

HIV and the Antiviral Role of Mushroom Nutraceuticals

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ABSTRACT

Mushrooms, environment and human health are interconnected. Mushrooms' essential role in the environment and bioremediation have attracted market attention because they are also a potential source of bioactive compounds able to perform several functions in organisms with benefits for the health of the consumer. The HIV/AIDS epidemic poses an inescapable challenge to the world at large and to Africa in particular and more specifically in Mozambique. A brief outline of the historical background discusses the present knowledge of mushrooms containing antiviral factors. Antiviral factors generally do not destroy their target pathogen; rather, they inhibit the development or reproduction of the virus. Administration of mushrooms, also used as dietary supplement extracts or biomass, supplies active immunoceuticals that may block virus cell-to-cell infection, modify viral receptors, prevent the adhesion of the virus to lymphocytes and stimulate interferon which has a general antiviral effect production and may inhibit HIV infection. Current strategies in the therapy of AIDS include antiretroviral drugs and complementary nutritional support considered beneficial. Nutrition is a fundamental part of a comprehensive package of care for people living with HIV/AIDS and mushrooms supply known bioactive molecules that may help HIV positive patients.

Keywords: mushrooms; HIV; immunoceuticals; antiviral activity; bioactive compounds

1 Introduction

Although mushrooms have been consumed since earliest history, their use as food, extracts, biomass and dietary supplements to promote human health and control deleterious effects on the environment, through their vast and unique degradative enzymatic potential, is quite recent.

The HIV/AIDS epidemic is spreading at a fearsome rate having an overwhelming and unfortunate impact on health, agriculture, malnutrition, food security and socioeconomic progress in countries that have been most seriously affected by the disorder namely in rural areas of Sub-Saharan Africa (1).

The interrelationship between nutrition and HIV is a vicious cycle and despite vast efforts, malnutrition in this area of the globe does not show any improvement (2,3).

Malnutrition has been associated with a decrease in immune function (4). Impairment of immune function may lead to increased susceptibility to infection with viruses (5).

Human immunodeficiency virus type 1 (HIV-1) is a member of the Lentivirus from the *Retroviridae* family and is the aetiological agent of AIDS being classified into the types 1 and 2 (HIV-1, HIV-2) (6).

The HIV/AIDS epidemic poses an inescapable challenge to the world at large and to Africa in particular and more specifically in Mozambique (7).

To cushion the repercussion of the disease widespread, action taken must integrate all elements involved, including nutritional care. To assess and reduce the severity of the complex interaction between HIV/AIDS and malnutrition have on each other, with wasting and weight loss as common features of HIV infection, is essential to predict disease progression and higher risk of morbidity and mortality (8,9).

Most of the children affected live in Sub-Saharan Africa and were infected by their HIV-positive mothers during pregnancy, childbirth or breastfeeding (10).

There is not an accurate number of people being affected globally by AIDS but of the estimated 37.9 million people (2.1 million children) living with HIV worldwide at the end of 2018 (10–12), most have been submitted to generic antiretroviral medicines.

Our own studies regarding sexual and physical intimate partner violence among women showed the prevalence of these co-infections among pregnant women, in the north of Mozambique and it was estimated that some 2 to 4 million people also had Hepatitis B Virus (HBV) and 4 to 5 million people had Hepatitis C virus (HCV) infections (13). HCV co-infection is a strong risk factor for immune dysfunction affecting the clinical course of acute Hepatitis C. In Mozambique, a National Antenatal Care HIV Surveillance Survey, conducted by the National Institute of Health in 2011, showed a national prevalence of 15.4% (14). Due to shared modes of transmission HIV, HBV, HCV and Syphilis pose major public health concerns in Africa (15,16).

Prevention of mother to child transmission cascade have established in most African countries. A comprehensive study on HIV/AIDS in Mozambique involved routine data collection from prevention of mother-to-child HIV transmission. It was conducted in order to evaluate if the observed results were of sufficient quality, coverage and of continuous availability to eventually complement or even replace biannual sentinel serosurveys that currently serve as the primary HIV surveillance system in Mozambique (17,18).

In the present review, we aim at examining the relationship between viral infection and the nutritional status of the host when mushroom nutrition is involved and the possible role of mushrooms on HIV/AIDS.

2 The HIV - Human Immunodeficiency Virus

A virus is composed of a DNA or RNA genome inside a protein shell called a capsid. Some viruses have an external lipid membrane envelope. Viruses can be divided into those containing a lipid envelope and those whose genome is only covered by a protein shell (19).

Chimpanzee virus is a hybrid of the Simian Immunodeficiency Virus (SIV) naturally infecting different monkeys and as a result of cross-species (zoonotic) transmission, HIV jumped from chimpanzees to humans in the 1920s in Congo, Africa, probably as a result of people eating the meat from chimps carrying this similar virus (20).

The immune system comprises the network of vessels and lymphoid tissue, including the bone marrow, thymus gland, lymph nodes, spleen, tonsils, adenoids, appendix, blood, and lymphatic vessels (21).

The virus can hide and integrate the genome of different body cells and can bind to the CD4 molecule and penetrating these cells. Within the cell, a viral enzyme (reverse transcriptase) transcribes viral

RNA into double-stranded DNA, which is then integrated into the human cell's DNA, enabling further replication to take place (22,23).

HIV has the ability to infect a variety of cells and tissues spreading through body fluids (e.g. blood, semen, breast milk and vaginal fluid) although not by tears, sweat, nasal discharge, saliva, faeces, vomit or urine. It affects the body's immune system, causing severe damage and eventually destroying it, targeting and reducing the CD4 cells (24).

For AIDS, the most critical of the T cells is CD4. The HIV infection results in the depletion of B and CD4 bearing T-helper/inducer lymphocytes which are produced from stem cells and matured in the bone marrow and their number is used to monitor the progression of the disease (25). HIV virus attacks macrophages and dendritic cells (26) in lymph nodes and the skin, blocking the mechanism that informs the immune system and more T lymphocytes have to be produced to fight the infection (Figure 1).

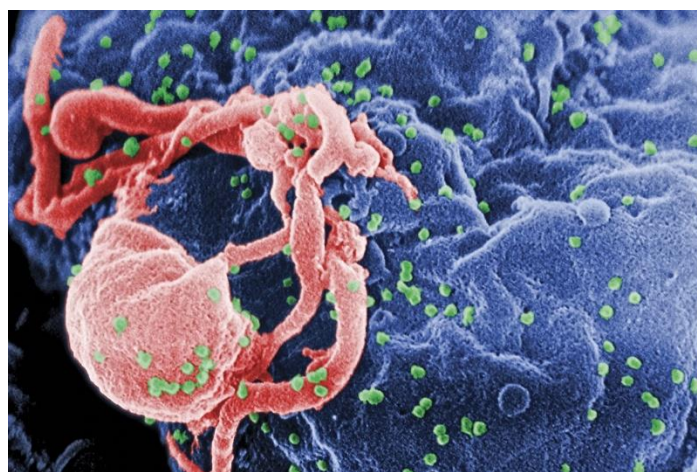


Figure 1. Coloured electron microscope image of immune system cell lymphocyte (red) protecting the cell (blue) from HIV virus (green). Mushrooms increase the number of lymphocytes (27).

New viruses generally do not emerge *de novo* rather they evolve all the time and rapidly from existing viruses from different animal species. Presently there are few antivirals (28) and the occurrence of HIV/AIDS in the 80's triggered a remarkable engagement on research for new antiviral drugs. As the propagation of viruses depends on the metabolic activity of the host cells, objective of antiviral chemotherapy is the discovery of agents that are specific for the inhibition of viral multiplication without affecting normal cell metabolism (29).

The human immunodeficiency virus type 1 (HIV-1) being lymphotropic and highly cytopathogenic has been associated with HTLV (Human T-Lymphotropic Virus)(30) increasing the susceptibility to leukaemia or lymphoma causing anaemia and immunodeficiency (31).

Macrophages and CD4+ T cells are the principal targets of HIV-1 and being present in every organ system the virus may be disseminated to many tissue reservoirs (32). Although HIV can be controlled and merely prevent progression by antiviral therapy (ART), through avoiding replication but not curing patients, it remains inactive in the body and cannot be eliminated (33). HIV evades the normal immune system mechanisms and promotes the destruction of the anti-viral interferon signalling pathway (34–36).

HIV escape immune system and antiretroviral therapies (37) by establishing latent reservoirs in host tissues and by intercellular mucosal viral transmission (38–40).

3 Mushroom Nutrition

Fungi and bacteria are major decomposers of nature in most complex ecosystems and crucial for the entire food chain in association with many organisms, being essential in the ecosystem flow of nutrient and energy cycling (41).

The number of fungi on the Earth is estimated to be 5,1 million, some 140,000-160,000 known species of [yeasts](#), [rusts](#), [smuts](#), [mildews](#), [moulds](#), and [mushrooms](#). Only 2,000 species are identified as edible mushrooms their global market estimated to be \$48 billion in 2018 growing to \$62 by 2023 (42).

Mushrooms have been used for health objectives for countless generations throughout the history of mankind, namely in Asia, although only a small proportion has been scientifically investigated (43). Medicinal mushrooms are presently used as food, nutritional supplement, medicament, nutraceutical/pharmanutrient, natural bio-control promoter in modern agriculture plant protection and cosmeceuticals (44–47).

Every mushroom species possesses literally thousands of compounds, with more or less powerful effects (48). This is the reason medicinal mushroom drugs may not be as effective as more refined dietary supplements. Thus our ongoing debate comparing mushroom extracts with mushroom biomass (49).

Besides the nutritional characteristics of low fat/energy and high in functional proteins and polyunsaturated fatty acids, mushrooms are potential sources of bioactive molecules able to achieve several functions in human organisms with benefits for consumer health. Two main divisions of edible mushrooms are: 1) *Ascomycota* – spores produced inside asci (e.g. *Penicillium*, *Cordyceps*, Truffles); 2) *Basidiomycota* – spores produced on cells called basidia which include most of the so-called “Medicinal Fungi” (e.g. Shiitake - *Lentinula edodes*, Maitake - *Grifolia frondosa*, Reishi - *Ganoderma lucidum*)(50).

Fungi are immensely diverse in relation to its genetics, shape, conservation, environment, and metabolism (51). While marine fungi still remain an underexplored resource of natural products (52,53).

Mushrooms produce numerous bioactive metabolites (e.g. selenium, vitamin D₂, antioxidants ergothioneine, glutathione, nucleoside compounds, saponins, tannins, anthraquinones, lectins, β -D-glucans, terpenes, polyketides, and steroids) (48,54,55), which make them very useful as nutraceuticals and pharmaceutical applications. Despite their significance, the research on rapid and correct identification of mushroom species is ongoing using morphological and molecular techniques extracting the genomic DNA of mushroom fruiting body(51,56–58) .

There is no borderline to differentiate between edible and medicinal mushrooms. Medicinal mushrooms have vast number of described health functions (43),including antitumour (59,60), immunomodulating (61), antioxidant (62), radical scavenging (63), cardiovascular (64), antihypercholesterolemia (65), antiviral (66), antibacterial (67), antiparasitic (68) , antifungal (69), antiallergic (70), anti-atherosclerotic (71), anti-inflammatory (72), detoxification (73), hepatoprotective (74), antidiabetic (75,76), anti-human papillomavirus (HPV) (77), parainfluenza and rhinoviruses (the common cold), influenza (the flu), HSV= Herpes simplex virus, mononucleosis (EBV-Epstein-Barr virus), cytomegalovirus, hepatitis viruses and other effects (78)

The increased concentration of these antiviral and anticancer compounds in mushrooms is an adaptation to their saprotrophic/lysotrophic nutrition meaning mushrooms live on dead and decaying substances, exposing them to attack from numerous parasites and fighting for nutrients (79). Mushrooms use growth inhibitors to combat the growth of these parasites and secure the nutrient rich areas (45)

4 Mushroom compounds with potential biological activity

The potential of mushroom compounds has been demonstrated on the modulation of the immune system, both humoral (antibody-mediated) and cellular immunity (mediated by T lymphocytes). They increase the capacity to reduce the frequency of mutation and counteracting carcinogenic agents, as well as rejuvenate the immune system following radio/chemotherapies in cancer biotherapy (80–82).

Mushroom β -glucans increases CD4 cells production and stimulates the immune system macrophages. Even when infected with HIV, the macrophages fight effectively and reduce HIV replication (83–85).

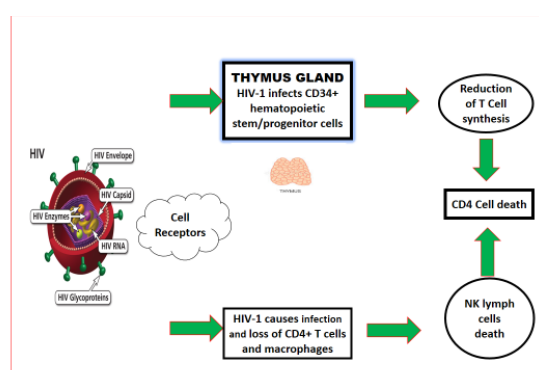


Figure 2. Retroviruses infect cells without killing their hosts but causing massive loss of bystander CD4 T cells elicited by caspase-1-mediated pyroptosis.

Coriolus versicolor, *Inonotus obliquus*, *Fomitopsis pinicola* and *Hericius erinaceus* are edible fungus that grow naturally in the bark of trees or on the dead wood of coniferous and broad-leaved trees and are well known for its immune boosting capabilities and anticancer properties (43).

Mushrooms (e.g. *Ganoderma lucidum*, *Pleurotus tuber-regium*, *Flammulina velutipes* and *Agaricus blazei*) have a large quantity of unique bioactive molecules such as a variety of high-molecular-weight polysaccharides and triterpenoids displaying a variety of medicinal properties (86,87).

Several triterpenes (e.g. lucidumol A, ganodermanondiol, ganodermanontriol, ganoderic acid beta), from the spores of *Ganoderma lucidum* are active as antiviral agents against human immunodeficiency virus type 1 (HIV-1) (66,88–92).

Mushrooms also contain many activities including antimicrobial, antiviral, antitumour, antiosteoclastic differentiation, anti-HIV-1, hepatoprotection, antioxidation, antihypertension, cholesterol reduction factors (e.g. lentinan, ganaderiol-F, ganoderic acid- β , lucidumol, PSP, coprinol, campestrin, sparassol, armillaric acid, cortinellin and ustilagic acid) (93–96).

Pulmonary Kaposi's sarcoma is still one of the most common malignancies in patients with human immunodeficiency virus (HIV) infection (97). Krestin and Lentinan are registered anticancer medical drugs from mushrooms in Japan. Studies regarding lentinan from the shiitake mushroom (*Lentinus edodes*) found that this polysaccharide (β -1, 3-D-glucan polymer) can halt sarcoma 180 (Lewis lung

sarcoma) with great effectiveness and lead to its complete regression, depending on the dosage (98,99)

Equally effective is PSK, an immunostimulating proteinbound polysaccharide K (Krestin) from the mushroom *Coriolus versicolor* (100,101). This compound found to be safe, used from the mid 1980 in Japan is still used as a medical drug and cancer cure from mushrooms. Its popularity due to the fact that in 1987 it accounted for 25% of all anticancer drug used in Japan. This drug is remarkably similar to Chinese PSP-polysaccharide peptide (registered as an anticancer drug in China), and is its predecessor (102–104).

Their modes of action suggested as due to the strengthening of the immune system, or directly by inhibition of viral enzymes, synthesis of viral nucleic acids or adsorption and uptake of viruses into mammalian cells (85,105).

Other powerful agents have also been discovered in the mycelium of certain species of mushrooms, such as polysaccharide KS-2 and glycoprotein LEM (*Lentinula edodes*) from the shiitake mushroom (106,107). It was also claimed that small molecular compounds with antiviral activities such as several triterpenes from *Ganoderma lucidum* are active as antiviral agents against human immunodeficiency virus type 1 (HIV-1) and dengue virus (93,108).

It has been established that in human clinical trials, the effect of using medicinal mushrooms (mycotherapy) for a longer period of time (on average 3 months) results in stronger improvements (109–111).

The exact mechanism of action of interferons (IFNs) is unknown, however it is understood the general molecular basis of their antiviral functions and the approaches developed by viruses to oppose the actions of IFNs (**Figure 3**). These are particles modulators of the immune response that increase secretion of human interferons, i.e. the body reacts to them as if they were of viral origin and boosts the immune system response (112–114).

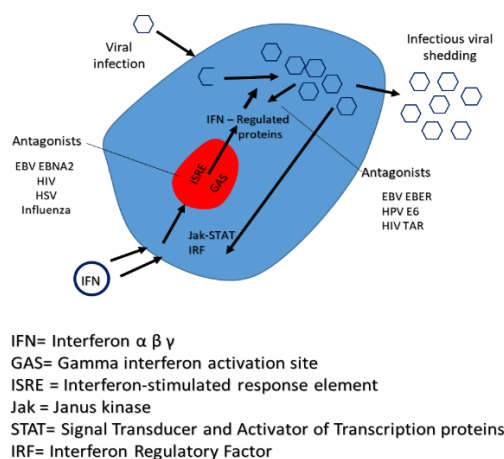


Figure 3. Virus entry and primary replication, viral spread, virus shedding (transmission of the virus).

The lymphotropic nature of the virus HIV-1, initially called lymphadenopathy-associated virus, infects humans and the function of the lymph node is disrupted while the production of and response to IFN-I may be severely altered (115,116).

The nucleobases, nucleosides and nucleotides found in mushrooms play important physiological roles and RNA found in shiitake spores stimulates interferon production (117,118).

Also, shiitake mushroom mycelia extract contains a polysaccharide KS-2- α -mannan peptide, which helps prevent and treat the flu via interferon-inducing activity (119–121).

Sporadic cases of breast cancer in HIV-infected women is recorded in the literature. A case in 1983 was reported of a 57-year old HIV-positive woman treated with mushroom lentinan the active ingredient of lentinan being β -1, 3-D-glucan polymer with β -1, 6 or β -1, 4 branches. After a 5-month treatment, she became HIV negative, the number of T helper lymphocyte cells (CD4 T-cells) greatly increased, while the activity of natural killer (NK) cells enhanced significantly. Three years later, she was still healthy and needed no further medical treatment (88,122–125).

It is well recognised the central role of anomalous immunity in a wide variety of diseases, including viral infections. The antiviral activity of lentinan, a common biological response modifier on HIV patients and adjuvant of conventional therapies, has shown that patients often feel healthy after only 2 weeks. However, the symptoms nearly always return, if lentinan is not used for a least 6 months, meaning its sustained efficacy on combined therapy is still unclear (126–128).

5 The antiviral mechanisms of medicinal mushrooms

HIV-1 infected people eliminate *CD4⁺ T cell population and naturally induced cell-mediated immune responses rarely eradicate infection* (129).

Some studies have suggested that direct viral infection of T cells may be responsible for much of the hallmark of CD4 cell loss in infected individuals (130,131).

The replication cycle of HIV has been well described (132) but precisely how HIV-1 kills cells *in vivo* is still an area of debate, probably by exhausting its resources triggering a process known as programmed cell death (apoptosis) (133–137).

B-cells are activated by the binding of their receptor (BCR) to an antigen and establishing a signalling pathway. Many molecules regulate the activation state of B cells and acquired deficiencies on B cell activation, essential for their selection and differentiation, and interact with CD40 signalling in B cells which is required for a proper immune response (138). Viral (HIV) infections and the access of extracellular nutrients (glucose and glutamine) regulates the Krebs cycle and oxidative phosphorylation thus the HIV-1 infection in CD4 T lymphocytes (139–143).

With infection of CD4⁺ T cells with HIV-1 considerable changes in the cellular metabolism occurs altering the substrates (e.g. glutamine) for the citric acid or tricarboxylic acid cycle and characterized by mitochondrial fusion, lipid accumulation, and reduced mitochondrial ATP production (144,145).

The survival of HIV inside the CD4⁺ lymphocytes depends on cells properly signalling pathways (146) and the immune system has its fundamental property to expand rapidly the antigen specific lymphocytes to combat pathogens such as HIV (147).

Mushroom lectins are a group of proteins that possess antiviral properties and act as immunomodulators as well as direct cytotoxic activity toward cancer cells and HIV. The mechanisms of anti-HIV activity of lectins has been described (148–151).

As the most abundant free amino acid in serum, glutamine is a readily available nutrient for most cells, and is involved in providing nitrogen and carbon for synthesis of many amino acids. It is used as supplement in many therapeutic uses including for complications of HIV/AIDS (152–154).

However, activation of B cells triggered by the binding of specific antigen to the B-cell receptor (BCR) is accompanied by increased glycolysis and glutaminolysis (155).

The human host has also multiple immune defence functions that can eliminate virus and/or viral disease (156). Cell culture (*in vitro*), animal (*in vivo*), and human (clinical) trials helped scientists to determine the antiviral mechanisms of specific medicinal mushrooms (92). Their active compounds fight viruses in two major ways: a) they boost the immune system: directly (specific response) and/or through various factors of humoral and cellular immunity; and b) attack the virus directly, which prevents the proliferation of viruses and can stop viral infections from developing (92,157).

Mushrooms offer a wide and undetermined variety of bioactive molecules and to be considered effective as an antiviral supplement should not cause any hepatotoxicity or exert minimal side effects to the host cells (74).

Most research on the health benefits of medicinal mushrooms focused on cancer, but in traditional medicine they were also used to prevent, alleviate, and treat viral infections (82). Nutritional status is closely associated with immunity and host resistance to infection and further to the well-known basic 50 nutrients, there are a wide variety of thousands of non-nutritive phytochemicals and functional foods (158). Antiviral and anticancer effects of mushrooms overlap as mushrooms stimulates the immune system and modulates immunity, essential for maintaining cell homeostasis (44,159).

Besides nutrition, factors such as genetics, environment, lifestyle, and their interaction should be taken into account (160).

Specific pharmaceuticals are required as antivirals since accepted antibiotics cannot treat viral diseases. Antiviral effects have been discovered for whole mushrooms, and for their extracts and biomass (161–163).

Direct antiviral effects, exhibited especially by smaller molecules, include the inhibition of viral enzymes, reduction of synthesis of viral nucleic acids and adsorption or uptake of viruses (164,165).

Indirect antiviral effects, result of the immunomodulation activity of polysaccharides or other complex molecules, are achieved by stimulating the immune response against the viral invasion and promoting biochemical factors, such as alkalinity, that discourage viral replication (166–168).

As eukaryotes, fungal cells contain a membrane-bound nucleus and rigid layers of fungal/mushroom cell walls containing complex polysaccharides (e.g. chitin, galactomannan and β -glucans) and proteins giving them a specific tension capacity but a dynamic structure providing both protective and aggressive functions (169,170).

β -glucans and other factors from mushrooms (e.g. proteins, glycoproteins, phenolic compounds, melanins, terpenoids and nucleosides) display antiviral activity against many zoonotic viruses (171–174).

Mushrooms yield bioactive metabolites in the fruiting bodies and or mycelia, and this being the basis for several biotechnological developments and production of new drugs including those carrying antiviral activity (175,176).

The data on antiviral and anti-tumour actions of mushroom-derived active compounds against many viruses pathogenic in humans indicate a predictive relationship of these properties although correlation between two attributes does not imply cause-and-effect relationship between the variables (177). Enzyme preparations from higher Basidiomycetes may prevent cancers with a viral aetiology (178–180).

Besides prevention of viral diseases, mushrooms reinforce the body on the inhibition, fight of infection, and trigger rehabilitation. The mechanisms of antiviral effects include improving the immunological response (114,181), enhanced antibody production and generation of several types of interferons (182), and direct antiviral activity, mostly by inhibiting their ability to multiply (183,184)

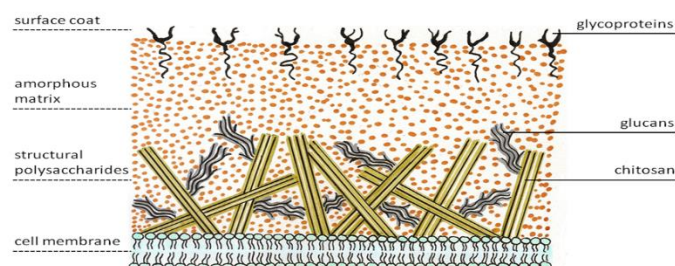


Figure 4. Mushroom cell structure. The thin cell wall, contains almost all active ingredients

Mushrooms fight viral infections and there are studies on anti-viral activities of several mushrooms against herpes (HHV-causing skin infections), orthopoxviruses (variola agent), West Nile (mosquito-borne disease), influenza (H1N1), hepatitis (HAV), and human immunodeficiency (HIV) (185,186).

Mushrooms have a history of medicinal use for millennia in parts of Asia. The most studied mushroom strains for producing antiviral medicines include *Daedaleopsis confragosa*, *Datronia mollis*, *Ischnoderma benzoinum*, *Trametes gibbosa*, *Coriolus versicolor*, *Laricifomes officinalis*, *Lenzites betulina*, *Rozites caperata*, *Lentinula edodes*, *Grifola frondosa*, *Ganoderma lucidum*, *Hericium erinaceus*, *Pleurotus ostreatus*, *Cordyceps sinensis* (187–189).

Medical, paramedical and nutritional uses of mushrooms have been described since the 1920's (190,191).

On the 1950's Cochran and Lucas reported medicinal mushrooms, more specifically *Calvatia gigantea* (giant puffball) and *Agaricus campestris* (meadow mushroom), to have protection effects from poliomyelitis virus colonizing the gastrointestinal tract of mice (192)

In the early 60's it was discovered that *Boletus edulis* (porcini), *Calvatia gigantea* (giant puffball), *Suillus luteus* (slippery jack), *Lentinus edodes* (shiitake), and *Piptoporus betulinus* (birch polypore) are mushrooms that effectively fight the flu-causing influenza viruses (193).

Influenza viruses, members of the family Orthomyxoviridae, may be inhibited by an active compound Ac2P (acetone precipitation) from shiitake mushrooms, a high molecular weight polysaccharide composed mainly of pentose sugars, and distinct from lentinan (194,195)

The antiviral research increased dramatically in the 1980s, since the onset of the AIDS epidemic in 1981. In 1983, scientists discovered the virus that causes AIDS and named HIV (human immunodeficiency virus), a virus that attacks the immune system, specifically CD4 cells (or T cells). Scientists have traced the origin of HIV back to chimpanzees and simian immunodeficiency virus (SIV), an HIV-like virus that attacks the immune system of monkeys and apes (28,196).

Scientific research in the West, concerning medicinal mushrooms, has significantly expanded from 1999 when Solomon Wasser in Israel started the "International Journal of Medicinal Mushrooms" and the biennially held "International Medicinal Mushroom Conferences" (197). However, the majority of

research in the medicinal mushroom field, involving many mushrooms (e.g. *Fomitopsis pinicola*, *Hericium erinaceus*, *Inonotus obliquus*, and *Coriolus versicolor*) is still mainly conducted by Asian scientists (198).

6 HIV/AIDS prevention and therapy

Unlike the present Covid 19, the majority of viral infections disappears spontaneously and do not need specific therapy although not all antivirals are effective against all viruses. Unlike most antibiotics that kill bacteria, antiviral compounds generally do not destroy directly the virus rather they inhibit the virus's ability to reproduce.

Viruses cannot multiply but may be replicated in the internal environment of cells that they invade. Specific viral enzymes (polymerases) for viral nucleic acids replication may be the target of effective antiviral agents.

Some obstacles are the toxicity of drugs (199), high cost of drugs and the capability of HIV-1 to develop resistance to antiviral drugs (200). There are no anti-HIV proprietary drugs prepared from medicinal mushrooms and plant-derived natural products continue to serve as a reservoir for the discovery of new medicines including anti-HIV agents. Ganodermediol, lucidadiol and applanoxidic acid isolated from mushroom *Ganoderma pfeifferi* show some activity against HIV-1, HSV-1 and influenza virus type A (201)

Antiviral drugs if combined with lentinan and/or other active mushroom compounds may inhibit HIV 5-24 times more effectively than AZT alone (depending on strain of virus) (202).

The World Health Organization (WHO) has suggested that ethnomedicines and other natural products should be regularly tested for antiviral properties and specifically against HIV as they may produce active agents more efficient and less costly than established pharmaceuticals (203–205).

Besides, current therapies to treat autoimmune diseases often result in side effects such as nonspecific immunosuppression (206).

We have reviewed the potential role of mushroom nutrition supplementation in other diseases including the prevention and the link between Herpes Simplex Virus (HSV) and Alzheimer's disease (207). Medicinal mushroom *Coriolus versicolor*, also used as dietary supplement biomass, contains the active compound PSK that blocks virus cell-to-cell infection, prevents the adhesion of the virus to lymphocytes and stimulates interferon production (208).

HIV infects by delivering its genome into the host cell cytoplasm (209) and PSK from *Coriolus versicolor* was shown to inhibit HIV infection by reshaping viral chemokine co-receptors and hampering the attachment of the virus to leucocytes (210).

Ganoderma lucidum (reishi) polysaccharides help seropositive patients through its anti-inflammatory properties linking the regulation and expression profiles of cytokines as biomarkers with differentiation of macrophages (211–215).

These are fundamental players in the maintenance of intestinal homeostasis and as key sentinels of the intestinal immune system (216).

Furthermore, people infected with HIV are more susceptible to invasive cervical cancer, lymphoma, Kaposi's sarcoma and many other symptoms of AIDS (stage 3 HIV) while several physicians reported improvements in patients with these cancers after using *Grifola frondosa* (maitake) extract justified by its immunotherapeutic potential (217–219).

7 Alternative and Complementary Medicine for HIV/AIDS

Non-traditional therapies include complementary and alternative medicines (CAM) also called complementary and integrative medicine. Complementary medicine is designated when these therapies (e.g. meditation, yoga, herbs, acupuncture and massage) are used not substituting but along with standard conventional traditional Western medicine. Alternative medicine comprising these approaches are used instead of standard medicine. Some CAM therapies are supported by scientific evidence, others are not based on the belief that a medical care provider has to treat the whole person i.e. body, mind, and spirit (220,221).

Anti-retroviral therapies have brought renewed hope for people living with HIV/AIDS extending and improving the quality of life for infected people and preventing pregnant people with HIV from transmitting the virus to their children (222). However, complete cure of this chronic illness may not be achieved and this medication may cause several adverse side effects. For these and other health and social issues, many HIV-positive people have turned to complementary or alternative medicine for help (223)

Some people use alternative medicine instead of standard Western medicine while the great debate continues on its values and regulations of usage. However, most people choose to use natural or alternative medicine along with standard Western medicine (224,225).

Alternative medicine includes many types of therapy. The goals of these therapies are to: a) Strengthen your immune system; b) Provide relief from symptoms and drug side effects; c) Improve your quality of life. With most complementary therapies, the body health is looked at from a holistic point of view with emphasis on health rather than on disease (226,227).

The FDA does not require that herbal remedies and dietary supplements (e.g. mushroom products) be tested in the same way of safety and effectiveness that standard medicines, before they are sold (228). Many of the treatments have not been studied as much as the HIV drugs being a risk to take something or try something that has not been fully studied or researched (229).

In Europe EFSA established for ingredients other than vitamins and minerals, proposed harmonised rules to protect consumers against potential health risks and maintains a list of substances which are known or suspected to have adverse effects on health and the use of which is therefore controlled (230).

Phytochemicals in some foods are a potential source of bioactive safe compounds for cancer chemoprevention and suppression of tumour initiation, promotion, and metastasis. The results indicate that *Hericium erinaceus* mushrooms may have therapeutic potential against human leukaemia (231).

Several mushrooms (e.g. *Leucopaxillus giganteus*) possesses various active substances (e.g. clitocine) that induce apoptosis through activation of several enzymes including caspases and polymerases via the mitochondrial-mediated caspase-dependent pathway (232,233).

Medicinal mushrooms (e.g. *Hericium erinaceum*, *Coriolus versicolor*, *Pleurotus eryngii*, *Ganoderma lucidum* and *Lentinus edodes*) contain in their extracts, ribosome inactivating proteins, lectins, ubiquitin-like proteins and laccases with strong antiviral effects (234,235)

Antiviral compounds from mushrooms (e.g. triterpenes, phenolic compounds, ergosterol peroxide, and purine derivatives) are strong biotherapeutics acting directly on the pathways of enzymatic

system of the human host, regulating the interactions between viral and components of the human cell (236).

These compounds may also act by inhibiting viral enzymes (reverse transcriptase, integrase, and protease) are all good drug targets. carried within the capsid and on the viral envelope, while some are only produced in the infected cell (237). The synthesis of viral nucleic acids or adsorption and uptake of viruses into mammalian cells are also affected by antiviral compounds in mushrooms (92,238,239).

Antiviral mushroom proteins are produced by *Pleurotus eryngii*, *Cortinarius caperatus* (Gypsy Mushroom) and *Pseudoplectanus nigrella* (240). Neogrifolin, an active substance from the edible bodies of the mushroom *Albatrellus confluens* from temperate zones, has been demonstrated to have diverse therapeutical effects (231). Results also suggested that neogrifolin is a potential candidate for osteosarcoma and Epstein-Barr virus (EBV) which is associated with several malignancies (241–243).

Among the active principles isolated from the mycelia of *Coriolus versicolor* is the polysaccharide peptide (PSP) which has proven its benefits in many clinical trials in China and Japan. Another active principle of *Coriolus* is protein bound polysaccharide Krestin (PSK- Protein-bound polysaccharide Kureha) (101,244).

Polysaccharopeptide (PSP) isolated from the edible mushroom *Coriolus versicolor* demonstrated inhibition of the interaction between HIV-1 gp120 and immobilized CD4 receptor, potent inhibition of recombinant HIV-1 reverse transcriptase, and inhibition of a glycohydrolase enzyme associated with viral glycosylation (241,245,246).

Natural compounds are a good source for the development of antiretroviral drugs with low cytotoxicity. The ability of a combination of phytochemical compounds for the prevention and treatment of HIV/AIDS and/or immune disorders was the subject of an application for a patent in the USA in 2008, a complex issue (247).

The kingdom Fungi represents a rich source of various biologically active compounds (**Table 1**), from high-molecular weight compounds to small organic molecules (secondary metabolites) (92,248).

Table 1. Bioactive compounds of some edible mushrooms

Mushroom	Common name	Compound/extract
<i>Agaricus bisporus</i>	White button	Polysaccharides, lectin
<i>Ganoderma lucidum</i>	Reishi	Polysaccharides, PSP
<i>Coriolus versicolor</i>	Yun Zhi	Krestin, PSK, PSP
<i>Lentinus edodes</i>	Shiitake	Lentinan
<i>Grifola frondosa</i>	Maitake Grifolan	Maitake D fraction
<i>Agaricus blazei</i>	Brazilian blazei	Agaricus polysaccharides
<i>Pleurotus tuber-regium</i>	King tuber	Pleuran
<i>Flammulina velutipes</i>	Winter	Flammulin

8 *Coriolus versicolor*



The health-promoting properties of polysaccharides (PSK and PSP) from mushroom *Coriolus versicolor* (*Trametes versicolor*, Turkey Tail), individually and as blended mixtures, has been the subject of considerable research on the prophylaxis and treatment of various human diseases (120,241,249).

PSK and PSP have antiviral effects on human immunodeficiency virus (HIV) inhibiting reverse transcriptase in vitro (250) attributable to the inhibition of binding of HIV with lymphocytes (251,252).

PSK is an inhibitory belonging to the enzyme-binding (reverse transcriptase) class of compound (253,254). The enzyme reverse transcriptase mode of action as an essential enzyme in the viral replication cycle and antiretroviral has been reviewed (255–258).

The capacity of polysaccharide PSK and sulphated (lentinan and dextran) polysaccharides from mushrooms to inhibit four different strains of HIV-1, a strain of HIV-2, and a human T-cell lymphotropic virus type I (HTLV-1) was tested. Cell-free infection of HIV-1 and HIV-2 was almost completely blocked. Cell-to-cell infection by HIV-1, HIV-2, and HTLV-1 may also be inhibited (259–261).

PSK, a biological response modifier, almost completely blocks the heterogenic cytopathogenic effect through strong cell proliferation and HIV-specific antigen expression proved inhibitory to a variety of HIV-1 strains and HIV-2 in acutely infected T-cell lines (MOLT-4 and MT-4). Indeed, treatment with PSK may specifically interfere with early stages of HIV infection by modifying the viral receptor (235,262–264).

The potential use of polysaccharide peptide (PSP) from *Coriolus versicolor* as immunoadjuvant for cancer immunotherapy and as anti-HIV agent was studied and showed that it exerts an anti-HIV activity mediated by toll-like receptor-4 (TLR4) adjuvant activities in stimulating expressions of cytokines (260,265).

9 *Ganoderma lucidum*



Ganoderma lucidum (Reishi) is an edible mushroom containing elements such as bioactive polyglycans (polysaccharides), such as β -glucans, triterpenoids, sterols, lectins, coumarins, and alkaloids which are found in all parts of the mushroom, including the mycelium (266). They increase the phagocytotic

capacity of macrophages, and increase the production - and lifetime - of CD4 lymphocytes as well (267). The laccase enzyme, produced by fungi of the genera *Ganoderma* sp. and *Lentinus* sp., inhibits the reverse transcriptase (RT) of the human immunodeficiency virus 1 (HIV-1) (164,212,268).

10 *Grifola frondosa*



Grifola frondosa (Maitake) contains the primary polysaccharide, β -D-glucan recognized as an effective immune-stimulator which increases the activity of macrophages and other immunocompetent cells (269). The substance also improves the immunological efficiency of these cells by increasing production of cytokines IL-1, IL-2 and others. The final result is an increase of the defences against HIV infection (270).

Also, D-Fraction, a polysaccharide extracted from *Grifola frondosa*, has been reported to exhibit an antitumoural effect through activation of immunocompetent cells, including macrophages and T cells, with modulation of the balance between Th-1 and Th-2 cells (271).

Results suggests that D-Fraction can decrease the effective dosage in tumour-bearing mice by increasing the proliferation, differentiation, and activation of immunocompetent cells and thus provide a potential clinical benefit for patients with cancer. Use of *Grifola* has demonstrated to diminish side effects of chemotherapy in test conducted in animals and in particular as immunomodulating agents, and as an adjunct to cancer and HIV therapy (217,272).

Antiretroviral therapy (ART) alone cannot eradicate HIV and its latent, persisting reservoirs and novel approaches have been tested such as the use of chimeric antigen receptor (CAR) T cells (273,274).

11 *Lentinula edodes*



From *Lentinula edodes* (Shiitake) it is obtained a β -1-3, β -1-6 δ -glucan named lentinan, which boosts the immune system (275). Thus, the active principles are mostly present as glucans of different glycoside links, such as (1 $\rightarrow$ 3), (1 $\rightarrow$ 6)- β -glucans γ (1 $\rightarrow$ 3)- α -glucans and as true heteroglucans. They constitute appropriate substrates for gut microbe digestion and metabolism (276).

They act as immune modulators due to the increase in concentration of humoral mediators, such as TNF- α , gamma interferon, Interleukin-2, Interleukin-6, and the production of nitric oxide and activity of catalase, in macrophages and T lymphocytes (277). They also increase the cytotoxicity of NK cells and macrophages (278).

Another active principle obtained from *Lentinula* is AHCC (Active Hexose Correlated Compound) an acylated α -1,4 -glucan standardized extract of cultured *Lentinula edodes* and other mushrooms. This compound is a functional food supplement which offers immune-modulating and antineoplastic activity namely in the prevention of cancer caused by HPV-human papilloma virus and shown in “in vitro” studies to kill off the HIV. Lentin exerts an inhibitory activity on HIV-1 reverse transcriptase (88,279,280).

To be noted are also an improvement in lymphocyte and erythrocyte count, anaemia and appetite, and as an immune-enhancer to decrease these adverse events of chemotherapy.

12 *Inonotus obliquus*



This mushroom, known as Chaga, has proven to be effective in fighting HIV and viral cancers namely in Siberia, Russia, justified by its high concentration on betulinic acid thought to be very toxic to cancers and other viruses (281).

13 *Hericium erinaceus*



Mushroom antiviral activities have been reported towards human immunodeficiency virus (HIV) using lectin isolated from *Hericium erinaceus* (282) and laccase isolated from edible mushroom *Clitocybe maxima* (Big Cup Umbrella) (186).

14 Pleurotus Ostreatus



Pleurotus ostreatus also known as oyster mushroom, have been used as source of substances with documented medicinal properties including anti HIV properties (283,284).

15 Synergistic effect

Dietary supplements with a single compound or combined with several pharmaceutical compositions is usually given for the co-treatment of HIV/AIDS, immune disorders and others. However, it is believed that the best efficacy of mushrooms, herbs, and plant products used in HIV/AIDS prevention and treatment is achieved with the use of the entire herbs, mushroom biomass and plant or its extracts, rather than with the use of isolated active ingredients (285–287).

The synergistic or additive pharmacological effect can be beneficial by eliminating the problematic side effects associated with the predominance of a single xenobiotic compound in the body. Indeed, synergistic interactions underlie the effectiveness of a number of phytomedicines (288).

However, there is also mounting evidence which demonstrate that medical plants contain synergistic and/or side-effect neutralizing combinations (289).

Oxidative stress associated with human immunodeficiency virus type-1 (HIV-1) infection and massive reactive oxygen species (ROS) production has been extensively studied (290), and the benefits of mushrooms as antioxidant supplementation have been demonstrated (291–293).

16 Conclusions

Nutrition comprises a fundamental part of an overall cluster of interventions on people living with HIV/AIDS as the epidemic is occurring mostly in communities where poor appetite, weight loss, wasting and general malnutrition is already endemic. Improvement of dietary quality and food diversity must be encouraged, as they are the major constraints in these populations while national control and treatment programmes must include nutritional elements or strategies designed to produce behaviour changes and improve health status.

In face of these challenges, it is crucial to consider how different therapies work on the management of HIV/AIDS, namely the utilization of some foodstuffs. Plant materials and mushrooms known to contain functional bioactive metabolites should be investigated. Mushroom products remain an untapped resource with enormous health and industrial potential as the dietary intake of antioxidants from mushrooms potentially regulate the oxidative homeostasis.

CONFLICT OF INTEREST

THF drafted and all authors contributed equally, and all declare no conflict of interest. Any fund or institution supported this work.

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