Recreational Mushroom Therapy for Cancer Treatment – A Boon

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Abstract: Different types of diseases and infections have jeopardized the life of human beings over a centenary. However, one disease that is considered pernicious and has highest standard of recurrence is cancer. Cancer, a major pandemic disease in the world, though considerably lower in India is frequently reported to grow in an alarming rate. The type and advancement in cancer decides the type of treatment amongst which includes surgery, chemotherapy, radiation, immunotherapy, targeted therapy, hormone therapy, stem cell transplant and precision medicine. Apart from the above conventional methods of therapy, the traditional medicines practiced for thousands of years till date are also used in therapy. Mushrooms are powerful sources of nutritional attributes which appear to reduce risk of obesity, diabetes, heart diseases and overall mortality. Some treasured and edible mushrooms like button, oyster, shiitake, etc. with effective antineoplastic effect and their active compounds of immense clinical interest are studied. The Chinese doctor Wu Ri (also, known as Wu Shui), who lived at the era of the "Ming Dynasty" (1368–1644 CE) discovered that *Shiitake* mushroom had an antitumor effect. Mushrooms (*Shiitake, Maiitake, Reishi, Pleurotus,* etc.) and mushroom-derived substances (lentinans, polysaccharides, AHCC, etc.) are effective anticancer drugs. Some mushroom-derived polysaccharides possess direct cytotoxic effect on tumor growth while the others trigger strong immune responses. The extracts from these edible varieties of mushrooms appeared to have reduced the side effects of both chemotherapy and radiotherapy.

Keywords: Mushrooms; antineoplastic effect; extracts; polysaccharides; cytotoxic activity; apoptosis.

I. INTRODUCTION

Lifestyle has great influence in human health. Healthy and balanced lifestyle with sufficient nutritional attribute is vital for maintaining hormonal balance. Amongst 30% of all diagnosed cancers caused due to poor nutritional supplies can be cured by having healthy food rich with nutrition. Cancer is the second leading cause of death in the world next to cardiovascular diseases. Around 8.8 million people die globally due to this epidemic disease, in spite of the best treatments available. More than 100 different types of cancer with their symptoms have been identified. The recommended treatments like surgery, chemotherapy, radiotherapy, targeted cancer drug therapy, hormone replacement therapy, and nanotechnology are efficient but these options are very expensive and also have side effects (both long-term and short term).

II. NEED FOR A HOLISTIC DRUG PRODUCT

It is often mentioned that both emotional and physical side effects occur based on the types of cancer, its stages and the treatment given which may last for weeks, months or even years. For some people, there may be late or permanent side effects; one such is cancer recurrence and second cancers. Surgical removal of tumors results in sudden acceleration of metastatic process resulting in recurrence/secondary cancers. Targeted drug therapy, chemotherapy and radiotherapy are the conventional cancer treatment options practised to stop cancer cells from dividing rapidly but practise also causes collateral damage, which includes stimulating initiation of new and secondary cancers. However, cancer becoming a

bigger business and the conventional treatments becoming costlier, natural products with less toxicity and nil side effects are designed to treat cancer and prevent their recurrence. Thus, holistic medicine/drugs are designed to eliminate any possibility of second cancers. "Holistic medicine" refers to dealing with or treating the whole of something or someone and not just a part. In other words, medicine used in the treatment that deals with the whole person, not just the injury/disease.

About 3.5 million people worldwide have switched to a healthier lifestyle by opting dietary supplements/plant-based medicines for primary health care. Mushrooms are primary source of unique nutrients enjoyed by people from ancient era, rich in vitamins, minerals (selenium, ergothioneine, copper, and potassium), beta-glucans, and antioxidants to protect and enhance health. Once referred as delicacy of gods, forbidden to common people, valued as herbal tonic by ancient Chinese; considered plant of immortality by ancient Egyptians; natural healers by ancient Greeks and Roman; mushrooms are now considered the safest recreational drug.

The fossil records of the lower cretaceous time period shows the very existence of the mushrooms even before human beings. Mycophagy, which refers to the act of consuming mushrooms dates back to the Neolithic era (3350–3100 BC) (last period of Stone Age), when edible mushrooms were considered the functional foods. Then, slowly and steadily, functional foods of the people got upgraded to a medicine/tonic of life, more appropriately the holistic mushroom medicine.

III. MYCOTHERAPY

Mycotherapy deals with the use of extracts or compounds extracted from medicinal mushrooms in order to treat different diseases/disorders. Mycotherapy of cancer/tumor deals with the use anti-carcinogens, compounds or extracts from mushrooms. Bioactive compounds of mushrooms have emerged as efficient nutraceutical with immense medicinal values. Progressive consumption of mushroom extracts as nutritive supplements enhance immune function and anti-tumor activity. Different species in the genera of *Agaricus, Pleurotus, Flammulina, Ganoderma, Polyporus, Tricholoma, Lentinula, Poria*, etc. are of great potential due to their anti-microbial, antioxidant, cardiovascular disease preventive, liver protective, anti-fibrotic, anti-inflammatory, anti-cancer properties.

A. History of Medicinal Mushrooms

As mentioned earlier, the use of medicinal mushrooms dates backs to Neolithic and Palaeolithic era[1]. Approximately around 450 BCE, Hippocrates, a Greek physician categorized amadou mushrooms to be potent anti-inflammatory drugs and wound healers. Sheh Nong, who was believed to have taught the ancient Chinese their practices of agriculture, as well as the use of herbal drugs laid the foundation of traditional Chinese medicine. He discovered and classified some 365 species of herbs and medicinal plants and is often referred to as the 'God of Chinese Herbal Medicine'. Around the 2nd century AD, a book named *Sheh Nong Ben Cao Jing (The Divine Farmer's Materia Medica/The Herbal Classic of the Divine Farmer*), charted some superior herbs (Fu Ling (*Poria cocos*), Yun Zhi (*Coriolus versicolor*), Ling Zhi (*Ganoderma lucidum*) and Bai Mu Er (*Tremella fuciformis*)) having excellent therapeutic action with few or no side effect. These may be safely taken for long periods and prolonged usage lightens the body and confers longevity. One the oldest human mummy, dating back 4000–5000 years ago, carried mushroom (*Piptoporus betulinus*) in his medicine kit for it is an natural antibiotic and a parasite killer. Mushrooms like reishi, cordyceps, agaricus, maiitake, phellinus, trametes, shiitake, and hericum are some which work on tumors as an anti-cancer agent in its own specific way. Yang *et al.* reported that mushrooms are biological response modifiers promoting and eliminating positive and negative factors, respectively[2]. Hence it is regarded the fourth principle form of the conventional cancer treatment.

B. Why Mycotherapy?

Cancer treatment has become a trade with the prevalence of this vulnerable disease which affects the children, teenagers and aged population each day. World Health Organization reported five lakh annual deaths due to cancer which rose to seven lakh by 2015 and was projected to rise five-fold by 2025. A research on "the economic burden of cancer on Indian households" concluded the average expenditure on treatment (drugs, chemotherapy, radiations) in a cancer-affected home was 36–44% more compared to other houses with relevant population[3]. In the past 10–15 years, the treatment costs had a radical difference that it will shoot out of reach for millions of Indians. Millions of people even spend their entire life savings on it and yet suffer side effects (recurrence/second cancers).

Anticancer drug prices goes up from Rs. 8,000–1.08 lakh per course; chemotherapy, hormonal drug therapy can cost anything from Rs. 10,000–4 lakh per cycle depending on the drugs used and the duration of treatment. Cost of radiation is comparatively low, package from 1 lakh to around 2.5 lakh. Apart from the conventional treatments, some unnecessary screening and over-screening processes adds up to the expenditure. With increasing expenditure, the population tends to switch to a cheaper treatment though being a long-term process. Thus, after years of experiments in conventional treatment, researchers having regained interest in the age-old mushroom therapy.

C. Decline in conventional cancer therapy

Cancer treatment has become a business these days. Conventional cancer treatment have been declined by cancer patients since the early 1980s and replaced with complementary and alternative medicine (CAM)[4]. During 1991–2002, Verhoef and white customized a qualitative analysis on 31 cancer subjects, suspended all predominant cancer treatments and used CAM[5]. Infinite inclinations reported for CAM usage is in accordance inclusive of all the pessimistic experience with the dominant mainstream medicine, death of family members or friends to cancer.

Factors influencing the criteria of decline in treatment after diagnosis include poor doctor-patient communication; emotive effects after diagnosis; anticipated rigorous side effects of predominant treatments; and of all are the increasing medical cost and hidden costs. Cancer patients from below poverty line, commoners often delay or skip the prescribed drugs/treatment because it is way too expensive. Journal "The Oncologist" once mentioned in the year 2013 that one-quarter of cancer patients either chose not to fill in their respective prescriptions or to only fill a part of a prescription due to cost issues. As per "Express Scripts", a pharmacy benefits manager, the list prices of cancer drugs (oral) spiked from 2011 to 2016. Of the 39 most commonly used oral drugs in the market in 2010, some prices have been tripled, quadrupled or even increased eight-fold by the end of 2015.

The American Cancer Society acknowledged that the conventional cancer treatments like chemotherapy and radiation actually promotes cancer. Chemotherapy and radiation are carcinogens and may enhance the risk for developing a second cancer. The risk is even surpassing when both the treatments are given simultaneously. Secondary malignancies are caused even after treatment with radiation or chemotherapy. These are totally unrelated to the first cancer that was treated and may occur even years after the initial cancer treatment. Etoposide, a chemotherapeutic drug; radiation therapy for lymphomas and leukaemia or treatment with both chemo and radiation together prominently intensifies secondary cancers.

Shaked Yuval once said "chemotherapy creates the effect of a double-edged sword, i.e. although chemotherapy kills cancer cells, it also causes the secretion of substances that confer resistance to the tumor". Alkylating agents such as mechlorethamine, chlorambucil, cyclophosphamide, melphalan, lomustine, carmustine, busulfan, and ethylenimines (thiotepa) are chemo drugs that has its effect on cancer cells during every phase of its life cycle, but these agents also cause secondary cancers, most commonly, acute myeloid leukemia (AML). Radioactive exposure surely causes chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), Hodgkin lymphoma and many more kinds of leukemia. The effect of radiation on the risk of developing a solid tumor cancer depends on factors such as:

- ➤ the dose of radiation (dose-volume dependences),
- \triangleright genetics,
- ➤ the area treated (tissue and organ dependences) and
- > the age of the patient when they were treated with radiation.

Generally, the risk of developing a solid tumor after radiation therapy goes up as the dose of radiation increases considerably. Organs such as the breast and thyroid, seems more likely to develop cancer after radiation than others. IMRT, VMAT, proton radiotherapy led to extreme uncertainties regarding second cancer risks in patients treated radiotherapy.

IV. CURRENT SCENARIO

Screening of mushroom extracts for anticancer activity is the current situation by NCI. Ikekawa *et al.* published in one of the reports the antitumor activity of mushroom extracts against Sacroma 180 in animals[6]. Not long after the discovery in 1969, three major anticancer drugs, krestin, lentinan and schizophyllan from cultured mycelium of *Trametes (Coriolus*)

versicolor), fruiting bodies of *Lentinus edodus* and *Schizophyllum commune*, respectively were developed[7–9]. In the past two-to-three decades, several scientific studies were carried out in Japan, China and Korea; and recently in USA and India using compounds and extracts of medicinal mushrooms. There are many pharmaceutical and healthcare centres namely Zhejiang Fangge Pharmaceutical and Healthcare Products Co. Ltd., FineCo Ltd., Aloha medicinal Inc., Hanmi Science Co. Ltd., etc. These companies specialize in development of effective mushroom drugs (anticancer formulation), array of mushroom products including the cancer-inhibiting activity. *Ganoderma lucidum, Phellinus rimosus, Pleurotus florida* and *Pleurotus pulmonaris* are medicinal mushrooms in South India with profound antioxidant and antitumor activities.

Figure 1 below shows the medicinal usage of mushrooms increasing in the past years.





V. MUSHROOMS IN CANCER THERAPY: MUSHROOM EXTRACTS

Polysaccharides from mushrooms are acknowledged as "biological response modifiers"—substances that activate the body's immune response. Pharmaceutical-grade polysaccharides have been introduced as adjuvants alongside standard cancer treatments, i.e., surgery, radio- and chemotherapy. Fungal β -glucans which includes lentinan, grifolan, GL-1, polysaccharide peptides (PSP and PSK), glycan (ganoderans A, B and C), proteoglycans, triterpenes, triterpenoids, and flavonoids are the most important anticancer compounds in mushrooms.

Apart from supporting the immune system and suppressing the chemotherapy-induced immune response, there are evidences that these mushroom polysaccharide extracts contribute to the efficacy of the chemotherapeutic drugs themselves through enhanced production of reactive oxygen species (ROS). Some genetically modified mushroom products namely, lentinan, schizophyllan/sizofiran/sonifilan, krestin (polysaccharide-k), GanoPoly, astragalan, GCS-100 and PectaSol which exhibits potential anti-cancer/anti-tumor activity with low toxicity.

A. Clinical trials

Problems of treating human cancers are still far from being solved. Between 30–40% of cancers can be currently be prevented by avoiding risk factors and implementing existing evidence-based prevention strategies. Early detection of cancer and management of patients developing cancer are ways to reduce the burden of cancer. Chances of curing cancer increases by every single percentage when diagnosed early and treated adequately. Besides tens of thousands cell cultures and animal studies, anti-cancer effects of medicinal mushrooms have been observed in human studies, including clinical trials. Official anti-cancer drugs from mushrooms include PSK (Krestin; since 1977), Lentinan (1985) and SPG (Sonifilan, 1986) in Japan and PSP (1983) in China. Many clinical trials also examined the simultaneous use of these drugs with various chemotherapy and radiotherapy, for many types of cancer. Clinical studies have shown that the extracts/active compounds from medicinal mushrooms work best when combined with surgery, chemotherapy, and radiotherapy. In fact, adding medicinal mushroom drugs to conventional treatment greatly improves the outcome and tolerance to invasive treatments.

Table 1 shows the potential anti-cancer compounds in mushrooms (high-molecular weight compounds: polysaccharide, protein-binding polysaccharide PSK and polysaccharide-P PSP; low molecular weight compounds: mushroom-derived terpenes and enzymes) which inhibit the growth of cancer cell lines/tissues by stimulating immune response namely T-cell infiltrations in the cancer tissue.

Potential compounds High-molecular	anti-cancer Low- molecular	Mushroom	Cell-line studies (inhibits the growth of/suppress)	Epidemiolog -ical studies (inhibits the growth of/suppress)	Method of delivery	Country
Lentinan	_	Shiitake mushrooms (Lentinus edodes)		Gastric cancer patients	IV/oral, combined administration with chemotherapy.	Japan
	D- fraction/M D-fraction	Grifola frondosa		Lung cancer, liver cancer patients, pancreatic cancer, and breast cancer patients	Oral/IV	China and Japan
Polysaccharides		Agaricus blazei	Lung and ovarian cancers and breast			China and Japan
Polysaccharides	Lectins	Agracius bisporus	Colon, breast and prostate			United States
Krestin (PSK)		Trametes versicolor		Lung, breast, gastric, colorectal cancer cases	Oral, oral+chemo/rad iotherapy	Japan
PSP		Trametes versicolor		Lung	Oral+radiothera py	
Functional protein (PCP- 3A)		P. citrinopleatus, P. sajor-caju	U-937, human leukemia cells			
Polysaccharides		P. geesteranus	Human breast cancer cell line MCF-7			
Hot water and ethanol extracts from fruiting bodies		P. ferulae	Lung carcinoma (A549) and cervical carcinomas (SiHa and HeLa)			
Sizofiran/SPG		Schizophyllan commune		Cervical cancer patients	Oral/IV + radiotherapy	Japan

TABLE 1: Potential anti-cancer mushroom compounds and their trials

Lentinan was first isolated from *Shiitake* mushrooms (*Lentinus edodes*) in 1970s. β -glucans like lentinan inhibits sarcoma 180 and leads to its complete regression. Ever since 1985, lentinan is an official anti-cancer drug (stomach cancer) in Japan delivered via injection or is made orally available. Meta-analysis of five clinical trials with 650 participants showed that the addition of lentinan (2 mg/week) to standard chemotherapy offers greater advantage over treatment involving chemotherapy alone in terms of survival rate of advanced gastric cancer patients. Here, patients with lymph node metastasis showed better results compared to non-lymph node metastasis. Other additional trials confirm increase survival

rate, reduced side effects from chemotherapy and improved quality of life and patients with colorectal, hepatocellular, breast and metastatic prostate cancer. Lentinan extended the survival and reduced the incidence of adverse effects in inoperable or recurrent gastric cancer patients in combination with tegafur as well as S-1-based chemotherapy (gimeracil and oteracil).

D-fraction/MD-fraction from *Grifola frondosa* is a popular anticancer mushroom drug in Japan and China. A nonrandomized study of 165 patients with stage III and stage IV cancers who were administered MD-fraction with Maitake fruiting bodies exhibited tumor regression/significant symptomatic improvement in 66% of lung cancer patients, 54% of liver cancer patients, 56% of pancreatic cancer patients, and 74% breast cancer patients. Combination of MD-fraction and whole Maitake fruiting body powder showed similar results: tumor regression in 58.3% of liver cancer patients, 68.8% of breast cancer patients, and 62.5% of lung cancer patients[10].

Polysaccharide extracts from *Agaricus blazei* showed strong *in vivo* and *in vitro* activities against some cancer cell lines; namely, lung and ovarian cancers. Mizuno reported positive clinical results in a number of breast cancer patients at unspecified dosage while Ahn reported increased NK-cell activity and reduced chemotherapy-related side effects. A study from 2008 confirmed that NK-cell activity increased in patients administered with *A. blazei* polysaccharide extract of dosage 3 g/day[11].

In 1977, oral administration of the extract krestin (PSK) from *Trametes versicolor* mycelium is registered as a drug for treating several types of cancer (digestive, lung, and breast) in Japan. A disease-free survival for five whole years in colorectal cancer cases were significantly higher with PSK and oral tegafur/uracil (UFT) than with UFT alone (73% vs. 58.8%) and increased survival rate (73.0% vs. 60.0%) in gastric cancer with given along with mitomycin and fluoracil. Enhanced oral administration of *T. versicolor* extract PSP with radiotherapy remarkably increased the percentage of apoptotic cells at 24 h compared to radiation alone and reduced radiotherapy induced reduction in WBC count. In a clinical trial with 136 patients undergoing radiotherapy, oral intake of *T. fuciformis* polysaccharide extract (3 g/day) resulted in reduction of WBC count (13.2%) compared to the control group and mycelial biomass of *T. versicolor* (6 g/day) prevented reduction in RBC and WBC count in lung cancer patients undergoing radiotherapy.

Polysaccharide extracts from *A. subrufescens* reduced chemotherapy-related side effects such as appetite, alopecia, emotional stability and general weakness in 100 cervical, ovarian, and endometrial cancer patients treated either with carboplatin plus VP16 (etoposide) or with carboplatin plus taxol.

Polysaccharide fraction from *Grifola frondosa* potentiated the action of carmustine and increased efficacy when given in combination with chemotherapy across a range of cancers, as well as reduced cisplatin-induced nephrotoxicity. Grifron-D, a polysaccharide extract from *G. frondosa* has direct cytotoxic effect on cancer cells through the oxidative membrane damage leading to apoptosis.

Polysaccharides extracted from sclerotia and mycelia of *P. tuber-regium* exhibited anti-tumor effect on different cancer cells[12]. Water soluble proteoglycan fraction isolated from mycelia of oyster mushroom (*P. ostreatus*) exhibited immunomodulatory functions and also displayed effective anti-cancer activity[13]. Functional protein (PCP-3A), a glycoprotein isolated from golden oyster mushroom exhibited anti-proliferative effect against U-937, human leukemia cells[14]. Ubiquinone-9 extracted from *P. sajor-caju* induced apoptosis of cancer cells (human leukemia cells, U937) by inhibiting the activity of topoisomerase-I[15]. Polysaccharides from the hot water extracts of *P. geesteranus* caused cytotoxic effect in human breast cancer cell line MCF-7. Choi *et al.* investigated hot water and ethanol extracts from fruiting bodies of *P. ferulae* which exerted positive effect on solid carcinomas—lung carcinoma (A549) and cervical carcinomas (SiHa and HeLa). Ethanol extracts had higher anti-tumor activity towards lung cancer cells (A549)[16].

Sizofiran/SPG from *Schizophyllan commune* culture medium came to use in Japan since 1986 for treating cervical cancer. Corresponding relation between infiltration of Langerhans cells (ILC) in tumor tissues and the radiation curability were studied in 449 patients with cervical cancer having radiotherapy alone, among them 390 had squamous cell carcinoma and 59 had adenocarcinoma. Sizofiran elevated ILC which in turn was associated to T-cell infiltration in tumor tissues[17].

VI. RESULT

Conventional cancer treatments like chemotherapy and radiation actually promotes cancer and are also carcinogens that may enhance the risk for developing a second cancer. Since the risk is even surpassing when both the treatments are given simultaneously, mushroom-derived extracts causing programmed cell death (PCD) of cancer cell lines by inducing signal

transfer, enhancing immune response and reducing proliferation of cancer cells. With increased economic burden, consuming effective anti-cancer mushroom drugs commonly found in India (prepared from *Ganoderma lucidum*, *Phellinus rimosus*, *Pleurotus florida* and *Pleurotus pulmonaris*) would be a boon.

A. Mushroom extracts and their properties

Immunodeficiency diseases like tumors/cancers are overcome naturally by stimulating/modulating the immune response. About 30 different species of mushrooms (edible/medicinal) are labeled as antecedents of biologically active metabolites with promising anti-cancer properties. Bioactive principles in the extracts are complex fraction of substances isolated/purified from medicinal/edible mushrooms. Cytotoxic mechanisms of different mushroom extracts against various carcinoma cell lines are studied[18]. Hence, mushrooms complement conventional cancer treatments like chemotherapy and radiation therapy. Some biologically active metabolites/compounds i.e., lentinan, hispolon, theanine, illudin-S, psilobycin, ganoderic acid, cordycepin, grifolin and antroquinonol bestows anti-cancer property. Polysaccharides, various polysaccharide–peptide/protein complexes, terpenoids, sterols, lectins, etc. are a few constituents of complex fractions of the mushroom extracts which attributes to cancer preventive activities.

Amongst these bioactive principle constituents, polysaccharides (α -, β -glucans) are of immense importance/interest due to their immunomodulatory activity; also shows direct anti-cancer effects and prevent tumor metastasis. Lentinans, schizophyllan, ganoderan and grifolan are specific β -glucan polysaccharides which induces activation and modification of haematopoietic stem cells (HSCs), complement pathways, immune cells like macrophages, dendritic cells (DCs), natural killer cells (NK), T_h and T_c cells, and B cells. Proteins contribute 10%–40% of mushroom dry weight. Lectins (specialized lectins, i.e., ABL) are protein constituents that recognize cancer cells and prevent the cells from proliferating. Polysaccharide–peptide/protein complexes namely proteoglycan polysaccharide peptide (PSP), polysaccharide–krestin (PSK), *Ganoderma* polysaccharide peptide (GPP), fungal immunomodulatory proteins (FIMs), glucan–protein complexes and many more complexes exerted the highest tumor inhibition properties.

Phenolic extracts (gallic acid, protocatechuic acid, vanillic acid, caffeic acid, catechin, epicatechin, cinnamic acid, abscisic acid, coumaric acid, ferulic acid, benzoic acid, etc.) from mushrooms act as antioxidants which play an important role in cancer prevention by neutralizing free radicals. Hispolon, an active polyphenol component possess anti-neoplastic effect and enhances the potential cytotoxicity of chemotherapeutic agents.

Apart from all these, selenium, a mineral present in mushrooms detoxifies cancer causing compounds in body by regulating enzyme functions in liver. It is an anti-inflammatory agent, and reduces the size of tumor cells. Vitamin D inhibits growth of cancer cells by regulating the cell growth cycle. Folate obtained from mushroom regulates DNA synthesis and repair, hindering the growth of cancer cells formed by mutation of DNA. Thus, the bioactive components in mushroom extracts describe their role as complementary medicines in conventional cancer therapy.

VII. CONCLUSION

There is *n*-number of clinical trials done to prove positive effect of medicinal mushrooms and the mushroom-derived products/supplements on various cancer types. Updated synoptic information on medicinal mushrooms posed many propitious therapeutic properties. Studies to date have analyzed a number of active compounds/principles/metabolites and exemplified underlying mechanisms which includes combination with chemo and radiotherapy, induction of signal transduction pathways, enhancing immune response, reducing tumor proliferation, finally causing PCD (apoptosis) of cancer cell lines. Since the effect of medicinal mushrooms and their supplements on various cancer types were positive, mushroom studies with *Pleurotus sp.* will result in positive trial in future.

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