genus and even across mammalian species: US 10702567, US 10729735, US 10596186, US 11007239, US 10874704, US 20200206287A1, US 11013776, US 10980852, WO 2018053123A1, WO 2019055119A1, WO 2020042009A1, Plant et al. ("Antiviral activity of oleandrin and a defined extract of Nerium oleander against SARS-CoV-2" in Biomed. Pharma. (2021), 138, 111457), Newman et al. ("Antiviral effects of Oleandrin" in J. Exp. Pharma. (2020), 12, 503-515), Avci et al. ("Determination of in vitro antiviral activity of Nerium oleander distillate against parainfluenza-3 virus" in Animal Vet. Sci. (2014), 2(5), 150-153) (the distillate does not contain oleandrin), Dey et al. ("Pharmacological aspects of Nerium indicum Mill: a comprehensive review" in Pharmacogn. Rev. (2014), 8(16), 156-162), Singh et al. (Nerium oleander derived cardiac glycoside is a novel inhibitor of HIV infectivity" in Fitoter. (2013), 84, 32-39), Hutchison et al. (The botanical glycoside oleandrin inhibits Human T-cell leukemia virus type-1 infectivity and Env-dependent virological synapse formation" in J. Antivir. Antiretrovir. (2019), 11(3), 184), Plante et al. ("Prophylactic and therapeutic inhibition of in vitro SARS-CoV-2 replication by oleandrin" in bioRxiv (2020), doi: 10.1101/2020.07.15.203489).

[0029] In particular, Yang et al. ("Identification of antiviral activity of the cardenolides, Na/K-ATPase inhibitors, against porcine transmissible gastroenteritis virus" in Toxic. Applied Pharma. (2017), 332, 129-137) demonstrate that some cardiac glycosides are active against some coronaviruses in some species but inactive against some coronaviruses in other species. Even within the same animal species, the cardiac glycosides can demonstrate substantially different levels of activity.

[0030] A need remains for improved pharmaceutical compositions containing oleandrin (and/or digoxin), optionally together with other compounds obtained from *Nerium sp.*, e.g. oleanolic acid, ursolic acid, betulinic acid or any combination thereof, that are therapeutically active against specific animal viral infections.

SUMMARY

[0031] The disclosure provides a pharmaceutical composition and method for treating and/or preventing viral infection in an animal; even though, it has been widely known that cardiac glycosides, in particular oleandrin and digoxin, are toxic to animals. The disclosure also provides a method of treating viral infection in animals by administration of the pharmaceutical composition. The inventors have succeeded in preparing antiviral compositions that exhibit sufficient antiviral activity to justify their use in treating viral

infection in animals, while at the same time being administered at doses that are not fatal to the animals. The inventors have developed corresponding treatment methods employing particular dosing regimens.

[0032] The disclosure also provides a prophylactic method of treating an animal at risk of contracting a viral infection, the method comprising chronically administering to the animal one or more doses of an antiviral composition on a recurring basis over an extended treatment period prior to the animal contracting the viral infection, thereby preventing the animal from contracting the viral infection; wherein the antiviral composition comprises oleandrin and/or digoxin. Alternatively, the disclosure also provides a prophylactic method of treating an animal at risk of having a viral disease, the method comprising chronically administering to the animal one or more doses of an antiviral composition on a recurring basis over an extended treatment period within 0-5 days of the animal having contracted a viral infection that causes said viral disease, thereby preventing the animal from exhibiting symptoms associated with said viral disease; wherein the antiviral composition comprises oleandrin and/or digoxin.

[0033] In some examples, the antiviral composition is administered to an animal having virally infected cells. In some examples, the viral infection is caused by any of the following virus families: Arterviridae, Astroviridae, Bornaviridae, Circoviridae, Coronaviridae, Chordopoxvirinae, Flaviviridae, Herpesviridae, Orthomyxoviridae, Papillomaviridae, Papovaviridae, Paramyxoviridae, Parvoviridae, Picornaviridae, Poxviridae, Reoviridae, Retroviridae, Rhabdoviridae, and Togaviridae.

[0034] The animal can be a domestic or livestock animal, e.g. pig, cow, horse, sheep, goat, llama, alpaca, buffalo, deer, elk, giraffe, camel, dog, cat, chicken, turkey, pigeon, duck, pheasant, guinea, or other animal.

[0035] Viral infections and diseases that can be treated include Venezuelan Equine Encephalomyelitis (encephalitis) (VEE) virus, Western Equine Encephalomyelitis (encephalitis) (WEE) virus, Eastern Equine Encephalomyelitis (encephalitis) (EEE) virus, bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), porcine reproductive and respiratory syndrome virus (PRRSV), porcine circovirus type-2 (PCV2), bovine herpes virus type 1 (BHV-1, e.g. infectious bovine rhinotracheitis (IBR)), bovine herpes virus type 2 (BHV-2, bovine herpes mamillitis), bovine herpes virus type 3 (BHV-3, catarrhal fever), bovine herpes virus type 5 (BHV-5, encephalitis), bovine papillomavirus, lyssavirus (rabies, a

Rhabdovirus), Foot and Mouth Disease virus (FMD; aphthovirus of the family Picornaviridae; e.g. serotypes A, O, C, SAT1,SAT2, SAT3, Asia1), lumpy skin disease virus (Capripoxvirus of the Poxviridae family), cowpox virus, pseudocowpox virus (paravaccinia), bovine leukemia virus, bovine lentivirus, respirovirus (bovine parainfluenza-3 virus), Morbillivirus (rinderpest virus), bovine ephemeral fever virus, vesicular stomatitis virus, African swine fever virus, African horse sickness virus (Reoviridae), sheeppox virus and goatpox virus (subfamily Chordopoxviridae, genus *Capripoxvirus*), equine influenza virus, equine infectious anemia virus, equine arteritis virus, classical swine fever virus, Nipah virus, swine vesicular disease virus, transmissible gastroenteritis virus of swine, avian infectious bronchitis virus, infectious laryngotracheitis virus (avian), duck hepatitis virus, avian influenza virus, infectious bursal disease virus (Gumboro), Marek's disease virus (visceral leukosis; Herpes virus), virulent Newcastle disease virus (vNDV, Paramyxoviridae, genus *Avulavirus*), avian metapneumovirus (in turkey), avian influenza virus, Poult Enteritis Mortality Syndrome (PEMS in turkey), columbid alphaherpesvirus-1 (CoHV-1), avian nephritis, arbovirus infections, turkey viral hepatitis, avian encephalomyelitis, avian hepatitis E virus, chicken cholera, fowl pox, fowl cholera, hemorrhagic enteritis in turkeys, canine parvovirus type 1 or type 2, infectious canine hepatitis (ICH, adenovirus 1), canine herpes, canine distemper virus (Morbillivirus), rotavirus intestinal viral in dogs, porcine herpesvirus 1 (pseudorabies, Aujeszky's disease), canine influenza, canine parainfluenza virus, feline herpes virus, feline immunodeficiency virus, feline parvovirus, feline infectious peritonitis virus, feline influenza virus, feline calicivirus, feline leukemia virus, feline viral rhinotracheitis, feline coronavirus, feline rotavirus, feline astrovirus, Torque teno sus virus (TTSuV), Porcine teschovirus (PTV), Porcine bocavirus 1 (PBoV1), swine influenza virus (e.g. type A), porcine endemic diarrhea virus (PEDV), porcine deltacoronavirus, and species and/or variants thereof.

[0036] In some examples, the disclosure provides an antiviral composition comprising (consisting essentially of): a) specific cardiac glycoside(s); b) plural triterpenes; or c) a combination of specific cardiac glycoside(s) and plural triterpenes. The specific cardiac glycoside can be selected from the group consisting of oleandrin and digoxin.

[0037] The disclosure provides a method of treating viral infection in an animal by chronic administration to the animal of an antiviral composition. The animal is treated by chronically administering to the animal a therapeutically effective amount

(therapeutically relevant dose) of the composition, thereby providing relief of symptoms associated with the viral infection or amelioration of the viral infection. Administration of the composition to the animal can begin immediately after infection or any time within zero to about 5 days after infection or at the earliest time after definite diagnosis of infection with virus. The virus can be any virus described herein; however, some viruses are preferred. Chronic administration can be achieved by repeated daily administration of rapid or immediate release dosage form(s) (or composition(s)) or by repeated administration (daily, weekly or monthly) of extended (controlled) release dosage form(s).

[0038] Accordingly, the disclosure also provides a method of treating viral infection in a mammal, the method comprising administering to the mammal one or more therapeutically effective doses of the antiviral composition. The one or more therapeutic dose(s) is(are) not lethal or fatal to the animal. One or more doses are administered on a daily, weekly, and/or monthly basis. One or more doses per day can be administered. The virus can be any virus described herein that is pathogenic to animals.

[0038a] One aspect of the disclosure provides use of an antiviral composition comprising oleandrin, digoxin, or a combination thereof in the manufacture of a medicament for treating viral infection in an animal in need thereof, wherein one or more doses of the antiviral composition comprising oleandrin, digoxin, or a combination thereof is to be administered to the animal, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

[0039] The disclosure also provides a method of treating viral infection in an animal in need thereof, the method comprising:

determining whether or not the animal has a viral infection;

indicating administration of antiviral composition;

administering an initial dose of antiviral composition to the animal according to a prescribed initial dosing regimen for a period of time;

periodically determining the adequacy of the animal's clinical response and/or therapeutic response to treatment with antiviral composition; and

if the animal's clinical response and/or therapeutic response is adequate, then continuing treatment with antiviral composition as needed until the desired clinical endpoint is achieved; or

if the animal's clinical response and/or therapeutic response are inadequate at the initial dose and initial dosing regimen, then escalating or deescalating the dose until the desired clinical response and/or therapeutic response in the animal is achieved.

[0040] Treatment of the animal with antiviral composition is continued as needed. The dose or dosing regimen can be adjusted as needed until the animal reaches the desired clinical endpoint(s) such as a reduction or alleviation of specific symptoms associated with the viral infection. Determination of the adequacy of clinical response and/or therapeutic response can be conducted by a clinician familiar with viral infections.

[0041] The individual steps of the methods of the disclosure can be conducted at separate facilities or within the same facility.

[0042] The disclosure provides alternate examples, for all the examples described herein, wherein the oleandrin is replaced with digoxin or used in combination with digoxin. The methods of the disclosure may employ oleandrin, digoxin, or a combination of oleandrin and digoxin. Accordingly, oleandrin, digoxin, oleandrin-containing composition, digoxin-containing composition, or oleandrin- and digoxin-containing composition may be used in the methods of the disclosure. Cardiac glycoside can be taken to mean oleandrin, digoxin or a combination thereof. A cardiac glycoside-containing composition comprises oleandrin, digoxin or a combination thereof.

[0043] The disclosure also provides a method of treating coronavirus infection, in particular an infection of coronavirus that is pathogenic to animals, e.g. BCV infection or PCV infection, the method comprising chronically administering to an animal, having said infection, therapeutically effective doses of cardiac glycoside (cardiac glycoside-containing composition).

[0044] The disclosure provides a method of preventing an animal from exhibiting one or more symptoms associated with viral infection, the method comprising administering to said animal one or more therapeutically effective doses of cardiac glycoside-containing composition, wherein said one or more doses are administered a) prior to said animal being infected with virus; or b) within a period of up to five days, up to four days, up to three days, up to two days, or up to one day of said animal having been infected with virus.

[0044a] Another aspect of the disclosure provides use of an antiviral composition comprising oleandrin, digoxin, or a combination thereof in the manufacture of a medicament for preventing viral infection in an animal at risk of contracting said viral infection, wherein one or more doses of the antiviral composition comprising oleandrin, digoxin, or a combination thereof is to be administered chronically to the animal on a recurring or continuous basis over an extended treatment period prior to the animal contracting the viral infection, thereby preventing the animal from contracting said viral infection, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV),

bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

[0045] The disclosure provides a method of preventing a viral infection in an animal from progressing to a disease state or from exhibiting one or more symptoms associated with viral infection, the method comprising administering to said animal one or more therapeutically effective doses of cardiac glycoside-containing composition within a period of up to seven days, up to six days, up to five days, up to four days, up to three days, up to two days, or up to one day of said animal having been infected with the virus. In other words, the composition might not stop the infection from occurring, but it would stop the infection from progressing to the disease state.

[0045a] Another aspect of the disclosure provides use of a cardiac glycoside-containing composition in the manufacture of a medicament for preventing an animal from exhibiting one or more symptoms associated with viral infection, wherein one or more doses of the cardiac glycoside-containing composition is to be administered to said animal, wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV), and wherein said one or more doses are to be administered a) prior to said animal being infected with virus; or b) within a period of up to five days, up to four days, up to three days, up to two days, or up to one day of said animal having been infected with virus.

[0045b] Another aspect of the disclosure provides use of an antiviral composition comprising oleandrin, digoxin, or a combination thereof in the manufacture of a medicament for preventing a viral infection in an animal from progressing to a disease state, wherein one or more doses of the antiviral composition is to be administered on a recurring or continuous basis to the animal having the viral infection that has not progressed to the disease state, thereby preventing progression of said viral infection to a disease state, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

[0045c] Another aspect of the disclosure provides use of a cardiac glycoside-containing composition in the manufacture of a medicament for preventing a viral infection in an animal from progressing to a disease state or from exhibiting one or more symptoms

associated with viral infection, wherein one or more therapeutically effective doses of the cardiac glycoside-containing composition is to be administered to said animal within a period of up to seven days, up to six days, up to five days, up to four days, up to three days, up to two days, or up to one day of said animal having been infected with the virus, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

[0046] In some examples, the animal has been in close contact (within six feet) with another animal having a viral infection. Close contact might also be due to said uninfected

animal living with, sharing food with, sharing shelter with, sharing air with, or sharing water with a virally infected animal.

[0047] The disclosure also provides a method of treating coronavirus infection, e.g. bovine coronavirus infection or porcine coronavirus infection, by repeatedly administering (through any of the modes of administration discussed herein) to an animal, having said infection, plural therapeutically effective doses of cardiac glycoside (cardiac glycoside-containing composition). One or more doses may be administered per day for one or more days per week and optionally for one or more weeks per month and optionally for one or more months per year.

[0048] The equivalent of plural daily doses of cardiac glycoside can be achieved by administering to said animal one or more extended-release dosage forms that release therapeutically effective daily doses of cardiac glycoside throughout a treatment period. Additional means of administering effective daily doses may be achieved through use of dosage forms suitable for use in water, milk, liquid feed, milk substitute, colostrum, colostrum substitute, or solid feed.

[0049] The disclosure also provides a method of treating viral infection in an animal, the method comprising administering to the animal 1-10 doses of cardiac glycoside (cardiac glycoside-containing composition) per day for a treatment period of 2 days to about 2 months. Two to eight, two to six, or four doses can be administered daily during the treatment period. Doses can be administered for 2 days to about 60 days, 2 days to about 45 days, 2 days to about 30 days, 2 days to about 21 days, or 2 days to about 14 days. Said administering can be through any of the modes of administration discussed herein. Systemic administration that provides therapeutically effective plasma levels of oleandrin and/or digoxin in said animal is preferred.

[0050] In some examples, one or more doses of cardiac glycoside are administered per day for plural days until the viral infection is cured. In some examples, one or more doses of cardiac glycoside (cardiac glycoside-containing composition) are administered per day for plural days and plural weeks until the viral infection is cured. One or more doses can be administered in a day. One, two, three, four, five, six or more doses can be administered per day.

[0051] A cardiac glycoside-containing composition comprises at least one cardiac glycoside. One or more pharmaceutical excipients are optionally included in said composition. The preferred cardiac glycosides are oleandrin or digoxin. If the cardiac

glycoside-containing composition comprises an extract of *Nerium* sp. or *Digitalis lanata* plant material(s), the extract can further comprise one or more components extracted from said plant material(s).

[0052] In some examples, the antiviral composition further comprises at least one cardiac glycoside-metabolism inhibitor, at least one cardiac glycoside-digestion inhibitor, at least one enzyme inhibitor, or a combination thereof.

[0053] A veterinary clinician will be able to use known dose escalation or de-escalation protocols to determine a safe and effective dose of oleandrin or digoxin to be administered to an animal.

[0054] The maximum tolerated dose (MTD) of cardiac glycoside may vary according to animal species. In some examples, a) said animal is a cow and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 1 ng/mL; b) said animal is a pig and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 5 ng/mL; c) said animal is a horse and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 5 ng/mL; d) said animal is a sheep and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 5 ng/mL; or e) said animal is a goat and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 10 ng/mL.

[0055] The pharmacokinetics of digoxin in animals allow for determination of suitable doses that provide target plasma concentrations of digoxin. The half-life of digoxin is as follows: a) in cattle- about 7-9 hours; b) in sheep- about 7-8 hours; c) in ewes and lambs- 13-15 hours; d) in horses- about 16-18 hours or about 10-23 hours; e) in puppies- about 20-30 hours or about 23 hours; f) in adult dogs- about 4-6 hours; g) in turkeys- about 10-12 hours; h) in cats- about 9-12 hours; i) in calves- about 5-7 hours; and j) in chickens- about 20-30 hours or about 25 hours.

[0056] Suitable nonlethal target plasma concentration of digoxin in animals are as follows: a) in horses- less than about 2 ng/ml or about 0.5-2 ng/ml; b) in dogs- less than about 2.5 ng/ml or about 0.5-2.5 ng/ml; c) in cattle- less than about 2.5 ng/ml or about 0.5-2 ng/ml; d) in chickens- less than about 2 ng/ml.

[0057] Suitable target doses (one to four times daily) for digoxin in animals are as follows: a) in dogs- less than about 100 microg/kg bodyweight or about 5-60 microg/kg

bodyweight; b) in turkeys- less than about 1 mg/kg bodyweight or about 0.05-0.5 mg/kg bodyweight; c) in cattle- less than about 100 micro/kg bodyweight or about 5-50 microg/kg bodyweight; d) in cats- less than about 100 micro/kg bodyweight or 0.5-50 micro/kg bodyweight; e) in horses- less than about 100 micro/kg bodyweight or 0.5-50 micro/kg bodyweight; and f) in chickens- less than 100 micro/kg bodyweight, about 1-50 microg/kg bodyweight, or about 4-20 microg/kg bodyweight.

[0058] Where oleandrin is administered to an animal in the form of Nerium species (Nerium sp.), e.g. *Nerium oleander* or *Nerium indicum*, leaf material, the amount of dried leaf material will preferably be a) less than 100 mg/Kg bodyweight or less than 50 mg/Kg bodyweight for a cow; b) less than 110 mg/Kg bodyweight for a goat; c) less than 110 mg/Kg bodyweight or less than 250 mg/Kg bodyweight for a sheep.

[0059] In some examples, the concentration of oleandrin and/or digoxin in the plasma of a treated animal is about 10 ng/mL or less, about 5 ng/mL or less, about 2.5 ng/mL or less, about 2 ng/mL or less, about 1 ng/mL, or about 0.5 ng/mL or less. In some examples, the concentration of oleandrin and/or digoxin in the plasma of a treated animal is about 0.0001 ng/mL or more, about 0.0005 ng/mL or more, about 0.001 ng/mL or more, about 0.0015 ng/mL or more, about 0.01 ng/mL or more, about 0.015 ng/mL or more, about 0.1 ng/mL or more, about 0.15 ng/mL or more, about 0.05 ng/mL or more, or about 0.075 ng/mL or more. The daily dose of antiviral composition administered to the animal will be sufficient to provide a plasma concentration of oleandrin or digoxin within at least one of the ranges set forth herein. The disclosure includes all combinations and selections of the plasma concentration ranges set forth herein.

[0060] The antiviral composition can be administered chronically, i.e. on a recurring basis, such as daily, every other day, every second day, every third day, every fourth day, every fifth day, every sixth day, weekly, every other week, every second week, every third week, monthly, bimonthly, semi-monthly, every other month every second month, quarterly, every other quarter, trimesterly, seasonally, semi-annually and/or annually. The treatment period one or more weeks, one or more months, one or more quarters and/or one or more years. An effective dose of cardiac glycoside (cardiac glycoside-containing composition) is administered one or more times in a day.

[0061] In some examples, the animal is administered 140 microg to 315 microg per day of cardiac glycoside. In some examples, a dose comprises 20 microg to 750 microg, 12 microg to 300 microg, or 12 microg to 120 microg of cardiac glycoside. The daily dose

of cardiac glycoside can range from 20 microg to 750 microg, 0.01 microg to 100 mg, or 0.01 microg to 100 microg of cardiac glycoside/day.

[0062] The dose of cardiac glycoside can be also about 0.5 to about 500 microg/day or less, about 0.5 to about 400 microg/day or less, about 0.5 to about 300 microg/day or less, about 0.5 to about 200 microg/day or less, about 0.5 to about 100 microg/day or less, about 1 to about 80 microg/day, about 1.5 to about 60 microg/day, about 1.8 to about 60 microg/day, about 1.8 to about 40 microg/day.

[0063] In some examples, the cardiac glycoside is administered in at least two dosing phases: a loading phase and a maintenance phase. The loading phase is continued until about achievement of steady state plasma level of cardiac glycoside. The maintenance phase begins at either the initiation of therapy or after about completion of the loading phase. Dose titration can occur in the loading phase and/or the maintenance phase.

[0064] All dosing regimens, dosing schedules, and doses described herein are contemplated as being suitable; however, some dosing regimens, dosing schedules, and doses may be more suitable for some subject than for others. The target clinical endpoints are used to guide said dosing.

[0065] The composition can be administered systemically. Modes of systemic administration include parenteral, buccal, enteral, intramuscular, subdermal, sublingual, peroral, pulmonary, or oral. The composition can also be administered via injection or intravenously. The composition may also be administered by two or more routes to the same subject. In some examples, the composition is administered by a combination of any two or more modes of administration selected from the group consisting of parenteral, buccal, enteral, intramuscular, subdermal, sublingual, peroral, pulmonary, and oral.

[0066] The cardiac glycoside may also be included in a feed and/or a liquid and administered orally to the animal. The solid feed may comprise cardiac glycoside and at least one feedstuff. The liquid feed may comprise cardiac glycoside, at least one liquid, and at least one nutrient. Cardiac glycoside may also be administered in a milk substitute product or in water. The cardiac glycoside may also be administered to the animal by feeding the animal leaf material from the *Nerium* sp. plant. The leaf material may be dried or undried. In some examples, the antiviral composition excludes *Nerium* sp. or *Digitalis lanata* plant material.

[0067] The disclosure also provides a sublingual dosage form comprising oleandrin (or digoxin) and liquid carrier. The disclosure also provides a method of treating viral infection

comprising sublingually administering plural doses of an oleandrin-containing (digoxin-containing) composition to an animal having said viral infection. One or more doses can be administered per day for two or more days per week and for one or more weeks per month, optionally for one or months per year. The liquid carrier can comprise water, oil, liquid feed, or a combination of any thereof.

[0068] In some examples, the antiviral composition comprises oleandrin (or digoxin or a combination of oleandrin and digoxin) and oil. The oil can comprise medium chain triglycerides (MCT). The antiviral composition can comprise one, two or more oleandrin-containing extracts and one or more pharmaceutical excipients.

[0069] In some examples, the glycoside-containing composition comprises an extract of *Nerium sp.*, said extract comprising a) at least oleandrin; b) at least oleandrin, oleanolic acid, ursolic acid, and betulinic acid; or c) at least oleandrin, oleanolic acid, ursolic acid, betulinic acid, kanerocin, kanerodione, oleandrigenin, Nerium F, neritaloside, odoroside, adynerin, odoroside-G-acetate, and gitoxigenin.

[0070] The cardiac glycoside-containing composition (or the extract) may further comprise polyphenol(s), carbohydrate(s), flavonoid(s), amino acid(s), soluble protein(s), cellulose, starch, alkaloid(s), saponin(s), tannin(s), and any combination thereof.

[0071] The amino acid can be selected from the group consisting of aspartic acid, glutamic acid, asparagine, serine, glutamine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, cysteine, isoleucine, leucine, phenylalanine, tryptophan, and lysine. In some examples, the amino is selected from the group consisting of asparagine, arginine, threonine, alanine, proline, tyrosine, valine, isoleucine, leucine, phenylalanine, tryptophan, and lysine.

[0072] If present in the antiviral composition, additional cardiac glycoside can be further included: odoroside or neritaloside. The aglycone oleandrigenin can also be further included. In some examples, the composition further comprises a) one or more triterpenes; b) one or more steroids; c) one or more triterpene derivatives; d) one or more steroid derivatives; or e) a combination thereof. In some examples, the composition comprises cardiac glycoside and a) two or three triterpenes; b) two or three triterpene derivatives; c) two or three triterpene salts; or d) a combination thereof. In some examples, the triterpene is selected from the group consisting of oleanolic acid, ursolic acid, betulinic acid, and salts or derivatives thereof.

[0073] Some examples of the disclosure include those wherein a pharmaceutical composition comprises at least one pharmaceutical excipient and the antiviral composition. In some examples, the antiviral composition comprises a) at least one cardiac glycoside and at least one triterpene; b) at least one cardiac glycoside and at least two triterpenes; c) at least one cardiac glycoside and at least three triterpenes; d) at least two triterpenes and excludes cardiac glycoside; e) at least three triterpenes and excludes cardiac glycoside; or f) at least one cardiac glycoside, e.g. oleandrin, digoxin. As used herein, the generic terms triterpene and cardiac glycoside also encompass salts and derivatives thereof, unless otherwise specified.

[0074] The cardiac glycoside can be present in a pharmaceutical composition in pure form or as part of an extract containing one or more cardiac glycosides. The triterpene(s) can be present in a pharmaceutical composition in pure form or as part of an extract containing triterpene(s). In some examples, the cardiac glycoside is present as the primary therapeutic component, meaning the component primarily responsible for antiviral activity, in the pharmaceutical composition.

[0075] In some examples, an oleandrin-containing extract is obtained by extraction of plant material. The extract can comprise a hot-water extract, cold-water extract, supercritical fluid (SCF) extract, subcritical liquid extract, organic solvent extract, or combination thereof of the plant material. In some examples, the extract has been (biomass) prepared by subcritical liquid extraction of *Nerium* plant mass (biomass) using, as the extraction fluid, subcritical liquid carbon dioxide, optionally comprising alcohol. In some examples, the oleandrin-containing composition comprises two or more different types of oleandrin-containing extracts.

[0076] Examples of the disclosure include those wherein the oleandrin-containing biomass (plant material) is *Nerium* sp., e.g. *Nerium oleander*, *Nerium oleander* L (Apocynaceae), *Nerium odourum*, *Nerium indicum* Mill, white oleander, pink oleander, *Agrobacterium tumefaciens*, cell culture (cellular mass) of any of said species, or a combination thereof. In some examples, the biomass comprises leaves, stems, flowers, bark, fruits, seeds, sap, and/or pods.

[0077] In some examples, the extract comprises at least one other pharmacologically active agent, obtained along with the cardiac glycoside during extraction, that contributes to the therapeutic efficacy of the cardiac glycoside when the extract is administered to an animal. In some examples, the composition further

comprises one or more other non-cardiac glycoside therapeutically effective agents, i.e. one or more agents that are not cardiac glycosides. In some examples, the composition further comprises one or more antiviral compound(s). In some examples, the antiviral composition excludes a pharmacologically active polysaccharide.

[0078] For each example of the disclosure, the preferred cardiac glycoside is a) oleandrin, b) digoxin, or c) a combination of oleandrin and digoxin.

[0079] In some examples, the extract comprises one or more cardiac glycosides and one or more cardiac glycoside precursors (such as cardenolides, cardadienolides and cardatrienolides, all of which are the aglycone constituents of cardiac glycosides, for example, digitoxin, acetyl digitoxin, digitoxigenin, digoxin, acetyl digoxin, digoxigenin, medigoxin, strophanthins, cymarine, ouabain, or strophanthidin). The extract may further comprise one or more glycone constituents of cardiac glycosides (such as glucoside, fructoside, and/or glucuronide) as cardiac glycoside precursors. Accordingly, the antiviral composition may comprise one or more cardiac glycosides and two more cardiac glycoside precursors selected from the group consisting of one or more aglycone constituents, and one or more glycone constituents. The extract may also comprise one or more other non-cardiac glycoside therapeutically effective agents obtained from *Nerium* sp. plant material.

[0080] In some examples, a composition containing oleandrin (OL), oleanolic acid (OA), ursolic acid (UA) and betulinic acid (BA) is more efficacious than pure oleandrin, when equivalent doses based upon oleandrin content are compared.

[0081] In some examples, the molar ratio of total triterpene content (OA + UA + BA) to oleandrin ranges from about 15:1 to about 5:1, or about 12:1 to about 8:1, or about 100:1 to about 15:1, or about 100:1 to about 50:1, or about 100:1 to about 75:1, or about 100:1 to about 80:1, or about 100:1 to about 90:1, or about 10:1.

[0082] In some examples, the molar ratios of the individual triterpenes to oleandrin range as follows: about 2-8 (OA) : about 2-8 (UA) : about 0.1-1 (BA) : about 0.5-1.5 (OL); or about 3-6 (OA) : about 3-6 (UA) : about 0.3-8 (BA) : about 0.7-1.2 (OL); or about 4-5 (OA) : about 4-5 (UA) : about 0.4-0.7 (BA) : about 0.9-1.1 (OL); or about 4.6 (OA) : about 4.4 (UA) : about 0.6 (BA) : about 1 (OL).

[0083] In some examples, the other therapeutic agent, such as that obtained by extraction of *Nerium* sp. plant material, is not a polysaccharide obtained during preparation of the extract, meaning it is not an acidic homopolygalacturonan or arabinogalaturonan. In some examples, the extract excludes another therapeutic agent and/or excludes an

acidic homopolygalacturonan or arabinogalaturonan obtained during preparation of the extract.

[0084] In some examples, the other therapeutic agent, such as that obtained by extraction of *Nerium* sp. plant material, is a polysaccharide obtained during preparation of the extract, e.g. an acidic homopolygalacturonan or arabinogalaturonan. In some examples, the extract comprises another therapeutic agent and/or comprises an acidic homopolygalacturonan or arabinogalaturonan obtained during preparation of the extract from said plant material.

[0085] In some examples, the extract comprises oleandrin and at least one other compound selected from the group consisting of cardiac glycoside, glycone, aglycone, steroid, triterpene, polysaccharide, saccharide, alkaloid, fat, protein, neritaloside, odoroside, oleanolic acid, ursolic acid, betulinic acid, oleandrigenin, oleaside A, betulin (urs-12-ene-3β,28-diol), 28-norurs-12-en-3β-ol, urs-12-en-3β-ol, 3β,3β-hydroxy-12-oleanen-28-oic acid, 3β,20α-dihydroxyurs-21-en-28-oic acid, 3β,27-dihydroxy-12-ursen-28-oic acid, 3β,13β-dihydroxyurs-11-en-28-oic acid, 3β,12α-dihydroxyoleanan-28,13β-olide, 3β,27-dihydroxy-12-oleanan-28-oic acid, homopolygalacturonan, arabinogalaturonan, chlorogenic acid, caffeic acid, L-quinic acid, 4-coumaroyl-CoA, 3-O-caffeoylquinic acid, 5- O-caffeoylquinic acid, cardenolide B-1, cardenolide B-2, oleagenin, neridiginoside, nerizoside, odoroside-H, 3-beta-O-(D-diginosyl)-5-beta, 14 beta-dihydroxy-card-20(22)-enolide pectic polysaccharide composed of galacturonic acid, rhamnose, arabinose, xylose, and galactose, polysaccharide with MW in the range of 17000-120000 D, or MW about 35000 D, about 3000 D, about 5500 D, or about 12000 D, cardenolide monoglycoside, cardenolide N-1, cardenolide N-2, cardenolide N-3, cardenolide N-4, pregnane, 4,6-diene- 3,12,20-trione, 20R-hydroxypregna-4,6-diene-3,12-dione, 16beta,17beta-epoxy-12beta-hydroxypregna-4,6-diene-3,20-dione, 12beta-hydroxypregna-4,6,16-triene-3,20-dione (neridienone A), 20S,21-dihydroxypregna-4,6-diene-3,12-dione (neridienone B), neriucoumaric acid, isoneriucoumaric acid, oleanderoic acid, oleanderen, 8alpha-methoxylabdan-18-oic acid, 12-ursene, kaneroside, neriumoside, 3β-*O*-(D-diginosyl)-2α- hydroxy-8,14β-epoxy-5β-carda-16:17, 20: 22- dienolide, 3β-*O*-(D-diginosyl)-2α,14β- dihydroxy-5β- carda-16:17,20:22-dienolide, 3β,27-dihydroxy-urs-18-en-13,28-olide, 3β,22α,28-trihydroxy-25-nor-lup-1(10),20(29)-dien-2-one, *cis*-karenin (3β-hydroxy-28-Z-p-coumaroyloxy-urs-12-en-27-oic acid), *trans*-karenin (3-β-hydroxy-

28-E-p-coumaroyloxy-urs-12-en-27-oic acid), 3beta-hydroxy-5alpha-carda-14(15),20(22)-dienolide (beta- anhydroepidigitoxigenin), 3 beta-O-(D-digitalosyl)-21-hydroxy-5beta-carda-8,14,16,20(22)-tetraenolide (neriumogenin-A-3beta-D-digitaloside), proceragenin, neridienone A, 3beta,27-dihydroxy-12-ursen-28-oic acid, 3beta,13beta-dihydroxyurs-11-en-28-oic acid, 3beta-hydroxyurs-12-en-28-aldehyde, 28- orurs-12-en-3beta-ol, urs-12-en-3beta-ol, urs-12-ene-3beta,28-diol, 3beta,27-dihydroxy-12-oleanen-28-oic acid, (20S, 24R)-epoxydammarane-3beta,25-diol, 20beta,28-epoxy-28alpha-methoxytaraxasteran-3beta-ol, 20beta,28-epoxytaraxaster-21-en-3beta-ol, 28-nor-urs-12-ene-3beta,17 beta-diol, 3beta-hydroxyurs-12-en-28-aldehyde, alpha-neriursate, beta-neriursate, 3alpha-acetophenoxy-urs-12-en-28-oic acid, 3beta-acetophenoxy-urs-12-en-28-oic acid, oleanderolic acid, kanerodione, 3β-*p*-hydroxyphenoxy-11α-methoxy-12α-hydroxy-20-ursen-28-oic acid, 28-hydroxy-20(29)-lupen-3,7-dione, kanerocin, 3alpha-hydroxy-urs-18,20-dien-28-oic acid, D-sarmentose, D-diginose, neridiginoside, nerizoside, isoricinoleic acid, gentiobiosylnerigoside, gentiobiosylbeaumontoside, gentiobiosyloleandrin, folinerin, 12β-hydroxy-5β-carda-8,14,16,20(22)-tetraenolide, 8β-hydroxy-digitoxigenin, Δ16-8β- hydroxy-digitoxigenin, Δ16-neriagenin, uvaol, ursolic aldehyde, 27(p-coumaroyloxy)ursolic acid, oleanderol, 16-anhydro-deacteyl-nerigoside, 9-D-hydroxy-cis-12-octadecanoic acid, adigoside, adynerin, alpha-amyrin, beta-sitosterol, campestrol, caoutchouc, capric acid, caprylic acid, choline, cornerin, cortenerin, deacetyloleandrin, diacetyl-nerigoside, foliandrin, pseudocuramine, quercetin, quercetin-3-rhamnoglucoside, quercitrin, rosaginin, rutin, stearic acid, stigmasterol, strospeside, urehitoxin, and uzarigenin. Additional components that may be present in the extract are disclosed by Gupta et al. (IJPSR (2010(, 1(3), 21-27, the entire disclosure of which is hereby incorporated by reference).

[0086] Oleandrin may also be obtained from extracts of suspension cultures derived from *Agrobacterium tumefaciens*-transformed calli. Hot water, organic solvent, aqueous organic solvent, subcritical liquid extract, or supercritical fluid extract of agrobacterium may be used according to the disclosure.

[0087] Oleandrin may also be obtained from extracts of *Nerium sp.* microculture in vitro, whereby shoot cultures can be initiated from seedlings and/or from shoot apices of the *Nerium sp.* cultivars, e.g. Splendens Giganteum, Revanche or Alsace, or other cultivars. Hot water, organic solvent, aqueous organic solvent, or supercritical fluid extracts of microcultured *Nerium sp.* may be used according to the disclosure.

[0088] The extract may also be obtained by extraction of cellular mass (such as is present in cell culture) of any of said plant species.

[0089] The disclosure also provides use of a cardiac glycoside in the manufacture of a medicament for the treatment of viral infection in an animal. In some examples, the manufacture of such a medicament comprises: providing one or more antiviral compounds of the disclosure; including a dose of antiviral compound(s) in a pharmaceutical dosage form; and packaging the pharmaceutical dosage form. In some examples, the manufacture can be conducted as described in PCT International Application No. PCT/US06/29061. The manufacture can also include one or more additional steps such as: delivering the packaged dosage form to a vendor (retailer, wholesaler and/or distributor); selling or otherwise providing the packaged dosage form to an animal having a viral infection; including with the medicament a label and a package insert, which provides instructions on use, dosing regimen, administration, content and toxicology profile of the dosage form. In some examples, the treatment of viral infection comprises: determining that an animal has a viral infection; indicating administration of pharmaceutical dosage form to the animal according to a dosing regimen; administering to the animal one or more pharmaceutical dosage forms, wherein the one or more pharmaceutical dosage forms is administered according to the dosing regimen.

[0090] The pharmaceutical composition can further comprise a combination of at least one material selected from the group consisting of a water soluble (miscible) co-solvent, a water insoluble (immiscible) co-solvent, a surfactant, an antioxidant, a chelating agent, and an absorption enhancer.

[0091] The solubilizer is at least a single surfactant, but it can also be a combination of materials such as a combination of: a) surfactant and water miscible solvent; b) surfactant and water immiscible solvent; c) surfactant, antioxidant; d) surfactant, antioxidant, and water miscible solvent; e) surfactant, antioxidant, and water immiscible solvent; f) surfactant, water miscible solvent, and water immiscible solvent; or g) surfactant, antioxidant, water miscible solvent, and water immiscible solvent.

[0092] The pharmaceutical composition optionally further comprises a) at least one liquid carrier; b) at least one emulsifying agent; c) at least one solubilizing agent; d) at least one dispersing agent; e) at least one other excipient; or f) a combination thereof.

[0093] In some examples, the water miscible solvent is low molecular weight (less than 6000) PEG, glycol, or alcohol. In some examples, the surfactant is a pegylated surfactant, meaning a surfactant comprising a poly(ethylene glycol) functional group.

[0094] The disclosure includes all combinations of the aspects and examples of the disclosure disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

[0095] The following figures form part of the present description and describe exemplary embodiments of the claimed invention. The skilled artisan will, in light of these figures and the description herein, be able to practice the invention without undue experimentation.

[0096] FIGS. 1A and 1B depict charts summarizing the in vitro dose response therapeutic antiviral activity of oleandrin (FIG. 1A) and extract containing oleandrin (FIG. 1B; PBI-oleandrin) as compared to control (DMSO vehicle) against bovine coronavirus as determined in HRT cells. (Example 6)

[0097] FIGS. 2A and 2B depict charts summarizing the in vitro dose response prophylactic antiviral activity of oleandrin (FIG. 2A) and extract containing oleandrin (FIG. 2B: PBI-oleandrin) against bovine coronavirus as determined in HRT cells. (Example 22)

[0098] FIGS. 3A and 3B depict charts summarizing the in vitro dose response therapeutic antiviral activity of oleandrin (FIG. 3A) and extract containing oleandrin (FIG. 3B; PBI-oleandrin) as compared to control (DMSO vehicle) against BVDV as determined in MDBK cells. (Example 13)

[0099] FIGS. 4A and 4B depict charts summarizing the in vitro dose response prophylactic antiviral activity of oleandrin (FIG. 4A) and extract containing oleandrin (FIG. 4B: PBI-oleandrin) against BVDV as determined in MDBK cells. (Example 22)

[00100] FIGS. 5A and 5B depict charts summarizing the in vitro dose response therapeutic antiviral activity of oleandrin (FIG. 5A) and extract containing oleandrin (FIG. 5B; PBI-oleandrin) as compared to control (DMSO vehicle) against PRRSV as determined in MARC 145 cells. (Example 14)

[00101] FIGS. 6A and 6B depict charts summarizing the in vitro dose response prophylactic antiviral activity of oleandrin (FIG. 6A) and extract containing oleandrin (FIG. 6B: PBI-oleandrin) against PRRSV as determined in MARC 145 cells. (Example 23)

CLAIMS

1) Use of an antiviral composition comprising oleandrin, digoxin, or a combination thereof in the manufacture of a medicament for treating viral infection in an animal in need thereof, wherein one or more doses of the antiviral composition comprising oleandrin, digoxin, or a combination thereof is to be administered to the animal, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

2) Use of an antiviral composition comprising oleandrin, digoxin, or a combination thereof in the manufacture of a medicament for preventing viral infection in an animal at risk of contracting said viral infection, wherein one or more doses of the antiviral composition comprising oleandrin, digoxin, or a combination thereof is to be administered chronically to the animal on a recurring or continuous basis over an extended treatment period prior to the animal contracting the viral infection, thereby preventing the animal from contracting said viral infection, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

3) Use of a cardiac glycoside-containing composition in the manufacture of a medicament for preventing an animal from exhibiting one or more symptoms associated with viral infection, wherein one or more doses of the cardiac glycoside-containing composition is to be administered to said animal, wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV), and wherein said one or more doses are to be administered a) prior to said animal being infected with virus; or b) within a period of up to five days, up to four days, up to three days, up to two days, or up to one day of said animal having been infected with virus.

4) Use of an antiviral composition comprising oleandrin, digoxin, or a combination thereof in the manufacture of a medicament for preventing a viral infection in an animal from progressing to a disease state, wherein one or more doses of the antiviral composition is to be administered on a recurring or continuous basis to the animal having the viral infection that has not progressed to the disease state, thereby preventing progression of said viral infection to a disease state, and wherein the viral infection is selected from the group consisting of bovine

coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

5) Use of a cardiac glycoside-containing composition in the manufacture of a medicament for preventing a viral infection in an animal from progressing to a disease state or from exhibiting one or more symptoms associated with viral infection, wherein one or more therapeutically effective doses of the cardiac glycoside-containing composition is to be administered to said animal within a period of up to seven days, up to six days, up to five days, up to four days, up to three days, up to two days, or up to one day of said animal having been infected with the virus, and wherein the viral infection is selected from the group consisting of bovine coronavirus (BCV), porcine coronavirus (PCV), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and porcine reproductive and respiratory syndrome virus (PRRSV).

6) The use of any one of the above claims, wherein the antiviral composition is to be administered systemically.

7) The use of any one of the above claims, wherein the animal has been in close contact (within six feet) with another animal having a viral infection, and/or wherein the uninfected animal has been living with, sharing food with, sharing shelter with, sharing air with, or sharing water with a virally infected animal.

8) The use of any one of the above claims, wherein

a) said animal is a cow and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 1 ng/mL;

b) said animal is a pig and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 5 ng/mL;

c) said animal is a horse and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 5 ng/mL;

d) said animal is a sheep and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 5 ng/mL; or

e) said animal is a goat and the dose of antiviral composition provides a maximum plasma concentration of digoxin or oleandrin of no more than 10 ng/mL.

9) The use of any one of the above claims, wherein a dose of said antiviral composition comprises about 0.05-0.5 microg/kg/day, about 0.05-0.35 microg/kg/day, about 0.05-0.22 microg/kg/day, about 0.05-0.4 microg/kg/day, or about 0.05-0.3 microg/kg/day, based upon the unit amount of oleandrin and/or digoxin per kg of bodyweight per day.

10) The use of any one of the above claims, wherein the cardiac glycoside is to be administered in at least two dosing phases: a loading phase and a maintenance phase.

11) The use of any one of claims 1-7, wherein following administration of said one or more doses, the plasma concentration of oleandrin in said subject is in the range of about 0.05 to about 2 ng/ml, about 0.005 to about 10 ng/mL, about 0.005 to about 8 ng/mL, about 0.01 to about 7 ng/mL, about 0.02 to about 7 ng/mL, about 0.03 to about 6 ng/mL, about 0.04 to about 5 ng/mL, or about 0.05 to about 2.5 ng/mL, in terms of the amount of oleandrin per mL of plasma.

12) The use of any one of the above claims, wherein a) plural doses are one or more doses to be administered per day for two or more days per week; b) 1-10 doses of cardiac glycoside (cardiac glycoside-containing composition) per day are to be administered for a treatment period of 2 days to about 2 months; or c) one or more doses of cardiac glycoside (cardiac glycoside-containing composition) are to be administered per day for plural days and plural weeks until the viral infection is cured.

13) The use of claim 12, wherein dosing is to be continued for one or more weeks per month.

14) The use of claim 13, wherein dosing is to be continued for one or more months per year.

15) The use of any one of the above claims, wherein said antiviral composition comprises a) oleandrin; b) a combination of oleandrin, oleanolic acid (free acid, salt, or prodrug) and ursolic acid (free acid, salt, or prodrug); c) a combination of oleandrin, oleanolic acid (free acid, salt, or prodrug) and betulinic acid (free acid, salt, or prodrug); d) a combination of oleandrin, oleanolic acid (free acid, salt, or prodrug), ursolic acid (free acid, salt, or prodrug), and betulinic acid (free acid, salt, or prodrug); e) a combination of oleandrin, oleanolic acid (free acid or salt thereof), ursolic acid (free acid or salt), and betulinic acid (free acid or); f) a combination of oleandrin and at least two triterpenes selected from the group consisting of oleanolic acid (free acid, salt, or prodrug), ursolic acid (free acid, salt, or prodrug), betulinic acid (free acid, salt, or prodrug); or g) a combination of at least oleandrin, oleanolic acid, ursolic acid, betulinic acid, kanerocin, kanerodione, oleandrigenin, Nerium F, neritaloside, odoroside, adynerin, odoroside-G-acetate, and gitoxigenin.

16) The use of any one of the above claims, wherein said antiviral composition further comprises polyphenol(s), carbohydrate(s), flavonoid(s), amino acid(s), soluble protein(s), cellulose, starch, alkaloid(s), saponin(s), tannin(s), or any combination thereof.

17) The use of any one of the above claims, wherein said antiviral composition comprises an extract of biomass.

18) The use of claim 17, wherein said extract is prepared by hot-water extraction, cold-water extraction, organic solvent extraction, supercritical fluid extraction, subcritical liquid extraction, or a combination thereof.

19) The use of claims 17 or 18, wherein said extract comprises a combination of oleandrin and one or more compounds extracted from said biomass.

20) The use of claim 19, wherein said biomass is plant material from *Nerium* species or *Agrobacterium* species biomass.

21) The use of claim 19, wherein said extract further comprises one or more cardiac glycoside precursors, one or more glycone constituents of cardiac glycosides, or a combination thereof.

22) The use of any one of the above claims, wherein the animal is selected from the group consisting of pig, cow, horse, sheep, goat, llama, alpaca, buffalo, deer, elk, giraffe, camel, dog, cat, chicken, turkey, pigeon, duck, pheasant, and guinea.

23) The use of any one of the above claims, wherein said antiviral composition is included in a feed and/or liquid administered orally to the animal.