International Journal of Medicinal Mushrooms, 21(2):105–119 (2019)

Cancer without Pharmacological Illusions and a Niche for Mycotherapy (Review)

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ABSTRACT: In this review we outline a framework in which mycotherapy is effective in the field of oncology. We suppose that irreversible epigenomic changes in cancer cells and achieving their replicative immortality when cancer-specific targets are absent should take away any illusions about a fundamental possibility of pharmacological blockage of the cancer process once ontogenesis begins. At the same time, however, we believe that effects of both traditional and alternative medicines on cancer clonogenic units within a particular range can lead to prolonged remission; with this in mind, we carefully consider the various possibilities of mycotherapy in controlling cancer activity. The aforementioned range is limited to nondisseminated cancer processes and depends on the absence of large secondary tumor nodes and the inexhaustibility of immune depots after chemotherapeutic treatment. The main therapeutic effect of fungal bioactive complexes is dectin-1–mediated immunity, including the reprogramming of dendritic cells, which significantly increases the period during which tumors generate immune tolerance. An inhibitory effect of fungal bioactive complexes on some molecular mediators of proliferative signaling and components of proinflammatory (synergistic with cancer) immunity can be considered less significant. The effect of fungal bioactive complexes on vital (including overexpressed) targets of cancer cells is even more limited. The results of this study stress that mycotherapy is only one of the tools that can be used to balance remission. Palliative mycotherapy is associated with polyphenolic composites, which contribute to detoxification and to the suppression of inflammation and pain sensation.

KEY WORDS: cancer hallmarks, immune tolerance, immunotherapy, medicinal mushrooms, targeted cancer therapy

ABBREVIATIONS: COX, cyclooxygenase; **DC**, dendritic cell; **EGF**, epidermal growth factor; **EpCAM**, epithelial cell adhesion molecule; **FGF**, fibroblast growth factor; ***IJMM***, *International Journal of Medicinal Mushrooms*; **MAPK**, mitogen-activated protein kinase; **MM**, medicinal mushroom; **MMP**, matrix metalloproteinase; **NF-κB**, nuclear factor-κB; **NKC**, natural killer cell; **PcG**, polycomb-group; **RNase**, ribonuclease; **VEGF**, vascular endothelial growth factor

I. INTRODUCTION

A respectable mycological journal, *Fungal Biology*, recently published an article with the provocative headline, "Are Mushrooms Medicinal?"[1] This article's remarkable summarizing lines stated:

> The worst of the advertisements for medicinal mushrooms recall the era of medical quackery that tolerated patent medicines including 'Dr. Bonker's Celebrated Egyptian Oil', which was advertised as a cure for colic and cramps in humans and farm animals, and 'Dr. Solomon's Cordial Balm of Gilead' that was praised as a treatment for venereal disease and a plethora of other maladies. Putting aside the current fantasies about mushrooms, there are good reasons for surveying the galaxy of metabolites in these organisms. After all, other kinds of fungi are the source of antibiotics old (penicillin) and new (cephalosporins), the cholesterol-lowering drug lovastatin, and

1521-9437/19/$35.00

> cyclosporins for supporting patients after organ transplants. Miraculous drugs may be sitting in the least prepossessing fruit bodies. And with a choice of 16 000 or more species of basidiomycetes that form mushrooms, there are lots of places to look. It is time to treat anti-aging tonics made from mushrooms as a sad phase in the history of mycology and proceed with the exploration of novel compounds with the potential to change the course of our modern plagues.

This article is remarkable to us for 2 reasons. First, a strong message in that article shows how the flow of scientific information has intensified and diversified over the past few decades and how the entire range of research activities was disconnected in an "information environment." It is strange, and a pity, that Senior Editor N. Money would publish in a respectable journal like *Fungal Biology* amateur articles without any scientific basis or evidence from the field of medicinal mushroom (MM) science.[1] The article "Are Mushrooms Medicinal?" is a superficial mixture of heterogeneous facts, truths, and lies; the selection of references from the literature is somewhat random, for example, mentioning fungal toxins, possible allergic reactions, and pure knowledge in biochemistry (imagining that all mushroom glucans have the same chemical structure). "This indicates that the author ignored both patent literature and the journal dealing specifically with medicinal mushrooms" (Prof. V. Sasek, personal communication, August 2018). The author of the published review is not familiar with data and references in the *International Journal of Medicinal Mushrooms* (*IJMM*). The article by Money[1] does not stand up; the author is not familiar with the new class of drugs called "mushroom pharmaceuticals or mushroom drugs" (e.g., krestin and polysaccharide peptide from *Trametes versicolor*; lentinan isolated from *Lentinus edodes*; schizophyllan [sonifilan, sizofiran, or SPG] from *Schizophyllum commune*; befungin from *Inonotus obliquus*; D-fraction from *Grifola frondosa*; polysaccharide fraction from *Ganoderma lucidum*; active hexose-correlated compound).

Unlike the article from *Fungal Biology*, the *IJMM*, beginning in 1999, aimed to bring together knowledge and scientists, using the burst of advances in computer technology and the ease with which information can be found within seconds to solve problems in the fields of pharmacology and to identify biotechnology and biomedical aspects pertaining to the use of higher fungi. *IJMM* has played a leading role in activating research on the medicinal properties of Basidiomycetes. For 20 years *IJMM* has disseminated important information and results from studies of chemical properties of MMs and on the biomedical aspects of their use.[2–15]

Hundreds of articles in the literature describe human clinical studies involving MMs. Clinical studies of the effects of various MM preparations on humans have been published in more than 1000 papers and reports.[14] Approximately 300 clinical studies were conducted on *G. lucidum* alone, and some on other species of genus *Ganoderma*.[14] Most clinical trials have studied mainly *G. lucidum*, *L. edodes*, *G. frondosa*, *T. versicolor*, *Sch. commune*, *Phellinus linteus*, and *Agaricus brasiliensis* (=*A. blazei* sensu Heinem.) in treating cancers and oncoimmunological and immunological diseases, and as immune-adjuvant therapies. Fruiting bodies of mushrooms and their biomass from submerged cultivated mycelia, various types of extracts, rare spores (from *G. lucidum*), glucans (pure β-glucans [e.g., lentinan or schizophyllan isolated from culture broth], proteoglucan (polysaccharide K), and polysaccharide peptide have been used in clinical trials for treating cancer. β-glucans have been used as an adjuvant therapy in clinical trials, mainly in Asian countries, with positive effects on patients' survival and quality of life. In many cases mushrooms have been used as adjuvant treatments with conventional chemotherapy or radiotherapy for various kinds of cancer. On the basis of this use of MMs in treatment in clinical trials, MMs show a significant advantage over chemotherapy and radiotherapy in reducing these therapies' adverse effects (loss of appetite, hair loss, nausea), and they have been proven to potentiate human immunity against health conditions.[2–15]

The suggested mechanism of action of MMs occurs through stimulation of the immune system. Some clinical studies have clarified the basic mechanisms involved in the immunomodulatory activity of

β-D-glucans, especially those providing data on dectin-1 and C3-iCR3 involvement. Dectin-1 is expressed on macrophages, neutrophils, dendritic cells (DCs), and T lymphocytes. Clinical trials have shown that MMs activate cytotoxic macrophages, monocytes, neutrophils, natural killer cells (NKCs), DCs, and chemical messengers (cytokines such as interleukins, interferons, and colony-stimulating factors) that trigger complementary and acute-phase responses. Also, MM products can be considered as multicytokine inducers that are able to induce the expression of various immunomodulatory cytokines and cytokine receptors.

Clinical studies have shown that MMs can be used not only as strong immunoceuticals but also as sources of potent metabolites that are capable of penetrating cell membranes and interfering with particular signal transduction pathways linked to processes such as inflammation, cell differentiation and survival, carcinogenesis, and metastasis. One such crucial pathway is the activation of the nuclear transcription factor κB (NF-κB). In some studies, levels of interleukin 1 and tumor necrosis factor-α decreased. Clinical studies showed that mushrooms had immunostimulatory and immunosuppressive effects on various parameters and can be part of oncoimmunological adjuvant therapy in many cancer cases. In some studies, regression of lung cancer metastasis was observed (which could be helpful for preventing tumor metastasis without causing any cellular toxicity), and chemotherapy- and radiotherapy-associated adverse effects and quality of life improved. Clinical studies have shown that MMs are an important part of cancer prevention and therapy. When used with conventional cancer therapies, MM products are intended to enhance patient tolerance of chemotherapy and radiotherapy and to reduce their toxicity and damaging adverse effects.[2]

Authors have published in *IJMM* the results of studies of antitumor drugs from MMs; these drugs have been called "biological response modifiers."[2,3] The application of biological response modifiers has become a new kind of cancer treatment, together with surgery, chemotherapy, and radiotherapy. Currently, more than 200 medicinal functions are known to be produced by MMs and fungi. Recently studied medicinal actions of mushrooms include antitumor, immunomodulatory, antioxidant, radical scavenging, cardiovascular, cholesterol-lowering, antiviral, antibacterial, antiparasitic, antifungal, detoxicative, hepatoprotective, antidiabetes, antiobesity, neuroprotective, and neuroregenerative effects, among others. Also, substances derived from MMs can be used as painkillers or analgesics. The best implementation of MM drugs and MM dietary supplements has been in preventing immune disorders and maintaining a good quality of life, especially in people who are immunodeficient or immunodepressed; are receiving chemotherapy or radiotherapy; have cancer, chronic blood-borne hepatitis B, C, and D infections, anemia, HIV/AIDS, herpes simplex virus infection, chronic fatigue syndrome, Epstein-Barr virus, or chronic gastritis and gastric ulcers caused by *Helicobacter pylori*; or are suffering from dementia (especially Alzheimer disease).[1–15]

Here, we demonstrate recent successes in studying the effects of fungal metabolites on neoplastic (cancer) cells. Nowadays, cancer is 1 of 2 leading causes of death worldwide (cardiovascular disease is the other). These top 2 causes accounted for 46.1% of all deaths in the United States in 2013. Among the 4 main categories of noncommunicable diseases (cardiovascular disease, chronic diabetes, respiratory disease, and cancer), cancer is recognized as the main cause of death at national, regional, and global levels. Figures for and projections of the global cancer burden presented in the new edition of the World Cancer Report[16] alerted the public to current frightening tendencies. The data show that the prevalence of cancer increased from 12.7 million cases in 2008 to 14.1 million in 2012. Unfortunately, this trend is projected to continue, with the number of new cases expected to increase by 75%: more than 40 million new cancer cases worldwide are predicted by 2015. Estimates reported by the World Health Organization indicate that 84 million people died of cancer between 2005 and 2015. Thus, cancer is killing more people than AIDS, malaria, and tuberculosis combined. In addition, in China and India (the most populated countries, with total populations now exceeding 2.6 billion people), cancer deaths are increasing largely because of smoking, unhealthy and unbalanced diets, and ecological problems such as air and water pollution.

In 2016, Siegel et al.[17] published projected cancer statistics for the United States: 1,685,210 new cancer cases and 595,690 cancer deaths will occur. According to the World Health Organization, the total number of global cancer-related deaths could reach 17 million per year by 2030.[16]

The 5 most common sites of cancer diagnosed in men in 2012 were the lung (16.7%), prostate (15.0%), colorectum (10%), stomach (8.5%), and liver (7.5%). Lung cancer demonstrated the highest incidence rate, at 34.2% per 100,000 cases, and prostate cancer, the second highest incidence rate, at 31.1% per 100,000 cases. The 5 most common sites of cancer among women were the breast (25.2%), colorectum (9.2%), lung (8.7%), cervix (7.9%), and stomach (4.8%). Breast cancer had a significantly higher incidence rate (43.3% per 100,000 cases) than any other cancer; the next highest incidence in women was recorded for colorectal cancer (14.3% per 100,000 cases).

Along with standard treatment schedules, approaches to targeting cancer therapy are being increasingly used. These approaches are based on known molecular mechanisms of action of metabolites of neoplastic cells. Successes and problems in this area are reviewed below.

II. CANCER WITHOUT PHARMACOLOGICAL ILLUSIONS

A. Essence of Cancer

A sufficient feature of cancer is a persisting shift in the balance between survival/proliferation of cells and cytostasis and tissue integration. Neoplastic cell transformation captures both the cell genome and epigenome. Once appearing in a multicellular organism, highly adaptive, epigenetically heterogeneous and replicative immortal cancer clones persist, gradually increasing immune tolerance and their own malignant potential.

From a cell biology viewpoint, cancer can be interpreted as an adaptive syndrome, when a basic "protozoan" program of cell survival is unpacked, whereas various suppressive or apoptotic stimuli emanating from a multicellular consortium are blocked. This occurs because integrative signaling networks are more ephemeral than basal networks associated with proliferative signaling and the working of the heat shock protein system of an individual cell.[18] From an evolutionary biology viewpoint, cancer can be considered as a remnant modular intention of a unitary organism, and as a kind of rudimentary new module that initiates the death of the host organism.[19] Nonmalignant tumors are considered to be morphogenetic sources of evolutionary innovations.[20]

B. Cancer Epigenome

The cancer process can be described through abnormal changes in gene expression in ontogenesis, associated with mostly irreversible activation of cell survival programs. The most significant epigenetic change during malignant transformation is the removal of "suppressive tags" of DNA via demethylation.[21] With a general decrease in methylation, local aberrant, redundant methylation is characteristic of some 5′-C-phosphate-G-3′ islets, leading to the repression of a number of tumor suppressors.[22] Repressing the expression of tumor suppressors through methylation is the most important epigenetic disorder, leading to the growth of tumor cells. Hundreds of genes with aberrantly methylated promotors can be detected for just one type of tumor.

In addition to gene-specific methylation, which can occur in a coding region of the gene, methylation of the genome decreases globally in tumor cells, especially during metastasis, mainly reflecting changes in the methylation of 5′-C-phosphate-G-3′ sites in noncoding sequences. Sequences of satellite DNA, located in centromeric heterochromatin, are strongly methylated. Insufficient DNA methylation in the centromeric regions of human chromosomes can make them unstable—a result of decondensation

of heterochromatin and enhancement of recombination in these regions. Violations of the structure of centromeric regions lead to nondissociation of chromosomes and aneuploidy, both of which are highly characteristic for tumor cells.[22,23]

Another important epigenomic change in cancer cells is histone modifications. Particularly characteristic of these changes is the loss of acetylation of K16 and trimethylation of K20 in histone H4. The reduction of histone methyltransferase activity at NZK27 and NZK9 sites correlates with *Rb* gene defects and deviations in cell cycle regulation, which are characteristic of tumor cells.

Research has revealed an increase in the expression of the polycomb-group (PcG) protein complex in some types of cancer.[24] One protein of the PcG protein complex is histomethyltransferase. PcG proteins in mammalian embryonic stem cells are necessary to maintain cell pluripotency; the proteins temporarily (reversibly) suppress the activity of those genes that begin to be expressed during differentiation. In cancer cells, methylation increases sharply for the promoters of genes that are targets of PcG proteins. This leads to strong gene silencing, which prevents differentiation and supports stem cell proliferation, predisposing cells to malignancy.[25]

C. Cancer Hallmarks

An increase in expression of oncogenes and early response proteins associated with adaptive epigenetic events determines cancer phenomenology, which is described by canonical manifestations known as "cancer hallmarks." These include a high degree of cell autonomy in generating proliferative signals and insensitivity to exogenous growth regulators. These occur because the expression of cyclin genes is violated, leading to the destruction of balanced cell cycle control. The phosphorylation of Rb and Cdk allows the cell to pass the $G_1 \rightarrow S$ checkpoint. As a result of the de-repression of the E2F transcription factors, the dependence of cell proliferation on negative regulation by means of exogenous signal molecules is lost, and the cell develops its own growth factors (platelet-derived growth factor, fibroblast growth factor [FGF]), receptors for exogenous growth factors (epidermal growth factor [EGF] receptor, Ret, Ras), and transcription factors (Myc, Jun).[26,27]

Other important cancer hallmarks are a decrease in a cell's sensitivity to proapoptotic stimuli and the avoidance of apoptosis, due to the insufficient function of p53[28] and overexpression of NF-κB, which blocks apoptosis on pathways initiated by the "death domains." Proliferating clones manifest other tactics that allow them to evade apoptosis by selecting cells with damaged Bax, Bad, Apaf-1, or cytochrome c-dependent caspases; cells with a blocked mitochondrial-mediated apoptotic pathway[29]; cells that overexpress Bcl-2, MDM2 products inhibiting Bax, and p53 proapoptotic factors; and cells with suppressed expression of the "death domain" receptors, which allows them to avoid Fas-mediated apoptosis.[30]

Neovascularization and the incorporation of endothelial cells into complex tumor tissue are highly characteristic of cancer. This is realized by increases in the overexpression of vascular endothelial growth factor (VEGF) and FGF, the molecules that induce angiogenic signals.[31] Endothelial cells within the microenvironment of the tumor node receive an angiogenic signal through VEGF receptors 1–3, and then proliferate.

D. Tolerogenic Signaling

In addition to canonical "hallmarks," cancer is characterized by a variety of secretory activities associated with proliferative signaling (EGF, VEGF, and transforming growth factor) and outward migration of survival factors (heat shock proteins) and proinflammatory cytokines. A number of tumor-releasing factors can attract DCs to a neoplastic area and disrupt their maturation, differentiation, and functional

activity, thereby leading to a deficient antitumor immune response or DC-mediated tolerance of the tumor. These factors include interleukin 10, which impairs maturation and differentiation of DCs and induces their tolerogenic phenotype[32]; lactic acid, which inhibits differentiation of DCs[33]; a human chorionic gonadotropin, which induces the tolerogenic phenotype of DCs[34]; and RANKL (receptor activator of NF-κB ligand), which polarizes DCs into a tolerogenic phenotype.[35]

E. The Illusory Nature of Pharmacological Victory over Cancer

The most common reason for the impossibility of annihilating cancer through the use of pharmaceuticals after it emerges is that cancer is a bioprocess involved in ontogenesis. The main limitation of drug therapy is the lack of vital targets specific to cancer cells and the toxic systemic effects of most drugs. During chemotherapy, mostly immune cells (including clonogenic) and cancer cells with reduced proliferative potential disappear, whereas cancer cells with hyperactive proliferative circuits persist, as a rule.[36] During *in vitro* experiments, a tremendous variety of substances, both synthetic and natural, induce a cytotoxic effect, but *in vivo*, only a limited fraction of cancer cells within complex cancer tissues demonstrate sensitivity to these substances.

Surgical removal of large nodes of malignant cells, when possible, leads the body into remission, the duration of which is related to the quality of immune surveillance for micrometastases remaining in regional and more distant lymph nodes associated with pathways of hematogenous and lymphogenous dissemination. However, the advantage of cancer cells relative to immunocytes is their replicative immortality, tolerogenic signaling, and active (gene expression changes) and passive (clonal heterogeneity) responses to immune and drug stimuli.

Targeted cancer therapy associated with inhibiting or destroying various molecular targets has the same restriction as drug therapy: almost no targets specific for cancer exist.[36] Concerning the inhibition of processes, recall that

> . . . in fact, automatic mechanisms exist in the body, negative for the therapy, by which artificial inhibition induced with exogenous agents will inevitably evoke an opposite response (promotion)[,] which will cancel and thus causes [*sic*] a deadly reaction for the patient in the application of the inhibitory factor. A strong inhibition evokes an even stronger promotion.[37]

Cancer tissue, like any other adaptogenic matter, obeys the Le Chatelier-Brown principle and capably strengthens compensatory processes. For example, cell cycle arrest leads the paracrine mechanism to realize its malignant potential: the cells begin active proliferative signaling.[38]

In fact, in pharmacotherapy, striving to defeat cancer as an ideal really solves more local problems, such as destroying inactive "determined" cancer derivatives in tumor parenchyma and increasing the duration of remission after surgical removal of the primary node. The success of pharmacotherapy and immunotherapy (including mycotherapy) in the latter cannot be ignored.

III. NICHE FOR MYCOTHERAPY

From an oncology point of view, most molecular stimuli transmitted by bioactive complexes of MMs are weak; that is, they are not destructive but rather have an inhibitory effect, although a number of these substances can have an apoptotic effect on cancer cells, both directly and, in many cases, mediated by NKCs (Table 1).

An important function of fungal glucans is their reprogramming of DCs, which helps to extend the period of development of immune tolerance to the tumor. The effective use of extracts from MMs

TABLE 1: Therapeutic Targets of Cancer and Niche for Mycotherapy

Cancer Aspect	Therapeutic Approach	Pharmaceuticals
Cell proliferation	Cdk inhibition	Letrozole, *ganoderic acids*, *genistein*
Resistance to apoptosis	Activation of apoptosis pathways	Vincristine, doxorubicin, interferon, TNF-α (NK-mediated: β-glucans)
Proliferation signaling	Blockage of EGF receptors	Gefitinib, erlotinib, β-glucans
Angiogenic signaling	Blockage of VEGF receptors	Angiostatin, endostatin, vasostatin, β-glucans
Replicative immortality	Telomerase inhibition	Rubromycin, costunolide, *thielavin b*
Inflammation	NF-κB inhibition	Resveratrol, triptolide, *panepoxidone*, *polyporenic acid*
Invasion	Metalloproteinase inhibition	Marimastat, rebimastat, metastat, *polyporenic acid*, *(E)-2-(4-hydroxy-3-methyl-2-butenyl)-hydroquinone*
Tolerogenic signaling	Stimulation of dendritic cells	Flt3 ligand, β-glucans
Genome instability	PARP inhibition, free radical scavenging	Iniparib, talazoparib, olaparib, veliparib, 3-aminobenzamide, *polyphenolic lignin-derived composites*
Downshift of catabolic potential	Inhibition of aerobic glycolysis	Iodoacetate, oxamic acid
Total RNA overproduction	RNA degradation	*RNAses*
Nonspecific (vital) targets	Destruction	
Heat shock proteins		Geldanamycin, radicicol
DNA polymerases		Foscarnet
RNA polymerases		*Amanitin*
COX1, COX2		Catechols
Tubulin		Colchicine
Actin		*Phalloidin*

Pharmaceuticals of fungal origin are italicized. EGF, epidermal growth factor; NF, nuclear factor; NK, natural killer cell; PARP, poly(ADP-ribose) polymerase; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

is fundamentally limited by the absence of large nodes of malignant cells and the nondepleted state of immunocyte depots.

A. Induction of Apoptosis Mediated by Reprogramming of NKCs and DCs

The cytotoxic activity of immunocytes against a wide range of target cancer cells, preceding directed immunization, was discovered relatively recently and is referred to as natural killer activity. Cells demonstrating such an activity pattern are referred to as NKCs,[39] which are a phylogenetically ancient species of T cells. Other subpopulations of T lymphocytes, however, have a similar effect. Cytotoxic lymphocytes recognize malignant cells through a significant decrease in the expression of the last major histocompatibility complex antigens. During contact with cancer cells, killer cells induce either Fas (tumor necrosis factor)–dependent apoptosis or nonspecific cell lysis through contamination with cytolytic granules containing perforin and granzyme B.[40,41]

This is a prevailing type of anticancer activity generated by substances of fungal origin, such as β-D-glucans and glycoprotein complexes. Biological activity of these substances depends on their solubility in water,[42] their molecular weight,[43] the degree of branching, and the presence of β-(1→6)-bonds along the main β-(1→3) chains.[44] Innate immune cells incorrectly recognize polysaccharides of the fungal cell as invasive clones of microorganisms, because this group of immunocytes has a whole class of receptors tuned to recognize a wide range of molecular fragments in cell walls. Substances such as glucans, mannans, and chitosans, which are the main hydrophilic components of the fungal cell wall, act as one of the so-called pathogen-associated molecular patterns for immune cells and complement a number of these cells' receptors (Toll-like receptors, dectin-1).[45] The immune system recognizes these fragments and is substantially activated.

Phagocytes such as macrophages and DCs express several types of C-type lectin receptors on their cell surfaces for capturing antigens. Dectin-1 is an example of a C-type lectin receptor that recognizes fungal β-glucan and is critical for its biological effects. β-glucans are carbohydrate polymers found primarily in fungal cell walls but also in plants and some bacteria. The dectin-1 agonist β-glucan acts as an adjuvant and an immunotherapeutic agent in treating a number of diseases.[45,46] Recent studies of mice suggest that β-glucans bind to dectin-1 on phagocytes and signal via Syk kinase independent of the Toll-like receptor pathway. They prime T_H17 responses.[47] A recent study found that DCs activated via dectin can convert T-regulatory cells to interleukin 17–producing cells.[48] They also prime and mount potent cytotoxic T-lymphocyte responses.[49]

In addition to provoking a direct immune response, activation of dectin-1 and its intermediates prevents the development of tolerogenic phenotypes of DCs and induces reproduction of immune phenotypes over a long period.[50]

B. Inhibition of Mitogenic Activity

Fungal metabolites had direct actions on experimental sets of cancer cells, showing that their ability to inhibit mitogenic activity can be associated with several important actions: 1) inhibition of protein kinases, the main generators of proliferative signals; 2) cell cycle arrest; and 3) violation of some circuits in the mitogen-activated protein kinase (MAPK) signaling cascade. The action of fungal benzoquinone metabolites was studied, showing the effect of clavilactones A, B, and D (produced by *Clitocybe clavipes*) on cancer cells and their pronounced ability to inhibit Ret/Ptc1, Abl-1, serine/threonine kinases, and, most important, the EGF receptor proliferative cascade.[51] Cell cycle arrest by fungal metabolites has mostly been studied in triterpenoids produced by *G. lucidum*; the effect of these metabolites leads to cell cycle arrest in the G_1/S[52,53] or G_2/M phase.[54] To date, 316 triterpenoids produced by *Ganoderma* species have been revealed, including ganoderic acids, lucidumols, and lucidodiols.[55] Their effects on the passage of cell cycle checkpoints are mediated through inhibition of Cdk2, CdkB, and CdkD1 and protein kinase C, and stimulation of the expression of the cyclin-dependent kinase gene (*p21*) inhibitor. The glycoside genistein, produced particularly by *Flammulina velutipes*, can also arrest the cell cycle.[56] In hepatocellular carcinoma cells, genistein regulates the activity of Cdk2 kinase and the cell cycle inhibitor p21, which leads to arrest in the G_2/M phase.[57] In cancer cells with intact tumor suppressor p53, ergosterol- and lanostane-containing extracts of *Fomitopsis pinicola* arrested the cell cycle in the G_1/S and G_2/M phases; the action of these extracts, however, is mediated by amounts of intracellular glutathione, which regulates p53 activity.[58]

MAPKs are unique integrators of signals from various receptor and nonreceptor tyrosine kinases, cytokine receptors, and transforming growth factor receptors. They are also key participants in the response to stress signals, depending on the cellular and intracellular contexts. Some oncogenic proteins (Ras, Raf) inevitably become involved in the MAPK cascade, which is why cells becomes substantially less sensitive to proapoptotic signals.[59] Molecular activation or inhibition involved in the MAPK signaling

network can lead to both increased proliferation and prolongation of the G_2 phase of the cell cycle. The greatest hope for violating the proliferative signaling pathways is associated with protein p38.[60] The effect of a triterpenoid fraction of *G. lucidum* mycelia was positively correlated with an arrest of growth (G_2 phase) of human hepatoma Huh-7 cells and with p38 expression.[61] In modulating the hyperactivation of mitogenic signaling pathways, bioactive complexes from *Inonotus linteus* can enhance the action of p38.[62] Panepophenanthrin (produced by *Panus lecomtei*) inhibits the epigenetic switch-off of the mitogen-activated cell tumor suppressor p27 and the avoidance of apoptosis associated with it.[63]

C. Blocking Neoangiogenesis

Bioactive complexes from MMs were studied to determine their antiangiogenic activity. The most active of these complexes were found in *Amyloporia xantha* and *Rigidoporus ulmarius*, and to a lesser degree in *G. lucidum*, *Taiwanofungus camphoratus*, and *A. murrilli*. The fucose and mannose fragments of polysaccharide complexes produced by these fungi supposedly bind to regulatory sites of VEGF and block its effect, triggering genetic angiogenesis.[64] Recall, however, that the reverse of angiogenesis blockage is the activation of cancer cells with a locomotor phenotype, which begin to extensively break away from the starving tumor.

D. Inhibition of Proinflammatory Cytokines and Apoptosis Blockers

Rudolf Virchow, the founder of cellular pathology, defined cancer as a chronically nonhealing wound. Data accumulated over the past decade indicate that, among immune cells, unconditioned cancer antagonists include only certain macrophage subpopulations, cytotoxic T lymphocytes, and NKCs, whereas other cellular participants in immune responses (such as neutrophils, mast cells, and even individual subpopulations of T and B lymphocytes) have diverse functions and, as a whole, are included in tumor progression. During the development of inflammatory responses, these cells propagate signaling molecules such as growth factors (EGF, VEGF, and FGF), chemokines and proinflammatory cytokines, and proteolytic enzymes that reduce tissue density (e.g., matrix metalloproteinases [MMPs]) and promote tumor invasion.[65–67]

In the development of mycotherapy, the role of the immune system in both cancer progression and tumor control requires fungal bioactive complexes to be profiled for both immunostimulatory and anti-inflammatory components.

The main proinflammatory factor fundamentally associated with cancer progression is the NF-κB chemokine, which blocks both JNK and p53-mediated apoptotic pathways. Erkel et al.[68] researched mushrooms such as *Lentinus crinitus* and some species of the genus *Panus* (*P. conchatus*, *P. lecomtei*) and found that they released the terpenoid panepoxidone, which prevents the degradation of inhibitory particles of NF-κB (IκBα) that inactivate this transcriptional factor.[68] Cyclopanepoxidone was isolated from the *Xylaria* 45-93 strain (an ascomycete),[69] and isopanepoxidone was isolated from *P. conchatus*[70]; both substances have a similar effect. In addition to panepoxidone and similar substances, a lipopolysaccharide isolated from *T. camphoratus* inhibited the degradation of inhibitory IκBα particles.[71,72] Mattilla et al.[73] showed that *L. edodes* fruiting bodies contain caffeic acid phenethyl ester, which inhibits NF-κB, even during binding with DNA. Caffeic acid phenethyl ester was detected later in extracts of *I. linteus*.[74]

E. Reduction of the Invasion Potential of Cancer Cells

The second important direction in restraining tumor promotion in the immune system is by inhibiting MMPs. Various cancer cells and granulocytes release zinc-containing endopeptidases that contribute to

the softening of the fibrillar and nonfibrillar connective tissue matrix, which significantly facilitates tumor invasion and metastasis. Polyporenic acid C and (E)-2-(4-hydroxy-3-methyl-2-butenyl)-hydroquinone isolated from the Basidiomycetes *Piptoporus betulinus* and *Daedalea dickinsii* showed inhibitory effects on collagenase in MMP-1, stromelysin in MMP-3, and gelatinase in MMP-9.[75–77]

F. Destruction of Vital Overexpressed Molecular Targets

A range of fungal metabolites manifest toxicity aimed at disabling basic cell survival systems; this cytotoxicity has the same limitations as chemotherapy: most of its targets are nonspecific for cancer. In some cases, however, the overexpression of some vital substances (RNA, cyclooxygenase [COX], and hydroquinones in hypoxic regions) by cancer tissue justifies their inhibition by fungal metabolites. In addition, some methods for targeting delivery of vital poisons while minimizing systemic toxicity have been developed in immunotherapy.

A fatty acid fraction of a hexane extract of *G. frondosa* mycelia (ergosterol, ergosta-4,6,8(14),22-tetraen-3-one,1-oleoyl-1-linoyl-3-palmitoglycerol) showed strong inhibitory activity against COX1 and COX2.[78] Bis-catechols of gerronemins A–F isolated from *Gerronema* sp. mycelia and lanostane triterpenoids from *P. betulinus*[79] have similar effects. Lanostane triterpenoids isolated from *Wolfiporia cocos* sclerotia inhibited DNA topoisomerases.[80] A triterpenoid component isolated from *Perenniporia fraxinea*, designated as fomitic acid, and triterpenoids 1, 2, and 3 from *G. lucidum* have shown inhibitory activity against DNA polymerases.[81,82]

Quinone bioreduction in hypoxic tumor regions leads to the formation of an intermediate half-quinone or hydroquinone. As a consequence, the covalent bond in quinone is metabolically stable, the effector quinone substance is released only in the hypoxic regions of tumors, and a desired large differential between the quinone effects is achieved. Lactases and peroxidases with soft action, isolated from culture medium of the fungus *Funalia trogii*, can oxidize semiquinone radicals, thereby reducing catabolic potential and enhancing the resorption of tumors, as was shown by Ünyayar et al.[83]

Special attention has recently been devoted to the cytotoxicity of ribonuclease (RNase) in relation to viruses and malignant tumors. A study of the action of fungal RNases showed that they can inhibit HIV-1 reverse transcriptase and have an antiproliferative effect on a number of cancer lines. RNases from such species as *Amanita hemibapha, Hygrophorus russula, Lactarius flavidus, Lyophyllum shimeji, Panellus serotinus, Ramaria formosa, Sch. commune, Thelephora ganbajun*, and *Tuber indicum* inhibited HIV-1 reverse transcriptase and cancers *in vitro*. Anticancer activity of RNase from *Cyclocybe cylindracea*, *L. flavidus*, *Pleurotus* spp., *Russula delica*, and *T. indicum* was observed when testing Hep G2 liver cancer cells. RNAses from *Calvatia caelata, L. shimeji, P. djamor, R. delica*, and *T. indicum* had inhibitory activity against MCF-7 breast cancer cells. Anticancer activity was noted for RNases from *Hypsizygus marmoreum* and *Pleurotus* species when testing L1210 leukemia in mice.[84]

RNA polymerase II was the target of the cyclic peptide α-amanitin, produced by *A. phalloides*, which Moldenhauer et al.[85] used as a vital poison. Amanitin binds the RNA polymerase II enzyme, blocking its work, which in turn terminates protein synthesis and destroys the cell. To avoid a systemic toxic effect, α-amanitin was delivered to cancer cells in an antibody-bound form. Epithelial cell adhesion marker (EpCAM), a protein expressed by many cancers and thus a tumor marker, was chosen as the binding object. Amanitin-conjugated antibody can carry 4 to 8 toxin molecules, delivering them to cells expressed on the surface of EpCAM. Despite possible errors (EpCAM is expressed by active cancer cells but not by "sleeping" cancer cells), the described effect is impressive: 2 injections of a high dose of amanitin-conjugated antibody led tumor regression in 90% of the tested animals.[85]

G. Oncoprevention and Palliative Therapy

In disseminated cancers, the main task is to provide palliative treatment, which reduces pain sensation and absorbs toxic products, circulating ligands, and mediators of cancer progression. Here, so-called xanthochroid polypores, particularly *I. obliquus* (chaga), are an indispensable raw material. Our previous publication provides a detailed review of the medicinal properties of *I. obliquus*.[86] Polyphenolic fragments with various molecular weights have the most sufficient effect on disseminated cancers. The use of *I. obliquus* extracts significantly improved both blood counts, which had been inhibited by the growth of metastases, and patients' overall well-being.[87]

These substances also have antioxidant and radical scavenging properties, which are important for preventing cancer. As cancer progresses, however, antioxidants and radical scavengers act in synergy with the cancer.[88]

IV. DISCUSSION AND CONCLUSIONS

In this article we outline how mycotherapy is effective in oncology. Such an emphasis is important to us because, on one hand, the traditional oncological triad can often oppose new immunotherapeutic approaches[89] and, on the other hand, new approaches (mycotherapy in particular) are subjected to nonconstructive criticism.[1]

We suppose that irreversible epigenomic changes in cancer cells, accompanied by their replicative immortality when no cancer-specific targets are available, should take away any illusions about the fundamental possibility of pharmacologically blocking—through immunotherapeutic and particularly mycotherapeutic means—the cancer process once ontogenesis begins. New developments such as monoclonal antibodies against specific antigens on tumor cells or against VEGF, and hybrid drugs consisting of antibodies (against tumor cells) and strong, cytostatic tyrosin kinase inhibitors, have considerably improved tumor therapies. We need an integrated system for preventing and treating oncological diseases; mushrooms and mushroom-derived compounds should be included in this system. In this context, we believe that effects of both traditional and alternative medicines on cancer clonogenic units within a particular range can lead to prolonged remission. In light of this, we carefully consider the possibilities for mycotherapeutic control of cancer activity.

The aforementioned range is limited to nondisseminated cancer processes, the absence of large secondary tumor nodes, and inexhaustible immune depots available after chemotherapeutic treatment. For example, a prospective immunotherapeutic approach using immune checkpoint inhibitors (i.e., receptor antagonists that keep the immune system from attacking cancer cells) successfully enhanced antitumor T-cell–mediated cytotoxicity.[90] After immune depots are depleted and bone marrow malfunctions, the last approach is to reboot immune control of the cancer process—namely, through xenotransplantation of bone marrow.[91]

The main therapeutic effect of fungal bioactive complexes is dectin-1–mediated immunity. This includes reprogramming DCs, which significantly increases the amount of time in which a tumor generates immune tolerance.[92–95]

An additional enactment can be considered an inhibitory effect of fungal bioactive complexes on some molecular mediators of proliferation signaling and proinflammatory (synergistic with cancer) immunity. Even more limiting is the effect of fungal bioactive complexes on vital targets of cancer cells, including overexpressed targets. Inhibition of processes and exposure to vital targets increases cellular stress and often provokes the neoplasm to retaliate after use of the treatment drug is suspended or discontinued. In this sense, mycotherapy is only one of the tools that can be used to balance remission. Palliative mycotherapy

is associated with polyphenolic composites, which contribute to detoxification, suppression of inflammation, and reductions in pain sensation.

ACKNOWLEDGMENTS

The work of I.V.Z. and M.A.B. was carried out in a framework according to State Task AAAA-A18-118031290108-6 of the Komarov Botanical Institute, Russian Academy of Sciences. The work of N.V.B. was carried out according to State Task AAAA-A18-118030190098-4 of the Komarov Botanical Institute, Russian Academy of Sciences.

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