviridae is a new virus family, which was formerly known as a subfamily of paramyxoviridae with five species divided between two genera (Metapneumovirus and Orthopneumovirus). Viruses in the Pneumoviridae family are often associated with respiratory infections and are transmitted through respiratory secretions, such as human metapneumovirus (HMPV), human respiratory syncytial virus A2 (HRSV-A2) and human respiratory syncytial virus B1 (HRSV-B1). Young children, the elderly, and patients with compromised cardiac, pulmonary, or immune systems are at greatest risk for serious disease associated with these RNA virus respiratory infections. Current estimates in developing and industrialized countries suggest as many as 33 million cases of RSV worldwide in the pediatric population less than 5 years old, 10% of which require hospitalization and 2% to 18% of hospitalized cases result in mortality. This amounts to between 66,000 and 600,000 deaths in young children annually. As the virus is ubiquitous, avoidance of infection is not possible. However, palivizumab, a moderately effective prophylactic drug (a monoclonal antibody directed against RSV surface fusion protein), is available for infants at high risk. To date, treatment of RSV and HPMV infections is still limited to supportive measures.

In the context it was surprisingly found, that an extract of black currants and bilberries, can mediate inhibition of Pneumoviridae virus infection and replication. Thus, the present invention is based on the use of Healthberry® 865 as anti-viral agent in the treatment and prophylaxis of Pneumoviridae e.g. hRSV infection. Therefore, an extract of black currants and bilberries could be an important solution for these respiratory infections by combining the antiviral effect with its positive influence on cell viability and no toxicity.

The present invention is related to a composition for use in treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family and wherein the composition comprises an extract of black currants and bilberries.

- 5 The composition according to the present invention is especially for use in treating or preventing a virus infection in human hosts selected from
- human metapneumovirus (HMPV),
 - human respiratory syncytial virus A2 (HRSV-A2) and
 - human respiratory syncytial virus B1 (HRSV-B1).

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It is also preferred to use the composition according to the present invention for treating or preventing a virus infection with avian metapneumovirus (AMPV), bovine respiratory syncytial virus (BRSV) or murine pneumonia virus (MPV). In a preferred configuration, the composition inhibits viral replication.

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In a preferred embodiment, the black currants are the fruit of *Ribes nigrum* and/or the bilberries are the fruit of *Vaccinium myrtillus*. It is further preferred, when the composition contains an extract from black currants and bilberries in a weight ratio of 0.5:1 to 1:0.5. In an advantageous configuration of the present invention, the composition is an extract of the pomaces from black

20 currants and bilberries.

25

It is particularly preferred, when the composition comprises anthocyanins and the anthocyanins are present in the composition at a concentration of at least 25 weight-%, preferably at least 30 weight-%, or at least 35 weight-%, or at least 40 weight-%, or at least 45 weight-%, or at least 50 weight-%.

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It is preferred, according to the present invention, when the extract is an alcoholic extract, preferably a methanol extract. The extract is preferably produced by a process comprising the steps of

- extraction of black currants and/or bilberries,
- purification via chromatography,
- mixing of the extract(s) with water and
- spray-drying of the mixture.

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One example of such a process is disclosed in EP1443948.

In a preferred embodiment, maltodextrin is added to the composition.

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The composition according to the present invention preferably contains at least three monosaccharide anthocyanins. Moreover, it preferably contains at least one monosaccharide anthocyanin in which the saccharide is arabinose or at least one disaccharide anthocyanin in which the disaccharide is rutinose. The composition preferably contains anthocyanins with at least two

different aglycones, more preferably at least four. Especially preferably the composition contains anthocyanins in which the aglycone units are cyanidin, peonidin, delphinidin, petunidin, malvidin and optionally also pelargonidin. In one preferred embodiment, the composition also contains at least one trisaccharide anthocyanin. The disaccharide anthocyanins are more water soluble than the monosaccharides; moreover, cyanidin and delphinidin anthocyanins are amongst the most water soluble anthocyanins.

In an advantageous embodiment of the present invention anthocyanins are selected from cyanidin-3-glucoside, cyanidin-3-galactoside, cyanidin-3-arabinoside, delphinidin-3-glucoside, delphinidin-3-galactoside, delphinidin-3-arabinoside, petunidin-3-glucoside, petunidin-3-galactoside, petunidin-3-arabinose, peonidin-3-glucoside, peonidin-3-galactoside, peonidin-3-arabinose, malvidin-3-glucoside, malvidin-3-galactoside, malvidin-3-arabinose, cyanidin-3-rutinoside, delphinidin-3-rutinoside. The anthocyanins are preferably selected from cyanidin-3-glucoside, cyanidin-3-rutinoside, delphinidin-3-glucoside, delphinidin-3-rutinoside, cyanidin-3-galactoside, delphinidin-3-galactoside.

The anthocyanins can be from natural sources or from synthetic productions. Natural sources are preferably selected from fruits, flowers, leaves, stems and roots, preferably violet petal, seed coat of black soybean. Preferably anthocyanins are extracted from fruits selected from: açai, black currant, aronia, eggplant, blood orange, marion blackberry, black raspberry, raspberry, wild blueberry, cherry, queen Garnet plum, red currant, purple corn (*Z. mays L.*), concord grape, norton grape, muscadine grape, red cabbage, okinawan sweet potato, Ube, black rice, red onion, black carrot. Particularly suitable fruit sources for the anthocyanins are cherries, bilberries, blueberries, black currants, red currants, grapes, cranberries, strawberries, black chokeberry, and apples and vegetables such as red cabbage. Bilberries, in particular *Vaccinium myrtillus*, and black currants, in particular *Ribes nigrum*, are especially suitable. It is further preferred to use plants enriched with one or more of anthocyanins as natural sources, preferably plants enriched with delphinidin-3-rutinoside.

The counterion in the anthocyanins in the composition of the invention may be any physiologically tolerable counter anions, e.g. chloride, succinate, fumarate, malate, maleate, citrate, ascorbate, aspartate, glutamate, etc. Preferably however the counterion is a fruit acid anion, in particular citrate, as this results in the products having a particularly pleasant taste. Besides the anthocyanins, the composition may desirably contain further beneficial or inactive ingredients, such as vitamins (preferably vitamin C), flavones, isoflavones, anticoagulants (e.g. maltodextrin, silica, etc.), desiccants, etc.

It is preferred when the composition comprises anthocyanins and is to be administered to the subject in a dose of the anthocyanins / regimen of 1 to 10 oral dosages of at least 80 mg anthocyanins each per day, preferably 3 to 6 oral dosages of at least 80 mg anthocyanins each per day.

In a further advantageous configuration, the composition is to be administered to the subject as parenteral bolus injection or infusion or parenteral nutritional solution. It is also preferred to use the composition to stabilize critical patients, where lifesaving treatments are not effective, and no last-line treatment is available (due to lack of treatment options).

The composition according to the present invention is to be administered to the subject, reaching a concentration in the target compartment at least 30 µg/ml, preferably at least 100 µg/ml. Target compartment are blood and lymph, specifically the medium surrounding the cells of the immune system, preferably Peripheral Blood Mononuclear Cells (PBMCs) or cells of the respiratory tract.

In a preferred embodiment, the subject is a human and preferably the subject is pregnant, or younger than 2 years or 65 years old or more.

The composition according to the present invention is preferably used when the subject suffers from asthma, chronic obstructive pulmonary disease or congestive heart failure.

A further aspect of the present invention is related to a liquid composition comprising an extract of black currants and bilberries, wherein the composition is comprised in a nebulizer, preferably a throat spray liquid composition comprising an extract of black currants and bilberries, wherein the composition further comprises an pharmaceutically acceptable excipient suitable for a liquid composition that is to be administered to the mucosal surfaces of the mouth and throat, preferably wherein the excipient comprises one or more of a tonicity adjusting agent, a buffering agent, a preservative, an antioxidant, a stabilizer, a pH adjusting agent, a penetration enhancer, a surfactant and a humectant.

The invention also provides a composition formulated as a throat spray, a throat lozenge or a mouthwash, further comprising a pharmaceutically acceptable carrier suitable for a composition that is to be administered to the mucosal surfaces of the mouth and throat.

The invention also provides a composition comprising an extract of black currants and/or bilberries, wherein the composition further comprises saline, and preferably wherein the composition is comprised in a nebulizer. The composition may comprise a tonicity adjusting agent, a buffering agent, a preservative, an antioxidant, a stabilizer, a pH adjusting agent, a penetration enhancer, a surfactant and a humectant. Preferably the composition is isotonic.

The present invention also refers to

- a composition comprising an analgesic or an anti-inflammatory agent or topical anesthetic and an extract of black currants and bilberries, preferably wherein the analgesic is ibuprofen or paracetamol/acetaminophen,

- a composition according for use in treating pain associated with an RSV infection in a subject,
- a combined preparation comprising an analgesic or topical anesthetic, and an extract of black currants and bilberries, for simultaneous, separate or sequential use in medicine,
- 5 – a throat lozenge comprising a topical anesthetic, and an extract of black currants and bilberries, preferably wherein the topical anesthetic is benzocaine or menthol,
- a composition comprising an antipyretic, and an extract of black currants and bilberries,
- a composition for use in treating fever associated with an RSV infection in a subject,
- a combined preparation comprising an antipyretic, and an extract of black currants and bilberries, for simultaneous, separate or sequential use in medicine,
- 10 – a combined preparation comprising palivizumab and an extract of black currants and bilberries for preventive treatment of RSV infection,
- combination preparation comprising one or more of the following adrenaline, bronchodilators, steroids, antibiotics, ribavirin, salbutamol and an extract of black currants and bilberries for a treatment after RSV infection.
- 15

A combined preparation is one which comprises separately packaged active components which are to be combined in use, i.e. by being administered simultaneously, separately or sequentially to the subject.

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Analgesic compounds are preferably selected from acetylsalicylic acid, Diclofenac, Dexibuprofen, Dexametoprofen, Flurbiprofen, Ibuprofen, Indometacin, Ketoprofen, Meloxicam, Nabumeton, Naproxen, Phenylbutazon, Piroxicam, Phenazon, Propyphenazon, rofecoxib, Celecoxib, Etoricoxib, Parecoxib, Metamizol, Paracetamol/Acetaminophen.

25

For all the compositions described above it is advantageous, when the black currants are the fruit of *Ribes nigrum* and/or the bilberries are the fruit of *Vaccinium myrtillus*. It is further preferred, when the composition contains an extract from black currants and bilberries in a weight ratio of 0.5:1 to 1:0.5. In an advantageous configuration of the present invention, the composition is an extract of the pomaces from black currants and bilberries. It is particularly preferred, when the composition comprises anthocyanins and the anthocyanins are present in the composition at a concentration of at least 25 weight-%, preferably at least 30 weight-%, or at least 35 weight-%, or at least 40 weight-%, or at least 45 weight-%, or at least 50 weight-%. It is preferred, according to the present invention, when the extract is an alcoholic extract, preferably a methanol extract.

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The present invention is also related to an antiviral agent for treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family with a level of efficacy of 1 log level, and an antiviral agent which is non-toxic.

40 The invention is also referring to an antiviral agent for treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family with a level of efficacy of 1 log level,

which is not killing more than 30%, preferably not more than 20%, more preferably not more than 10% of cells in a cell-based assay in mammalian cells, preferably HepG2 cells.

This antiviral agent preferably comprises one or more anthocyanins selected from cyanidin-3-glucoside, cyanidin-3-galactoside, cyanidin-3-arabinoside, delphinidin-3-glucoside, delphinidin-3-galactoside, delphinidin-3-arabinoside, petunidin-3-glucoside, petunidin-3-galactoside, petunidin-3-arabinose, peonidin-3-glucoside, peonidin-3-galactoside, peonidin-3-arabinose, malvidin-3-glucoside, malvidin-3-galactoside, malvidin-3-arabinose, cyanidin-3-rutinoside, delphinidin-3-rutinoside. The anthocyanins are preferably selected from cyanidin-3-glucoside, cyanidin-3-rutinoside, delphinidin-3-glucoside, delphinidin-3-rutinoside, cyanidin-3-galactoside, delphinidin-3-galactoside.

It is known that viral infections can occur when a medical device is used on a subject. This is particularly the case when the device, such as a catheter or feeding tube, is to be retained in the subject for any length of time, e.g. the dwell time of the device in the subject is more than 24 hours.

Accordingly, the present invention is also related to a composition for use, wherein the composition is for use with a medical device which is to be inserted into the subject, or wherein the subject has had a medical device inserted, optionally wherein the device is inserted via the nose or mouth. It is preferred, when the medical device is a needle, a catheter, a port, an intubation device or tube, or a nebulizer. It is further preferred, when a dwell time of the medical device in the subject is more than 24 hours, more than 48 hours, more than 72 hours, more than one week, more than 2 weeks, more than 3 weeks, preferably wherein the dwell time is more than one week, more than 2 weeks or more than 3 weeks.

The invention further refers to a medical device suitable for insertion into a subject, the medical device comprising a coating composition on an exterior surface of the device, wherein the coating composition comprising an extract of black currants and bilberries. It is preferred, when the medical device is a needle, a catheter, an intubation device or tube, or a nebulizer, preferably wherein the exterior surface of the medical device is plastic.

It is further preferred, when the black currants are the fruit of *Ribes nigrum* and/or the bilberries are the fruit of *Vaccinium myrtillus*. It is further preferred, when the composition contains an extract from black currants and bilberries in a weight ratio of 0.5:1 to 1:0.5. In an advantageous configuration of the present invention, the composition is an extract of the pomaces from black currants and bilberries. It is particularly preferred, when the composition comprises anthocyanins and the anthocyanins are present in the composition at a concentration of at least 25 weight-%, preferably at least 30 weight-%, or at least 35 weight-%, or at least 40 weight-%, or at least 45 weight-%, or at least 50 weight-%. It is preferred, according to the present invention, when the extract is an alcoholic extract, preferably a methanol extract.

The invention also covers a method of making the medical device as described, the method comprising applying the coating composition to the exterior surface of the medical device, optionally wherein the coating composition is formulated as a cream, a hydrogel cream, or a spray.

5 Moreover, the invention refers to a deep-lung particle comprising a composition comprising an extract of black currants and bilberries, which is dispensed into the deeper respiratory tract of an individual and a device for dispensing a deep-lung particle into the deeper respiratory tract of an individual.

10 The composition may comprise a formulation of extracts of black currants and bilberries with nanoparticles, preferably liposomes. Such formulations may be inhaled to maximize the delivery of nanoparticles into the lung. Inhalation facilitates the localized delivery of compositions directly to the lungs via the oral or nasal inhalation route. For example, aerosolized delivery of liposomal interleukin-2 (IL-2) in dogs has been shown to be effective against pulmonary metastases from
15 osteosarcoma (Khanna C, Anderson PM, Hasz DE, Katsanis E, Neville M, Klausner JS. Interleukin-2 liposome inhalation therapy is safe and effective for dogs with spontaneous pulmonary metastases. *Cancer* 1997; 79: 1409–21.) Moreover, the delivery of anticancer drugs via nanoparticles has been shown to be efficacious and safe in a variety of cancers. Anticancer drugs can also be formulated into drug nanocrystals with high drug loading and minimal use of excipients.
20 (Sharad M, Wei G, Tonglei L, Qi Z, Review: Pulmonary delivery of nanoparticle chemotherapy for the treatment of lung cancers: challenges and opportunities, *Acta Pharmacologica Sinica* (2017) 38: 782–797).

In a preferred embodiment, a nanoparticle suspension comprising the composition according to the
25 present invention is aerosolized into droplets with appropriate aerodynamic diameters using currently available inhalation devices. Such inhalation devices are preferably selected from nebulizers and pressurized metered dose inhalers (pMDI).

Therefore, in an advantageous configuration, the composition according to the present invention
30 may also be formulated as nanoparticle suspension for use in a nebulizer. Such nebulizers convert suspension of nanoparticles into inhalable droplets and may be used for the delivery of the composition into the deep lungs without compromising liposome integrity. An alternative configuration refers to pMDIs, which create small inhalable droplets of drugs suspended in compressed propellant (such as hydrofluoroalkane (HFA)).

35 The present invention also refers to a nanoparticle formulation as a dry powder, which offers greater long-term stability than a suspension. Controlling the size of nanoparticles is central for their formulation into reliable and efficient inhalable dry powders. Nanoparticles can be dried with/without excipients via spray-drying, freeze-drying and spray freeze-drying to generate stable
40 and uniformly sized inhalable particles.

In an alternative embodiment, nanoparticles may be co-dried with excipients, which leads to the formation of inhalable nanoparticle aggregates in an excipient matrix. It is possible to utilize particle engineering and ensure consistent and highly efficient delivery of nanoparticles to the lungs through nano-aggregates, large porous particles, and other formulation techniques.

Item list

Preferred embodiments of the present invention are summarized in the following item list:

5

1. A composition for use in treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family and wherein the composition comprises an extract of black currants and bilberries.

10

2. The composition for use according to item 1, wherein the black currants are the fruit of *Ribes nigrum* and/or the bilberries are the fruit of *Vaccinium myrtillus*.

3. The composition for use according to any preceding item wherein the composition contains an extract from black currants and bilberries in a weight ratio of 0.5:1 to 1:0.5.

15

4. The composition for use according to any preceding item wherein the composition is an extract of the pomaces from black currants and bilberries.

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5. The composition for use according to any preceding item, wherein the composition comprises anthocyanins and the anthocyanins are present in the composition at a concentration of at least 25 weight-%.

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6. The composition for use according to any preceding item, wherein the extract is an alcoholic extract, preferably a methanol extract.

7. The composition for use according to any preceding item, wherein the extract is prepared by a process comprising the steps of extraction of black currants and bilberries, purification via chromatography, mixing of the extract(s) with water and spray-drying of the mixture.

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8. A composition for use in treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family and wherein the composition comprises one or more of the following anthocyanins:

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cyanidin-3-glucoside, cyanidin-3-galactoside, cyanidin-3-arabinoside, delphinidin-3-glucoside, delphinidin-3-galactoside, delphinidin-3-arabinoside, petunidin-3-glucoside, petunidin-3-galactoside, petunidin-3-arabinose, peonidin-3-glucoside, peonidin-3-galactoside, peonidin-3-arabinose, malvidin-3-glucoside, malvidin-3-galactoside, malvidin-3-arabinose, cyanidin-3-rutinoside, delphinidin-3-rutinoside.

40

9. A composition for use in treating or preventing a virus infection in a subject, wherein the virus is from the Pneumoviridae family and wherein the composition comprises:

cyanidin-3-glucoside, cyanidin-3-rutinoside, delphinidin-3-glucoside, delphinidin-3-rutinoside, cyanidin-3-galactoside and delphinidin-3-galactoside.

- 5 10. The composition for use according to any preceding item wherein the virus is selected from avian metapneumovirus (AMPV), human metapneumovirus (HMPV), bovine respiratory syncytial virus (BRSV), human respiratory syncytial virus A2 (HRSV-A2), human respiratory syncytial virus B1 (HRSV-B1), murine pneumonia virus (MPV).
- 10 11. The composition for use according to any preceding item wherein the virus is from the genus Orthopneumovirus or wherein the virus is human metapneumovirus.
12. The composition for use according to any preceding item wherein the virus is human respiratory syncytial virus.
- 15 13. The composition for use according to any preceding item wherein the composition inhibits viral replication.
- 20 14. The composition for use according to any preceding item wherein the composition comprises anthocyanins and is to be administered to the subject 1 to 10 oral dosages of at least 80 mg anthocyanins each per day, preferably 3 to 6 oral dosages of at least 80 mg anthocyanins each per day.
- 25 15. The composition for use according to any preceding item wherein the composition is to be administered to the subject as parenteral bolus injection or infusion or parenteral nutritional solution to stabilize critical patients.
- 30 16. The composition for use according to any preceding item wherein the composition is to be administered to the subject, reaching a concentration in the target compartment of at least 30 µg/ml, preferably at least 100 µg/ml.
- 35 17. The composition for use according to any preceding item wherein the subject is a human.
18. The composition for use according to any preceding item wherein the subject is human and is younger than 2 years old or is 65 years old or more.
- 40 19. The composition for use according to any preceding item wherein the subject suffers from asthma, chronic obstructive pulmonary disease or congestive heart failure.
20. The composition for use according to any preceding item, wherein the composition is for use with a medical device which is to be inserted into the subject, or wherein the subject

has had a medical device inserted, optionally wherein the device is inserted via the nose or mouth.

- 5 21. The composition for use according to item 20, wherein the medical device is a needle, a catheter, a port, an intubation device or tube, or a nebulizer.
- 10 22. The composition for use according to item 20 or 21, wherein a dwell time of the medical device in the subject is more than 24 hours, more than 48 hours, more than 72 hours, more than one week, more than 2 weeks, more than 3 weeks, preferably wherein the dwell time is more than one week, more than 2 weeks or more than 3 weeks.
23. A liquid composition comprising an extract of black currants and bilberries, wherein the composition is comprised in a nebulizer.
- 15 24. A throat spray liquid composition comprising an extract of black currants and bilberries, wherein the composition further comprises a pharmaceutically acceptable excipient suitable for a liquid composition that is to be administered to the mucosal surfaces of the mouth and throat, preferably wherein the excipient comprises one or more of a tonicity adjusting agent, a buffering agent, a preservative, an antioxidant, a stabilizer, a pH adjusting agent, a penetration enhancer, a surfactant and a humectant.
- 20 25. A composition comprising an analgesic or topical anesthetic or anti-inflammatory agent, and an extract of black currants and bilberries, preferably wherein the analgesic is ibuprofen or paracetamol/acetaminophen.
- 25 26. A composition according to the previous item for use in treating pain associated with an RSV infection in a subject.
- 30 27. A combined preparation comprising an analgesic or topical anesthetic, and an extract of black currants and bilberries, for simultaneous, separate or sequential use in medicine.
28. A throat lozenge comprising a topical anaesthetic, and an extract of black currants and bilberries, preferably wherein the topical anesthetic is benzocaine or menthol.
- 35 29. A composition comprising an antipyretic, and an extract of black currants and bilberries.
30. A composition according to the previous item for use in treating fever associated with an RSV infection in a subject.
- 40 31. A combined preparation comprising an antipyretic, and an extract of black currants and bilberries, for simultaneous, separate or sequential use in medicine.

32. A medical device suitable for insertion into a subject, the medical device comprising a coating composition on an exterior surface of the device, wherein the coating composition comprising an extract of black currants and bilberries.
- 5 33. The medical device according to item 32, wherein the medical device is a needle, a catheter, an intubation device or tube, or a nebulizer, preferably wherein the exterior surface of the medical device is plastic.
- 10 34. A method of making the medical device according to item 32 or 33, the method comprising applying the coating composition to the exterior surface of the medical device, optionally wherein the coating composition is formulated as a cream, a hydrogel cream, or a spray.
- 15 35. A method for treating or preventing a virus infection in a subject in need thereof, comprising administering to the subject an effective amount of a composition comprising an extract of black currants and bilberries, wherein the virus is from the Pneumoviridae family.
- 20 36. A method for preventing a device-associated virus infection in a subject, comprising: (a) inserting a device into the subject and administering an effective amount of a composition comprising an extract of black currants and bilberries at a site of insertion of the device; and/or (b) applying an effective amount of a composition comprising an extract of blackcurrants and bilberries to an external surface of a device and inserting the device into the subject, wherein the virus is from the Pneumoviridae family.
- 25 37. The method according to items 35 or 36 wherein the extract is as defined in any of items 2 to 8.
38. The method according to any of items 35 to 37, wherein the virus is as defined in item 9.
- 30 39. The method according to any of items 35 to 38, wherein the composition is to be administered as defined in items 10 or 11.

Examples

5 The berry extracts composition (Healthberry® 865; Evonik Nutrition & Care GmbH, Darmstadt, Germany) used in the present study is a dietary supplement consisting of 17 purified anthocyanins (all glycosides of cyanidin, peonidin, delphinidin, petunidin, and malvidin) isolated from black currant (*Ribes nigrum*) and bilberries (*Vaccinium myrtillus*).

10 The relative content of each anthocyanin in the Healthberry® 865 product was as follows: 33.0% of 3-O-b-rutinoside, 3-O-b-glucosides, 3-O-b-galactosides, and 3-O-b-arabinosides of cyanidin; 58.0% of 3-O-b-rutinoside, 3-O-b-glucosides, 3-O-b-galactosides, and 3-O-b-arabinosides of delphinidin; 2.5% of 3-O-b-glucosides, 3-O-b-galactosides, and 3-O-b-arabinosides of petunidin; 2.5% of 3-O-b-glucosides, 3-O-b-galactosides, and 3-O-b-arabinosides of peonidin; 3.0% of 3-O-b-glucosides, 3-O-b-galactosides, and 3-O-b-arabinosides of malvidin.

15 The 3-O-b-glucosides of cyanidin and delphinidin constituted at least 40–50% of the total anthocyanins.

20 The major anthocyanins contained in the berry extract used are cyanidin-3-glucoside, cyanidin-3-rutinoside, delphinidin-3-glucoside, delphinidin-3-rutinoside, cyanidin-3-galactoside and delphinidin-3-galactoside.

25 In addition to the anthocyanins mentioned above, the product also contained maltodextrin (around 40 weight-% of the composition), and citric acid (to maintain stability of anthocyanins). The amount of anthocyanin citrate is at least 25 weight-% of the composition. The composition is prepared from black currants and bilberries by a process comprising the steps of alcoholic extraction of black currants and bilberries, purification via chromatography, mixing of the extracts with maltodextrin citrate and water and spray-drying of the mixture. The product composition contains extracts of black currants and bilberries mixed in a weight ratio of around 1:1.

30

Materials:**Table 1:** Materials used for the measurement of cell survival and metabolism

Material	Supplier
RealTime-Glo™ MT Cell Viability Assay	Promega GmbH, Mannheim (Germany)
Dulbecco's Modified Eagle's medium (DMEM)	Gibco Life technologies, Carlsbad (USA)
Fetal bovine serum	Gibco Life technologies, Carlsbad (USA)
HepG2 cells	ATCC/American Type Culture Collection in Partnership with LGC standards, Wesel (Germany)
Healthberry® 865 (anthocyanin content 29.7%)	Evonik Nutrition & Care GmbH, Darmstadt (Germany)

5

Table 2: Devices used for the measurement of cell survival and metabolism.

Device	Supplier
Centro LB 960 microplate luminometer	Berthold Technologies, (Germany)

Table 3: Materials used for anti-viral assay

Material	Supplier
hRSV serotype B	patient derived isolate (Institute of Virology Würzburg)
Influenza virus serotype A	patient derived isolate (Institute of Virology Würzburg)
Dulbecco's Modified Eagle's medium (DMEM)	Gibco Life technologies, Carlsbad (USA)
Fetal bovine serum	Gibco Life technologies, Carlsbad (USA)
HepG2 cells	ATCC/American Type Culture Collection in Partnership with LGC standards, Wesel (Germany)
MDCK cells	ATCC/American Type Culture Collection in Partnership with LGC standards, Wesel (Germany)
HP Viral Nucleic Acid Kit	Hoffman-La-Roche Ltd., Basel (Switzerland)
LightMix® Modular Respiratory Syncytial kit (Cat. No. 07 766 343 001)	Hoffman-La-Roche Ltd., Basel (Switzerland)

LightCycler 480 RNA Master Hydrolysis Probes kit (Cat. No. 04991885001)	Hoffman-La-Roche Ltd., Basel (Switzerland)
RTqPCR LightMix® Modular Influenza A kit (Cat. No. 07 792 182 001)	Hoffman-La-Roche Ltd., Basel (Switzerland)
LightCycler® Multiplex RNA Virus Master kit (Cat. No. 07 083 173 001)	Hoffman-La-Roche Ltd., Basel (Switzerland)
Healthberry® 865 (anthocyanin content 29.7%)	Evonik Nutrition & Care GmbH, Darmstadt (Germany)
Bilberry extract, Vaccinium myrtillus (anthocyanin content 38.8%)	Evonik Nutrition & Care GmbH, Darmstadt (Germany)
Black currant extract, Ribes nigrum (anthocyanin content 30%)	Evonik Nutrition & Care GmbH, Darmstadt (Germany)
GLUCIDEX IT 19 (maltodextrin)	ROQUETTE GmbH, Frankfurt (Germany)
Delphinidin 3-rutinoside / D3R	Polyphenols AS, Sandnes (Norway)
Delphinidin 3-glucoside / D3G	Polyphenols AS, Sandnes (Norway)
Cyanidin 3-rutinoside / C3R	Polyphenols AS, Sandnes (Norway)
Cyanidin 3-glucoside / C3G	Polyphenols AS, Sandnes (Norway)

Table 4: Devices used for the anti-viral assay

Device	Supplier
LightCycler480 II qPCR machine	Hoffman-La-Roche Ltd., Basel (Switzerland)
LightCycler96 qPCR 20 machine	Hoffman-La-Roche Ltd., Basel (Switzerland)
LightCycler96 Application software V1.1	Hoffman-La-Roche Ltd., Basel (Switzerland)

5

Methods:**Test compound preparation:**

All test compounds were dissolved and diluted in cell culture medium. The overall amount of anthocyanins was normalized between Healthberry® 865 and the single anthocyanins (e.g.

10 500µg/mL of Healthberry® 865 corresponds to 150µg/mL of anthocyanins tested for the single test compounds) or as well the single berry extracts (taken into account that Healthberry® 865 also contains maltodextrin besides the anthocyanins). The medium served as control for viral inhibition or cytotoxicity.

15 **Cell viability assay:**

Cell viability was measured by RealTime-Glo™ MT Cell Viability Assay (Cat. No. G9712, Promega, Germany). HepG2 cells (2x10⁴) were incubated with decreasing amounts of the test compound solubilized in DMEM. Wells with DMEM alone served as control. The MT Cell Viability Substrate

and the NanoLuc luciferase were added according to the manufacturer's instructions. The assays were performed in triplicates. After 1h, and then every six or 12h, the luminescence was measured with Centro LB 960 microplate luminometer (Berthold Technologies, Germany). Luminescence values after 1h were set to 1 and changes over time were calculated.

5

Anti-viral assay:

RSV titer determination (RTqPCRs):

To analyze the influence of the test compounds on RSV replication, cells were seeded in 48 well plates. After 24h test compounds were added, and cells were subsequently infected with RSV. Cell culture supernatants were harvested three days post-infection and centrifuged at 2000 rpm to remove detached cells. Viral nucleoid acids were isolated from 200µl cell culture supernatants using the Roche HP Viral Nucleic Acid Kit according to the manufacturer's manual. Viral genome copy numbers were determined using 5µl of the eluted RNA and the RTqPCR using the LightMix® Modular Respiratory Syncytial kit (Cat. No. 07 766 343 001, Roche) in combination with the LightCycler 480 RNA Master Hydrolysis Probes kit (Cat. No. 04991885001, Roche). All reactions were performed in triplicates on Roche LightCycler96 or Roche LightCycler480 II qPCR machines. The genome copy numbers were determined with the respective cycler software. Quality of the RTqPCRs was ensured by following the MIQE guidelines [Bustin, S. A. et al. (2009). The MIQE Guidelines: Minimum Information for Publication of Quantitative Real-Time PCR Experiments. Clinical Chemistry, 55, 611–622. <http://doi.org/10.1373/clinchem.2008.112797>]. In brief: 1st. The recursion coefficient of the relative-standard curve r^2 had to be >0.95 . 2nd. Triplicate assays with a standard deviation of >0.5 were excluded from the analyses. Resulting genome copy numbers were expressed as genome copies per ml of the cell culture supernatants.

From the first identification till now, antiviral compounds are initially identified via screening assay either *in vitro* or in cell culture using replication assays. Even the activities of compounds identified by *in vitro* enzyme screening tests need to be verified in cell culture-based assays. These assays are state of the art methods to identify and confirm antiviral activities since they allow the quantification of the inhibition of viral replication and ensure the cellular uptake of compounds. For example, aciclovir, the gold standard in the treatment of HSV-1, was identified by screening of antiviral substances in sponges (Elion et al., 1977 Selectivity of action of an antihherpetic agent, 9-(2-hydroxyethoxymethyl)guanine. PNAS 74. 5716). Later, the antiviral activity of aciclovir inhibiting other members of the Herpesviridae was shown in cell culture-based assays as well (AKESSON-JOHANSSON et al., 1990 Inhibition of Human Herpesvirus 6 Replicationby9-[4-Hydroxy-2-(Hydroxymethyl)Butyl]Guanine (2HM-HBG) and Other Antiviral Compounds. AAC 34. 2417). Moreover, all compounds used as clinical drugs against HIV-1, such as 3TC and Lopinavir (ABT-378), were initially tested *in vitro* to demonstrate their antiviral effects (Coates et al., 1992. The Separated Enantiomers of 2'-Deoxy-3'-Thiacytidine (BCH 189) Both Inhibit Human Immunodeficiency Virus Replication In Vitro. AAC 36. 202; Sham et al. 1998. ABT-378, a Highly Potent Inhibitor of the Human Immunodeficiency Virus Protease. AAC 42. 3218).

Influenza genome determination:

MDCK cells were seeded in 48 well plates. After 24h test compounds were added, and cells were subsequently infected with influenza A virus. All infections were performed in triplicates. Cell culture supernatants were harvested three days post-infection and centrifuged at 2000 rpm to remove detached cells and analyze viruses secreted to the supernatant. Viral RNAs were isolated from 200µl cell culture supernatants using the Roche HP Viral Nucleic Acid Kit according to the manufacturer's manual. Viral genome copy numbers were determined using 5µl of the eluted RNA and the RTqPCR LightMix® Modular Influenza A kit (Cat. No. 07 792 182 001, Roche) in combination with the LightCycler® Multiplex RNA Virus Master kit (Cat. No. 07 083 173 001, Roche). All PCR reactions were performed in triplicates from a RNAs with a Roche LightCycler96 qPCR 20. The Cq values were determined with the respective cyclers software (Roche LightCycler96 Application software V1.1). The internal standard of the Modular Influenza A kit with 1000 genome copies served as positive control. Quality was ensured by following the MIQE guidelines.

Example 1: Influence of berry extracts on cell viability

To exclude cellular toxicity and adverse side effects, cellular viabilities of the test compounds on
5 HepG2 cells (96 well-plate: 650 cells/well) were determined with the RealTime-Glo™ MT Cell
Viability Assay kit. This assay measures the intracellular ATP content and therefore provides
information on the cellular viability and metabolism. The cells were incubated with decreasing test
compound concentration in triplicate assays. Subsequently, both the MT Cell Viability Substrate
and NanoLuc® Enzyme were added, and the luciferase activities were measured after 1h. These
10 measurements were repeated every 6h or 12h, and changes to the luciferase activity at the start of
the experiment were calculated per individual well. The luminescence was normalized on the mean
of the medium control wells for each time-point. These compensations result in values of 1 for the
medium control at each time point. Values less than 1 indicate a lower number of cells or a
decrease in metabolic activity compared to the appropriate controls.

15

Figure 1 displays the influence of Healthberry® 865 on the viability of HepG2 cells. The increase of
luciferase activity, measured at nine different time-points, was normalized to the increase of control
cells incubated with the medium. Error bars represent the standard deviation.

20 Healthberry® 865 did not negatively influence cellular growth or metabolic activity at any
concentration analysed, indicating the test compound were non-toxic at these concentrations.
Healthberry® 865 even led to increased metabolic activity and viability of the cells when incubated
with increasing concentrations of the extract.

25

Example 2: Anti-viral effects of berry extracts on hRSV virus

To analyze effects of Healthberry® 865 on hRSV replication, cells were incubated with Healthberry®
865 in different concentrations, and subsequently infected with hRSV subtype B. All experiments
30 were performed in triplicates. After three days the cell culture medium was centrifuged to remove
cells, and viral RNA was isolated from 200µl. Viral loads were determined by RTqPCR using the
LightMix® Modular Respiratory Syncytial kit (Roche). Positive controls with 1000 hRSV genome
copies were included in the RTqPCR. All RTqPCR reactions were performed in triplicates.
Berry extracts of black currants and bilberries, such as Healthberry® 865 inhibited viral replication
35 to approx. 37% even at the lowest concentration. This indicates that even the lowest
concentrations inhibited hRSV replication efficiently.

Figure 2 shows that Healthberry® 865 reduces RSV replication (log scale). HepG2 cells were
incubated with Healthberry® 865, subsequently infected with RSV and viral load was determined
40 using RTqPCR. Error bars indicate the standard deviation of three independent samples.

Similar experiments were performed to analyze effects of the main single anthocyanins present in Healthberry® 865. All four single anthocyanins did not influence hRSV replication at the concentrations examined indicating that the active component of Healthberry® 865 was not present or not applied in a sufficient concentration.

5

Figure 3 shows that single anthocyanins did not inhibit viral replication (log scale). HepG2 cells were incubated with single anthocyanins, subsequently infected with RSV and viral titers were determined with RTqPCR. Error bars indicate the standard deviation of three independent samples.

10

Example 3: Anti-viral effects of berry extracts on Influenza A virus (comparative)

The influence of Healthberry® 865 and single anthocyanins on the replication of Influenza A virus were analyzed. MDCK cells were incubated with the test compounds and subsequently infected with a patient-derived isolate of Influenza virus serotype A. All reactions were performed in triplicates. Cell culture supernatants were harvested after three days, and viral genomic RNAs were isolated from 200µl cell culture supernatants. Viral loads were determined by RTqPCR using the LightMix® Modular Influenza A kit (Roche). Positive controls with 1000 Influenza genome copies were included in the RTqPCR. All RTqPCR reactions were performed in triplicates.

All test materials, including Healthberry® 865, showed similar amounts of virus in the supernatant as the negative control, with only minor differences indicating that none of the components inhibited influenza virus replication.

Figure 4 shows that the replication of influenza virus is not influenced by Healthberry® 865. MDCK cells were pretreated with Healthberry® 865, infected with influenza virus (serotype A). Viral RNAs were isolated and quantified by RTqPCR (Cq-values; note: lower Cq values correspond to higher viral loads).

The results displayed no effect of Healthberry® 865 on Influenza A virus confirming the specificity of the anti-viral effects of berry extracts of black currants and bilberries on specific viruses or virus families, respectively. Other compounds as the single anthocyanins also did not show any influence on the replication of influenza virus.

35

Claims

1. A composition for use in treating or preventing a virus infection in a subject, wherein the virus is
5 from the Pneumoviridae family and wherein the composition comprises an extract of black
currants and bilberries.
2. The composition for use according to claim 1, wherein the black currants are the fruit of *Ribes
nigrum* and/or the bilberries are the fruit of *Vaccinium myrtillus* and preferably, wherein the
10 composition contains an extract from black currants and bilberries in a weight ratio of 0.5:1 to
1:0.5.
3. The composition for use according to any preceding claim wherein the composition is an extract
of the pomaces from black currants and bilberries.
- 15 4. The composition for use according to any preceding claim, wherein the composition comprises
anthocyanins and the anthocyanins are present in the composition at a concentration of at least
25 weight-%.
- 20 5. The composition for use according to any preceding claim, wherein the extract is an alcoholic
extract, preferably a methanol extract.
6. The composition for use according to any preceding claim, wherein the extract is prepared by a
process comprising the steps of extraction of black currants and bilberries, purification via
25 chromatography, mixing of the extract(s) with water and spray-drying of the mixture.
7. The composition for use according to any preceding claim, wherein the composition comprises
one or more of the following anthocyanins:
cyanidin-3-glucoside, cyanidin-3-galactoside, cyanidin-3-arabinoside, delphinidin-3-glucoside,
30 delphinidin-3-galactoside, delphinidin -3-arabinoside, petunidin-3- glucoside, petunidin-3-
galactoside, petunidin-3-arabinose, peonidin-3-glucoside, peonidin-3-galactoside, peonidin-3-
arabinose, malvidin-3-glucoside, malvidin-3-galactoside, malvidin-3-arabinose, cyanidin-3-
rutinoside, delphinidin-3-rutinoside.
- 35 8. The composition for use according to any preceding claim, wherein the composition comprises:
cyanidin-3-glucoside, cyanidin-3-rutinoside, delphinidin-3-glucoside, delphinidin-3-rutinoside,
cyanidin-3-galactoside and delphinidin-3-galactoside.
9. The composition for use according to any preceding claim wherein the virus is selected from
40 avian metapneumovirus (AMPV), human metapneumovirus (HMPV), bovine respiratory

syncytial virus (BRSV), human respiratory syncytial virus A2 (HRSV-A2), human respiratory syncytial virus B1 (HRSV-B1), murine pneumonia virus (MPV).

- 5 10. The composition for use according to any preceding claim wherein the composition comprises anthocyanins and is to be administered to the subject 1 to 10 oral dosages of at least 80 mg anthocyanins each per day, preferably 3 to 6 oral dosages of at least 80 mg anthocyanins each per day.
- 10 11. The composition for use according to any preceding claim wherein the composition is to be administered to the subject, reaching a concentration in the target compartment of at least 30 µg/ml, preferably at least 100 µg/ml.
- 15 12. The composition for use according to any preceding claim wherein the subject is a human, preferably younger than 2 years old or 65 years old or more.
13. The composition for use according to any preceding claim wherein the subject suffers from asthma, chronic obstructive pulmonary disease or congestive heart failure.
- 20 14. The composition for use according to any preceding claim, wherein the composition is for use with a medical device which is to be inserted into the subject, or wherein the subject has had a medical device inserted, optionally wherein the device is inserted via the nose or mouth.
- 25 15. The composition for use according to claim 14, wherein the medical device is a needle, a catheter, a port, an intubation device or tube, or a nebulizer.
- 30 16. The composition for use according to claim 14 or claim 15, wherein a dwell time of the medical device in the subject is more than 24 hours, more than 48 hours, more than 72 hours, more than one week, more than 2 weeks, more than 3 weeks, preferably wherein the dwell time is more than one week, more than 2 weeks or more than 3 weeks.
- 35 17. A liquid composition comprising an extract of black currants and bilberries, wherein the composition is comprised in a nebulizer, preferably a throat spray liquid composition comprising an extract of black currants and bilberries, wherein the composition further comprises an pharmaceutically acceptable excipient suitable for a liquid composition that is to be administered to the mucosal surfaces of the mouth and throat, preferably wherein the excipient comprises one or more of a tonicity adjusting agent, a buffering agent, a preservative, an antioxidant, a stabilizer, a pH adjusting agent, a penetration enhancer, a surfactant and a humectant.
- 40 18. A combined preparation comprising an analgesic or topical anesthetic, and an extract of black currants and bilberries, for simultaneous, separate or sequential use in medicine, preferably wherein the analgesic is ibuprofen or paracetamol/acetaminophen.

19.A medical device suitable for insertion into a subject, the medical device comprising a coating composition on an exterior surface of the device, wherein the coating composition comprising an extract of black currants and bilberries.

5

20.The medical device according to claim 19, wherein the medical device is a needle, a catheter, an intubation device or tube, or a nebulizer, preferably wherein the exterior surface of the medical device is plastic.

10

21.A method of making the medical device according to claim 19 or claim 20, the method comprising applying the coating composition to the exterior surface of the medical device, optionally wherein the coating composition is formulated as a cream, a hydrogel cream, or a spray.

15

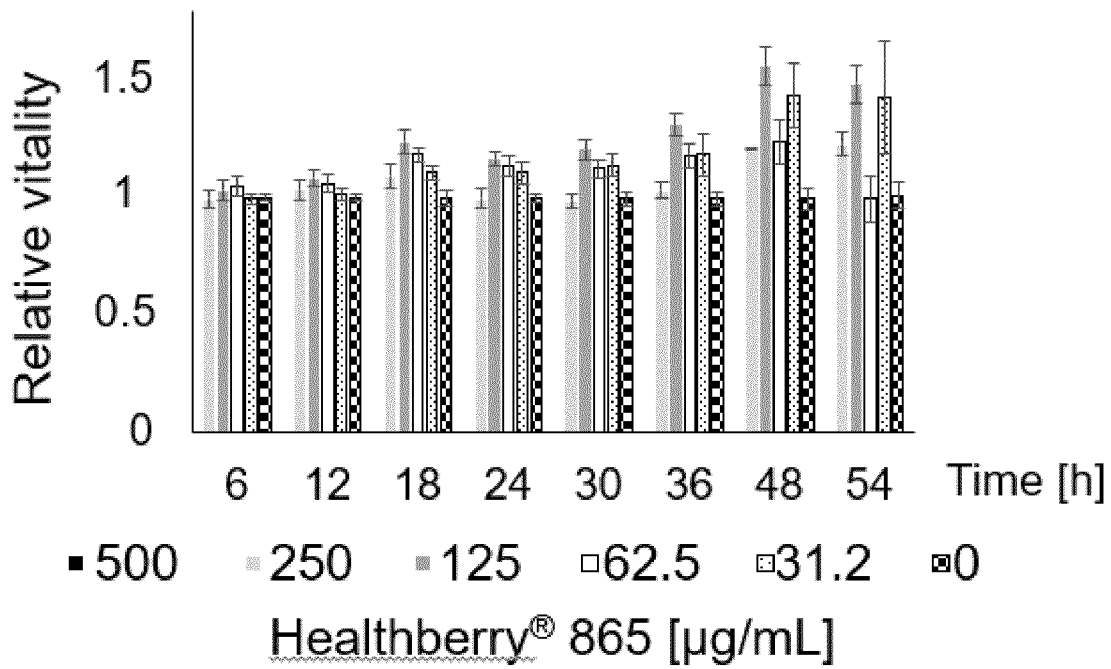


Figure 1: Influence of Healthberry® 865 on the viability of HepG2 cells. The increase of luciferase activity, measured at nine different time-points, was normalized to the increase of control cells incubated with the medium. Error bars represent the standard deviation.

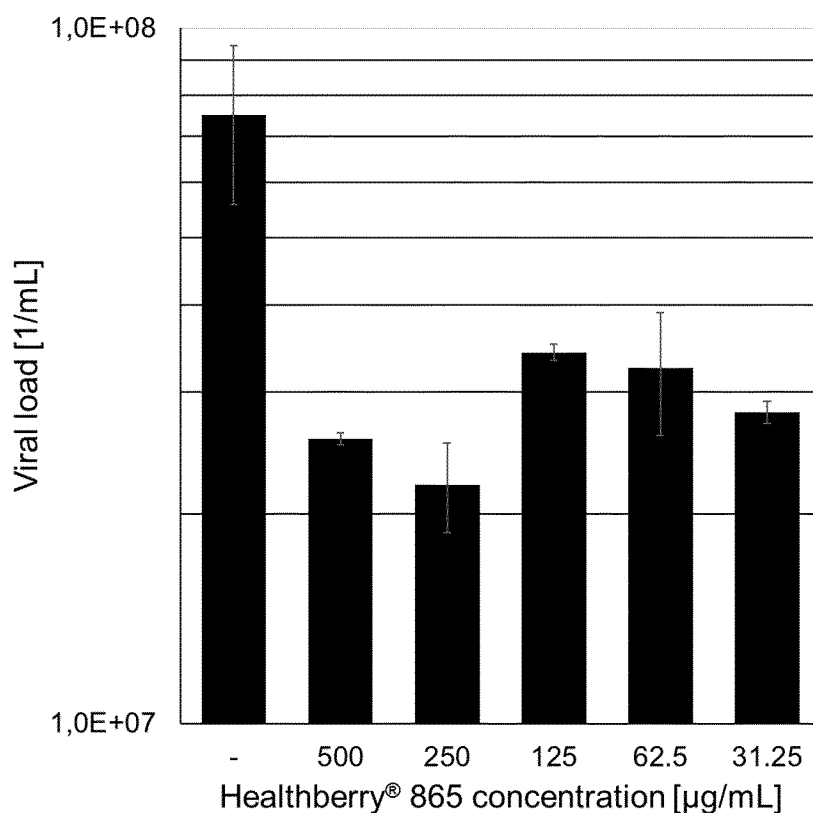


Figure 2: Healthberry® 865 reduces RSV replication (log scale). HepG2 cells were incubated with Healthberry® 865, subsequently infected with RSV and viral load was determined using RTqPCR. Error bars indicate the standard deviation of three independent samples.

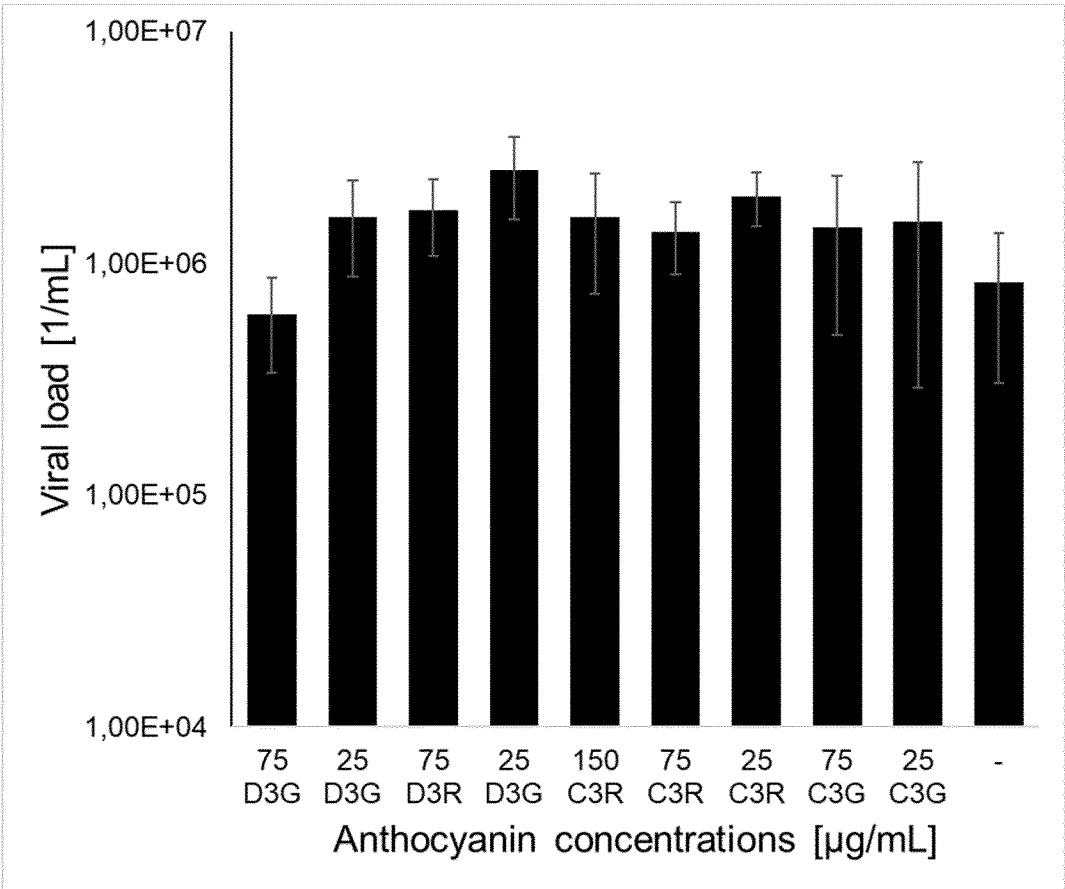


Figure 3: Single anthocyanins did not inhibit viral replication (log scale). HepG2 cells were incubated with single anthocyanins, subsequently infected with RSV and viral titers were determined with RTqPCR. Error bars indicate the standard deviation of three independent samples.

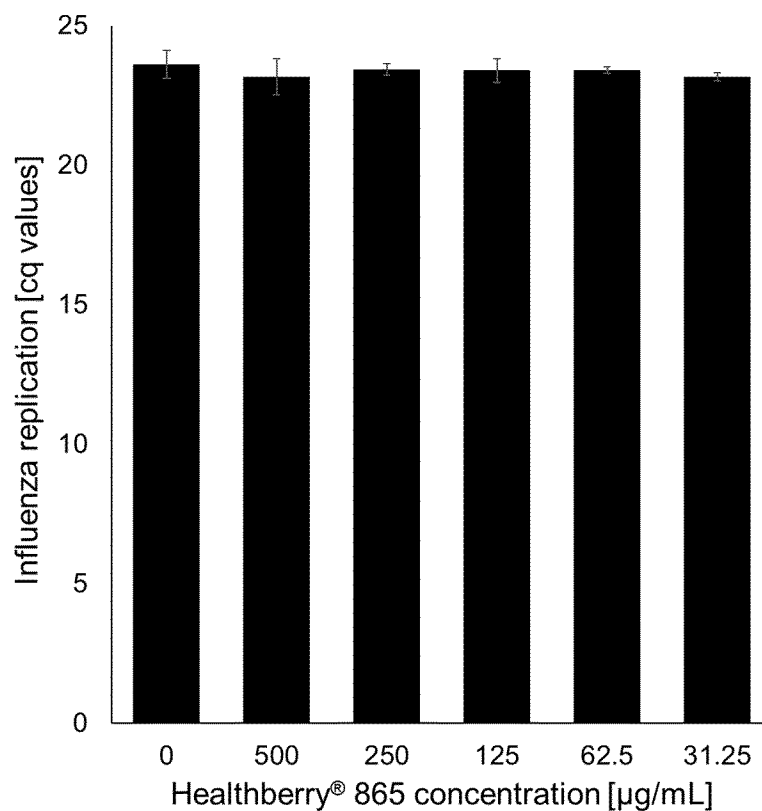


Figure 4: Replication of influenza virus is not influenced by Healthberry® 865. MDCK cells were pretreated with Healthberry® 865, infected with influenza virus (serotype A). Viral RNAs were isolated and quantified by RTqPCR (Cq-values). Note: lower Cq values correspond to higher viral loads.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/058656

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/185 A61K36/45 A61K31/7048 A61P31/14
ADD.

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)
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)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/41137 A1 (UNIFOB [NO]; ANDERSEN OEYVIND MOKSHEIM [NO] ET AL.) 6 November 1997 (1997-11-06) page 9, line 14 - page 10, line 11; tables 1,2 page 18, line 1 - page 27, line 17; example 1 page 36, line 4 - page 38, line 20; claims 1-33	1-21
Y	----- GB 2 562 260 A (SIS SCIENCE IN SPORT LTD [GB]) 14 November 2018 (2018-11-14) page 3, paragraph 3 page 17, paragraph 3 - page 19, paragraph 1 page 31, paragraph 2 ----- -/-	1-21



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

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Date of the actual completion of the international search

19 June 2020

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/058656

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 9 168 276 B2 (BOMBARDELLI EZIO [IT]; RONCHI MASSIMO [IT] ET AL.) 27 October 2015 (2015-10-27) columns 2-3; claims 1,4; examples 1-4 -----	1-21
Y	IKUTA KAZUFUMI ET AL: "Anti-viral and anti-bacterial activities of an extract of blackcurrants (Ribes nigrum L.).", MICROBIOLOGY AND IMMUNOLOGY DEC 2012, vol. 56, no. 12, December 2012 (2012-12), pages 805-809, XP009516099, ISSN: 1348-0421 Antiviral assays - Results - Discussion -----	1-21
Y	NIKOLAEVA-GLOMB LUBOMIRA ET AL: "In vitro antiviral activity of a series of wild berry fruit extracts against representatives of Picorna-, Orthomyxo- and Paramyxoviridae.", NATURAL PRODUCT COMMUNICATIONS JAN 2014, vol. 9, no. 1, January 2014 (2014-01), pages 51-54, XP009516100, ISSN: 1934-578X page 51, column 2 - page 53, column 1 -----	1-21
X	"Nasal Spray", GNPD 1 January 2009 (2009-01-01), XP002757968, Retrieved from the Internet: URL:www.gnpd.com [retrieved on 2009-01-01] the whole document -----	17
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A	WO 03/039569 A1 (MEDPALETT PHARMACEUTICALS AS [NO]; COCKBAIN JULIAN [GB]) 15 May 2003 (2003-05-15) claims 1-10; examples 1-3 -----	1-21
Y	US 2017/333491 A1 (SOLEY ASTALS ALBERT [ES] ET AL) 23 November 2017 (2017-11-23) paragraphs [0030], [0056], [0059], [0060], [0070], [0072] -----	14-16, 19-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/058656

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