arthritis, uveitis, keratoconjunctivitis, sicca syndrome, Sjögren's syndrome, and HAM/TSP, among others. HAM/TSP is clinically characterized by chronic progressive spastic paraparesis, urinary incontinence, and mild sensory disturbance. While ATLL is etiologically linked to viral latency, oncogenic transformation, and the clonal expansion of HTLV-1-infected cells, the inflammatory diseases, such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), are caused by autoimmune and/or immunopathological responses to proviral replication and the expression of viral antigens. HAM/TSP is a progressive neuroinflammatory disease that results in the deterioration and demyelination of the lower spinal cord. HTLV-1-infected circulating T-cells invade the central nervous system (CNS) and cause an immunopathogenic response against virus and possibly components of the CNS. Neural damage and subsequent degeneration can cause severe disability in patients with HAM/TSP. The persistence of proviral replication and the proliferation of HTLV-1-infected cells in the CNS leads to a cytotoxic T-cell response targeted against viral antigens, and which may be responsible for the autoimmune destruction of nervous tissues.

[0022] Even though cardiac glycosides have been demonstrated to exhibit some antiviral activity against a few viruses, the specific compounds exhibit very different levels of antiviral activity against different viruses, meaning that some exhibit very poor antiviral activity and some exhibit better antiviral activity when evaluated against the same virus(es).

[0023] A need remains for improved pharmaceutical compositions containing oleandrin, oleanolic acid, ursolic acid, betulinic acid or any combination thereof that are therapeutically active against specific viral infections.

SUMMARY ~~OF THE INVENTION~~

[0024] The ~~invention~~ disclosure provides a pharmaceutical composition and method for treating and/or preventing viral infection in a mammalian subject. The disclosure ~~invention~~ also provides a pharmaceutical composition and method for treating viral infection, e.g. Viral hemorrhagic fever (VHF) infection, in a mammalian subject. The disclosure ~~invention~~ also provides a method of treating viral infection in mammals 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 humans and animals. The inventors have developed corresponding treatment methods employing particular dosing regimens. The disclosure ~~invention~~ also provides a prophylactic method of treating a subject at risk of

contracting a viral infection, the method comprising chronically administering to the subject one or more doses of an antiviral composition on a recurring basis over an extended treatment period prior to the subject contracting the viral infection, thereby preventing the subject from contracting the viral infection; wherein the antiviral composition comprises oleandrin.

[0025] In some ~~embodiments~~examples, the antiviral composition is administered to subjects having virally infected cells, wherein the cells exhibit an elevated ratio of alpha-3 to alpha-1 isoforms of Na,K-ATPase.

[0026] In some ~~embodiments~~examples, the viral infection is caused by any of the following virus families: Arenaviridae, Arterviridae, Bunyaviridae, Filoviridae, Flaviviridae, Orthomyxoviridae, Paramyxoviridae, Rhabdoviridae, Retroviridae (in particular, Deltaretrovirus genus), Coronaviridae, or Togaviridae. In some embodiments, the viral infection is caused by (+)-ss-envRNAV or (-)-ss-envRNAV.

[0027] Some ~~embodiments~~ examples of the disclosure ~~invention~~ are directed to compositions for and methods of treating Filovirus infection, Flavivirus infection, Henipavirus infection, alphavirus infection, or Togavirus infection. Viral infections that can be treated include, at least, Ebolavirus, Marburgvirus, Alphavirus, Flavivirus, Yellow Fever, Dengue Fever, Japanese Enchephalitis, West Nile Viruses, Zikavirus, Venezuelan Equine Encephalomyelitis (encephalitis) (VEE) virus, Chikungunya virus, Western Equine Encephalomyelitis (encephalitis) (WEE) virus, Eastern Equine Encephalomyelitis (encephalitis) (EEE) virus, Tick-borne Encephalitis, Kyasanur Forest Disease, Alkhurma Disease, Omsk Hemorrhagic Fever, Hendra virus, Nipah virus, Deltaretrovirus genus, HTLV-1 virus, and species thereof.

[0028] Some ~~embodiment~~examples~~ ~~ of the disclosure ~~invention~~ are directed to compositions for and methods of treating viral infections from viruses of the Arenaviridae family, Arterviridae, Bunyaviridae family, Filoviridae family, Flaviviridae family (Flavivirus genus), Orthomyxyoviridae family, Paramyxoviridae family, Rhabdoviridae family, Retroviridae family (Deltaretrovirus genus), Coronaviridae family, (+)-ss-envRNAV, (-)-ss-envRNAV, or Togaviridae family.

[0029] Some ~~embodiment~~examples~~ ~~ of the disclosure ~~invention~~ are directed to compositions for and methods of treating viral infections from viruses of the Henipavirus genus, Ebolavirus genus, Flavivirus genus, Marburgvirus genus, Deltaretrovirus genus, Coronavirus (CoV), or Alphavirus genus.

[0030] In some ~~embodiments~~examples, the (+)-ss-envRNAV is a virus selected from the group consisting of Coronaviridae family, Flaviviridae family, Togaviridae family, and Arterviridae family.

[0031] In some ~~embodiment~~examples, the (+)-ss-envRNAV is a coronavirus that is pathogenic to humans. In some ~~embodiment~~examples, the coronavirus spike protein binds to ACE2 (angiotensin converting enzyme 2) receptors in human tissue. In some ~~embodiment~~examples, the coronavirus is selected from the group consisting of SARS-CoV, MERS-CoV, COVID-19 (SARS-CoV-2), CoV 229E, CoV NL63, CoV OC43, CoV HKU1, and CoV HKU20.

[0032] In some ~~embodiment~~examples, the (+)-ss-envRNAV is a virus selected from the group consisting of flavivirus, Yellow Fever virus, Dengue Fever virus, Japanese Encephalitis virus, West Nile virus, Zikavirus, Tick-borne Encephalitis virus, Kyasanur Forest Disease virus, Alkhurma Disease virus, Omsk Hemorrhagic Fever virus, and Powassan virus.

[0033] In some ~~embodiment~~examples, the (+)-ss-envRNAV is a Togaviridae family virus selected from the group consisting of arborvirus, eastern equine encephalomyelitis virus (EEEV), western equine encephalomyelitis virus (WEEV), Venezuelan equine encephalomyelitis virus (VEEV), Chikungunya virus (CHIKV), O'nyong'nvirus (ONNV), Pogosta disease virus, Sindbis virus, Ross River fever virus (RRV) and Semliki Forest virus.

[0034] In some ~~embodiment~~examples, the (-)-(ss)-envRNAV is a virus selected from the group consisting of Arenaviridae family, Bunyaviridae family (Bunyavirales order), Filoviridae family, Orthomyxoviridae family, Paramyxoviridae family, or Rhabdoviridae family.

[0035] In some ~~embodiment~~examples, Arenaviridae family virus is selected from the group consisting of Lassa virus, aseptic meningitis, Guanarito virus, Junin virus, Lujo virus, Machupo virus, Sabia virus and Whitewater Arroyo virus.

[0036] In some ~~embodiment~~examples, Bunyaviridae family virus is selected from the group consisting of Hantavirus, and Crimean-Congo hemorrhagic fever orthonairovirus.

[0037] In some ~~embodiment~~examples, Paramyxoviridae family virus is selected from the group consisting of Mumps virus, Nipah virus, Hendra virus, respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), and Newcastle disease virus (NDV).

[0038] In some ~~embodiment~~examples, Orthomyxoviridae family virus is selected from the group consisting of influenza virus (A through C), Isavirus, Thogotovirus, Quaranjavirus, H1N1 virus, H2N2 virus, H3N2 virus, H1N2 virus, Spanish flu virus, Asian flu virus, Hong Kong Flu virus, and Russian flu virus.

[0039] In some ~~embodiment~~examples, Rhabdoviridae family virus is selected from the group consisting of rabies virus, vesiculovirus, Lyssavirus, and Cytorhabdovirus.

[0040] The disclosure ~~invention~~ also provides ~~embodiment~~examples for the treatment of HTLV-1-associated condition or neuro-inflammatory disease. In some ~~embodiment~~examples, the HTLV-1-associated condition or neuro-inflammatory disease is selected from the group consisting of myelopathy/tropical spastic paraparesis (HAM/TSP), adult T-cell leukemia/lymphoma (ATLL), autoimmune condition, inflammatory condition, infectious dermatitis, rheumatoid arthritis, uveitis, keratoconjunctivitis, sicca syndrome, Sjögren's syndrome, and Strongyloides stercoralis.

[0041] The disclosure ~~invention~~ also provides a method of inhibiting the infectivity of HTLV-1 particles released into the culture supernatants of treated cells and also reducing the intercellular transmission of HTLV-1 by inhibiting the Env-dependent formation of virological synapses, the method comprising administering to a subject in need thereof an effective amount of the antiviral composition.

[0042] In some ~~embodiment~~examples, the disclosure ~~invention~~ 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.

[0043] ~~One aspect of t~~The disclosure ~~invention~~ provides a method of treating viral infection in a subject by chronic administration to the subject of an antiviral composition. The subject is treated by chronically administering to the subject 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 subject can begin immediately after infection or any time within one day to 5 days after infection or at the earliest time after definite diagnosis of infection with virus. The virus can be any virus described herein.

[0044] Accordingly, the disclosure ~~invention~~ 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. One or more doses are administered on a daily, weekly or monthly basis. One or more doses per day can be administered. The virus can be any virus described herein.

[0045] The disclosure ~~invention~~ also provides a method of treating viral infection in a subject in need thereof, the method comprising:

determining whether or not the subject has a viral infection;

indicating administration of antiviral composition;

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

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

if the subject'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 subject'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 subject is achieved.

[0046] Treatment of the subject with antiviral composition is continued as needed. The dose or dosing regimen can be adjusted as needed until the patient 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.

[0047] The individual steps of the methods of the disclosure ~~invention~~ can be conducted at separate facilities or within the same facility.

[0048] The disclosure ~~invention~~ provides alternate ~~embodiment~~examples, for all the ~~embodiment~~examples described herein, wherein the oleandrin is replaced with digoxin or used in combination with digoxin. The methods of the disclosure ~~invention~~ 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~~invention~~. 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.

[0048a] In one aspect, the present disclosure relates to use of oleandrin in the preparation of a medicament: (a) for treating COVID-19 (SARS-CoV-2) coronavirus infection in a subject, wherein the medicament is to be administered to the subject in one or more therapeutically effective doses per day for a treatment period of at least about 5 days to about one or more months; or (b) for preventing COVID-19 (SARS-CoV-2) coronavirus

infection in a subject, wherein the medicament is for chronic administration to the subject in one or more doses per day over an extended treatment period.

[0048a] In another aspect, the present disclosure relates to use of oleandrin in the preparation of a medicament for treating or preventing COVID-19 (SARS-CoV-2) coronavirus infection in a subject, wherein the medicament is to be administered to the subject in plural therapeutically effective doses.

[0049] The disclosure ~~invention~~ also provides a method of treating coronavirus infection, in particular an infection of coronavirus that is pathogenic to humans, e.g. SARS-CoV-2 infection, the method comprising chronically administering to a subject, having said infection, therapeutically effective doses of cardiac glycoside (cardiac glycoside-containing composition).

[0050] The disclosure ~~invention~~ also provides a dual pathway method of treating coronavirus infection, in particular an infection of coronavirus that is pathogenic to humans, e.g. SARS-

CoV-2 infection, the method comprising chronically administering to a subject, having said infection, therapeutically effective doses of cardiac glycoside (cardiac glycoside-containing composition), thereby inhibiting viral replication of said coronavirus and reducing the infectivity of progeny virus of said coronavirus.

[0051] The disclosure ~~invention~~ also provides a method of treating coronavirus infection, in particular SARS-CoV-2 infection, by repeatedly administering (through any of the modes of administration discussed herein) to a subject, 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.

[0052] The disclosure ~~invention~~ also provides a method of treating coronavirus infection in a human, the method comprising administering to the subject 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 subject is preferred.

[0053] In some ~~embodiment~~examples, one or more doses of oleandrin are administered per day for plural days until the viral infection is cured. In some ~~embodiment~~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.

[0054] In some ~~embodiment~~examples, the concentration of oleandrin and/or digoxin in the plasma of a treated infected subject, e.g. with coronavirus infection, is about 10 microg/mL or less, about 5 microg/mL or less, about 2.5 microg/mL or less, about 2 microg/mL or less, or about 1 microg/mL or less. In some ~~embodiment~~examples, the concentration of oleandrin and/or digoxin in the plasma of a treated subject with coronavirus infection is about 0.0001 microg/mL or more, about 0.0005 microg/mL or more, about 0.001 microg/mL or more, about 0.0015 microg/mL or more, about 0.01 microg/mL or more, about 0.015 microg/mL or more, about 0.1 microg/mL or more, about 0.15 microg/mL or more, about 0.05

microg/mL or more, or about 0.075 microg/mL or more. In some ~~embodiment~~examples, the concentration of oleandrin and/or digoxin in the plasma of a treated infected subject is about 10 microg/mL to about 0.0001 microg/mL, about 5 microg/mL to about 0.0005 microg/mL, about 1 microg/mL to about 0.001 microg/mL, about 0.5 microg/mL to about 0.001 microg/mL, about 0.1 microg/mL to about 0.001 microg/mL, about 0.05 microg/mL to about 0.001 microg/mL, about 0.01 microg/mL to about 0.001 microg/mL, about 0.005 microg/mL to about 0.001 microg/mL. The disclosure ~~invention~~ includes all combinations and selections of the plasma concentration ranges set forth herein.

[0055] 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.

[0056] In some ~~embodiment~~examples, the subject is administered 140 microg to 315 microg per day of cardiac glycoside. In some ~~embodiment~~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. The recommended daily dose of oleandrin, present in the SCF extract, is generally about 0.25 to about 50 microg twice daily or about 0.9 to 5 microg twice daily or about every 12 hours. The dose can be about 0.5 to about 100 microg/day, 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. The maximum tolerated dose can be about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day of oleander extract containing oleandrin and the minimum effective dose can be about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day. Suitable doses comprising cardiac glycoside and triterpene can be about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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. In some ~~embodiment~~example**s**, the dose of oleandrin is about 1 mg to about 0.05 mg, about 0.9 mg to about 0.07 mg, about 0.7 mg to about 0.1 mg, about 0.5 mg to about 0.1 mg, about 0.4 mg to about 0.1 mg, about 0.3 mg to about 0.1 mg, about 0.2 mg. The disclosure ~~invention~~ includes all combinations of the doses set forth herein.

[0057] In some ~~embodiment~~example**s**, 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.

[0058] 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.

[0059] 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 ~~embodiment~~example**s**, 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.

[0060] The disclosure ~~invention~~ also provides a sublingual dosage form comprising oleandrin and liquid carrier. The disclosure ~~invention~~ also provides a method of treating viral infection, in particular coronavirus infection, e.g. as defined herein, comprising sublingually administering plural doses of an oleandrin-containing (digoxin-containing) composition to a subject 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.

[0061] In some ~~embodiment~~example**s**, the antiviral composition comprises oleandrin (or digoxin or a combination of oleandrin and digoxin) and oil. The oil can comprise medium chain triglycerides. The antiviral composition can comprise one, two or more oleandrin-containing extracts and one or more pharmaceutical excipients.

[0062] If present in the antiviral composition, additional cardiac glycoside can be further included: odoroside, neritaloside, or oleandrigenin. In some ~~embodiment~~example**s**, 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 ~~embodiment~~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 ~~embodiment~~examples, the triterpene is selected from the group consisting of oleanolic acid, ursolic acid, betulinic acid and salts or derivatives thereof.

[0063] Some ~~embodiment~~examples of the disclosure ~~invention~~ include those wherein a pharmaceutical composition comprises at least one pharmaceutical excipient and the antiviral composition. In some ~~embodiment~~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.

[0064] 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 ~~embodiment~~examples, the cardiac glycoside is present as the primary therapeutic component, meaning the component primarily responsible for antiviral activity, in the pharmaceutical composition. In some ~~embodiment~~examples, the triterpene(s) is/are present as the primary therapeutic component(s), meaning the component(s) primarily responsible for antiviral activity, in the pharmaceutical composition.

[0065] In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the oleandrin-containing composition comprises two or more different types of oleandrin-containing extracts.

[0066] ~~Embodiment~~Examples of the disclosure ~~invention~~ include those wherein the oleandrin-containing biomass (plant materia) is *Nerium* sp., *Nerium oleander*, *Nerium oleander* L (Apocynaceae), *Nerium odourum*, white oleander, pink oleander, *Thevetia* sp., *Thevetia*

peruviana, yellow oleander, *Thevetia nerifolia*, *Agrobacterium tumefaciens*, cell culture (cellular mass) of any of said species, or a combination thereof. In some ~~embodiment~~examples, the biomass comprises leaves, stems, flowers, bark, fruits, seeds, sap, and/or pods.

[0067] In some ~~embodiment~~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 a subject. In some ~~embodiment~~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 ~~embodiment~~examples, the composition further comprises one or more antiviral compound(s). In some ~~embodiment~~examples, the antiviral composition excludes a pharmacologically active polysaccharide.

[0068] In some ~~embodiment~~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 digitoxins, digitoxigenin, digoxin, acetyl digoxins, 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 presursors. 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. or *Thevetia* sp. plant material.

[0069] In some ~~embodiment~~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.

[0070] In some ~~embodiment~~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.

[0071] In some ~~embodiment~~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).

[0072] In some ~~embodiment~~examples, the other therapeutic agent, such as that obtained by extraction of *Nerium* sp. or *Thevetia* sp. plant material, is not a polysaccharide obtained during preparation of the extract, meaning it is not an acidic homopolygalacturonan or arabinogalaturonan. In some ~~embodiment~~examples, the extract excludes another therapeutic agent and/or excludes an acidic homopolygalacturonan or arabinogalaturonan obtained during preparation of the extract.

[0073] In some ~~embodiment~~examples, the other therapeutic agent, such as that obtained by extraction of *Nerium* sp. or *Thevetia* sp. plant material, is a polysaccharide obtained during preparation of the extract, e.g. an acidic homopolygalacturonan or arabinogalaturonan. In some ~~embodiment~~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.

[0074] In some ~~embodiment~~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-

organic solvent, or supercritical fluid extracts of agrobacterium may be used according to the disclosure~~invention~~.

[0076] Oleandrin may also be obtained from extracts of *Nerium oleander* microculture in vitro, whereby shoot cultures can be initiated from seedlings and/or from shoot apices of the *Nerium oleander* 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 oleander may be used according to the disclosure~~invention~~.

[0077] The extract may also be obtained by extraction of cellular mass (such as is present in cell culture) of any of said plant species.

[0078] The disclosure ~~invention~~ also provides use of a cardiac glycoside in the manufacture of a medicament for the treatment of viral infection in a subject. In some ~~embodiment~~examples, the manufacture of such a medicament comprises: providing one or more antiviral compounds of the disclosure~~invention~~; including a dose of antiviral compound(s) in a pharmaceutical dosage form; and packaging the pharmaceutical dosage form. In some ~~embodiment~~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 a subject 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 ~~embodiment~~examples, the treatment of viral infection comprises: determining that a subject has a viral infection; indicating administration of pharmaceutical dosage form to the subject according to a dosing regimen; administering to the subject one or more pharmaceutical dosage forms, wherein the one or more pharmaceutical dosage forms is administered according to the dosing regimen.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] In some ~~embodiment~~examples, the water miscible solvent is low molecular weight (less than 6000) PEG, glycol, or alcohol. In some ~~embodiment~~examples, the surfactant is a pegylated surfactant, meaning a surfactant comprising a poly(ethylene glycol) functional group.

[0083] The disclosure ~~invention~~ includes all combinations of the aspects, ~~embodiment~~examples and sub-~~embodiment~~examples of the disclosure ~~invention~~ disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

[0084] 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.

[0085] FIGS. 1-2 depict charts summarizing the in vitro dose response antiviral activity of various compositions against Ebolavirus.

[0086] FIGS. 3-4 depict charts summarizing the in vitro dose response antiviral activity of various compositions against Marburgvirus.

[0087] FIG. 5 depicts a chart summarizing the in vitro dose response antiviral activity of oleandrin against Zikavirus (SIKV strain PRVABC59) in Vero E6 cells.

[0088] FIG. 6 depicts a chart summarizing the in vitro dose response antiviral activity of digoxin against Zikavirus (SIKV strain PRVABC59) in Vero E6 cells.

[0089] FIG. 7 depicts a chart summarizing the in vitro dose response antiviral activity of various compositions (oleandrin, digoxin and PBI-05204) against Ebolavirus in Vero E6 cells.

[0090] FIG. 8 depicts a chart summarizing the in vitro dose response antiviral activity of various compositions (oleandrin, digoxin and PBI-05204) against Marburgvirus in Vero E6 cells.

[0091] FIG. 9 depicts a chart summarizing the in vitro cellular viability of Vero E6 cells in the presence of various compositions (oleandrin, digoxin and PBI-05204).

CLAIMS

1) Use of oleandrin in the preparation of a medicament:
(a) for treating COVID-19 (SARS-CoV-2) coronavirus infection in a subject, wherein the medicament is to be administered to the subject in one or more therapeutically effective doses per day for a treatment period of at least about 5 days to about one or more months; or
(b) for preventing COVID-19 (SARS-CoV-2) coronavirus infection in a subject, wherein the medicament is for chronic administration to the subject in one or more doses per day over an extended treatment period.

2) The use according to claim 1, wherein oleandrin is present in a composition comprising at least one extract obtained from oleandrin-containing biomass.

3) The use according to claim 2, wherein said extract is independently selected upon each occurrence from the group consisting of hot-water extract, organic solvent extract, aqueous organic solvent extract, and supercritical fluid extract.

4) Use of oleandrin in the preparation of a medicament for treating or preventing COVID-19 (SARS-CoV-2) coronavirus infection in a subject, wherein the medicament is to be administered to the subject in plural therapeutically effective doses.

5) The use according to claim 4, wherein said plural therapeutically effective doses are one or more doses to be administered per day for two or more days per week.

6) The use according to claim 4 or claim 5, wherein dosing is to be continued for one or more weeks per month.

7) The use according to any one of claims 4 to 6, wherein dosing is to be continued for one or more months per year.

8) The use according to any one of claims 4 to 7, wherein oleandrin is present in a composition comprising at least one extract obtained from oleandrin-containing biomass.

9) The use according to claim 8, wherein said extract is independently selected upon each occurrence from the group consisting of hot-water extract, organic solvent extract, aqueous organic solvent extract, and supercritical fluid extract.

10) The use according to claim 8 or claim 9, wherein said extract comprises a combination of oleandrin and one or more compounds extracted from said biomass.

11) The use according to claim 10, wherein said one or more compounds comprises one or more cardiac glycoside precursors, one or more glycone constituents of cardiac glycosides, or a combination thereof.

12) The use according to claim 8 or claim 9, wherein said extract comprises oleandrin and one or more compounds 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.

13) The use according to any one of claims 4 to 12, wherein the medicament is to be administered via systemic, parenteral, buccal, enteral, intramuscular, subdermal, sublingual, peroral, oral, or a combination thereof.

14) The use according to any one of claims 4 to 13, wherein when said oleandrin is for said treating, said oleandrin is to be administered immediately after infection or any time within one day to 5 days after infection or at the earliest time after diagnosis of infection with virus.

15) The use according to any one of claims 1 to 14, wherein when said oleandrin is for said treating, said oleandrin is to be administered as primary antiviral therapy, adjunct antiviral

therapy, or co-antiviral therapy, or wherein said administration comprises separate administration or coadministration of said oleandrin with at least one other antiviral composition or with at least one other composition for treating symptoms associated with said viral infection.

16) The use according to any one of claims 1 to 15, wherein the total of the therapeutically effective doses of oleandrin per day is independently selected upon each occurrence from 1 microg to 180 microg, 1 microg to 120 microg, 5 microg to 100 microg, 10 microg to 80 microg, 10 microg to 75 microg, 15 microg to 120 microg, 15 microg to 100 microg, 15 microg to 80 microg, 30 microg to 120 microg, 30 microg to 100 microg, 30 micro to 90 microg, 40 microg to 70 microg, about 1 microg, about 5 microg, about 10 microg, about 20 microg, about 30 microg, about 40 microg, about 50 microg, about 60 microg, about 70 microg, about 80 microg, about 90 microg, about 100 microg, about 110 microg, about 120 microg, about 130 microg, about 140 microg, about 150 microg, about 160 microg, about 170 microg, about 180 microg, 140 microg to 315 microg, 20 microg to 750 microg, 12 microg to 300 microg, 12 microg to 120 microg, 0.01 microg to 100 mg, 0.01 microg to 100 microg, 0.5 to 100 microg, 1 to 80 microg, 1.5 to 60 microg, 1.8 to 60 microg, and 1.8 to 40 microg.

17) The use according to any one of claims 1 to 15, wherein
a) the therapeutically effective dose comprises 0.05-0.5 mg/kg/day, 0.05-0.35 mg/kg/day, 0.05-0.22 mg/kg/day, 0.05-0.4 mg/kg/day, 0.05-0.3 mg/kg/day, 0.05-0.5 microg/kg/day, 0.05-0.35 microg/kg/day, 0.05-0.22 microg/kg/day, 0.05-0.4 microg/kg/day, or 0.05-0.3 microg/kg/day, based upon the unit amount of oleandrin per kg of bodyweight of subject per day;
b) the daily therapeutically effective dose of oleandrin is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day; and/or
c) the daily dose of oleandrin is a minimum of about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

18) The use according to any one of claims 1 to 15, wherein the therapeutically effective dose is to be administered twice daily or about every 12 hours, and the amount of oleandrin in said dose is 0.25 to 50 microg or 0.9 to 15 microg.

19) The use according to any one of claims 1 to 15, wherein said therapeutically effective doses are 2 to 10 doses per day, 2 to 8 doses per day, 2 to 6 doses per day, 2 to 4 doses per day, 2 doses per day, 3 doses per day, 4 doses per day, 5 doses per day, 6 doses per day, 7 doses per day, 8 doses per day, 9 doses per day, or 10 doses per day.

20) The according to any one of claims 1 to 19, wherein following administration of said therapeutically effective doses, the plasma concentration of oleandrin in said subject is in the range of 0.05 to 2 ng/ml, 0.005 to 10 ng/mL, 0.005 to 8 ng/mL, 0.01 to 7 ng/mL, 0.02 to 7 ng/mL, 0.03 to 6 ng/mL, 0.04 to 5 ng/mL, or 0.05 to 2.5 ng/mL, in terms of the amount of oleandrin per mL of plasma.

CLAIMS

1) A method of treating viral infection in a subject in need thereof, the method comprising administering to the subject one or more doses of an antiviral composition comprising oleandrin, digoxin, or a combination thereof, wherein said viral infection is caused by a positive-sense single-stranded enveloped RNA virus ((+)-ss-envRNA-V).

2) A prophylactic method of treating a subject at risk of contracting a viral infection, the method comprising chronically administering to the subject one or more doses of an antiviral composition on a recurring basis over an extended treatment period prior to the subject contracting the viral infection, thereby preventing the subject from contracting the viral infection; wherein the antiviral composition comprises oleandrin, digoxin, or a combination thereof, and wherein said viral infection is caused by a positive-sense single-stranded enveloped RNA virus ((+)-ss-envRNA-V).

3) The method of claim 1 comprising:

determining whether or not the subject has said viral infection;

indicating administration of said antiviral composition;

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

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

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

if the subject'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 subject is achieved.

4) The method of any one of the above claims, wherein a dose comprises about 100-1000 mg or about 100-1000 microg of antiviral composition per Kg of body weight of said subject.

5) The method of any one of the above claims, wherein the amount of oleandrin as part of said composition administered per day is selected from the group consisting of 140 microg to 315 microg, 20 microg to 750 microg, 12 microg to 300 microg, 12 microg to 120 microg, 0.01 microg to 100 mg, 0.01 microg to 100 microg, about 0.5 to about 100 microg,

about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, or about 1.8 to about 40 microg.

6) The method of any one of the above claims, wherein a dose of said antiviral composition is administered twice daily or about every 12 hours, and the amount of oleandrin in said dose is about 0.25 to about 50 microg or about 0.9 to 5 microg.

7) The method of any one of the above claims, wherein a dose of said antiviral composition comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 antiviral composition per kg of body weight of subject per day.

8) The method of any one of the above claims, wherein a) the daily dose of oleandrin in said antiviral composition is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day; and/or b) the daily dose of oleandrin in said antiviral composition is a minimum of about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

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

10) The method of claim 9, wherein the cardiac glycoside is digoxin and the dosing regimen for the loading phase and maintenance phase is as follows:

Human age	Oral Loading phase dose, mcg/kg/day	Oral maintenance phase dose, mcg/kg/day	
Premature	20 to 30 or 15-25	4.7 to 7.8	2.3 to 3.9 Twice Daily
Full-Term	25 to 35 or 20-30	7.5 to 11.3	3.8 to 5.6 Twice Daily
1 to 24 months	35 to 60 or 30-50	11.3 to 18.8	5.6 to 9.4 Twice Daily
2 to 5 years	30 to 45 or 25-35	9.4 to 13.1	4.7 to 6.6 Twice Daily
5 to 10 years	20 to 35 or 15-30	5.6 to 11.3	2.8 to 5.6 Twice Daily
Over 10 years	10 to 15 or 8-12	3.0 to 4.5 or 2.4 to 3.6 or 3.4 to 5.1	3.0 to 4.5 Once Daily .

11) The method of any one of the above claims, 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) A method of treating viral infection in a subject in need thereof, the method comprising administering to the subject one or more doses of an antiviral composition comprising oleandrin, wherein said viral infection is is caused by a positive-sense single-stranded enveloped RNA virus ((+)-ss-envRNA-V), wherein

a dose comprises about 100-1000 mg or about 100-1000 microg of antiviral composition per Kg of body weight of said subject; or the amount of oleandrin administered per day is selected from the group consisting of 140 microg to 315 microg, 20 microg to 750 microg, 12 microg to 300 microg, 12 microg to 120 microg, 0.01 microg to 100 mg, 0.01 microg to 100 microg, about 0.5 to about 100 microg, about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, or about 1.8 to about 40 microg; or a dose of said antiviral composition comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 antiviral composition per kg of body weight of subject per day; and

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.

13) The method of any one of the above claims, wherein the (+)-ss-envRNAV is a virus selected from the group consisting of Coronaviridae family, Flaviviridae family, Togaviridae family, and Arterviridae family.

14) The method of any one of the above claims, wherein the (+)-ss-envRNAV is a coronavirus that is pathogenic to humans.

15) The method of claim 14, wherein the coronavirus is selected from the group consisting of SARS-CoV, MERS-CoV, COVID-19 (SARS-CoV-2), CoV-229E, CoV-NL63, CoV-OC43, CoV-HKU1, and CoV-HKU20.

16) The method of any one of claims 1-13, wherein the (+)-ss-envRNAV is a virus selected from the group consisting flavivirus, Yellow Fever virus, Dengue Fever virus, Japanese Enchephalitis virus, West Nile virus, Zikavirus, Tick-borne Encephalitis virus, Kyasanur Forest Disease virus, Alkhurma Disease virus, Omsk Hemorrhagic Fever virus, and Powassan virus.

17) The method of any one of claims 1-13, wherein the (+)-ss-envRNAV is a Togaviridae family virus selected from the group consisting arborvirus, eastern equine encephalomyelitis virus (EEEV), western equine encephalomyelitis virus (WEEV), Venezuelan equine encephalomyelitis virus (VEEV), Chikungunya virus (CHIKV), O'nyong'nvirus (ONNV), Pogosta disease virus, Sindbis virus, Ross River fever virus (RRV) and Semliki Forest virus.

18) A method of treating viral infection in a subject in need thereof, the method comprising administering to the subject one or more doses of an antiviral composition comprising oleandrin, digoxin or a combination thereof, wherein said viral infection is caused by a negative-sense single-stranded enveloped RNA virus ((-)-ss-envRNA-V).

19) A prophylactic method of treating a subject at risk of contracting a viral infection, the method comprising chronically administering to the subject one or more doses of an antiviral composition on a recurring basis over an extended treatment period prior to the subject contracting the viral infection, thereby preventing the subject from contracting the viral infection; wherein the antiviral composition comprises oleandrin, digoxin or a combination thereof, and wherein said viral infection is caused by a negative-sense single-stranded enveloped RNA virus ((-)-ss-envRNA-V).

20) The method of claim 18 comprising:

determining whether or not the subject has said viral infection;

indicating administration of said antiviral composition;

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

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

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

if the subject'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 subject is achieved.

21) The method of any one of the claims 18-20, wherein a dose comprises about 100-1000 mg or about 100-1000 microg of antiviral composition per Kg of body weight of said subject.

22) The method of any one of claims 18-21, wherein the amount of oleandrin as part of said composition administered per day is selected from the group consisting of 140 microg to 315 microg, 20 microg to 750 microg, 12 microg to 300 microg, 12 microg to 120 microg, 0.01 microg to 100 mg, 0.01 microg to 100 microg, about 0.5 to about 100 microg, about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, or about 1.8 to about 40 microg.

23) The method of any one of claims 18-22, wherein a dose of said antiviral composition is administered twice daily or about every 12 hours, and the amount of oleandrin in said dose is about 0.25 to about 50 microg or about 0.9 to 5 microg.

24) The method of any one of claims 18-23, wherein a dose of said antiviral composition comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 antiviral composition per kg of body weight of subject per day.

25) The method of any one of claims 18-24, wherein a) the daily dose of oleandrin in said antiviral composition is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day; and/or b) the daily dose of oleandrin in said antiviral composition is a minimum of about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

26) The method of any one of claims 18-25, 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.

27) A method of treating viral infection in a subject in need thereof, the method comprising administering to the subject one or more doses of an antiviral composition comprising oleandrin, wherein said viral infection is is caused by a negative-sense single-stranded enveloped RNA virus ((-) ss-envRNA-V), wherein

a dose comprises about 100-1000 mg or about 100-1000 microg of antiviral composition per Kg of body weight of said subject; or the amount of oleandrin administered per day is selected from the group consisting of 140 microg to 315 microg, 20 microg to 750 microg, 12 microg to 300 microg, 12 microg to 120 microg, 0.01 microg to 100 mg, 0.01 microg to 100 microg, about 0.5 to about 100 microg, about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, or about 1.8 to about 40 microg; or a dose of said antiviral composition comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 antiviral composition per kg of body weight of subject per day; and

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.

28) The method of any one of claims 18-27, wherein the (-)-ss-envRNAV is a virus selected from the group consisting of Arenaviridae family virus, Bunyaviridae family (Bunyavirales order) virus, Filoviridae family virus, Orthomyxoviridae family virus, Paramyxoviridae family virus, and Rhabdoviridae family virus.

29) The method of any one of claims 18-28, wherein the (-) ss-envRNAV is an Arenaviridae family virus selected from the group consisting of Lassa virus, aseptic mengitis, Guanarito virus, Junin virus, Lujo virus, Machupo virus, Sabia virus and Whitewater Arroyo virus.

30) The method of any one of claims 18-28, wherein the (-)-ss-envRNAV is a Bunyaviridae family virus selected from the group consisting of Hantavirus, Crimean-Congo hemorrhagic fever orthonairovirus.

31) The method of any one of claims 18-28, wherein the (-)-ss-envRNAV is a Paramyxoviridae family virus selected from the group consisting of Mumps virus, Nipah virus, Hendra virus, respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), and NDV.

32) The method of any one of claims 18-28, wherein the (-)-ss-envRNAV is a Orthomyxoviridae family virus selected from the group consisting of influenza virus (A through C), Isavirus, Thogotovirus, Quaranjavirus, H1N1, H2N2, H3N2, H1N2, Spanish flu, Asian flu, Hong Kong Flu, Russian flu.

33) The method of any one of claims 18-28, wherein the (-)-ss-envRNAV is a Rhabdoviridae family virus selected from the group consisting of rabies virus, vesiculovirus, Lyssavirus, Cytorhabdovirus.

34) A method of treating viral infection according to any of the claims herein comprising sublingually administering to a subject having a viral infection one or more doses of cardiac glycoside comprising oleandrin, digoxin or a combination thereof.

35) A method of treating coronavirus infection comprising administering to a subject, having said infection, plural therapeutically effective doses of oleandrin, digoxin or a combination thereof.

36) The method of claim 34 or 35, wherein said plural doses are one or more doses administered per day for two or more days per week.

37) The method of claim 36, wherein dosing is continued for one or more weeks per month.

38) The method of claim 37, wherein dosing is continued for one or more months per year.

39) The method of any one of claims 34-38, wherein said coronavirus is pathogenic to humans.

40) The method of any one of claims 34-39, wherein said coronavirus is selected from the group consisting of SARS-CoV, MERS-CoV, COVID-19 (SARS-CoV-2), CoV 229E, CoV NL63, CoV OC43, CoV HKU1, and CoV HKU20.

41) The method of any one of claims 34-40, wherein the concentration of oleandrin in the plasma of said subject after administration of oleandrin is a) about 10 microg/mL or less,

about 5 microg/mL or less, about 2.5 microg/mL or less, about 2 microg/mL or less, or about 1 microg/mL or less; b) about 0.0001 microg/mL or more, about 0.0005 microg/mL or more, about 0.001 microg/mL or more, about 0.0015 microg/mL or more, about 0.01 microg/mL or more, about 0.015 microg/mL or more, about 0.1 microg/mL or more, about 0.15 microg/mL or more, about 0.05 microg/mL or more, or about 0.075 microg/mL or more; c) a combination of any upper limit of item a) with any lower limit of item c); or d) 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.

42) The method of any one of the claims 34-40, wherein a dose comprises about 100-1000 mg or about 100-1000 microg of antiviral composition per Kg of body weight of said subject.

43) The method of any one of claims 34-42, wherein the amount of oleandrin as part of said composition administered per day is selected from the group consisting of 140 microg to 315 microg, 20 microg to 750 microg, 12 microg to 300 microg, 12 microg to 120 microg, 0.01 microg to 100 mg, 0.01 microg to 100 microg, about 0.5 to about 100 microg, about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, or about 1.8 to about 40 microg.

44) The method of any one of claims 34-43, wherein a dose of said antiviral composition is administered twice daily or about every 12 hours, and the amount of oleandrin in said dose is about 0.25 to about 50 microg or about 0.9 to 5 microg.

45) The method of any one of claims 34-44, wherein a dose of said antiviral composition comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 antiviral composition per kg of body weight of subject per day.

46) The method of any one of claims 34-45, wherein a) the daily dose of oleandrin in said antiviral composition is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day; and/or b) the daily dose of oleandrin in said antiviral composition is a minimum of about

0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

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

48) The method of claim 47, wherein the cardiac glycoside is digoxin and the dosing regimen for the loading phase and maintenance phase is as follows:

Human age	Oral Loading phase dose, mcg/kg/day	Oral maintenance phase dose, mcg/kg/day	
Premature	20 to 30 or 15-25	4.7 to 7.8	2.3 to 3.9 Twice Daily
Full-Term	25 to 35 or 20-30	7.5 to 11.3	3.8 to 5.6 Twice Daily
1 to 24 months	35 to 60 or 30-50	11.3 to 18.8	5.6 to 9.4 Twice Daily
2 to 5 years	30 to 45 or 25-35	9.4 to 13.1	4.7 to 6.6 Twice Daily
5 to 10 years	20 to 35 or 15-30	5.6 to 11.3	2.8 to 5.6 Twice Daily
Over 10 years	10 to 15 or 8-12	3.0 to 4.5 or 2.4 to 3.6 or 3.4 to 5.1	3.0 to 4.5 Once Daily .

49) The method 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); 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).

50) The method of claim 49, wherein, in a dose of antiviral composition, the molar ratio of oleandrin to said triterpenes is selected from any of the following

Antiviral Composition	Oleandrin (moles)	Oleanolic acid (moles)	Ursolic acid (moles)	Betulinic acid (moles)	Suitable dose
B	0.5-1.5	4-6	4-6	-	0.05 to 0.35 mg/kg/day
C	0.5-1.5	4-6	4-6	0.1-1	0.05 to 0.22 mg/kg/day
AC	About 1	About 4.7	About 4.5	-	0.05 to 0.4 mg/kg/day
AD	About 1	About 4.7	About 4.5	About 0.6	0.05 to 0.22 mg/kg/day.

51) The method of claims 49, wherein the molar ratio of total triterpene content (oleanolic acid + ursolic acid + betulinic acid) 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.

52) The method of claim 49, wherein the molar ratios of the individual triterpenes (oleanolic acid (OA) : ursolic acid (UA) : betulinic acid (BA)) to oleandrin (OL) range as follows: 2-8 (OA) : 2-8 (UA) : 0.1-1 (BA) : 0.5-1.5 (OL); or 3-6 (OA) : 3-6 (UA) : 0.3-8 (BA) : 0.7-1.2 (OL); or 4-5 (OA) : 4-5 (UA) : 0.4-0.7 (BA) : 0.9-1.1 (OL); 4.6 (OA) : 4.4 (UA) : 0.6 (BA) : 1 (OL); about 9-12 (OA) : up to about 2 (UA) : up to about 2, or about 10 (OA) : about 1 (UA) : about 1, or about 9-12 (OA) : about 0.1-2 (UA) : about 0.1-2 (BA), or about 9-11 (OA) : about 0.5-1.5 (UA) : about 0.5-1.5 (BA), or about 9.5-10.5 (OA) : about 0.75-1.25 (UA) : about 0.75-1.25 (BA), or about 9.5-10.5 (OA) : about 0.8-1.2 (UA) : about 0.8-1.2 (BA), or about 9.75-10.5 (OA) : about 0.9-1.1 (UA) : about 0.9-1.1 (BA).

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

54) The method of claim 53, 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.

55) The method of claim 53 or 54, wherein said biomass is plant material from *Nerium* species or *Agrobacterium* species biomass.

56) The method of any one of claims 53-55, wherein said extract comprises a combination of oleandrin and one or more compounds extracted from said biomass.

57) The method of any one of claims 53-56, wherein said extract further comprises one or more cardiac glycoside precursors, one or more glycone constituents of cardiac glycosides, or a combination thereof.

58) The method of any one of claims 53-57, wherein said extract comprises oleandrin and one or more compounds 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, urchitoxin, and uzarigenin.

59) The method of any one of claims 53-58, wherein the daily dose of said extract is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day.

60) The method of any one of claims 52-58, wherein the daily dose of said extract is a minimum of about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

61) The method of any one of the above claims, wherein the viral titre in the subject's blood or plasma is reduced or does not increase as a result of the treatment.

62) The method of any one of the above claims, wherein the administration is systemic, parenteral, buccal, enteral, intramuscular, subdermal, sublingual, peroral, oral, or a combination thereof.

63) The method of any one of the above claims, wherein one or more doses are administered on a daily, weekly or monthly basis.

64) The method of any one of the above claims, wherein said antiviral composition is administered immediately after infection or any time within one day to 5 days after infection or at the earliest time after definite diagnosis of infection with virus.

65) The method of any one of the above claims, wherein said antiviral composition is administered as primary antiviral therapy, adjunct antiviral therapy, or co-antiviral therapy.

66) The method of any one of the above claims, wherein said administration comprises separate administration or coadministration of said antiviral composition with at least one other antiviral composition or with at least one other composition for treating symptoms associated with said viral infection.

67) The method of claim 66, wherein said symptoms are selected from the group consisting of inflammation, vomiting, nausea, headache, fever, diarrhea, nausea, hives, conjunctivitis, malaise, muscle pain, joint pain, seizure, and paralysis.

68) A sublingual dosage form comprising oleandrin, digoxin or a combination thereof.

69) The dosage form of claim 68 further comprising at least one liquid carrier.

70) An extract comprising oleandrin, said extract having been prepared by subcritical liquid extraction of biomass of *Nerium* sp. or *Thevetia* sp.

71) The extract of claim 70, wherein said subcritical liquid comprises carbon dioxide and optionally further comprises alcohol.

72) A method of preparing an extract comprising oleandrin, said method comprising the step of

subjecting oleandrin-containing biomass to extraction with subcritical liquid carbon dioxide, optionally further comprising alcohol, for a period of time sufficient to extract oleandrin from said biomass.

73) A method of preparing an extract comprising oleandrin, said method comprising

extracting oleandrin-containing biomass with extraction liquid comprising subcritical liquid carbon dioxide, optionally further comprising alcohol, for a period of time sufficient to extract oleandrin from said biomass;

separating said biomass from said extraction liquid while retaining said extraction liquid; and then

removing extraction liquid, thereby forming said extract.

74) A method of producing a combination oleandrin-containing extract, the method comprising

subjecting oleandrin-containing first biomass to organic solvent extraction to provide an oleandrin-containing organic solvent extract;

subjecting oleandrin-containing second biomass to subcritical liquid (SbCL) extraction (SbCLE) to provide an oleandrin-containing SbCL extract; and

combining said oleandrin-containing organic solvent extract and said oleandrin-containing SbCL extract to provide said combination oleandrin-containing extract.

75) An improved oleandrin-containing composition comprising a portion of oleandrin-containing organic solvent extract as defined herein and a portion of oleandrin-containing SbCL extract as defined herein.

76) A method of treating coronavirus infection, the method comprising administering to a subject in need thereof plural doses of oleandrin per day for a treatment period of at least about 5 days to about one month, wherein oleandrin is present in a pharmaceutical composition comprising at least one extract obtained from oleandrin-containing biomass.

77) The method of claim 76, wherein the total dose of oleandrin per day is independently selected upon each occurrence from about 1 microg to about 180 microg, about 1 microg to about 120 microg, about 5 microg to about 100 microg, about 10 microg to about 80 microg, about 10 microg to about 75 microg, about 15 microg to about 120 microg, about 15 microg to about 100 microg, about 15 microg to about 80 microg, about 30 microg to about 120 microg, about 30 microg to about 100 microg, about 30 micro to about 90 microg, about 40 microg to about 70 microg, about 1 microg, about 5 microg, about 10 microg, about 20 microg, about 30 microg, about 40 microg, about 50 microg, about 60 microg, about 70 microg, about 80 microg, about 90 microg, about 100 microg, about 110 microg, about 120 microg, about 130 microg, about 140 microg, about 150 microg, about 160 microg, about 170 microg, or about 180 microg.

78) The method of claim 76 or 77, wherein said plural doses of oleandrin per day are 2 to 10 doses per day, 2 to 8 doses per day, 2 to 6 doses per day, 2 to 4 doses per day, 2 doses per day, 3 doses per day, 4 doses per day, 5 doses per day, 6 doses per day, 7 doses per day, 8 doses per day, 9 doses per day, or 10 doses per day.

79) The method of any one of claims 76-78, wherein said pharmaceutical composition comprises at least two extracts obtained from *Nerium* species.

80) The method of claim 79, wherein said extract is independently selected upon each occurrence from the group consisting of hot-water extract, solvent extract, supercritical fluid extract, and subcritical liquid extract.

81) A method of treating viral infection as described herein.

82) A composition as described herein.

83) An antiviral composition as described herein.

84) An oleandrin-containing composition as described herein.

85) A method of treating coronavirus infection, the method comprising administering to a subject in need thereof one or more doses of oleandrin per day for a treatment period of at least about 5 days to about one or more months, wherein said coronavirus infection is pathogenic to humans.

86) The method of claim 85, wherein said coronavirus is selected from the group consisting of SARS-CoV, MERS-CoV, COVID-19 (SARS-CoV-2), CoV 229E, CoV NL63, CoV OC43, CoV HKU1, and CoV HKU20.

87) The method of claim 85, wherein the total dose of oleandrin per day is independently selected upon each occurrence from about 1 microg to about 180 microg, about 1 microg to about 120 microg, about 5 microg to about 100 microg, about 10 microg to about 80 microg, about 10 microg to about 75 microg, about 15 microg to about 120 microg, about 15 microg to about 100 microg, about 15 microg to about 80 microg, about 30 microg to about 120 microg, about 30 microg to about 100 microg, about 30 micro to about 90 microg, about 40 microg to about 70 microg, about 1 microg, about 5 microg, about 10 microg, about 20 microg, about 30 microg, about 40 microg, about 50 microg, about 60 microg, about 70 microg, about 80 microg, about 90 microg, about 100 microg, about 110 microg, about 120 microg, about 130 microg, about 140 microg, about 150 microg, about 160 microg, about 170 microg, about 180 microg, about 140 microg to about 315 microg, about 20 microg to about 750 microg, about 12 microg to about 300 microg, about 12 microg to about 120 microg, about 0.01 microg to about 100 mg, about 0.01 microg to about 100 microg, about 0.5 to about 100 microg, about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, and about 1.8 to about 40 microg.

88) The method of claim 85, wherein a dose comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 per kg of bodyweight of subject per day.

89) The method of claim 85, wherein a) the daily dose of oleandrin is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day,

about 38.4 microg/day or about 30 microg/day; and/or b) the daily dose of oleandrin is a minimum of about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

90) The method of claim 85, wherein a dose is administered twice daily or about every 12 hours, and the amount of oleandrin in said dose is about 0.25 to about 50 microg or about 0.9 to 15 microg.

91) The method of claim 85, wherein said one or more doses of oleandrin per day are 2 to 10 doses per day, 2 to 8 doses per day, 2 to 6 doses per day, 2 to 4 doses per day, 2 doses per day, 3 doses per day, 4 doses per day, 5 doses per day, 6 doses per day, 7 doses per day, 8 doses per day, 9 doses per day, or 10 doses per day.

92) The method of claim 85, wherein oleandrin is present in a composition comprising at least one extract obtained from oleandrin-containing biomass.

93) The method of claim 92, wherein said extract is independently selected upon each occurrence from the group consisting of hot-water extract, solvent extract, and supercritical fluid extract.

94) The method of claim 85, 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.

95) A method of treating coronavirus infection comprising administering to a subject, having said infection, plural therapeutically effective doses of oleandrin or oleandrin-containing composition.

96) The method of claim 95, wherein said plural therapeutically effective doses are one or more doses administered per day for two or more days per week.

97) The method of claim 96, wherein dosing is continued for one or more weeks per month.

98) The method of claim 97, wherein dosing is continued for one or more months per year.

99) The method of claim 95, wherein said coronavirus is pathogenic to humans.

100) The method of claim 99, wherein said coronavirus is selected from the group consisting of SARS-CoV, MERS-CoV, COVID-19 (SARS-CoV-2), CoV-229E, CoV NL63, CoV-OC43, CoV HKU1, and CoV HKU20.

101) The method of claim 95, wherein oleandrin is present in a composition comprising at least one extract obtained from oleandrin-containing biomass.

102) The method of claim 101, wherein said extract is independently selected upon each occurrence from the group consisting of hot-water extract, solvent extract, and supercritical fluid extract.

103) The method of claim 101, wherein said extract comprises a combination of oleandrin and one or more compounds extracted from said biomass.

104) The method of claim 103, wherein said one or more compounds comprises one or more cardiac glycoside precursors, one or more glycone constituents of cardiac glycosides, or a combination thereof.

105) The method of claim 95, wherein the administration is systemic, parenteral, buccal, enteral, intramuscular, subdermal, sublingual, peroral, oral, or a combination thereof.

106) The method of claim 95, wherein said antiviral composition is administered immediately after infection or any time within one day to 5 days after infection or at the earliest time after diagnosis of infection with virus.

107) The method of claim 95, wherein said antiviral composition is administered as primary antiviral therapy, adjunct antiviral therapy, or co-antiviral therapy, or wherein said administration comprises separate administration or coadministration of said composition with at least one other antiviral composition or with at least one other composition for treating symptoms associated with said viral infection.

108) The method of claim 95, wherein the total dose of oleandrin per day is independently selected upon each occurrence from about 1 microg to about 180 microg, about 1 microg to about 120 microg, about 5 microg to about 100 microg, about 10 microg to about 80 microg, about 10 microg to about 75 microg, about 15 microg to about 120 microg, about 15 microg to about 100 microg, about 15 microg to about 80 microg, about 30 microg to about 120 microg, about 30 microg to about 100 microg, about 30 micro to about 90 microg, about 40 microg to about 70 microg, about 1 microg, about 5 microg, about 10 microg, about 20 microg, about 30 microg, about 40 microg, about 50 microg, about 60 microg, about 70 microg, about 80 microg, about 90 microg, about 100 microg, about 110 microg, about 120 microg, about 130 microg, about 140 microg, about 150 microg, about 160 microg, about

170 microg, about 180 microg, about 140 microg to about 315 microg, about 20 microg to about 750 microg, about 12 microg to about 300 microg, about 12 microg to about 120 microg, about 0.01 microg to about 100 mg, about 0.01 microg to about 100 microg, about 0.5 to about 100 microg, about 1 to about 80 microg, about 1.5 to about 60 microg, about 1.8 to about 60 microg, and about 1.8 to about 40 microg.

109) The method of claim 95, wherein a dose comprises about 0.05-0.5 mg/kg/day, about 0.05-0.35 mg/kg/day, about 0.05-0.22 mg/kg/day, about 0.05-0.4 mg/kg/day, about 0.05-0.3 mg/kg/day, 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 per kg of bodyweight of subject per day.

110) The method of claim 95, wherein a) the daily dose of oleandrin is a maximum of about 100 microg/day, about 80 microg/day, about 60 microg/day, about 40 microg/day, about 38.4 microg/day or about 30 microg/day; and/or b) the daily dose of oleandrin is a minimum of about 0.5 microg/day, about 1 microg/day, about 1.5 microg/day, about 1.8 microg/day, about 2 microg/day, or about 5 microg/day.

111) The method of claim 95, wherein a dose is administered twice daily or about every 12 hours, and the amount of oleandrin in said dose is about 0.25 to about 50 microg or about 0.9 to 15 microg.

112) The method of claim 95, wherein said one or more doses of oleandrin per day are 2 to 10 doses per day, 2 to 8 doses per day, 2 to 6 doses per day, 2 to 4 doses per day, 2 doses per day, 3 doses per day, 4 doses per day, 5 doses per day, 6 doses per day, 7 doses per day, 8 doses per day, 9 doses per day, or 10 doses per day.

113) The method of claim 95, 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.

114) The method of claim 113, wherein said extract comprises oleandrin and one or more compounds 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, urechitoxin, and uzarigenin.