REVISÃO

Pharmacological effects of Agaricales fungi: a review of evidence

Efeitos farmacológicos dos fungos Agaricales: uma revisão de evidência

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ABSTRACT

Supplementary quantities of edible mushrooms can be used not only as a simple implement of nitrogen substrate, but also as aids in the treatment of cancer, given its pharmacological effects, especially the fungi from the Agaricales order. The aim of this study was to evaluate the pharmacological effects of fungi Agaricales in cancer patients through a systematical and critical review of literature using the following databases: Medline, Database, Nacional Center of Biotechnology Information, Lilacs and Cochrane. The use of medicinal mushrooms may consist in a new therapeutic approach for cancer treatment although clinical controlled and randomized trials are needed to establish the criteria of using them in cancer patients.

Indexing terms: *Agaricus. Neoplasms. Supplementary feeding.*

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RESUMO

Quantidades suplementares de cogumelos comestíveis podem ser usadas não somente como simples implemento de substrato nitrogenado, mas também como auxiliares no tratamento do câncer, devido a seus efeitos farmacológicos, especialmente os dos fungos da ordem Agaricales. O objetivo deste trabalho foi avaliar os efeitos farmacológicos de fungos Agaricales em pacientes com câncer, a partir de uma revisão sistemática e crítica da literatura, usando as seguintes bases de dados: *Medline*, *Database*, *Nacional Center of Biotechnology Information*, Lilacs e *Cochrane*. O uso de cogumelos comestíveis pode consistir em uma nova possibilidade terapêutica para o tratamento do câncer, embora sejam necessários estudos clínicos controlados e triagens randomizadas adicionais para estabelecer os critérios de uso em pacientes com câncer.

Termos de indexação: Agaricus. Neoplasias. Suplementação nutricional.

INTRODUCTION

Many cultures all over the world utilize the hot water decoctions from certain mushrooms, due to their recognized medicinal properties. In China and Japan, many of these fungi extracts became important ingredients in traditional medicine[1].

Reports and observations referring to empirical treatments with edible fungi of Agaricales order and other ones belonging to Hymenomycetes class has been attracting the attention of the researchers. Since 1980, effects of active substances of various species of fungi have been investigated *in vitro* and *in vivo* and in clinical trials *in anima nobile*, presenting promising results[2].

Nutritional properties of these medicinal mushrooms are already established, although Agaricales fungi have pharmacological effects that can improve life quality and cancer patients outcome, so these effects have to be detailed studied to establish the criteria of using them as an adjuvant of cancer treatment[2,3].

Agaricales used empirically as nutritional supplement for the treatment of cancer and other diseases with successful results have been related. *Lentinus edodes, Grifola frondosa, A. blazei* and *A. sylvaticus*, known in Brazil as Cogumelo do Sol®, are mushrooms belonging to Agaricales family which are known for their therapeutic properties[4].

Other species of fungi belonging to Basidiomycetes class but not to Agaricales family are also used because of medicinal properties, such as: *Ganoderma lucidum* (Amphyllophorales family), known in Brazil as king mushroom and in China as Ling Zhi and *Auricularia auricular-jude* (Auriculariaceae). Inside the Ascomycete order, the *Cordyceps sinens* species is the most important one considering its therapeutical effects[2].

Representatives of the genus Agaricus have been shown to contain polysaccharides and glucoproteins, steroids, riboglucans conditioning high antitumor, antimutagenic, bactericidal, antiangiogenic activities and ability to enhance immune system[4].

Nutraceutical fungi are being slowly incorporated to western medicine. They are legally sold in Japan as dietary supplementation as: Krestin® a polysaccharide peptide extracted from *Trametes* (or *Coriolus* or *Polyporus*) *versicolor* (Basidiomycete, Amphyllophorales order, Coriolaceae family) known as Kawaratake, Yun Zhi or Turkey tail; Schizophyllan® (PolyC), from the fungus *Schizophyllum commune* (Agaricales order, Schyzophylaceae family), also known as Suehirotake[5] and Lentinan®, extracted from Shiitake[6]. All of these products are commercialized in Japan as medicament with primary indication for cancer treatment: Krestin® for breast, digestive and lung cancer treatments; Schizophyllan® for cervical

cancer treatment and Lentinan® for gastric cancer treatment[6,7].

The aim of this study is to evaluate the nutritional activities and pharmacological effects of nutrients present in Agaricales mushrooms. In the present study, a systematic and critical review of the literature was made using the following data bases: Medline, Database, National Center for Biotechnology Information, Lilacs and Cochrane.

Biology of agaricales with medicinal properties

The taxonomic route of Agaricales order is: Eucariota (super-kingdom), fungi (Kingdom) Metazoa (group), Basidiomycota (phylum), Hymenomycetes (class), Homobasidiomycetes (sub-class) and Agaricales (order). Agaricaceae is a family belonging to Agaricales order which has a great number of important species[3].

Agaricales are considered cosmopolitan fungi. They grow easily in a wide variety of habitats, from the Artic to the Tropics. While some are strict to specific areas, others grow in geographically separated areas. Chemical substances existing in mushrooms may change according to soil and climate conditions of the region they are cultivated[3].

The knowledge of Agaricales morphology is of fundamental importance for the taxonomy of these basidiomycetes and the understanding of physiological and phylogenetic aspects. Morphology is studied in four degrees: macroscopic, microscopic, ultra structural and molecular biology[8]. Macro and microscopic morphological characteristics are the first parameters used for species classification, while ultra structural and molecular biology have been used for phylogenetics. The use of genetic analyses of DNA contributes to the taxonomic classification of Agaricales fungi[9].

The cellular walls of mycelia and fruiting bodies are important sources of beta-glucans, having a stratified structure composed of a fiber layer, proteins, beta-glucans, associated to chitin beta-glucans protein and plasmatic membrane[8].

Clinical trials

Studies concerning the anti-neoplastic effects of Agaricales fungi in induced tumors in animals, have evaluated the imunomodulator role in cells genetically altered, the cytostatic effect in tumor growth and the effect of vascular proliferation induced by tumors.

Although the results of clinical trials have not been consensual, most studies suggest that these fungi have favorable effects in cancer treatment (Chart 1). Several effects such as immunomodulation enhancement, reduction of tumor growth by cytostatic effect, and the inhibition of tumor vascularization are due to the different mechanisms of action of Agaricales fungi.

Estrogen production *in situ* is the main factor of breast cancer in postmenopausal women. Aromatase/estrogen synthesize is a P_{450} enzyme complex that converts androgens into estrogens. Aromatase activity occurs in tumors and may play a more dominant role in cell proliferation than in circulating estradiol. Enzyme kinetics has demonstrated mixed inhibition, suggesting the presence of multiple inhibitors or more than one inhibitory mechanism. Aromatase activity and cell proliferation were measured using MCF-7aro, and aromatase-transfected tested in breast cancer cell line. Phytochemical compounds in the mushroom aqueous extract inhibited aromatase activity and proliferation of MCF-7aro cells. These results suggest that ingestion of mushrooms may regulate aromatase activity and chemoprevention in post menopausal women by reducing *in situ* production of estrogen[10].

A clinical research was conducted with 56 patients, all were at a middle-late stage cancer. Patients were treated with chemotherapy and radiotherapy. Among them, 30 were in the experimental group and 26 in the comparison group. In the experimental group patients were treated with polysaccharides tablets 3 times/day, 4 tablets each time (total 6g/day) starting one week before chemotherapy and radiotherapy. Comparison group patients were treated with Polyactin-A (polysaccharide isolated from hemolytic *Streptococcus alpha* culture)

Chart 1. Clinical trials.

Reference	Mushroom specie	Substance	Dosage	Tumor	Results
Grube et al.[10] 2001	*Agaricus bisporus*	White fruiting bodies	2.5, 5 or 10μL liophylized extract solubilized in culture media ($10X_{CM}$)/mL de células (5mL/well)	Breast cancer	Suppression of aromatase activity *in situ* in a dose dependent manner; Inhibition of HCF-7aro cells proliferation.
Ruwei et al.[11]2001	*Agaricus blazei; Lentinus edodes; Grifola frondosa; Ganoderma lucidum; Coriolus versicolor; Cordyceps sinensis mycelium.*	Polysaccharides mixture of 6 medicinal mushrooms in tablets with de 500mg; Polyactin-A.	4 tablets each time, 3 times a day (total 6g/dia) of mushrooms mixture; 10mg, each time of Polyactin-A, 3 times daily (total 3mg/ day)*This treatment lasted two mouths	Gastric carcinoma, hepatic carcinoma, lung carcinoma, large intestines carcinoma, naso-pharingeal carcinoma	Little changes in digestive tract reaction after chemotherapy or radiotherapy in patients of control group and in this group the enhancement of total number of white blood cells was less expressive than in the patients of experimental group. Non specific immunity increased after treatment. The increase in IgA secretion and improvement of NK cells and monocytes activity were also observed.
Fortes et al.[13] 2007	*Agaricus sylvatcius*	Aqueous extract of *Agaricus sylvatcius*	30mg/kg/day for six months	patients with colorectal cancer during post-surgery phase	increase of adhesion to physical activity; improved disposition and good mood, reduction of complaints, pains, and alterations of sleep such as insomnia and bad nights of sleep when *Agaricus sylvaticus* and placebo groups were compared.
See et al.[27] 2001	*Agaricus blazei* Murill	1) *Agaricus blazei* Murill tea 2) Transfer Factor Plus 3) IMUPlus 4) intravenous and oral ascorbic acid 5) Imunomudualor Mix, nitrogenated soy extract and *Andrographis Paniculata*	1)10mg/dia 2) 3 tablets 3 times daily 3) 40mg/day 4) 50 a 100gm/day) intravenous e 1-2mg/day orally 5) 500mg twice a day	1 Urinary blader , 5 breast, 2 prostate, 1 neuroblastoma, 2 lung, 3 colon, 1 mesotelioma, 2 limphomas, 1 ovary, 1 gastric and 1 osteosarcoma	Enhancement of NK cells function and other immunological parameters and hemoglobin of PBMC or plasma in late stage cancer patients.
Hui et al.[12] 1988	*Agaricus blazei*	Aqueous extract of *Agaricus blazei* (supplemented by Iwakin Co., Ltd. Laboratory of Japan)	20g of *A. blazei* twice daily for 3 mounths	Non-lymphocytic Leukemia	Cellular rates of bone marrow recovered to normal levels within 7-8 days after chemoterapy. IgM quantity of test group increased while IgG and IgA levels presented no changes in test group. Psychological condition and appetite increased in patients of test group and 6 pacientes of this same group had infections against 13 of control group.
Jing et al.[29] 1988	*Agaricus blazei*	*Agaricus blazei* solubilized in water	20g of *A. blazei* solubilized in water during 3 mouths	Digestive tract carcinoma	Fatigue, anorexia, discomfort and nausea reduced gradually in test group while no changes or an aggravation were observed in control group. After 3 months hematological analyses of test group improved qualitatively. The quantity of IgG did not alter but the IgM and IgE quantities increased in test group

30mg/day, starting a week before radiotherapy and chemotherapy. After 2 months, the comparison group had little change in the reaction of the digestive tract and had decreased the number of blood white cells when compared to the experimental group. The researchers concluded that polysaccharides can alleviate toxic reactions caused by conventional therapies, improve nonspecific immunity and secretion of IgA, stimulate macrophages and monocytes function, increase cellular immunity (natural killer cells, LAK cells and Th/Ts cells) presenting better immunomodulating effects when compared to Polyactin-A[11].

Another clinical study evaluated the effects of *A. blazei* in 20 patients with acute nonlymphocytic leukemia which were divided in two groups. The experimental group was treated with *A. blazei* (20g, 3 times daily) and the comparison group received placebo. All of them were being treated with chemotherapy. Tumors were in remission and the ratio of erythrocytes and granulocytes recovered to normal levels within 7-8 days in the experimental group when compared to the placebo group[12].

Clinical study evaluated the effects of the dietary supplementation with *Agaricus sylvaticus* fungus in relation to the quality of life in 56 patients with colorectal with gastrointestinal cancer during post-surgery phase. The patients were treated in the randomized study separated as placebo and *Agaricus sylvaticus* (30mg/kg/day) supplemented groups. After six months of treatment, it was observed an increase of adhesion to physical activity; improved disposition and good mood, reduction of complaints, pains, and alterations of sleep such as insomnia and bad nights of sleep when *Agaricus sylvaticus* and placebo groups were compared[13].

Mushrooms's substances with pharmacological effects

Ergosterol

Ergosterol or provitamin D2 is found in lipid fraction of Agaricales extracts and is an important substrate in biosynthesis of vitamin D.

Takaku et al. observed that when rats with Sarcoma 180 were treated with lipid fraction extracted from *A. blazei,* tumoral growth was delayed, although side effects such as decrease of thymus, spleen and in the number of lymphocytes which commonly occur as a consequence of chemotherapy were not noticed. The active substance responsible for these effects is believed to be ergosterol, whose substance has no direct cytotoxic effect on cancer cells of sarcoma 180 *in vitro*, though it can inhibit neovascularization induced by tumor[14].

In vivo studies were made about the action of ergosterol in cells of Lewis Hepatic Carcinoma (LHC) lineage. The administration of ergosterol in the peritoneal cavity inhibited neovascularization induced by tumor, suggesting that either ergosterol or its metabolites might be involved in this action[14].

Ergosterol peroxide can also be found in species of mushrooms and this compound is able to induce apoptosis. Takei et al.[15] observed that ergosterol peroxide inhibited the growth of HL60 human leukemia cells by induction of apoptosis. This substance can also be beneficial to the cancer treatment.

Lectin

Lectins are found in lipid fraction of Agaricales extracts. Phospholipids are found in all living organisms. In animals it is an important constituent of nervous tissues and the brain. It is generally synthesized by an association of stearic, palmitic or oleic acids linked to colinic ester of phosphoric acid. Lectin acid contains palmitic, estearic, palmitoleic, oleic, linolenic, linoleic and aracdonic acids, besides 20 to 22 other fat acids.

Some mushroom's lectins have antiproliferative, antitumor and immunoenhancing activity[16]. Antitumoral effects of fat acids in lipid fraction of Agaricales fungi have already been described in the scientific literature[17]. Some authors attribute this action to oleic acid[18]. According to Kimura, the inhibitory action of oleic acid in the growth of LHC

tumors may be due to angiogenesis inhibition induced by tumor[18].

Fungal lectins presented antitumoral activity *in vitro* and *in vivo*. *Volvariella volvacea* lectin show antitumor activity against sarcoma S-180 cells, *Grifolla frondosa* lectin is citotoxic to HeLa cells, *Agaricus bisporus* lectins possesses antiproliferative activity against colon cancer cell line HT29 and the breast cancer cell line MCF-7 and *Tricholoma mongolicum* lectin inhibits mouse mastocytoma P815 cells *in vitro* and sarcoma S-180 cells *in vivo*[19]. The antiproliferative activity of this substance can also be useful to the treatment of psoriasis[7].

Terpenes

The classification of terpenes is made according to the number of isoprene units in: hemiterpenoides, C5; monoterpenoides, C10; sesquiterpenoides, C15; diterpenoides, C20; triterpenoides, C30 and carotenoides, C40[20].

In vegetables, the function of terpenoides is related to antitumoral action in Agaricales fungi. Monoterpenes, diterpenes, sesquiterpenes have many different roles. Triterpenes and other derivatives which include steroids, have a wide variety of functions such as: the protection of plants against herbivores; antimitotic; induction of seed germination and inhibition of root growth. Cholesterol, vitamins A, D and E and sexual hormones (estradiol and testosterone) are triterpenes of special importance. Steroids with C_{27} and C_{29} belong to the terpene group but aren't true terpenes, since they are synthesized from the same precursor squalene, that has 30 carbon atoms in its structure[20].

Some researchers have reported that triterpenes possess the bioactivity of hepatoprotection, cholesterol stasis and anti-hipertension due to the inhibition of enzymes such as β-galactosidase, cholesterol synthase, angiotension converting enzyme. A triterpene extracted from *Ganoderma tsugae* was found to induce cell apoptosis and the cell cycle arrest in human hepatoma Hep 3B by mechanisms that were not yet investigated[21].

Considering their antitumoral activity, the group of triterpenes is the most important among terpenoides. The mechanism of antitumoral action of triterpenes extracted from Agaricales fungi is related to the inhibition of tumor induced by angiogenesis[22].

Beta-glucans

The β-D-glucans are indigestible polysaccharides occurring naturally in various organic sources such as yeasts, bacteria, algae and mushrooms as a component of cellular wall. Their chemical composition consists of a β-D-glucopiranose units, bound through (1→4) or (1→3), glucosidic bonds[23,24].

Different species of mushroom produce different types of β-D-glucans that can vary according to the degree of polymerization, molecular weight, branching frequency and solution formation[24]. The branching side chains can be fructose, mannose, xilose and galactose, amino-acids and polypeptide chains[25].

Besides the primary structure, beta-glucans with 1-3 bond present secondary and tertiary structures, which form triple helix and multimers supporting cell structure[25].

When beta-glucans are administered orally or during the purification process if prepared to intravenous administration, a number of fragmentations of multimeric chains occur. Each fragmented component will akin to different beta-glucans receptors. The binding with receptors on the surface of macrophages, are responsible for stimulating the immunological system[25].

Two membrane β-1,3-glucan receptors have been characterized at a molecular level. The first one to be reported was the CR3 receptor which is highly expressed on neutrophils, monocytes and NK cells, whereas less is present on macrophages. Dectin-1 was the second β-1,3-glucan to be described at a molecular level. This receptor is expressed mainly on macrophages and mediates the phagocytosis of yeasts[26].

Macrophages stimulation and immunomodulator effects are due to β-1,3 glucan which has molecular weight of 6500 Daltons[2]. The β-1,3 glucan has a number of effects on the immunological system such as increase of cellular and humoral immunity, in phagocytic and chemiostatic activity of macrophages, in the number of monocytes, in the depuration of antigens and in the cytolytic activity on human tumoral cells *in vitro*[10].

The β-D-glucans function as pseudo-antigens in the activation of the immune system. The antigen is phagocyted by thymus dependent cells which are suppressor and auxiliary lymphocytes, and bursa dependent cells, the plasmocytes that secretes antibodies. They also activate Th-1 cells and thymus dependent cells which stimulate T lymphocytes to secrete isoleukines. These isoleukines stimulate natural killer cells responsible for the destruction of neoplasic cells. In the presence of antigen the CD-8 lymphocytes acquire higher specific cytotoxicity, contributing to the process of cellular destruction[13,27].

The β-D-glucans are responsible by the hematopoietic activity of the new cultivable mushroom *Sparassis crispa*. The 6-branched 1,3-β-glucan of *S. crispa*, named SCG enhance the hematopoietic response CY-induced leukopenic mice from a qualitative as well as quantitative point of view[28]. Among products commercialized in Japan containing β-D-glucans extracted from medicinal mushrooms, Lentinan® and Schizophyllan® are available in the market[11].

Protein-glucans

Protein-glucans are formed by the association of amino-acids or peptides with branches major chains of glucans. These covalent bindings form polysaccharides linked to peptides (polysaccharide peptide- PSP) generally with amino-acids in the neutral or acid form[25]. Polysaccharides linked to peptides are also known as polysaccharide protein complex (ATOM).

PSP have higher opsonizing action compared to isolated polysaccharides and act as better epitopes. Krestin® PSK has been prescribed for oral use. Its active substance is beta-glucan linked protein, extracted from mushrooms[11,29]. When administered orally, peptide linked polysaccharides have better absorption if compared to non associated polysaccharides[30].

Arginine

Arginine is known to increase immunity by releasing HGH, human growth hormone - which would act in the gain of muscular mass, and through the improvement of cicatricial response in wounds - a result of the increase of hydroxyproline production and the T- lymphocyte function[31-37].

Arginine has an important regulatory role in cardiovascular function for being the precursor of nitric oxide, a potent neurotransmitter that has the vital function of dilatating and constricting small brain blood vessels[38]. Therefore, there is an increasing interest in the use of L-arginine in the treatment and prevention of the endothelium-dependent relaxation associated to diabetes, hypercholesterolemia and hypertension[31].

Polyamine itself has a fundamental role in the proliferation of normal and that of cancer cells. Experiments show that when blocking the polyamine synthesis by inhibiting ornithine descarboxylase, or by combining a limited polyamine diet source, an inhibitory effect on tumor growth is produced[14]. Arginine may prove helpful to improve the clinical conditions of Alzheimer's patients because it raises polyamine levels, which have an important action on cellular proliferation[17,38,39].

Studies report that dietary supplementation with arginine in adult cancer patients shows possible positive effects through the decrease of tumoral growth and increase of life expectation[5,39,40].

Fibers

The antitumoral action of agaricales fungi is also due to the protective activity of some nutrients.

From a nutritional point of view, mushrooms contain appreciable amounts of dietary fiber, particularly important for the regulation of physiological functions in human organism[41]. Fibers can absorb bile acids or hazardous materials in the intestine, and thus decrease the chances of developing tumors[4].

CONCLUSION

All revised studies showed that nutritional supplementation with Agaricales fungi have beneficial effects in patients, suggesting that it may consist in a new therapeutic perspective to cancer treatment. Before establishing the criteria for a dietary supplementation with medicinal fungi as co-adjuvant to traditional cancer therapy, the pharmacokinetics, the action mechanisms, toxicology and other aspects of these fungi, will have to undergo detailed studies. Additional researches such as clinical controlled randomized trials are of fundamental importance.

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