ANTIVIRAL ACTIVITY FROM MEDICINAL MUSHROOMS

Inventor: Paul Edward Stamets, Shelton, WA (US)

Correspondence Address:
William R. Hyde
1833 10th Street
Penrose, CO 81240 (US)

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ABSTRACT

Compounds having unique antiviral properties are prepared from medicinal mushroom mycelium, extracts and derivatives. The compositions are derived from Fomitopsis and blends of medicinal mushroom species and are useful in preventing and treating viruses including Poxviridae and Orthopox viruses.
ANTIVIRAL ACTIVITY FROM MEDICINAL MUSHROOMS

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention relates to methods and products useful in restricting the growth, spread and survivability of viruses in animals, especially humans. More particularly, the invention relates to methods and medicinal mushroom mycelium products for treating Orthopox viruses.

[0003] 2. Description of the Related Art

[0004] Despite advances in modern medicine, microbes and viruses continue to kill millions of people, stimulating the search for new antimicrobial and antiviral agents, some of which have proven to be of significant commercial value. A major difficulty in the discovery of antimicrobial and antiviral agents is their inherent toxicity to the affected host organism. For instance, a novel agent or treatment that kills the virus but also harms the human host is neither medically practicable nor commercially attractive. Hence, many new antiviral drugs have never made it past preliminary screening studies as they have failed to prove non-toxicity and are unsafe to consume.

[0005] That medicinal mushrooms have been ingested for hundreds, and in some cases, thousands of years, is strong support for their non-toxicity, making them appealing candidates in the search for new antimicrobial and antiviral agents. The cell surface of mycelium secretes antibiotics in a kind of “sweat” which are known in the field as exudates or secondary metabolites. These antibiotics and enzymes target distinct sets of microbes. Useful antibiotics isolated from mushrooms include calvacin from the Giant Puffball (Calvatia gigantea), armillariic acid from Honey Mushrooms (Armillaria mellea), campestrin from Agaricus campestris (The Meadow Mushroom), coprinol from Inky Caps (Coprinus species) corolin from Turkey Tail Mushrooms (Trametes versicolor—Coriolus versicolor), cortinelin from Shiitake (Lentinula edodes), ganomycin from Reishi (Ganoderma lucidum) and sparrasol from Cauliflower mushrooms (Sparassid crispa).

[0006] Suzuki et al. (1990) characterized an antiviral water-soluble lignin in an extract of the mycelium of Shiitake mushrooms (Lentinula edodes) isolated from cultures grown on rice bran and sugar cane bagasse which limited HIV replication in vitro and stimulated the proliferation of bone-marrow cells. Clinical trials with laminarin in the treatment of HIV patients showed inhibitory activity. (Gordon et al., 1998).

However, Abrams (2002) found no significant advantage in using laminarin in treating AIDS patients. Another mushroom recognized for its antiviral activity is Fomes fomentarius, a hoof-shaped wood conk growing trees, which inhibited the tobacco mosaic virus (Aoki et al., 1993). Collins & Ng (1997) identified a polysaccharopeptide inhibiting HIV type 1 infection from Turkey Tail (Trametes versicolor) mushrooms while Sarkar et al. (1993) identified an antiviral substance resident in an extract of Shiitake (Lentinula edodes) mushrooms. More recently, derivatives of the Gypsy mushroom, Rozites caperata, were found by Pirinino & Brandt (1999) to have significant inhibitory activity against the replication and spread of varicella zoster (the ‘shingles’ and ‘chickenpox’ virus), influenza A, and the respiratory syncytial virus but not against HIV and other viruses. Eo et al. (1999) found antiviral activity from the methanol-soluble fractions of Reishi mushrooms (Ganoderma lucidum), selective in inhibiting Herpes simplex and the vesicular stomatitis virus (HSV). Wang & Ng (2000) isolated a novel ubiquitin-like glycoprotein from Oyster mushrooms (Pleurotus ostreatus) that demonstrated inhibitory activity toward the HIV-1 reverse transcriptase. Arabinoxylane inhibits HIV indirectly through the enhancement of NK cells that target the virus. Arabinoxylanes are created from mushroom mycelia’s enzymatic conversion of rice bran (Ghoneum, M., 1998). Research by Dr. Byong Kak Kim showed that extracts of Reishi (Ganoderma lucidum) prevented the death of lymphocytes infected with HIV and inhibited the replication of the virus within the mother and daughter cells (Kim et al., 1994). In response to hot water extracts of Reishi mushrooms, preserved in ethanol, versus saline controls, NK cell activity was significantly augmented when cancer cells were co-cultured with human spleen cells. (Ohmoto, 2002). A mycelial combination of 7 species grown on rice achieved a similar result, greater than any one species at the same dosage. As the water extract of the fruitbodies is high in beta glucans while the mycelium-on-rice is low in beta glucans, but is high in arabinoxylanes, two causal agents are identified as NK effectors. Both the extract and the heat treated, freeze dried, powdered mycelium from 7 species share common activity levels of enhancing NK activity by 300%. These compounds may be synergistic. This same combination of 7 species fermented on rice had a strong effect against HIV, inhibiting replication by 99% while the water extract of Reishi fruitbodies was 70%, respectively. These results underscore that water extractations of fruitbodies and oral administration of myceliated rice positively influence the immune system, activating different subsets of immunological receptor sites. Maitake (Grifola frondosa) is currently the subject of research in the treatment of HIV. Mizuno et al. (1996) noted that crude fractions from Chaga (Inonotus obliquus) showed antiviral activity against HIV.

[0007] Fomitopsis officinalis (Villars) Bondarzew & Singer (=Agaricus officinalis, Fomes officinalis, Fomes larchis and Larici fomes officinalis) has the common names Agarikon, Quinine Conk, Larch Bracket Mushroom, Brown Trunk Rot, Eburiko, Adagan (“ghost bread”) and Taka’s di (“tree biscuit”). Once widespread throughout the temperate regions of the world, this perennial wood conk saprophyzes larch, Douglas fir and hemlock, preferring mature woodlands. Now nearly extinct in Europe and Asia, this mushroom is a resident of the Old Growth Forests of Oregon, Wash. and British Columbia. Known constituents include beta glucans, triterpenoids, agaricin and extracellular antibiotics. Forms used include mushroom fruitbodies and mycelium. F. officinalis has traditionally been used for centuries for the treatment of tuberculosis and/or pneumonia, the primary causal organisms being Mycobacterium tuberculosis, Bacillus pneumoniae and/or other microorganisms. Mizuno et al. (1995) and Hanssen (1996) include this mushroom in a group of polyproles, the hot water extracts of which provide a strong host mediated response. Agarikon was also applied topically, in a poultice, as an anti-inflammatory and to treat muscle/skeletal pain. Described by the first century Greek physician Dioscorides in Materia Medica, the first encyclopedic pharmacopoeia on the medicinal use of plants, in approximately 65 C.E., as a treatment for a wide range of illnesses, most notably consumption, later known as tuberculosis. A resident on the old growth conifers, especially spruce, hemlock, Douglas fir and on larch, this amazing mushroom produces a chalky cylindrical fruitbody that adds layers of spore-producing pores with each growth season, allowing for rough callousative page. Only lasts up to 50 years have been collected, and often times they resemble a woman, reminiscent of the Venus of Willendorf.
form. The Haida First Peoples of the Queen Charlotte Islands, and elsewhere on the coast of British Columbia, associated this mushroom, or debatably another polyopore species, with the powerful creator spirit Raven, and as a protector of women's sexuality (Blanchette et al., 1992; Stamets, 2002). This mushroom was carved into animalistic forms and placed on shamans' graves to protect them from evil spirits. Grzywnowicz (2001) described the traditional use of this mushroom by Polish peoples, as a treatment against coughing illnesses, asthma, rheumatoid arthritis, bleeding, infected wounds, and was known for centuries as a "elixir ad longam vitam": elixir of long life. The North Coast First Peoples of Northwestern North America also discovered the use of this mushroom as a poultice to relieve swellings and in teas for treating feverish illnesses. Called the Quinina Fungus in many forestry manuals because of its bitter taste, this mushroom is not the source of quinine, an alkaloid from the bark of the Amazonian Cinchona ledgeriana tree which was widely used since the late 19th century to treat malaria, caused by Plasmodium falciparum. Despite the long history of use, few modern studies have been published on its medicinally active compounds. F. officinalis merits further research as the number of strains is in rapid decline, especially in Europe, where it is on the verge of extinction (Leck, 1991).

The present inventor has suggested that it is thought, but not yet proven, that Fomitopsis officinalis provided aid in preventing the scourge of viral diseases such as smallpox among native populations of northwestern North America (Stamets, 2002). Upon further investigation, the inventor contacted Guqiaow (2004), President of the Haida People who told him "We did not have to develop a defense against smallpox. Our people went from 50,000 to 500 in three years. The smallpox came from a passenger dropped from the ship, the Queen Charlotte. Had we known of a cure, we would have used it." Moreover, tests of the hot-water extract from boiling this mushroom showed no antiviral activity with the U.S. Defense Department's Bioshield BioDefense Program whilst the water/ethanol extract from the in vitro grown mycelium originating from a tissue clone of this mushroom showed strong anti-pox virus activity (U.S. patent application Ser. No. 11/029,861).

Summaries of the antiviral properties of mushrooms were published by Sun et al. (2000), Brandt & Pirrino (2000) and Stamets (2001, 2002). Besides having a direct antiviral or antimicrobial effect, mushroom derivatives can also activate natural immune response, potentiating host defense, and in effect have an indirect but significant antimicrobial activity. (Stamets, 2003).

As mushrooms share a more common evolutionary history with animals than with any other kingdom, mushrooms and humans suffer from common pathogens in the microbial world, for instance, the bacterium Staphylococcus aureus and Pseudomonas fluorescens. Mushrooms have a vested evolutionary interest in not being rotted by bacteria, producing antibacterial agents to stave off infection. Work by Stay et al. (2000) showed that various mushroom species have anti-bacterially specific properties. Viral infections, as in viral pneumonia, can precede, for instance, infections from Streptococcus pneumoniae or Staphylococcus aureus, so the use of mushrooms having antibacterial properties can help forestall secondary infections from opportunistic pathogens. Mushrooms having both antibacterial and antiviral properties are especially useful for preventing infection. Furthermore, it is anticipated that some mushrooms will demonstrate anti-bacteriophageic properties, being dually antibacterial and antiviral.

Mushrooms have within them polysaccharides, glycoproteins, ergosterols, enzymes, acids and antibiotics, which individually and in concert can mitigate viral infection. As each species of mushrooms is unique, not only in its cellular architecture, but also in its innate response to viral antagonists, animals, especially humans, can benefit from these antiviral mushroom-derived agents. Since humans now face multiple threats from numerous viruses, including but not limited to HIV, flu (such as smallpox), West Nile virus, influenza and avian or bird flu viruses, coronaviruses such as SARS, hepatitis, Lyme disease, HELA, SARS, HIV, respiratory syncytial virus, hantaviruses, vesicular stomatitis, Herpes, Epstein Barr, Varicella-Zoster, Polio, Yellow Fever, Marburg, Ebola, VEE, Lassa and Dengue Fever, and numerous microbes including Plasmodium falciparum, Bacillus anthracis, Escherichia coli, anthrax, Mycobacterium tuberculosis, bacteriophages, fungi such as Candida albicans, as well as prions such as BSE, finding substances that afford a broad shield of protection against multiple viruses and microbes is difficult. Virologists are increasingly concerned about the threat of viral infection from animal hosts, thought to be the probable source of the 2003 SARS (Severe Acute Respiratory Syndrome) epidemic, likely to have originated in rural regions of China where humans and captured animals exist in close quarters. Furthermore, the concentration of animals in "factory farms" wherein thousands of chickens, hogs, cows and other animals are aggregated, provide a breeding environment for contagions as well as other environmental catastrophes. Viruses and bacteria can also breed when birds, dogs, prairie dogs, vermin, cats, primates, bats and other animals, including humans, have concentrated populations. These sources, and more yet to be discovered, present a microbial threat to human health.

Smallpox is a serious acute, contagious and infectious disease marked by fever and a distinctive progressive skin rash. The majority of patients with smallpox recover, but death may occur in up to 30% of cases. Many smallpox survivors have permanent scars on large areas of their body, especially their face, and some are left blind. Occasional outbreaks of smallpox have occurred for thousands of years in India, western Asia and China. European colonization in both the Americas and Africa was associated with extensive epidemics of smallpox among native populations in the 1500s and 1600s, including use as a biological weapon in the United States. Smallpox was produced as a weapon by several nations well past the 1972 Bioweapons convention that prohibited such actions.

There is no specific treatment for smallpox and the only prevention is vaccination. In 1980, the disease was declared eradicated following worldwide vaccination programs. However, in the aftermath of the terrorist and anthrax attacks of 2001, the deliberate release of the smallpox virus is now regarded as a possibility and the United States is taking precautions to deal with this possibility.

Smallpox is classified as a Category A agent by the Centers for Disease Control and Prevention. Category A agents are believed to pose the greatest potential threat for adverse public health impact and have a moderate to high potential for large-scale dissemination. Other Category A agents are anthrax, plague, botulism, tularemia, and viral hemorrhagic fevers. Even the remote potential for release of
a deadly communicable disease in an essentially non-immune population is truly frightening.

Orthopox (Orthopoxvirus) includes the virus that causes smallpox (Variola major). Smallpox infects only humans in nature, although other primates have been infected in the laboratory. Other members of the Orthopoxvirus genera capable of infecting humans include monkeypox, camelpox, cowpox, and vaccinia. Other poxviruses capable of infecting humans include the Parapoxvirus pseudocowpox and Orf (Parapoxvirus ovini) and the Molluscum contagiosum. Monkeypox is a rare smallpox-like disease encountered in villages in central and west Africa. It is transmitted by monkeys, primates and rodents. Camelopox is a serious disease of camels. The genetic sequence of the camelpox virus genome is most closely related to that of the Variola (smallpox) virus. Cowpox is usually contracted by milking infected cows and causes ulcerating “milker’s nodules” on the hands of dairy workers. Cowpox protects against smallpox and was first used for vaccination against smallpox. Pseudocowpox is primarily a disease of cattle. In humans it causes non-ulcerating “milker’s nodes.” Molluscum contagiosum causes minor warty bumps on the skin. It is transferred by direct contact, sometimes as a venereal disease. Orf virus occurs worldwide and is associated with handling sheep and goats afflicted with “scabby mouth.” In humans it causes a single painless lesion on the hand, forearm or face. Vaccinia, a related Orthopox of uncertain origin, has replaced cowpox for vaccination. Other viruses of the Poxviridae family include buffalopox virus, rabbitpox virus, avipox virus, sheep-pox virus, goatpox virus, lumpy skin disease (Neethling) virus, swinepox virus and Yaba monkey virus.

Poxviruses are very large rectangular viruses the size of small bacteria. They have a complex internal structure with a large double-stranded DNA genome enclosed within a “core” that is flanked by two “lateral bodies.” The surface of the virus particle is covered with filamentous protein components, giving the particle the appearance of a ball of knitting wool. The entire virus particle is encapsulated in an envelope derived from the host cell membranes, thereby “disguising” the virus immunologically. Most poxviruses are host-specific, but Vaccinia is a remarkable exception. True pox viruses are antigenically rather similar, so that infection by one elicits immune protection against the others.

With the flow of airline passengers from remote regions of the world, concentrating in airports and being re-routed to their destinations, the contagiousness of foreign-borne viruses carried by passengers is likely to be exacerbated in these types of locations, especially within the closed compartments of passenger airplanes, increasing the likelihood of cross-infection. Virtually anywhere humans concentrate provide opportunities for contagions to spread, whether by air or by physical contact. The history of viruses indicates the danger posed by new strains for which no immunities or vaccines exist. With the increased threat of bioterrorism from weaponized viruses, a readily available broad-spectrum antiviral serves the best interests of public health.

BRIEF SUMMARY OF THE INVENTION

Medicinal mushrooms having unique antiviral properties are described, including mushroom species, mycelium, extracts and derivatives useful in preventing, treating and ameliorating, mitigating, alleviating, reducing or curing infection from viruses. Particularly preferred are Fomitosipus and various combinations with other mushroom species. Extracts showing target specific antiviral properties are disclosed, as well as methods for preparation and isolation of active fractions.

Still further objects and advantages of this invention will become more apparent from the following detailed description and appended claims. Before explaining the disclosed embodiments of the present invention in detail, it is to be understood that the invention is not limited in its application to the details of the particular products and methods illustrated, since the invention is capable of other embodiments which will be readily apparent to those skilled in the art. Also, the terminology used herein is for the purpose of description and not of limitation.

DETAILED DESCRIPTION OF THE INVENTION

The extracts of the mushroom mycelium of Fomitosipus officinalis, Fomitosipus pinicola, Piptoporus betulinus and various combinations of species have been found by the present inventor to have unique antiviral properties, including activity against Orthopox viruses.

Orthopox viruses have a notorious reputation for their surviving outside of the carrier-host animal, surviving on surfaces such as blankets, on dead skin cells, and can be readily transmitted through bodily fluids, whether they are aspirated or not. That these viruses can survive long after their host cells have died makes orthopoxes especially capable of widespread distribution. Novel antiviral agents are needed to reduce the survivability of viruses beyond that of disinfectants currently in practice. Moreover, since the entry of viruses are commonly through the nasal and throat cavities, or through sexual contact, contact antivirals that limit the survivability of the virus, or kill the virus, and/or limit the susceptibility of human cells to infection by a pox virus while selectively not harming healthy human cells are needed. Such contact antivirals as disclosed herein could prove useful in many applications, closing some of the many vectors used by this virus for transmission to new hosts.

Rather than the mushrooms themselves, particularly preferred is the live mushroom mycelium (the “vegetative” state of the mushroom, containing at most only primordia or young mushrooms) and extracts thereof, particularly the cell free (centrifuged) extracts. The mycelium may be cultivated, grown or fermented on solid, semi-solid or liquid media. Preferred derivatives include frozen, dried or freeze-dried mycelium, extracts thereof and dried, solvent-free extracts (including both “crude” extracts and cell-free centrifuged extracts). It was unexpectedly found that boiling of the mushroom in water created water extracts that showed no activity against pox viruses whereas the mycelium grown from a clone of the same mushroom did.

Preferred antiviral species include the Fomitosipus species, particularly F. officinalis and F. pinicola, and the Piptoporus species, particularly P. betulinus.


[0025] The mycelial products of the present invention are preferably grown on grains; rice is very suitable. The mycelium may alternatively be grown on various agricultural and forestry products, by-products and waste products or synthetic media and the antiviral metabolites and products harvested using methods known to the art. Alternatively, the mycelium may be grown via liquid fermentation and the antiviral products harvested subsequent to colonization. The methods for cultivation of mycelium that are contemplated are covered within, for example, but are not limited to, the techniques described by Stamets (1993, 2000) in Growing Gourmet and Medicinal Mushrooms.

[0026] Although ethanol and water extracts are illustrated below, it will be obvious that the various solvents and extraction methods known to the art may be utilized. The extracts may optionally be prepared by methods including extraction with water, alcohols, organic solvents and supercritical fluids such as CO₂, etc. Extracts may also be prepared via steam distillation of volatile components, similar to the preparation of "essential oils" from flowers and herbs. Suitable alcohols include those containing from 1 to 10 carbon atoms, such as, for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, 2-butanol, 2-methyl-1-propanol (t-butyl), ethylene glycol, glycerol, etc. Suitable organic solvents include unsubstituted organic solvents containing from 1 to 16 carbon atoms such as alkanes containing from 1 to 16 carbon atoms, alkenes containing from 2 to 16 carbon atoms, alkenes containing from 2 to 16 carbon atoms and aromatic compounds containing from 5 to 14 carbon atoms, for example, benzene, cyclohexane, cyclopentane, methylecyclohexane, pentanes, hexanes, heptanes, etc., ketones containing from 3 to 13 carbon atoms such as, for example, acetone, 2-butanone, 3-pentanone, 4-methyl-2-pentanone, etc., esters containing from 2 to 15 carbon atoms such as t-butyl methyl ether, 1,4-dioxane, diethyl ether, tetrahydrofuran, etc., esters containing from 2 to 18 carbon atoms such as, for example, methyl formate, ethyl acetate and butyl acetate, nitriles containing from 2 to 12 carbon atoms such as, for example acetonitrile, propionitrile, benzonitrile, etc., amides containing from 1 to 15 carbon atoms such as, for example, formamide, N,N,N-dimethylformamide, N,N,N-dimethylacetamide, amines and nitrogen-containing heterocycles containing from 1 to 10 carbon atoms such as pyrroli-dine, 1-methyl-2-pyrrolidinone, pyridine, etc., halogen substituted organic solvents containing from 1 to 14 carbon atoms such as, for example, bromotrichloromethane, carbon tetrachloride, chloroform, etc., 1,2-dichloroethane, dichloromethane, 1-chlorobutane, trichloroethylene, 1,2-dichlorobenzene, 1,2,4-trichloro-

[0027] Preferred drying methods include freeze drying, air drying, spray drying and drum drying and the methods and apparatus for drying mycelium, extracellular metabolites, extracts and derivatives disclosed in U.S. Pat. No. 4,631,837 to Magoon (1986), herein incorporated by reference in its entirety. Extracts are preferably extracted from living mycelium and may be cell-free (filtered and/or centrifuged) or not.

[0028] The products from the culturing of the medicinal mushroom species and mycelia, extracts and derivatives can be deployed via several delivery systems as an effective antiviral control, including orally-active powders, pills, capsules, teas, extracts, dried extracts, sublinguals, sprays, dispersions, solutions, suspensions, emulsions, foams, syrups, lotions, ointments, gels, pastes, dermal patches, injectables, vaginal creams and suppositories.

[0029] The mycelium, extracts and derivatives of Fomitopsis officinalis, Piptoporus betulinus and/or Ganoderma resinaceum may optionally be combined with Agaricus bras-siliensis, Agrocybe arvalis, Agrocybe aegerita, Auricularia auricula, Auricularia polytricha, Calvitas gigantean, Cordyceps sinensis, Flammulina populclica, Flammulina velutipes, Fomes fomentarius, Fomitopsis cajanderi, Fomi-topsis pincola, Ganoderma applanatum, Ganoderma capsense, Ganoderma lucidum, Ganoderma oregone, Ganoderma sinense, Ganoderma neo-japonicum, Ganoderma tsugae, Gignanopsis gigantean, Grifola frondosa, Hericium abietis, Hericium erinaceus, Hericium ramosum, Hypoloma capnoides, Hypoloma sublateritum, Inonotus obliquus, Inonotus dryadeus, Inonotus dryophilus, Lentinula edodes, Lentinus pondersus, Lenzites betulina, Mycena alcalina, Phellinus linteus, Pholiota adipose, Pholiota nameko, Pleurotus citrinopileatus, Pleurotus cornucopiae, Pleurotus dryi-nus, Pleurotus eryngii, Pleurotus ostreatus, Pleurotus open-tinae, Pleurotus pulmonarius, Pleurotus tuberregium, Polyporus sulphureus (Laetiporus sulphureus), Laetiporus conifericola, Polyporus hirius, Polyporus tuberaster, Polyporus umbellatus, (=Grifola umbellata), Schizophyllum commune, Trametes versicolor (=Coriolus versicolor), and/or Wolfiporia cocos (=Porzia cocos) mycelium, extracts or derivatives.

[0030] Fomitopsis, Piptoporus and Ganoderma resinaceum may optionally be added to any formula or product in an amount sufficient to have the effect of preventing, treating, alleviating, mitigating, ameliorating or reducing infection.

[0031] The invention includes the combination of products from multiple mushroom species in a form to have the accumulated effect of restricting the growth, spread and survivability of viruses in animals, especially humans. Such forms may have the additional advantages of functioning as antibacterial, antiprotozoal, immunomodulators, nutraceutical-
als and/or probiotics as well as enhancing innate immunity defense mechanisms and host immune response, resulting in healing.

[0032] Optimizing dosage is dependent upon numerous variables. The difference between a medicine and poison is often dosage. Determining the proper dose for antiviral effects will only require routine experimentation because the concentrations of extracts can be simply diluted or concentrated by adjusting water content.

[0033] The term “effective amount” refers to an amount sufficient to have antiviral activity and/or enhance a host defense mechanism as more fully described below. This amount may vary to some degree depending on the mode of administration, but will be in the same general range. The exact effective amount necessary could vary from subject to subject, depending on the species, preventative treatment or condition being treated, the mode of administration, etc. The appropriate effective amount may be determined by one of ordinary skill in the art using only routine experimentation or prior knowledge in the art in view of the present disclosure. Typical therapeutic amounts of mycelium on rice (individual fungal species and/or combinations of species) are preferably 0.1-20 g/m/ day, more preferably 0.25-10 g/m/ day, and most preferably 0.5-5 g/m/ day. Typical therapeutic amounts of extracts (individual fungal species and/or combinations of species) preferably deliver 0.1-20 mg. extracted materials per kg. of body weight, more preferably 0.25-10 mg/kg, and most preferably 0.5-5 mg/kg.

[0034] The antiviral extracts, mycelium and/or other derivatives may be incorporated into foods to produce foods with antiviral properties, useful for protecting animals, including humans, dogs, cats, horses, cows, pigs, birds, fish, insects and other wild and domesticated animals, from infection.

[0035] The applicant anticipates that since DNA techniques and other advances in taxonomy will likely result in changes in names, the splitting of species, and even in the transfer of species to other genera, that the Polyporeaceae species mentioned in this patent application are those as understood by the most complete monograph on the subject, Ryvarden & Gilbertson’s North American Polypores. 1986 vol. 1 and 2, Fungi Flora, Oslo, Norway. As such, when we describe Fomitopsis officinalis, Piptoporus betulinus or any other mushroom species, we mean Fomitopsis officinalis sensu lato, Piptoporus betulinus sensu lato and a similar broad description of any other species, each of which means that this is the species concept as described within the broadest taxonomic interpretation, encompassing synonyms, varieties, forms and species that have or will be split from these species since original publication. As is known in the art, names change as new species concepts are constructed.

Example 1

[0036] Tissue cultures of the Polypore mushrooms, Fomitopsis officinalis, Fomitopsis pinicola and Piptoporus betulinus were cloned from wild specimens by the inventor and purified over time by successive transfers in a clean room laboratory using standard tissue culture techniques as described in Growing Gourmet and Medicinal Mushrooms Stamets (1993, 2000). Fomitopsis officinalis I is a strain collected from Morton, Wash., USA. Other species were either collected or obtained from culture banks. The Ganoderma resinaceum utilized is a strain formerly misidentified as G. lucidum. Phylogenetic analysis of Ganoderma based on nearly complete mitochondrial small-subunit ribosomal DNA sequences, Soon Gyu Hong and Hack Sung Jung, Mycologia, 96(4), 2004, pp. 742-745.

[0037] Mycelial cultures were grown in sterile Petri dishes containing sterilized malt yeast rice agar. After three weeks of colonization in a clean room laboratory, the cultures were aseptically transferred into a 1000 ml. BIBERBACH® stirrer containing 800 ml. of sterilized water. The BIBERBACH® container was activated using a WARING® blender base, chopping the mycelium into thousands of fragments. This mycelial broth was then transferred, under sterile conditions, into a sterilized glass 2000 ml. fermentation vessel containing a 3% concentration of malt sugar, 0.3% yeast and 0.3% powdered rice, stir bar and 800 ml. of sterilized water. Once transferred, the fermentation flask was placed on a magnetic stir plate, and stirred at 300-400 rpm for a period of 3-4 days in front of a laminar flow hood at a temperature of 70-75°F. During that time, three-dimensional colonies of mycelium appeared, increasing in numbers and in density. The fermentation was stopped prior to the coalescing of the mycelium into a contiguous mycelial mat. The dissociated fragmented mycelial mass allows for a multiple loci inoculation, resulting in accelerated colonization and allowing for the ease of further dilutions and inoculations. The fermented broth was then diluted 1:10 into sterilized water, and transferred, under sterile conditions, into polypropylene incubation bags containing approximately 6.6 lbs or 3 kg. moistened sterilized rice, adjusted to approximately 45-50% moisture content. Approximately 50-100 ml. of diluted fermented fluid was transferred into each of the 10 rice bags under sterile conditions. The fresh mycelial cultures were then incubated for 60-120 days in a class 100 clean room. Incubation times are preferably 7-180 days, more preferably 30-120 days.

[0038] Once colonization was determined to be sufficient, the mycelium-colonized rice was transferred to glass containers for extraction. The mycelium, being delicate in nature, was handled with utmost care so as not to cause cell damage in transfer and immediately covered with an approximately equal weight of 50% ethanol-water (prepared by mixing equal weights of 95% (190 proof) organic ethyl alcohol and spring water), agitated, and then allowed to rest for room temperature infusion-extraction for a total of 14 days. Cultures of Fomitopsis officinalis, Piptoporus betulinus, Ganoderma resinaceum and the various other species were treated separately in a similar fashion to the methods described herein. The clear fluid, the supernatant, was drawn off and decanted into 2 ounce amber bottles or other containers. Dilution for bioassay was from 1:100 to 1:1000.

[0039] It will of course be appreciated that differing concentrations and/or compositions of extracts may be easily prepared; e.g., 3 kg. of fresh mycelium on rice for every 3000 ml. of extract or 1 g. mycelium/1 ml. extract is an example of a therapeutically useful extract.

Example 2

[0040] Proprietary strains of Fomitopsis officinalis, Fomitopsis pinicola, Piptoporus betulinus, Ganoderma resinaceum and Ganoderma applanatum, sourced and/or originated by Stamets, were grown under Class 100 clean room conditions on sterilized, certified organic short grain brown rice, in accordance to methods described by Stamets (1993, 2000) in Growing Gourmet and Medicinal Mushrooms. The moistened rice was sterilized in high-density polypropylene bags and inoculated with mycelium, which was fermented in liquid
culture for several days. Each strain was grown to optimize the number of cell divisions (CFU’s—colony forming units) prior to transfer into grain. Once inoculated, each strain was incubated for a duration to optimize their CFU (colony forming units) maxima, and then flash frozen to -18°C. The frozen myceliated rice was then freeze-dried in a negative pressure vacuum of 1500-2000 millibars and then heated to 75°C. For 24 hours. The freeze-dried material was then milled to a fineness of 20-80 standard mesh (180-850 microns). This raw material can be filled into capsules, made into tablets, tinctures or further used as a base for a medicinal product effective as an antimicrobial and/or for potentiating a host mediated response. Products made from *Fomitopsis officinalis*, *Fomitopsis pinicola* and *Piptoporus betulinus* may be combined with other mushrooms, fungi, or plant based materials to positive affect immunity, host defense and resistance from infectious diseases. Grains other than rice may be additionally employed with similarly positive results.

Example 3

[0041] The general approach for determining antiviral activity and toxicity as described by E. Kern for orthopoxviruses (http://www.niaid.nih.gov/protocols/orthopox.htm) was utilized. The Selectivity Index (SI) values were determined by or under the direction of Dr. Earl Kern of the USAMRIID/NII/USAID Bioshield BioDefense Program.

[0042] An inexpensive, rapid assay such as a CPE-inhibition assay that is semi-automated was used initially to screen out the negatives. Screening assays were conducted in low-passaged human cells. Each assay system contained a positive control (CDV) and a negative control (ACV). Toxicity was determined using both resting and proliferating human fibroblast cells.

[0043] Screening Assay Systems for Determining Antiviral Activity Against VV and CV

[0044] Compounds were screened for activity against Vaccinia virus (VV) and Cowpox virus (CV) using the CPE assay in HFF cells. The screening assay systems utilized were selected to show specific inhibition of a biologic function, i.e., cytopathic effect (CPE) in susceptible human cells. In the CPE-inhibition assay, drug is added 1 hr prior to infection so the assay system will have maximum sensitivity and detect inhibitors of early replicative steps such as adsorption or penetration as well as later events. To rule out non-specific inhibition of virus binding to cells all compounds that show reasonable activity in the CPE assay can be confirmed using a classical plaque reduction assay in which the drug is added 1 hr after infection. These assay systems also can be manipulated by increasing the pre-treatment time in order to demonstrate antiviral activity with oligodeoxynucleotides and/or peptides. By delaying the time of addition of drug after infection, information regarding which step in the virus life cycle is inhibited (i.e., early vs. late functions) can be gained.

[0045] Efficacy: In all the assays used for primary screening, a minimum of six drug concentrations was used covering a range of 100 μg/ml to 0.03 μg/ml in 5-fold increments. These data allowed good dose response curves. From these data, the dose that inhibited viral replication by 50% (effect concentration 50; EC₅₀) was calculated using the computer software program MacSynergy II by M. N. Prichard, K. R. As saltine, and C. Shipman, Jr., University of Michigan, Ann Arbor, Mich.

[0046] Toxicity: The same drug concentrations used to determine efficacy were also used on uninfected cells in each assay to determine toxicity of each experimental compound. The drug concentration that is cytotoxic to cells as determined by their failure to take up a vital stain, neutral red, (cytotoxic concentration 50; CC₅₀) was determined as above. The neutral red uptake assay has been found to be reliable and reproducible and allows quantitation of toxicity based on the number of viable cells rather than cellular metabolic activity. It is important also to determine the toxicity of new compounds on dividing cells at a very early stage of testing. A cell proliferation assay using HFF cells is a very sensitive assay for detecting drug toxicity to dividing cells and the drug concentration that inhibits cell growth by 50% (IC₅₀) was calculated as described above. In comparison with four human diploid cell lines and vero cells, HFF cells are the most sensitive and predictive of toxicity for bone marrow cells.

[0047] Assessment of Drug Activity: To determine if each compound has sufficient antiviral activity that exceeds its level of toxicity, a selectivity index (SI) was calculated according to CC₅₀/EC₅₀. This index, also referred to as a therapeutic index, was used to determine whether or not a compound warrants further study. Compounds that had an SI of 2 or more are considered active, 10 or greater (≥10) is considered very active.

[0048] Laboratory Procedures for Determining Antiviral Efficacy and Toxicity

[0049] Preparation of compounds for in vitro testing: As the fungal extracts were water, ethanol and DMSO soluble, they were dissolved in tissue culture medium without serum at 1 mg/ml and diluted for use as indicated below in the description of the assay system. Noteworthy is that the extracts from the patient’s living mycelium, diluted from 100:1 to 1,000:1, showed effectiveness against the described viruses at dosages designed for testing pure pharmaceuticals, underscoring that the extracts as presented are potent against viruses.

[0050] Screening and Confirmation Assays for VV and CV

[0051] Preparation of Human Foreskin Fibroblast (HFF) Cells: Newborn human foreskins are obtained as soon as possible after circumcision and placed in minimal essential medium (MEM) containing vancomycin, fungizone, penicillin, and gentamicin at the usual concentrations, for 4 hr. The medium is then removed, the foreskin minced into small pieces and washed repeatedly with phosphate buffered saline (PBS) deficient in calcium and magnesium (PD) until red cells are no longer present. The tissue is then trypsinized using trypsin at 0.25% with continuous stirring for 15 min at 37°C in a CO₂ incubator. At the end of each 15-min. period the tissue is allowed to settle to the bottom of the flask. The supernatant containing cells is poured through sterile cheesecloth into a flask containing MEM and 10% fetal bovine serum. The flask containing the medium is kept on ice throughout the trypsinizing procedure. After each addition of cells, the cheesecloth is washed with a small amount of MEM containing serum. Fresh trypsin is added each time to the foreskin pieces and the procedure repeated until all the tissue is digested. The cell-containing medium is then centrifuged at 1000 RPM at 4°C for 10 min. The supernatant liquid is discarded and the cells resuspended in a small amount of MEM with 10% FBS. The cells are then placed in an appropriate number of 25 cm² tissue culture flasks. As cells become confluent and need trypsinization, they are expanded into larger flasks. The cells are kept on vancomycin and fungizone to passage four, and maintained on penicillin and gentamicin. Cells are used only through passage 10.
Cytopathic Effect Inhibition Assay: Low passage HFF cells are seeded into 96 well tissue culture plates 24 hr prior to use at a cell concentration of 2.5x10^4 cells per ml in 0.1 ml of MEM supplemented with 10% FBS. The cells are then incubated for 24 hr at 37°C in a CO2 incubator. After incubation, the medium is removed and 125 μl of experimental drug is added to the first row in triplicate wells, all other wells having 100 μl of MEM containing 2% FBS. The drug in the first row of wells is then diluted serially 1:5 throughout the remaining wells by transferring 25 μl using the BioMek 2000 Laboratory Automation Workstation. After dilution of drug, 100 μl of the appropriate virus concentration is added to each well, excluding cell control wells, which received 100 μl of MEM. The virus concentration utilized is 1000 PFU’s per well. The plates are then incubated at 37°C in a CO2 incubator for 7 days. After the incubation period, media is aspirated and the cells stained with a 0.1% crystal violet in 3% formalin solution for 4 hr. The stain is removed and the plates rinsed using tap water until all excess stain is removed. The plates are allowed to dry for 24 hr and then read on a BioTek Multplate Autoreader at 620 nm. The EC50 values are determined by comparing drug treated and untreated cells using a computer program.

Plaque Reduction Assay using Semi-Solid Overlay: Two days prior to use, HFF cells are plated into 6 well plates and incubated at 37°C with 5% CO2 and 90% humidity. On the date of assay, the drug is made up at twice the desired concentration in 2x MEM and then serially diluted 1:5 in 2x MEM using 6 concentrations of drug. The initial starting concentration is usually 200 μg/ml down to 0.06 μg/ml. The virus to be used is diluted in MEM containing 10% FBS to a desired concentration which will give 20-30 plaques per well. The media is then aspirated from the wells and 0.2 ml of virus is added to each well in duplicate with 0.2 ml of media being added to drug toxicity wells. The plates are then incubated for 1 hr with shaking every 15 min. After the incubation period, an equal amount of 1% agarose will be added to an equal volume of each drug dilution. This gives final drug concentrations beginning with 100 μg/ml and ending with 0.03 μg/ml and a final agarose overlay concentration of 0.5%. The drug/agarose mixture is applied to each well in 2 ml volume and the plates are incubated for 3 days, after which the cells are stained with a 0.01% solution of neutral red in phosphate buffered saline. After a 5-6 hr incubation period, the stain is aspirated, and plaques counted using a stereomicroscope at 10x magnification.

Screening and Confirmation Assays for Toxicity

Neutral Red Uptake Assay Twenty-four h prior to assay, HFF cells are plated into 96 well plates at a concentration of 2.5x10^4 cells per well. After 24 hr, the media is aspirated and 125 μl of drug is added to the first row of wells and then diluted serially 1:5 using the BioMek 2000 Laboratory Automation Workstation in a manner similar to that used in the CPE assay. After drug addition, the plates are incubated for 7 days in a CO2 incubator at 37°C. At this time the media/drug is aspirated and 200 μl/well of 0.01% neutral red in PBS is added. This is incubated in the CO2 incubator for 1 hr. The dye is aspirated and the cells are washed using a Nunc Plate Washer. After removing the PBS, 200 μg/well of 50% ETOH/1% glacial acetic acid (in H2O) is added. The plates are rotated for 15 min and the optical densities read at 540 nm on a plate reader. The EC50 values are determined by comparing drug treated and untreated cells using a computer program.

Independent cell cytotoxicity tests conducted by or under the direction of Dr. Susan Manly and/or Dr. Samir Ross of the National Center for Natural Products Research (NCNPR) at the University of Mississippi showed the mycelial extracts to be non-toxic at the high levels of exposure in three human cell culture lines. It is therefore possible that the Selectivity Index ratios may be understated, as SI is the CC50 (cytotoxicity) divided by EC (effective concentration) (the amount that will kill 50% of the human cells divided by the amount to kill 50% of the virus). If the SI values are understated, the products described herein could be loaded much higher than that shown before evidence of cytotoxicity would be seen and the actual antiviral activity may be much more than that shown by cell line biosassays described herein.

All strains below were incubated for approximately two months prior to extractions; some strains were incubated up to 7 months. Activity was seen consistently within this timespan of incubation. With those strains designated as “shaken,” the mycelium and ethanol/water were shaken and allowed to settle prior to decanting the extract.

The *Fomitisopsis officinalis* strain and extracts described above in Example 1 were utilized.

<table>
<thead>
<tr>
<th>Drug Name (Mycelium Extract)</th>
<th>CPE</th>
<th>CPE</th>
<th>CPE</th>
<th>CDV</th>
<th>CDV</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fomitisopsis officinalis</em> I</td>
<td>0.68</td>
<td>1.1</td>
<td>&gt;10</td>
<td>&gt;14.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Shaken</td>
<td>0.5</td>
<td>0.81</td>
<td>&gt;10</td>
<td>&gt;20</td>
<td>2.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name (Mycelium Extract)</th>
<th>CPE</th>
<th>CPE</th>
<th>CPE</th>
<th>CDV</th>
<th>CDV</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Vaccinia</em> Cells</td>
<td><em>F. officinalis</em> I</td>
<td>0.98</td>
<td>1.5</td>
<td>&gt;10</td>
<td>&gt;10.2</td>
</tr>
<tr>
<td><em>F. officinalis</em> I</td>
<td>4.9</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;20</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Bacteria | Mushroom Extracts-% Inhibition
---|---
*Mycobacterium tuberculosis* | *F. officinalis* extract-73%

From these data showing direct antiviral activity, it is reasonably predictable and expected that the compositions will have utility in humans in preventing, treating, alleviating, ameliorating, mitigating, reducing and/or curing infection and/or symptoms from viruses, including smallpox.

When the mycelial extracts were dried and fractionated, none of the 91 fractions showed any antiviral activity at the concentrations tested and yet the whole extracts continued to show significant antiviral activity, repeatedly and consistently, for more than two years from creation.

GC testing of the *Fomitisopsis* and *Pytoporus* extracts for agaric acid showed no agaric acid to be present. It will be noted that the activity of agaric acid does not correlate
well with the activity of the extracts in the bioassays herein. HPLC analysis of the *Fomitopsis* and *Piptoporus* extracts showed no betulinic acid to be present. It is, of course, possible that agamic acid and/or betulinic acid may be an intermediate in various cellular processes or may be found to be biologically incorporated into various cellular constituents. It is further possible that such molecular matrices may serve to detoxify the cytotoxicity while preserving antiviral properties. However, it does not appear that the antiviral properties of the present invention may be ascribed to either agamic acid or betulinic acid and it is expected that the extracts possess novel antiviral and antimicrobial compounds.

[0062] Although ethanol was used as the organic solvent, ethanol is clearly not the causal agent, as numerous samples of other mushroom species showed no activity although they were also presented in the same form (ethanol and water) as was *Fomitopsis officinalis*.

[0063] It will be understood that a supplement or extract composed of ingredients from the fungi *Fomitopsis officinalis*, *Fomitopsis pinicola*, *Piptoporus betulinus* and/or *Ganoderma resinaceum* and used in an amount sufficient to have the effect of preventing, treating, mitigating, reducing, alleviating, ameliorating or curing infection from viruses or their vectors, including Cowpox, Variola (smallpox) and other Orthopox viruses, coronaviruses including SARS, HIV, influenza, avian influenza, Venezuelan Equine Encephalitis, Yellow fever, West Nile, SARS, Rhinovirus New World and Old World arenaviruses including the American hemorrhagic fevers, Lassa and lymphocytic choriomeningitis, VEE, Hanavirus, Rift Valley fever, sandfly fever, yellow fever, West Nile, Dengue fever, respiratory viruses, Rhinoviruses, Herpes Simplex I, Herpes Simplex II, Lyme, HELA, Epstein Barr, Ebolavirus, Varicella-Zoster, adenoviruses, Polio, Hepatitis including Hepatitis A, B and C and/or from the microbes causing Tuberculosis, pneumonia (bacterial pneumonia, viral pneumonia, and mycoplasma pneumonia), such as *Plasmodium falciparum*, *Bacillus anthracis*, *Escherichia coli*, *Myco bacterium tuberculosis*, bacteriophages and fungi such as *Candida albicans* should be obvious to one skilled in the art and considered within the scope of the invention. As the products and methods of the present invention treat both viruses and opportunist pathogenic organisms such as *Mycobacterium tuberculosis* and other bacteria, it will be appreciated that the present invention is exceptionally advantageous insofar as viral infections can lead to bacterial infections and vice versa.

[0064] It will also be obvious to one skilled in the art that isolation, fractionation, purification and/or identification of DNA, RNA and protein sequences responsible for antiviral activity and antiviral agents from *Fomitopsis officinalis*, *Fomitopsis pinicola*, *Piptoporus betulinus* and/or *Ganoderma resinaceum* could be transferred to another organism, such as a bacterium or yeast, for the commercial production of antiviral agents and/or its antiviral or antimicrobial active derivatives and should be considered within the scope of the invention.

[0065] The publications and other materials used herein to illuminate the background of the invention and in particular cases, to provide additional details respecting the practice, are incorporated by reference.

[0066] It should be understood the foregoing detailed description is for purposes of illustration rather than limitation of the scope of protection accorded this invention, and therefore the description should be considered illustrative, not exhaustive. The scope of protection is to be measured as broadly as the invention permits. While the invention has been described in connection with preferred embodiments, it will be understood that there is no intention to limit the invention to those embodiments. On the contrary, it will be appreciated that those skilled in the art, upon attaining an understanding of the invention, may readily conceive of alterations to, modifications of, and equivalents to the preferred embodiments without departing from the principles of the invention, and it is intended to cover all these alternatives, modifications and equivalents. Accordingly, the scope of the present invention should be assessed as that of the appended claims and any equivalents falling within the true spirit and scope of the invention.

1 claim:

1. A composition for restricting the growth, spread and survivability of viruses comprising a derivative of a medicinal mushroom wherein the medicinal mushroom is a *Fomitopsis*, the derivative is selected from the group consisting of live mycelium, dried live mycelium, freeze dried mycelium, extracts of live mycelium, dried extracts of live mycelium and combinations thereof and the derivative has a selectivity index (SI) against an Orthopox virus of 10.

2. The composition of claim 1 wherein the Orthopox virus is selected from the group consisting of smallpox, monkeypox, camelpox, cowpox and vaccinia.

3. The composition of claim 1 wherein the *Fomitopsis* is *Fomitopsis officinalis*.


5. The composition of claim 1 wherein the live mycelium is grown on a grain.

6. The composition of claim 1 wherein the derivative is administered in a form selected from the group consisting of orally-active powders, pills, capsules, teas, extracts, dried extracts, sublinguals, sprays, dispersions, solutions, suspensions, emulsions, foams, syrups, lotions, ointments, gels, pastes, dermal patches, injectables, vaginal cremes and suppositories.

7. The composition of claim 1 wherein the extracts are extracted with ethanol and water.
8. The composition of claim 1 wherein the extracts are extracted with a solvent selected from the group consisting of water, steam, alcohols, organic solvents, carbon dioxide and combinations thereof.

9. The composition of claim 8 wherein the organic solvents are selected from the group consisting of alcohols containing from 1 to 10 carbon atoms, unsubstituted organic solvents containing from 1 to 16 carbon atoms, ketones containing from 3 to 13 carbon atoms, ethers containing from 2 to 15 carbon atoms, esters containing from 2 to 18 carbon atoms, nitriles containing from 2 to 12 carbon atoms, amides containing from 1 to 15 carbon atoms, amines and nitrogen-containing heterocycles containing from 1 to 10 carbon atoms, halogen substituted organic solvents containing from 1 to 14 carbon atoms, acids containing from 1 to 10 carbon atoms, and alkoxy, aryloxy, cyanoalkyl, aryl, alkaryl and aralkyl substituted organic solvents containing from 3 to 13 carbon atoms, DMSO and combinations thereof.

10. The composition of claim 1 wherein the composition additionally comprises a derivative selected from the group consisting of Piptoporus betulinus derivatives and Ganoderma resinaceum derivatives.

11. The composition of claim 1 wherein the derivative also inhibits tuberculosis bacteria (Mycobacterium tuberculosis).

12. A composition comprising an extract of Fomitopsis mycelium wherein the extract has antiviral activity and a Selectivity Index (SI=CC50/EC50) against a Poxviridae virus ≥10.

13. The composition of claim 12 wherein the Poxviridae virus is selected from the group consisting of smallpox, monkeypox, camelpox, cowpox, pseudocowpox, Molluscum contagiosum and Orf virus.

14. The composition of claim 12 wherein the Fomitopsis is Fomitopsis officinalis.


16. The composition of claim 12 wherein the extract is administered in a form selected from the group consisting of orally-active powders, pills, capsules, teas, dried extracts, sublinguals, sprays, dispersions, solutions, suspensions, emulsions, foams, syrups, lotions, ointments, gels, pastes, dermal patches, injectables, vaginal creams and suppositories.

17. The composition of claim 12 wherein the extract is extracted with ethanol and water.

18. The composition of claim 17 wherein the antiviral activity is due to contact with mycelial components and not due to contact with the ethanol.

19. The composition of claim 12 wherein the extract is extracted with a solvent selected from the group consisting of water, steam, alcohols, organic solvents, carbon dioxide and combinations thereof.

20. The composition of claim 19 wherein the organic solvents are selected from the group consisting of alcohols containing from 1 to 10 carbon atoms, unsubstituted organic solvents containing from 1 to 16 carbon atoms, ketones containing from 3 to 13 carbon atoms, ethers containing from 2 to 15 carbon atoms, esters containing from 2 to 18 carbon atoms, nitriles containing from 2 to 12 carbon atoms, amides containing from 1 to 15 carbon atoms, amines and nitrogen-containing heterocycles containing from 1 to 10 carbon atoms, halogen substituted organic solvents containing from 1 to 14 carbon atoms, acids containing from 1 to 10 carbon atoms, and alkoxy, aryloxy, cyanoalkyl, aryl, alkaryl and aralkyl substituted organic solvents containing from 3 to 13 carbon atoms, DMSO and combinations thereof.

21. The composition of claim 12 wherein the composition additionally comprises an extract selected from the group consisting of Piptoporus betulinus derivatives and Ganoderma resinaceum derivatives.

22. A composition comprising an extract of Fomitopsis officinalis mycelium wherein the extract has an antiviral activity Selectivity Index (SI=CC50/EC50) against pox viruses that is ≥10 and the survivability of the pox virus is limited upon contact with the extract of Fomitopsis officinalis.

23. A composition for limiting the survivability of pox viruses upon contact with the composition while selectively not harming healthy human cells comprising an extract of live Fomitopsis officinalis mycelium wherein the extract has a Selectivity Index (SI=CC50/EC50) against an Orthopox virus that is ≥10.

24. A composition that limits the susceptibility of human cells to infection by a pox virus via the composition contacting the pox virus prior to the pox virus contacting a living human cell, wherein the composition comprises an extract of Fomitopsis officinalis mycelium and the extract has a calculated Selectivity Index (SI=CC50/EC50) against a pox virus that is ≥10.

* * * * *