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

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(57) **ABSTRACT**

Compounds having unique antiviral properties are prepared from medicinal mushroom mycelium, extracts and derivatives. The compositions are derived from *Fomitopsis, Piptoporus, Ganoderma resinaceum* and blends of medicinal mushroom species and are useful in preventing and treating viruses including Pox and HIV viruses.

ANTIVIRAL ACTIVITY FROM MEDICINAL MUSHROOMS

[0001] This application 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 *Orthopox* and HIV 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 (*Sparassis 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 stomatitus 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] *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, 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 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 Colombia, 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 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 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).

[0010] *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*).

[0011] 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."

[0012] 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 derivatives can also activate natural immune response, potentiating host defense, and in effect have an indirect but significant antimicrobial activity. (Stamets, 2003).

[0013] 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 flourescens*. 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-bacteriophagic properties, being dually antibacterial and antiviral.

[0014] 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, bird flu viruses, hepatitis, Lyme disease, HELA cervical virus, respiratory syncytial virus, vesicular stomatitus, Dengue, Yellow Fever, Ebola, VEE, Punta Toro, Pichinde, Dengue Fever and others, *Plasmodium falciparum, Bacillus anthracis, Escherichia coli*, 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 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] *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, usually encountered in villages in central and west Africa. It is transmitted by monkeys 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 with a central indentation. 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 Poxyiridae family include buffalopox virus, rabbitpox virus, avipox virus, sheep-pox virus, goatpox virus, lumpy skin disease (Neethling) virus, swinepox virus and Yaba monkey virus.

[0019] 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 2 "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.

[0020] Human immunodeficiency virus ("HIV"), the causative agent of the disease known as acquired immunodeficiency syndrome ("AIDS"), is one of the principle threats to human life. Patients with illnesses that, in retrospect, were manifestations of AIDS were reported in the literature in 1981. A case definition of AIDS for national reporting was first published in 1982 and AIDS was declared a new epidemic. Since that time, deaths and new infections have numbered in the tens of millions worldwide.

[0021] HIV infection in humans causes general immunosuppression and involves other disorders in patients in advanced stages of infection. The clinical manifestations of AIDS may be directly attributable to infection with this virus or the result of secondary conditions occurring as a consequence of immune dysfunction caused by the underlying infection. A patient is generally diagnosed as having AIDS when a previously healthy adult with an intact immune system acquires an impaired immune system attributed to the systemic depletion of CD4+ T lymphocytes ("T cells") and the unresponsiveness and incompetence of the remaining T cells. The impaired immunity usually appears over a period of 18 months to 3 years. The level of T cells serves as a diagnostic indicator of disease progression. As a result of this impaired immunity, the patient becomes susceptible to opportunistic infections, various types of cancers such as Kaposi's sarcoma and non-Hodgkin's Lymphoma and other disorders associated with reduced functioning of the immune system.

[0022] HIV is an RNA retrovirus (such as HIV-1 and HIV-2) that replicates through a DNA intermediate. The HIV virus carries with it a polymerase (reverse transcriptase) that catalyzes transcription of viral RNA into double-helical DNA. Each HIV virus particle contains two identical, single-stranded RNA molecules surrounded by the viral nucleocapsid protein subunits. The remaining core of the virus is composed of the capsid and matrix proteins. Enzymes required for replication and integration of the viral genetic materials into the host cells are also contained within the capsid. The outer coat of the virus particle consists of viral envelope glycoprotein "spikes" and membrane derived from the host cell. As a result of this evasion, full recovery from infection is never observed in a natural situation and viral persistence results.

[0023] No effective treatment capable of preventing the disease is available. Despite vaccine development being a top priority of HIV and AIDS research, a vaccine that provides a complete and long lasting protective response against all forms of HIV has yet to be realized. In fact, it is considered by some to currently be beyond reach and in any

event likely to be a very difficult task. Such views arise because the lentiviruses, such as HIV, have developed very successful methods to evade the immune response, such as latency and antigenic variability. Although combinations of therapies including highly active anti-retroviral therapy have reversed the immunodeficiency of AIDS, problems and limitations such as side effects and development of drug resistant virus persist with available drugs that effectively and safely combat HIV.

[0024] 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. 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

[0025] Medicinal mushrooms having unique antiviral properties are described, including mushroom species, mycelium, extracts and derivatives useful in preventing and treating infection from Pox and HIV viruses. Particularly preferred are *Fomitopsis* and *Piptoporus* species and various combinations with other mushroom species against Pox and *Ganoderma Resinaceum* and various combinations against HIV. 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.

[0026] The present invention has been found to achieve these advantages. 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

[0027] The mushroom species *Fomitopsis officinalis, Fomitopsis pinicola, Piptoporus betulinus, Ganoderma resinaceum* and blends have been found by the inventor to have unique antiviral properties, including activity against *Orthopox* viruses by *F. officinalis, F. pinicola* and *P. betulinus* and blends and activity against HIV by *G. resinaceum* and blends. *G. resinaceum* is a species formerly misidentified as *G. lucidum.*

[0028] Rather than the mushrooms themselves, particularly preferred is the mushroom mycelium (the "vegetative" state of the mushroom, containing at most only primordia or young mushrooms) and derivatives thereof. 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 extracts. It was unexpectedly found that boiling in water of the mushroom created water extracts but these show no activity against pox viruses whereas the mycelium grown from a clone of the mushroom did.

[0029] Preferred anti-Pox species include the *Fomitopsis* species, particularly *F. officinalis* and *F. pinicola*, and the *Piptoporus* species, particularly *P. betulinus*. A preferred anti-HIV species are *Ganoderma resinaceum* and *Piptoporus betulinus*. A seven mushroom blend and a thirteen polypore mushroom blend (available from Fungi Perfecti LLC of Olympia, Wash., USA as STAMETS 7™ and MYCOSOFT® GOLD respectively) are also preferred for antiviral activity, including both anti-Pox and anti-HIV activity.

[0030] *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. 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. pinicolaf effusa, F. pinicolaf paludosa, F. pinicolaf resupinata, F. pseudopetchiin, 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* and *Laricifomes* species including *L. concavus, L. maire* and *L. officinalis. Piptoporus* species include *P. betulinus, P. choseniae, P. elatinus, P. fraxineus, P. helveolus, P. maculatissimus, P. malesianus, P. paradoxus, P. quercinus f. monstrosa, P. soloniensis, P. suberosus* and *P. ulmi.*

[0031] 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.*

[0032] 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 CO_2, 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, proprionitrile, 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, trifluroacetic acid, etc., carbon disulfide, dimethyl sulfoxide (DMSO), nitromethane and combinations 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.

[0033] Preferred drying methods include freeze drying, air drying, spray drying and drum drying. Particularly preferred methods and apparatus for drying mycelium, extracellular metabolites, extracts and derivatives are 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. As to dried or dehydrated extracts, particularly preferred are the unique dehydrated crystalline extracts obtained by use of the teachings of U.S. Pat. No. 4,631,837 and mixtures of dehydrated extract and dehydrated mycelium. Exemplary driers are available from MCD Technologies, Inc. of Tacoma, Wash. under the REFRACTANCE WINDOW® brand.

[0034] 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.

[0035] 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 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 adipose, 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.

[0036] *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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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, Ryvarden & 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

[0041] 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 and *Fomitopsis officinalis* IV are strains respectively collected from Morton and Elwha, Wash., USA. *Fomitopsis officinalis* V is a strain collected from Cortes Island, British Columbia, Canada. *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.

[0042] 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 WARING™ 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.

[0043] 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.

[0044] 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

[0045] Proprietary strains of *Fomitopsis officinalis, Fomitopsis pinicola* and *Piptoporus betulinus*, 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 maxima, and then flash frozen to −18 degrees 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 a antimicrobial and/or for potentiating a host mediated response. Products made from *Fomitopsis officinalis* 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

[0046] The general approach for determining antiviral activity and toxicity for orthopoxviruses as described by E. Kern (http://www.niaid-aacf.org/protocols/orthopox.htm) was utilized.

[0047] 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.

[0048] Screening Assay Systems for Determining Antiviral Activity Against VV and CV

[0049] Compounds were screened for activity against VV 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.

[0050] 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% (effective concentration 50; EC_{50}) was calculated using the computer software program MacSynergy II by M. N. Prichard, K. R. Asaltine, and C. Shipman, Jr., University of Michigan, Ann Arbor, Mich.

[0051] 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.

[0052] 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 CC_{50}/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 (~1.5-2.5) are considered active, 10 or greater is considered very active.

[0053] Laboratory Procedures for Determining Antiviral Efficacy and Toxicity

[0054] 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.

[0055] Screening and Confirmation Assays for VV and CV

[0056] 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.

[0057] 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 CO_2 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 CO_2 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 Autoreader at 620 nm. The EC_{50} values are determined by comparing drug treated and untreated cells using a computer program.

[0058] Plague 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% CO_2 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.

[0059] Screening and Confirmation Assays for Toxicity

[0060] 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 CO_2 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 CO_2 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 H_2O) is added. The plates are rotated for 15 min and the optical densities read at 540 nm on a plate reader. The EC_{50} values are determined by comparing drug treated and untreated cells using a computer program.

[0061] All strains below were incubated for approximately two months prior to extractions except for those designated "4 months," which were incubated for approximately four months prior to extraction. Those strains designated "Hot" were incubated for the final 48 hours at approximately 35° C. (95° F.). With those strains designated as "shaken," the mycelium and ethanol/water were shaken and allowed to settle prior to decanting the extract.

[0062] The *Fomitopsis officinalis* strains and extracts described above in Example 1 were utilized, as was *Fomitopsis pinicola* and two mushroom blends. The 7 mushroom blend was prepared from equal portions by weight of *Ganoderma resinaceum, Agaricus brasiliensis* (Himematsutake), *Cordyceps sinensis* (Cordyceps), *Grifola frondosa* (Maitake), *Hericium erinaceus* (Lion's Mane), *Polyporus umbellatus* (Zhu Ling) and *Trametes versicolor* (Turkey Tail) mycelium. The 13 mushroom blend was prepared from equal portions by weight of *Ganoderma resinaceum, Fomitopsis officinalis* (Agarikon), *Ganoderma applanatum* (Artists' Conk mycelium), *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).

	Vaccinia - HFF Cells					
Drug Name	CPE EC50	CPE EC90	CPE CC50	CPE SI	CPE CDV EC50	CPE CDV EC90
Fomitopsis officinalis I	3.4	4.8	>10	2.9	2.1	3.4
Fomitopsis officinalis I Hot	5.7	8.7	>10	>1.8	2.1	3.4
Fomitopsis officinalis I 4 months	1.9	3.3	>10	>5.3	2.5	5.4
Fomitopsis officinalis I 4 months	3	6.5	>10	>3.3	2.1	3.4
Fomitopsis officinalis I shaken	1.1	1.8	>10	>9.1	2.5	5.4
Fomitopsis officinalis IV	6.5	>10	>10	>1.5	2.1	3.4
Fomitopsis officinalis IV Hot	6.7	>10	>10	>1.5	2.1	3.4
Fomitopsis officinalis V	7.4	>10	>10	>1.4	2.1	3.4
Fomitopsis officinalis V Hot	5	8.9	>10	>2	2.5	5.4
Fomitopsis officinalis V Hot	2.8	4.7	>10	>3.6	2.1	3.4
Fomitopsis pinicola	2.7	3.6	>10	3.7	2.1	3.4
Piptoporus betulinus	1.4	>10	>10	>7.1	2.5	5.4
Piptoporus betulinus Hot	>0.4	>0.4	1.9	<4.8	2.1	3.4
Fomitopsis officinalis I and *Piptoporus betulinus*	1.7	2.8	>10	>5.9	2.5	5.4
7 mushroom blend	>2	>2	9.4	<4.7	2.1	3.4
13 mushroom blend	>2	>2	7.7	<3.9	2.1	3.4
13 mushroom blend	>2	>2	7.7	<3.9	2.1	3.4

	PR EC50	PR EC90	PR CC50	PR SI	PR CDV EC50	PR CDV EC90
Fomitopsis officinalis I shaken	1.3	7.5	>10	>7.7	4.9	17

	Cowpox - HFF Cells					
Drug Name	CPE EC50	CPE EC90	CPE CC50	CPE SI	CPE CDV EC50	CPE CDV EC90
Fomitopsis officinalis I	2.3	3.9	>10	4.3	2.7	76
Fomitopsis officinalis I Hot	7.1	>10	>10	1.4	2.7	76
Fomitopsis officinalis I 4 months	1.3	2.2	>10	>7.7	3.1	
Fomitopsis officinalis I 4 months	4.1	6.5	>10	>2.4	2.7	76
Fomitopsis officinalis I shaken	0.68	1.1	>10	>14.7	3.1	
Fomitopsis officinalis IV	>10	>10	>10	0	2.7	7.6
Fomitopsis officinalis IV Hot	6	>10	>10	2.7	7.6	
Fomitopsis officinalis V	7.1	>10	>10	>1.4	2.7	76
Fomitopsis officinalis V Hot	1.7	2.5	>10	>5.9	3.1	

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Fomitopsis officinalis V Hot	3.8	6.6	>10	>2.6	2.7	76
Fomitopsis pinicola	3.1	3.9	>10	3.2	2.7	76
Piptoporus betulinus	1.1	1.8	>10	>9.1	3.1	
Piptoporus betulinus Hot	>0.4	>0.4	1.9	<4.8	2.7	76
Fomitopsis officinalis I and *Piptoporus betulinus*	1.9	3	>10	>5.3	3.1	
7 mushroom blend	>2	>2	9.4	<4.7	2.7	76
13 mushroom blend	>2	>2	7.7	<3.9	2.7	76

	PR EC50	PR EC90	PR CC50	PR SI	PR CDV EC50	PR CDV EC90
Fomitopsis officinalis I shaken	3.6	8.7	>10	>2.8	10.3	18.1

	Neutral Red Toxicity Assay		
Drug Name	CC50	ACV CC50	CDV CC50
Fomitopsis officinalis I	>10	>100	>100
Fomitopsis officinalis I Hot	8.7	>100	>100
Fomitopsis officinalis I 4 months	>10	>100	>100
Fomitopsis officinalis I 4 months	>10	>100	>100
Fomitopsis officinalis I shaken	>10	>100	>100
Fomitopsis officinalis IV	8.9	>100	>100
Fomitopsis officinalis IV	>10	>100	>100
Fomitopsis officinalis V	>10	>100	>100
Fomitopsis officinalis V Hot	>10	>100	>100
Fomitopsis officinalis V	9.9	>100	>100
Fomitopsis pinicola	>10	>100	>100
Piptoporus betulinus	9.2	>100	>100
Piptoporus betulinus Hot	1.7	>100	>100
Fomitopsis officinalis I and *Piptoporus betulinus*	9.1	>100	>100
7 mushroom blend	7.2	>100	>100
13 mushroom blend	7.5	>100	>100

[0063] 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, mitigating, reducing or curing infection and/or symptoms from *Orthopox* viruses.

EXAMPLE 4

[0064] All strains below were incubated for approximately two months prior to extractions except for those designated "4 months," which were incubated for approximately four months prior to extraction. Those strains designated "Hot" were incubated for the final 48 hours at approximately 35° C. (95° F.). With those strains designated as "shaken," the mycelium and ethanol/water were shaken and allowed to settle prior to decanting the extract. For those strains designated as "dried," the extract was air dried prior to testing.

[0065] The *Fomitopsis officinalis* strains and extracts described above in Example 1 were utilized, as were *Ganoderma resinaceum, Grifola frondosa, Polyporus umbellatus, Trametes versicolor* and two mushroom blends. The 7 mushroom blend was prepared from equal portions by weight of *Ganoderma resinaceum, Agaricus brasiliensis* (Himematsutake), *Cordyceps sinensis* (Cordyceps), *Grifola frondosa* (Maitake), *Hericium erinaceus* (Lion's Mane), *Polyporus umbellatus* (Zhu Ling) and *Trametes versicolor* (Turkey Tail) mycelium. The 13 mushroom blend was prepared from equal portions by weight of mycelium of *Ganoderma resinaceum, Fomitopsis officinalis* (Agarikon), *Ganoderma applanatum* (Artists' Conk mycelium), *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).

[0066] The following procedure was utilized with virus HIV-1 NL4-3 (batch TL WS3 D5):

[0067] 1) Infect PBMC blasts in bulk (500 $TCID^{50}$/10^5 cells) for two hours with the specified virus.

[0068] 2) Wash out unadsorbed virus and resuspend cells at 2×10^6/ml.

[0069] 3) Seed 10^5 cells per well into plate containing drug dilutions (100 μl+100 μl).

[0070] 4) Assay supernatant 7 days after inoculation.

Sample/	NL4-3 Antiviral		PBMC Toxicity	
Drug	IC_{50}	IC_{90}	CC_{50}	CC_{90}
Piptoporus betulinus	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml
3TC	0.023 μM	0.066 μM	240 μM	>1,000 μM

Sample/	NL4-3 Antiviral (μM)		PBMC Toxicity (μM)	
Drug	IC_{50}	IC_{90}	CC_{50}	CC_{90}
Fomitopsis officinalis I	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml
Fomitopsis officinalis I	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml
Fomitopsis officinalis I 4 months	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml	>3,200 μg/ml

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3TC	0.010 μM	0.130 μM	430 μM	>1,100 μM
	0.011 μM	0.050 μM	310 μM	>1,000 μM
7 mushroom blend	43 μg/ml	390 μg/ml	<32 μg/ml	8,000 μg/ml
13 mushroom blend	23 μg/ml	19,000 μg/ml	6,000 μg/ml	7,400 μg/ml
3TC	<0.003 μM	0.190 μM	<0.32 μM	930 μM
3TC	0.005 μM	0.130 μM	<0.32 μM	>1,000 μM
7 mushroom blend	50 μg/ml	360 μg/ml	240 μg/ml	>100,000 μg/ml
13 mushroom blend	900 μg/ml	10,000 μg/ml	1,300 μg/ml	>100,000 μg/ml
3TC	0.006 μM	0.062 μM	250 μM	>1,000 μM
3TC	0.004 μM	0.031 μM	<0.32 μM	>1,000 μM
Ganoderma Resinaceum Dried	78 μg/ml	1,000 μg/ml	10,000 μg/ml	>100,000 μg/ml
Grifola frondosa Dried	5,100 μg/ml	18,000 μg/ml	6,000 μg/ml	>100,000 μg/ml
Polyporus umbellatus Dried	820 μg/ml	12,000 μg/ml	2,400 μg/ml	>100,000 μg/ml
Trametes versicolor Dried	440 μg/ml	3,000 μg/ml	870 μg/ml	>100,000 μg/ml
3TC	0.031 μM	0.490 μM	540 μM	>1,000 μM
3TC	0.031 μM	0.230 μM	380 μM	>1,000 μM

[0071] Similar results for the 7 mushroom blend showing HIV cell death percentages of 61.3±3.9, 78.4±4.1 and 98±1.9 from concentrations of 40, 200, and 1,000 μg/cultivated species blend respectively was provided by Ohtomo, M., (2001) "In vivo and in vitro test study: physiological activity in immune response system of representative basidiomycetes" Unpublished research report provided to the inventor and Fungi Perfecti from Tamagawa University, Japan. 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, mitigating, reducing or curing infection and/or symptoms from HIV viruses.

[0072] 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 the have the effect of preventing, mitigating, reducing, alleviating or curing infection from microbes including Cowpox, Variola (Small Pox), coronavirus SARS, HIV, Influenza, Herpes Simplex I, Herpes Simplex II, Bird Flu, Lyme, HELA, Epstein Barr, Ebola, VEE, Punta Toro, Pichinde, Yellow Fever, West Nile Virus, Dengue Fever, Respiratory viruses, Varicella-Zoster, Polio, Hepatitis, Tuberculosis, pneumonia (bacterial pneumonia, viral pneumonia, and mycoplasma pneumonia), *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.

[0073] 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.

[0074] 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.

[0075] 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 or reducing infection from an *Orthopox* 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, dried extracts of live mycelium and combinations thereof.

2. The method of claim 1 wherein the *Orthopox* virus is selected from the group consisting of smallpox, monkeypox, camelpox, cowpox, pseudocowpox, *Molluscum contagiosum* and Orf virus.

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

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

5. 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. annosa f.*

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. pinicolaf paludosa, F. pinicolaf resupinata, F. pseudopetchiin, 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. uiddringtoniae, F. zonalis* and *F. zuluensis*

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

7. 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.

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

9. 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.

10. The method of claim 9 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.

11. 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.

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

13. A method for providing defense from a viral infection wherein a Fomitopsis composition is administered in an amount sufficient to have an effect selected from the group consisting of preventing, reducing, mitigating, treating, alleviating preventing, treating, alleviating, mitigating, ameliorating or reducing infection and mitigating the viral infection and wherein the viral infection is an *Orthopox* virus.

14. The method of claim 13 wherein the *Orthopox* virus is selected from the group consisting of smallpox, monkeypox, camelpox, cowpox, pseudocowpox, *Molluscum contagiosum* and Orf virus.

15. The method of claim 13 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. annosa f. 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. pseudopetchiin, 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*

16. The method of claim 13 wherein the live mycelium is grown on a grain.

17. The method of claim 13 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.

18. The method of claim 13 wherein the extracts are extracted with ethanol and water.

19. The method of claim 13 wherein the extracts are extracted with a solvent selected from the group consisting of water, steam, alcohols, organic solvents, carbon dioxide and combinations thereof.

20. 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.

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