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(54) **ANTIVIRAL ACTIVITY FROM MEDICINAL MUSHROOMS**

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(76) Inventor: **Paul Stamets**, Shelton, WA (US)

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

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(57) **ABSTRACT**

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(63) Continuation-in-part of application No. 11/145,679, filed on Jun. 6, 2005, which is a continuation-in-part of application No. 11/029,861, filed on Jan. 4, 2005.

(60) Provisional application No. 60/534,776, filed on Jan. 6, 2004.

Compounds having unique antiviral properties are prepared from medicinal mushroom mycelium, extracts and derivatives. The compositions are derived from *Fomitopsis*, *Piptoporus*, *Ganoderma* and blends of medicinal mushroom species and are useful in preventing and treating viruses including *Orthopox* viruses, influenza, avian influenza, Venezuelan Equine Encephalitis, yellow fever, West Nile, Dengue, New World and Old World arenaviruses, hantavirus, Rift Valley fever, sandfly fever, hantavirus, SARS, Rhinovirus and other viruses.

ANTIVIRAL ACTIVITY FROM MEDICINAL MUSHROOMS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 11/145,679, filed Jun. 6, 2005, which is a continuation-in-part of U.S. patent application Ser. No. 11/029,861, filed Jan. 4, 2005, which claims the benefit of U.S. Provisional Application No. 60/534,776, filed Jan. 6, 2004.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] 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 viruses.

[0004] 2. Description of the Related Art

[0005] Despite advances in modern medicine, microbes, especially viruses, continue to kill millions of people, stimulating the search for new anti-microbial agents, some of which have proven to be of significant commercial value. A major difficulty in the discovery of anti-microbial 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 anti-viral drugs have never made it past preliminary screening studies as they have failed to prove non-toxicity and are unsafe to consume.

[0006] 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*), armilliaric 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*), cortinellin from Shiitake (*Lentinula edodes*), ganomycin from Reishi (*Ganoderma lucidum*) and sparassol from Cauliflower mushrooms (*Sparassia crispa*).

[0007] 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 lentinan in the treatment of HIV patients showed inhibitory activity. (Gordon et al., 1998). However, Abrams (2002) found no significant advantage in using lentinan 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 Piraino & Brandt (1999) to have significant inhibition 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*), selectively inhibiting Herpes simplex and the vesicular stomatitis virus (VSV). 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 extractions 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 anti-viral activity against HIV.

[0008] Betulinic acid and betulinic acid derivatives are a class of small molecules that exhibit anti-human immunodeficiency virus type 1 (anti-HIV-1) activity.

[0009] Agaricin (agaric acid, agaricic acid, agaricinic acid, laricic acid, alpha-hexadecylcitric acid, d-cetylcitric acid, n-hexadecylcitric acid, 2-hydroxy-1,2,3-nonadecanetricarboxylic acid), a white, microcrystalline, water-soluble powder first isolated in 1883 from *Fomitopsis officinalis*, is known to occur in various mushroom species including *F. officinalis* (= *Agaricum officinalis*, *Agaricum officinale*, *Fomes officinalis*, *Fomes laricis*, *Fomes albogriseus*, *Laricifomes officinalis*, *Leptoporus officinalis*, *Boletus agaricum*, *Boletus laricis*, *Boletus laricinus*, *Boletus officinalis*, *Boletus purgans*, *Ungulina officinalis* and *Polyporus officinalis*), *Piptoporus betulinus* (= *Polyporus betulinus*), *Phellinus linteus* and various *Polyporus* species. "Agaricin" has been used to refer to both pure agaric acid and extracts of *Fomitopsis officinalis* with larger or smaller amounts of impurities. In the present context, "agaricin" will be utilized

to refer to pure agaric acid, both synthetic and extracted, to salts of agaric acid such as, for example, the sodium, potassium, lithium and bismuth agaricines, and to extracts of mushroom fruitbodies or mushroom mycelium containing agaric acid. "Agaric acid" as used in the present context refers to the compound 2-hydroxy-1,2,3-nonadecanetricarboxylic acid. Agaricin, including extracts of *Fomitopsis officinalis* of greater or lesser purity, has been used both orally and topically for centuries to treat various ailments. Oral applications include the treatment of sweats in wasting conditions (agaricin has a powerful anhidrotic or antihydrotic effect) or treatment of hyperhidrosis (parasympatholytic or anticholinergic effect), treatment of consumption (tuberculosis), coughing illnesses, feverish illnesses and asthma and use as an emetic, purgative or laxative and use as a parasympatholytic (anticholinergic) agent. Agaricin also has been applied topically, in a poultice, as an anti-inflammatory, to treat muscle/skeletal pain including rheumatoid arthritis, to treat swelling, bleeding or infected wounds and as a counter-irritant applied to abraded surfaces or mucous membrane. Salts of agaricin, including sodium, lithium and bismuth agaricines have also found application.

[0010] *Fomitopsis officinalis* (Villars) Bondarzew & Singer (= *Agaricum officinalis*, *Fomes officinalis*, *Fomes laricis* and *Laricifomes officinalis*) has the common names Agarikon, Quinine Conk, Larch Bracket Mushroom, Brown Trunk Rot, Eburiko, Adagan ('ghost bread') and Tak'a di (tree biscuit). Once widespread throughout the temperate regions of the world, this perennial wood conk saprophytizes 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, Washington 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. (1995a) and Hanssen (1996) include this mushroom in a group of polypores, 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 a rough calculation of age. Conks 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 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 shaman's 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 "elixirium ad longam vitam": elixir of long life. The North Coast First Peoples of North-western North America also discovered the use of this mushroom as a poultice to relieve swellings and in teas for treating feverish illnesses. Called the Quinine 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).

[0011] *Piptoporus betulinus* (Bull.:Fr.) Karst (= *Polyporus betulinus* (Bull.:Fr.) Fr.) is commonly known as the Birch Polypore or Kanbatake. It is found throughout the birch forests of the world, circumboreal, and is one of the most common mushrooms on that host. Known constituents include betulin, betulinic acid, agaric acid, single stranded RNA, heteroglucans, and antibiotics. Forms used include mushrooms, mycelium on grain and fermented mycelium. Crude extracts and purified fraction are tumor inhibiting in vitro. The novel antibiotic, Piptamine, has been isolated from this fungus (Schlegel et al. 2000). Pisha et al. (1995) found, in mice studies, that betulinic acid, a pentacyclic triterpene, was specifically toxic to melanoma without adverse effects to the host. Farnsworth et al. (1995) found that betulinic acid facilitated apoptosis of melanoma. This compound has been further evaluated for the treatment or prevention of malignant melanoma. Manez et al. (1997) found that selected triterpenoids reduced chronic dermal inflammation. Found with the famous Ice Man, the use of *P. betulinus* transcends cultures and millennia. A fungus useful to stop bleeding, prevent bacterial infection, and as an antimicrobial agent against intestinal parasites, this species is one of the most prominent and frequently encountered mushroom seen on birch. Capasso (1998) postulated that the Ice Man used this fungus to treat infection from intestinal parasites (*Trichuris trichiura*).

[0012] The present inventor has suggested that it is thought, but not yet proven, that *Fomitopsis officinalis* provided an 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 Guujaaw (2004), President of the Haida People who told him "We did not have time 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).

[0013] Summaries of the antiviral properties of mushrooms were published by Suay et al. (2000), Brandt & Piraino (2000) and Stamets (2001, 2002). Besides having a direct antiviral or antimicrobial effect, mushroom deriva-

tives can also activate natural immune response, potentiating host defense, and in effect have an indirect but significant antimicrobial activity. (Stamets, 2003).

[0014] 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 Suay 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.

[0015] 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 anti-viral mushroom-derived agents. Since humans now face multiple threats from numerous viruses, including but not limited to HIV, Pox (such as small pox), West Nile virus, influenza and avian or bird flu viruses, coronaviruses such as SARS, hepatitis, Lyme disease, HELA cervical virus, respiratory syncytial virus, hantavirus, 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 (Sudden 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.

[0016] 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 over 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.

[0017] 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.

[0018] 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.

[0019] *Orthopox* (orthopoxviruses or poxviruses) includes the virus that causes smallpox (Variola). Smallpox infects only humans in nature, although other primates have been infected in the laboratory. Other members of the *Orthopox* genus of viruses capable of infecting humans include monkeypox, camelpox, cowpox, pseudocowpox, *Molluscum contagiosum* and Orf. Monkeypox is a rare smallpox-like disease encountered in villages in central and west Africa. It is transmitted by monkeys, primates and rodents. Camelpox 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.

[0020] 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 particles 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-species 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.

[0021] Influenza (“flu”) is an infection of the respiratory system characterized by fever, body aches, chills, dry cough, headache, sore throat and stuffy nose. The flu, which is caused by a variety of viruses, is notable for its ability to sweep through entire communities in both developed and developing countries and is associated with high morbidity and a significant death rate. Half the population of a community may be affected during an epidemic. Children are much more likely than adults to get sick from the flu, as are families with school-age children—schools are an excellent place for flu viruses to infect and spread. The risk of death from influenza is highest among persons aged 65 or older, although young children, particularly the newborn, and persons with certain chronic conditions are also at risk of death. The flu is particularly serious because of the rapidity of outbreaks, the large number of people affected and the possibility of serious complications such as pneumonia. The Centers for Disease Control and Prevention estimates that 5-20% of the population of the United States come down with the flu each flu season (typically late fall through winter). Although most recover from the illness, according to CDC estimates about 19,000-36,000 died from the flu and its complications each year during the epidemics occurring from 1976-1999. The 1918 Spanish flu pandemic is estimated to have caused 20-40 million deaths worldwide, including 500,00 in the United States. The 1957 Asian flu and the 1968 Hong Kong flu outbreaks killed hundreds of thousands in the United States.

[0022] The influenza viruses are RNA viruses belonging to the Orthomyxoviridae family. Influenza viruses are classified into types A, B and C. Type A is the most common and usually causes the most serious epidemics. Influenza A viruses are further divided into subtypes on the basis of two proteins found on the surface of the virus, hemagglutinin (H) and neuraminidase (N). Influenza A viruses are found in many different animals, including birds, pigs, whales and seals, with wild birds acting as the reservoir for all subtypes of influenza A viruses. The influenza A subtypes H1N1 and H3N2 have circulated widely among people (the Spanish flu was a H1N1 virus and the Hong Kong flu was a H3N2 virus). Type B can also cause epidemics, but generally produces a milder disease than that caused by type A. Type C viruses have never been connected with major epidemics. Yearly flu vaccines are available targeting new variant strains resulting from antigenic drift, but neither prior vaccination nor previous infection guarantees protection from the flu since the virus typically varies from year to year.

[0023] It is currently feared that a strain of avian influenza (“bird flu”), which naturally occurs in wild birds and can spread to domesticated birds, could mutate into a form easily transmissible by human-to-human and cause a worldwide pandemic. The H5N1 high pathogenicity avian influenza (HPAI) virus strain, which is becoming endemic in various Asian countries and has spread to a number of countries in the Middle East, Africa and Europe, has particularly concerned researchers because it is spread by migratory wild-fowl, because it is especially virulent and has caused the death of millions of animals worldwide, because it mutates rapidly and continues to evolve and because it has spread to domesticated birds and mammals including pigs and tigers and in limited circumstances to humans. As influenza type A H5 hemagglutinin viruses have not circulated among humans and most or all of the population has no protective antibodies, there is the potential that H5N1 could cause a

pandemic were it to mutate to a form easily transmissible by human-to-human contact. The H5N1 avian influenza strain has caused illness in more than 100 people in Asia and the Middle East, approximately half of whom have died (almost all cases are thought to be the result of bird-to-human infection, but it appears there may be rare cases of human-to-human transmission). A severe influenza pandemic could potentially result in unprecedented death, social disruption and economic loss as millions become seriously ill at the same time.

[0024] Venezuelan equine encephalitis (VEE) is a mosquito-borne enveloped RNA virus of the *Alphavirus* genus endemic to northern South America, Central America, Mexico and occasionally the United States, causing severe disease in humans as well as Equidae (horses, mules, burros and donkeys). VEE is characterized by fever that may be accompanied by severe headache, muscle and back pain, chills, nausea, vomiting and exhaustion or weakness that may progress to encephalitis (inflammation of the meninges of the brain and the brain itself). The incidence among humans during epidemics has been as high as 30-50% of the population, especially among children. Although most human infection is subclinical or mild and the fatality rate in humans is typically 0.5-1%, approximately 4% of children develop signs of central nervous system infection and the fatality rate in children and others manifesting severe encephalitis may reach 20%. Alphaviruses include a number of encephalitis and fever species in addition to VEE having characteristics suitable for weaponization, including the potential to be produced in large quantities, effective delivery via an aerosol vector and relative stability in the environment, and such weaponization is thought to have occurred in a number of countries as part of bioweapons programs.

[0025] West Nile virus (WNV) is a virus of the *Flavivirus* genus commonly found in Africa, West Asia and the Middle East which has spread to Europe and to the Western Hemisphere (including the United States in the last decade). The mosquito-borne virus can infect birds and mammals including humans and horses. In a few people (less than 1%), infection with WNV causes severe illness with symptoms that may include high fever, headache, stupor, coma, convulsions, vision loss and paralysis lasting several weeks. Specific types of severe neuroinvasive disease include West Nile encephalitis, West Nile meningitis and West Nile meningoencephalitis. Neurological effects may be permanent. Approximately 20% of the people who become infected have symptoms including fever, headaches, body aches, nausea and vomiting which may last from a few days to several weeks. Approximately 80% of those infected with WNV do not show any symptoms at all. People over the age of 50 are at higher risk to develop the serious symptoms of WNV.

[0026] Dengue (DF) and dengue hemorrhagic fever (DHF) are mosquito-borne diseases also caused by viruses of the *Flavivirus* genus. Dengue consists of four closely related but antigenically distinct virus serotypes. Infection with one serotype provides immunity for life to only that serotype, so a person can have been infected by dengue more than once during their lifetime. Dengue epidemics have historically occurred in Asia, Africa and North, Central and South America. Infections produce a spectrum of symptoms ranging from a nonspecific viral syndrome to fatal hemor-

rhagic disease. Symptoms of dengue include high fever, severe joint pain (the severity of the pain has given dengue the name “breakbone” fever), severe headache, muscle pain, pain behind the eyes, nausea, vomiting and rash. Dengue hemorrhagic fever is a severe, often fatal complication of dengue wherein the symptoms also include marked damage to blood vessels, bleeding from the nose, mouth, gums or under the skin and damage to the lymph system. DHF causes some deaths. Without prompt treatment DHF can progress to dengue shock syndrome, the most severe form, including all of the above symptoms plus massive bleeding, fluids leaking outside the blood vessels and shock from collapse of blood vessels. Dengue shock syndrome mostly occurs in children or young adults experiencing their second dengue infection and has a fatality rate of 5-15%. Dengue has emerged as a major health problem and the most important mosquito-borne viral disease affecting humans with tens of millions of cases of dengue fever and up to hundreds of thousands of cases of dengue hemorrhagic fever occurring each year. There is currently no vaccine (attenuated or recombinant viral vaccines may be available in 5-10 years) and no specific treatment beyond supportive care.

[0027] Yellow fever is a *Flavivirus* group viral hemorrhagic fever that has caused large epidemics in sub-Saharan Africa and South America (it is also present in the Caribbean Islands and Central America and formerly occurred in Europe and North America). Humans and monkeys can both be infected, and human infection may be via horizontal human-to-human transmission or by mosquito bite (the vector). There is also vertical transmission from mosquitoes to offspring via infected eggs, functioning as a reservoir for the virus and transmission from one year to the next. Infection may cause a wide spectrum of illness ranging from no or mild symptoms to severe illness and death. The “acute” phase, which occurs first, is characterized by fever, headache, muscle pain including backache, shivering, nausea and vomiting. Most patients improve and their symptoms disappear after three or four days; however, approximately 15% enter a “toxic” phase with reappearance of fever, jaundice (the “yellow” in yellow fever), bleeding from the orifices and deterioration of kidney function. Approximately 50% of those in the toxic phase die in 10-14 days. There are an estimated 200,000 cases and 30,000 deaths annually worldwide. Vaccination and mosquito control are the most important measures for control of yellow fever; there is no specific treatment beyond oral rehydration, acetaminophen and supportive care.

[0028] Arenaviruses are zoonotic pathogens generally associated in humans with rodent-borne human hemorrhagic fevers. The New World or Tacaribe arenavirus complex includes the Junin virus (Argentine hemorrhagic fever), Machupo virus (Bolivian hemorrhagic fever), Guanarito virus (Venezuelan hemorrhagic fever), Sabia virus (Brazilian hemorrhagic fever) and various other American hemorrhagic fever viruses occurring in Central and South America. The Old World or LCM/Lassa complex includes the lymphocytic choriomeningitis (LCM) virus and the Lassa fever virus (West African human hemorrhagic fever). The arenaviruses are spherical single-stranded RNA viruses enveloped in a lipid membrane. They show ribosomes acquired from their host cells when viewed in cross section. New virions are created by budding from the surface of their hosts' cells. Pichinde (PIC) is a species of the Arenavirus genus causing a fatal infection in the guinea pig (asymptomatic laboratory

infection has been reported in humans) which serves as the established animal model for Lassa Fever and as an animal model for the New World arenaviruses. Tacaribe (isolated from bats) also serves as an animal model for the New World arenaviruses.

[0029] Punta Toro virus (PTV) is a member of the *Phlebovirus* genus of the Bunyaviridae family of RNA viruses which causes a hemorrhagic disease in mice. PTV is closely related to the hanta, Rift Valley fever and sandfly fever viruses which infect humans. PTV serves as the animal model for studying the treatment of the human infections.

[0030] SARS is a new viral illness spread mainly by close person-to-person contact and possibly by infected surfaces or objects or an airborne vector or other means. SARS is believed to have originated in rural China in November 2002. In March 2003 the alarming spread of cases caused the World Health Organization and U.S. Centers for Disease Control and Prevention to issue a global alert over cases of atypical pneumonia that did not appear to respond to treatment. The illness was named Severe Acute Respiratory Syndrome (SARS). By the third week of March 2003, researchers from several countries had isolated a novel single-stranded RNA virus from the Coronavirus family (SARS-CoV) with contagiousness and high mortality rate unlike any other known human coronaviruses. Although coronaviruses account for about thirty percent of respiratory illnesses, most are moderate in course (such as common colds) with pneumonia being caused only in patients with poor immune systems; SARS-CoV seemed to be the first Coronavirus that consistently caused severe disease in humans. Before the outbreak was contained, it spread to more than two dozen countries. By December of 2003, 774 people had died and more than 8,000 had been infected. World airlines were hit hard by the SARS epidemic as several carriers slashed flights and axed jobs. The tourism industry suffered badly due to the fear unleashed by the outbreak, as did many other businesses and industries far from its epicenter. In many ways SARS caused the worst economic crisis in Southeast Asia since the wave of bank failures and currency devaluations that occurred there in 1988.

[0031] SARS was a form of lung injury characterized by increased permeability of the alveolar-capillary membrane, diffuse alveolar damage, the accumulation of proteinaceous pulmonary edema and pulmonary failure. Symptoms included high fever and one or more respiratory symptoms including, cough, shortness of breath and difficulty breathing. In addition to fever and respiratory symptoms, SARS was associated with other symptoms including headache, muscular stiffness, loss of appetite, malaise, confusion, rash, diarrhea and low oxygen levels in the blood (hypoxia). In many cases, those symptoms were followed by pneumonia in both lungs, sometimes requiring use of a respirator. The pathology of SARS is not yet fully understood and the clinical symptoms are unusual. The disease was mild in children and the mortality rate in that group almost nonexistent. Persons who suffered from chronic disease and the elderly had a much higher mortality rate. Patients who survived SARS infections recovered seemingly spontaneously while those who perished succumbed to rapid respiratory decline accompanied by extensive lung tissue damage. The tissue damage appeared to be driven by the patient's own immune system rather than the organism

itself. The mechanism of SARS pathogenesis may involve both direct viral cytocidal effects on the target cells and immune-mediated mechanisms. There are no specific therapies for SARS. The use of physiologically targeted strategies of mechanical ventilation and intensive care unit management including fluid management and glucocorticoids was the only supportive therapy available. Numerous antibiotic therapies were tried with no clear effect. Ribavirin with or without use of steroids was used in a number of patients. But, in the absence of clinical indicators, its effectiveness was not proven.

[0032] SARS was a much more virulent strain than most coronaviruses, leading scientists to believe that the virus had its origins in a non-human animal, where a coronavirus can have more severe effects. Although this virus most likely originated from a wild animal, perhaps the civet cat, the SARS virus was well adapted in humans as evidenced by the high person-to-person transmissibility of the virus. The critical questions are whether there is extensive horizontal transmission between animals, and whether the jump of the virus from animals to human was a rare and accidental event or portends frequent occurrences in the future. The answers to these questions will determine whether animals are viable reservoirs for future SARS outbreaks and whether person-to-person transmission of SARS-CoV might recur.

[0033] 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 are 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 anti-viral serves the best interests of public health.

BRIEF SUMMARY OF THE INVENTION

[0034] Medicinal mushrooms having unique antiviral properties are described, including mushroom species, mycelium, extracts and derivatives useful in preventing, treating ameliorating, mitigating, alleviating, reducing or curing infection from viruses. Particularly preferred are *Fomitopsis* and *Piptoporus* species 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. Products utilizing a single species or a plurality of medicinal mushrooms are also disclosed.

[0035] 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

[0036] The extracts of the mushroom mycelium of *Fomitopsis officinalis*, *Fomitopsis pinicola*, *Piptoporus betulinus* and various combinations of species have been previously found by the present inventor to have unique antiviral properties, including activity against *Orthopox* viruses (see U.S. patent application Ser. Nos. 11/029,861 and 11/031,699). As both *Fomitopsis officinalis* and *Piptoporus betulinus* are known to contain agaricin, the antiviral properties of the isolated compound were investigated. Agaricin was also found to have antiviral activity against *Orthopox* viruses (see U.S. patent application Ser. No. 11/145,679) but shows some latent cell toxicity that is not seen from the applicant's water-ethanol extracts of living mycelium from *Fomitopsis* and *Piptoporus* mushrooms.

[0037] The mushroom species *Fomitopsis officinalis*, *Fomitopsis pinicola*, *Piptoporus betulinus*, *Ganoderma resinaceum* and blends have been found by the inventor to have unique antiviral properties.

[0038] 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 but these show no activity against pox viruses whereas the mycelium grown from a clone of the mushroom did.

[0039] Preferred antiviral species include the *Fomitopsis* species, particularly *F. officinalis* and *F. pinicola*, and the *Piptoporus* species, particularly *P. betulinus*. A seven mushroom blend, a thirteen polypore mushroom blend and a 16 mushroom blend (available from Fungi Perfecti LLC of Olympia, Wash., USA as STAMETS 7™, MYCOSOFT® GOLD and HOST DEFENSE® respectively) are also preferred for antiviral activity.

[0040] *Fomitopsis* species include *F. africana*, *F. albomarginata* var. *pallida*, *F. albomarginata* var. *polita*, *F. albomarginata* var. *subvillosa*, *F. anhuiensis*, *F. annosa* f. *multistriata*, *F. annosa* var. *indica*, *F. arbitraria*, *F. avellanea*, *F. buchholtzii*, *F. cajanderi*, *F. caliginosa*, *F. castanea*, *F. cinerea*, *F. concava*, *F. connata*, *F. corrugata*, *F. cuneata*, *F. cupreorosea*, *F. cystina*, *F. cytisina*, *F. dochmia*, *F. durens*, *F. epileucina*, *F. euosma*, *F. feei*, *F. fulviseda*, *F. hainaniana*, *F. iberica*, *F. ibericus*, *F. kiyosumiensis*, *F. komatsuzakii*, *F. labyrinthica*, *F. latissima*, *F. lignea*, *F. lilacinogilva*, *F. maackiae*, *F. maire*, *F. marginata*, *F. mellea*, *F. minutispora*, *F. nigrescens*, *F. nivosa*, *F. odoratissima*, *F. officinalis* (= *Laricifomes officinalis*), *F. olivacea*, *F. palustris*, *F. pinicola*, *F. pinicola* f. *effusa*, *F. pinicola* f. *paludosa*, *F. pinicola* f. *resupinata*, *F. pseudopetchiini*, *F. pubertatis*, *F. quadrans*, *F. rhodophaea*, *F. rosea*, *F. roseozonata*, *F. rubidus*, *F. rufolaccata*, *F. rufopallida*, *F. samningensis*, *F. scalaris*, *F. semilaccata*, *F. sensitiva*, *F. spraguei*, *F. stellae*, *F. subrosea*, *F. subungulata*, *F. sulcata*, *F. sulcata*, *F. supina*, *F. unita*, *F. unita* var. *lateriha*, *F. unita* var. *multistratosa*, *F. unita* var. *prunicola*, *F. vinosa*, *F. widdringtoniae*, *F. zonalis*

and *F. zuluensis* and *Laricifomes* species including *L. concavus*, *L. maire* and *L. officinalis*. *Piptoporus* species include *P. betulinus*, *P. chosensiae*, *P. elatinus*, *P. fraxineus*, *P. helveolus*, *P. maculatissimus*, *P. malesianus*, *P. paradoxus*, *P. quercinus f. monstrosa*, *P. soloniensis*, *P. suberosus* and *P. ulmi*.

[0041] 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*.

[0042] 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-butanol), 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, alkynes containing from 2 to 16 carbon atoms and aromatic compounds containing from 5 to 14 carbon atoms, for example, benzene, cyclohexane, cyclopentane, methylcyclohexane, pentanes, hexanes, heptanes, 2,2,4-trimethylpentane, toluene, xylenes, etc., ketones containing from 3 to 13 carbon atoms such as, for example, acetone, 2-butanone, 3-pentanone, 4-methyl-2-pentanone, etc., ethers 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-dimethylformamide, N,N-dimethylacetamide, amines and nitrogen-containing heterocycles containing from 1 to 10 carbon atoms such as pyrrolidine, 1-methyl-2-pyrrolidinone, pyridine, etc., halogen substituted organic solvents containing from 1 to 14 carbon atoms such as, for example, bromotrichloromethane, carbon tetrachloride, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, 1-chlorobutane, trichloroethylene, tetrachloroethylene, 1,2-dichlorobenzene, 1,2,4-trichlorobenzene, 1,1,2-trichlorotrifluoroethane, etc., alkoxy, aryloxy, cyloalkyl, aryl, alkaryl and aralkyl substituted organic solvents containing from 3 to 13 carbon atoms such as, for example, 2-butoxyethanol, 2-ethoxyethanol, ethylene glycol dimethyl ether, 2-methoxyethanol, 2-methoxyethyl ether, 2-ethoxyethyl ether, etc., acids containing from 1 to 10 carbon atoms such as acetic acid, trifluoroacetic acid, etc., carbon disulfide, dimethyl sulfoxide (DMSO), nitromethane and combina-

tions thereof. Extracts may also be prepared via sequential extraction with any combination of the above solvents. The extracts may be further refined by means known to the art.

[0043] 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.

[0044] 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.

[0045] The mycelium, extracts and derivatives of *Fomitopsis officinalis*, *Piptoporus betulinus* and/or *Ganoderma resinaceum* may optionally be combined with *Agaricus brasiliensis*, *Agrocybe arvalis*, *Agrocybe aegerita*, *Auricularia auricula*, *Auricularia polytricha*, *Calvatia gigantean*, *Cordyceps sinensis*, *Flammulina populicola*, *Flammulina velutipes*, *Fomes fomentarius*, *Fomitopsis cajanderi*, *Fomitopsis pinicola*, *Ganoderma applanatum*, *Ganoderma capense*, *Ganoderma lucidum*, *Ganoderma oregonense*, *Ganoderma sinense*, *Ganoderma neojaponicum*, *Ganoderma tsugae*, *Giganopanus gigantean*, *Grifola frondosa*, *Hericium abietis*, *Hericium erinaceus*, *Hericium ramosum*, *Hypholoma capnoides*, *Hypholoma sublateritium*, *Inonotus obliquus*, *Lentinula edodes*, *Lentinus ponderosus*, *Lenzites betulina*, *Phellinus linteus*, *Pholiota adiposa*, *Pholiota nameko*, *Pleurotus ostreatus*, *Pleurotus tuberregium*, *Pleurotus eryngii*, *Polyporus sulphureus* (*Laetiporus sulphureus*), *Polyporus hirtus*, *Polyporus tuberaster*, *Polyporus umbellatus* (= *Grifola umbellata*), *Polyporus conifericola*, *Schizophyllum commune*, *Trametes versicolor* (= *Coriolus versicolor*), and/or *Wolfiporia cocos* (= *Poria cocos*) mycelium, extracts or derivatives.

[0046] *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. *Fomitopsis*, *Piptoporus* and *Ganoderma resinaceum* may optionally be added to any formula or product wherein the marketing of the product is substantially improved by the addition of *Fomitopsis* and/or *Piptoporus* and/or *Ganoderma resinaceum* mycelia, extracts or derivatives.

[0047] 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 antibacterials, antiprotozoals, immunomodulators, nutraceuticals and/or probiotics as well as enhancing innate immunity defense mechanisms and host immune response.

[0048] 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.

[0049] 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 gm./day, more preferably 0.25-10 gm./day, and most preferably 0.5-5 gm./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.

[0050] 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.

[0051] 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 Polyporaceae species mentioned in this patent application are those as understood by the most complete monograph on the subject, Ryvarde & Gilbertson's North American Polypores, 1986 vol. I and II, FungiFlora, 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

[0052] 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 strains collected from Morton, Wash., USA. *Piptoporus betulinus* is a strain collected in Idaho, 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.

[0053] 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. EBERBACH™ stirrer containing 800 ml. of sterilized water. The EBERBACH™ container was activated using a WARNING™ blender base, chopping the mycelium into thousands of fragments. This myceliated 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 class 100 clean room. Incubation times are preferably 7-180 days, more preferably 30-120 days.

[0054] 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 gentle care so as to 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; mushroom blends were treated in a similar fashion using a mixture of equal portions by weight of the mushroom species. 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.

[0055] It will of course be appreciated that differing concentrations and/or compositions of extracts may be easily prepared; 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

[0056] 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

[0057] The general approach for determining antiviral activity and toxicity as described by E. Kern for orthopoxviruses (<http://www.niaid-aacf.org/protocols/orthopox.htm>) was utilized. The Selectivity Index (SI) values were determined by or under the direction of Dr. Earl Kern of the USAMRIID/NIH/USAID Bioshield BioDefense Program. Similar bioassays were utilized for Dengue, SARS, VEE, West Nile, Yellow Fever, Rhinovirus, Pichinde, Punta Toro and Tacaribe. A similar bioassay was utilized by or under the direction of Dr. Robert W. Sidwell for influenza and respiratory viruses, Sidwell, R. W. and Smee, D. F., 2000. In vitro and in vivo assay systems for study of influenza virus inhibitors, *Antiviral Res.* 48, 1-16.

[0058] 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.

[0059] Screening Assay Systems for Determining Antiviral Activity Against VV and CV

[0060] Compounds were screened for activity against W and 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.

[0061] Efficacy: In all the assays used for primary screening, a minimum of six drug concentrations was used covering a range of 100 $\mu\text{g}/\text{ml}$ to 0.03 $\mu\text{g}/\text{ml}$, in 5-fold increments. These data allowed good dose response curves. From these data, the dose that inhibited viral replication by 50% (effective concentration 50; EC_{50}) was calculated using the computer software program MacSynergy II by M. N. Pritchard, K. R. Asaltine, and C. Shipman, Jr., University of Michigan, Ann Arbor, Mich.

[0062] 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; CC_{50}) 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% (IC_{50}) 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.

[0063] 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 $\text{CC}_{50}/\text{EC}_{50}$. This index, also referred to as a therapeutic index, was used to determine if a compound warrants further study. Compounds that had an SI of 2 or more are considered active, 10 or greater is considered very active.

[0064] Laboratory Procedures for Determining Antiviral Efficacy and Toxicity

[0065] Preparation of compounds for in vitro testing: As the fungal extracts were water 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 applicant'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.

[0066] Screening and Confirmation Assays for VV and CV

[0067] 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 CO_2 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 cm^2 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.

[0068] 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 2.5×10^5 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 Multiplate Auto-reader at 620 nm. The EC₅₀ values are determined by comparing drug treated and untreated cells using a computer program.

[0069] 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 2×MEM and then serially diluted 1:5 in 2×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 10× magnification.

[0070] Screening and Confirmation Assays for Toxicity

[0071] Neutral Red Uptake Assay Twenty-four h prior to assay, HFF cells are plated into 96 well plates at a concentration of 2.5×10^4 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.

[0072] 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 bioassays described herein.

[0073] 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.

[0074] The *Fomitopsis officinalis* strains and extracts described above in Example 1 were utilized, as was *Piptoporus betulinus*, *Ganoderma resinaceum*, *Fomitopsis pini-cola* and three mushroom mycelium blends. The 7 mushroom blend was prepared from equal portions by weight of *Ganoderma resinaceum* mycelium, *Agaricus brasiliensis* (Himematsutake) mycelium, *Cordyceps sinensis* (Cordyceps) mycelium, *Grifola frondosa* (Maitake) fruit-bodies, *Hericium erinaceus* (Lion's Mane) mycelium, *Polyporus umbellatus* (Zhu Ling) mycelium and *Trametes versicolor* (Turkey Tail) mycelium. The 13 mushroom blend was prepared from equal portions by weight of the mycelium of *Ganoderma resinaceum*, *Fomitopsis officinalis* (Agarikon), *Ganoderma applanatum* (Artists' Conk), *Ganoderma oregonense* (Oregon polypore), *Grifola frondosa* (Maitake), *Phellinus linteus* (Mesima), *Trametes versicolor* (Yun Zhi), *Fomes fomentarius* (Ice Man Fungus), *Inonotus obliquus* (Chaga), *Lentinula edodes* (Shiitake), *Polyporus umbellatus* (Zhu Ling), *Piptoporus betulinus* (Birch Polypore) and *Schizophyllum commune* (Suchirotake). The 16 mushroom blend was prepared from 13.49% *Grifola frondosa* mycelium, 11.56% *Agaricus brasiliensis* mycelium, 11.56% *Inonotus obliquus* mycelium, 10.60% *Ganoderma resinaceum* mycelium, 9.63% *Cordyceps sinensis* mycelium, 7.70% *Phellinus linteus* mycelium, 6.73% *Schizophyllum commune* mycelium, 4.82% *Trametes versicolor* mycelium, 4.82% *Polyporus umbellatus* mycelium, 4.82% *Hericium erinaceus* mycelium, 2.89% *Ganoderma applanatum* mycelium, 2.89% *Ganoderma oregonense* mycelium, 1.93% *Fomitopsis officinalis* mycelium, 1.93% *Fomes fomentarius* mycelium, 1.93% *Lentinula edodes* mycelium, 1.93% *Piptoporus betulinus* mycelium and 0.77% *Grifola frondosa* fruit body extract.

Viruses	Mushroom Extracts-Selectivity Index (SI) Values				
	<i>Ganoderma applanatum</i>	<i>Ganoderma resinaceum</i>	<i>Fomitopsis officinalis</i>	<i>Fomitopsis pinicola</i>	<i>Piptoporus betulinus</i>
Influenza viruses					
Flu A					
H1N1		>2.8	>3.1		
H3N2			>3.1		
H5N1			>2.5		
Flu B			2.8		
Orthopox Viruses					
Cowpox			14.7	4.3	9.1
Vaccinia			20.4	2.9	7.1
Smallpox					
West Nile			>1.7	>3.1	8.5
Yellow Fever			2.3		
Dengue					
VEE					
SARS					
Rhinovirus					
Pichinde	<3	3	<3		>5.2
Punta Toro		<3	3		
Tacaribe			>3		

[0075]

Viruses	Mushroom Extracts-Selectivity Index (SI) Values			Agaric Acid-SI Values
	7	13	16	
	Mushroom Blend	Mushroom Blend	Mushroom Blend	
Influenza Viruses				
Flu A				
H1N1		>2.7		
H3N2				3.2
H5N1				
Flu B	>3.2	>2.8	>3.2	
Orthopox Viruses				
Cowpox				
Vaccinia				
Smallpox	<3.6	<4.8		
West Nile	1.9			
Yellow Fever				>2.7
Dengue				>2.6
VEE		>4.7	>2.7	>2.8
SARS	1.4		>1.8	
Rhinovirus				>4
Pichinde		<3	<3	
Punta Toro	<3		<3	
Tacaribe				<3

[0076]

Bacteria	Mushroom Extracts-% Inhibition			
	<i>Fomitopsis officinalis</i>	7 Mushroom Blend	13 Mushroom Blend	16 Mushroom Blend
	<i>Mycobacterium tuberculosis</i>	73%	63%	70-87%

[0077] 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, influenza, West Nile, Dengue, yellow fever, the New World and Old World arenaviruses, VEE, hanta, Rift Valley fever, sandfly fever viruses and Rhinoviruses, and bacteria.

[0078] 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.

[0079] GC testing of the *Fomitopsis* and *Piptoporus* 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 agaric 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 agaric acid or betulinic acid and it is expected that the extracts possess novel antiviral and antimicrobial compounds.

[0080] 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 microbes 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, Hantavirus, Rift Valley fever, sandfly fever, yellow fever, West Nile, Dengue fever, respiratory viruses, Rhinoviruses, Herpes Simplex I, Herpes Simplex II, Lyme, HELA, Epstein Barr, Ebola, Varicella-Zoster, adenoviruses, Polio, Hepatitis including Hepatitis A, B and C, Tuberculosis, pneumonia (bacterial pneumonia, viral pneumonia, and *Mycoplasma pneumoniae*), *Plasmodium falciparum*, *Bacillus anthracis*, *Escherichia coli*, *Mycobacterium 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 opportunistic 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.

[0081] 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.

[0082] 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.

[0083] 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.

I claim:

1. A method for preventing, treating, ameliorating, mitigating, alleviating, reducing and curing infection from a virus comprising administering a therapeutically effective amount of a medicinal mushroom derivative wherein the medicinal mushroom is a *Fomitopsis* and the medicinal mushroom derivative is selected from the group consisting of live mycelium, dried live mycelium, freeze dried mycelium, extracts of live mycelium, solvent free extracts of live mycelium and combinations thereof.

2. The method of claim 1 wherein the virus is selected from the group consisting of influenza viruses, avian influenza viruses, Venezuelan Equine Encephalitis, West Nile virus, Dengue virus, yellow fever virus, New World and Old World arenaviruses, hantavirus, Rift Valley fever virus, sandfly fever viruses and Rhinoviruses.

3. The method of claim 1 wherein the virus is selected from the group consisting of Orthomyxoviridae, Alphavirus, Flavivirus, Arenavirus, Phlebovirus and Coronavirus viruses.

4. The method of claim 1 wherein the *Fomitopsis* is *Fomitopsis officinalis*.

5. The method of claim 1 wherein the *Fomitopsis* is *Fomitopsis pinicola*.

6. The method of claim 1 wherein the *Fomitopsis* is selected from the group consisting of *F. africana*, *F. albomarginata* var. *pallida*, *F. albomarginata* var. *polita*, *F. albomarginata* var. *subvillosa*, *F. anhuiensis*, *F. annosaf multistriata*, *F. annosa* var. *indica*, *F. arbitraria*, *F. avellanea*, *F. bucholtzii*, *F. cajanderi*, *F. caliginosa*, *F. castanea*, *F. cinerea*, *F. concava*, *F. connata*, *F. corrugata*, *F. cuneata*, *F. cupreorosea*, *F. cystina*, *F. cytisina*, *F. dochmia*, *F. durescens*, *F. epileucina*, *F. euosma*, *F. feei*, *F. fulviseda*, *F. hainaniana*, *F. iberica*, *F. ibericus*, *F. kiyosumiensis*, *F. komatsuzakii*, *F. labyrinthica*, *F. latissima*, *F. lignea*, *F. lilacinogilva*, *F. maackiae*, *F. maire*, *F. marginata*, *F. mellea*, *F. minutispora*, *F. nigrescens*, *F. nivosa*, *F. odoratissima*, *F. officinalis* (= *Laricifomes officinalis*), *F. olivacea*, *F. palustris*, *F. pinicola*, *F. pinicola* f. *effusa*, *F. pinicola* f. *paludosa*, *F. pinicola* f. *resupinata*, *F. pseudopetchiini*, *F. pubertatis*, *F. quadrans*, *F. rhodophaea*, *F. rosea*, *F. roseozonata*, *F. rubidus*, *F. rufolaccata*, *F. rufopallida*, *F. sanmingensis*, *F. scalaris*, *F. semilaccata*, *F. sensitiva*, *F. spraguei*, *F. stellae*, *F. subrosea*, *F. subungulata*, *F. sulcata*, *F. sulcata*, *F. supina*, *F. unita*, *F. unita* var. *lateritia*, *F. unita* var. *multistratosa*, *F. unita* var. *prunicola*, *F. vinosa*, *F. widdringtoniae*, *F. zonalis* and *F. zuluensis*.

7. The method of claim 1 wherein the live mycelium is grown on a grain.

8. The method of claim 1 wherein the live mycelium is grown on wood.

9. The method of claim 1 wherein the medicinal mushroom 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 creams and suppositories.

10. The method of claim 1 wherein the extracts are extracted with ethanol and water.

11. The method 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.

12. The method of claim 11 wherein the organic solvent is 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, nitrites 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, cyloalkyl, aryl, alkaryl and aralkyl substituted organic solvents containing from 3 to 13 carbon atoms, DMSO and combinations thereof.

13. The method of claim 1 wherein the medicinal mushroom derivative is added to an animal feed.

14. The method of claim 1 wherein the medicinal mushroom derivative is added to a food.

15. The method of claim 14 wherein the medicinal mushroom derivative additionally comprises a derivative selected from the group consisting of *Piptoporus betulinus* derivatives and *Ganoderma resinaceum* derivatives.

16. The method of claim 1 wherein the medicinal mushroom derivative additionally comprises a derivative selected

from the group consisting of *Piptoporus betulinus* derivatives and *Ganoderma resinaceum* derivatives.

17. The method of claim 1 wherein marketing of the medicinal mushroom derivative is improved by the claims herein.

18. A method for preventing, treating, ameliorating, mitigating, alleviating, reducing and curing infection from a virus comprising administering a therapeutically effective amount of a medicinal mushroom derivative wherein the virus is selected from the group consisting of influenza viruses, avian influenza viruses, Venezuelan Equine Encephalitis, West Nile virus, Dengue virus, yellow fever virus, New World and Old World arenaviruses, hantavirus, Rift Valley fever virus, sandfly fever viruses and Rhinoviruses, the medicinal mushroom is a *Fomitopsis* and the medicinal mushroom derivative is selected from the group consisting of live mycelium, dried live mycelium, freeze dried mycelium, extracts of live mycelium, solvent free extracts of live mycelium and combinations thereof.

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