REVIEW

The effects of dietary supplementation with Agaricales mushrooms and other medicinal fungi on breast cancer: Evidence-based medicine

Maria Rita Carvalho Garbi Novaes, Fabiana Valadares, Mariana Campos Reis, Daniella Rodrigues Gonçalves, Marilia da Cunha Menezes

Universidade de Brasília, School of Medicine, Institute of Health Science (ESCS), Brasilia/DF, Brazil.

Breast cancer is the most prevalent cancer in women. The most frequent therapeutic approaches for the treatment of this disease are chemotherapy, radiotherapy, hormone therapy, and surgery. Conventional pharmacological treatments cause many harmful side effects in patients. To improve the quality of life of breast cancer patients, researchers have sought alternative adjuvant treatment strategies. To assess the effects of fungi and other basidiomycetes Agaricales on the co-adjuvant treatment of breast cancer, we conducted a literary review of the available scientific evidence. We selected articles published in refereed journals from 1990 to 2011 in Medline, Lilacs, CAPES, Scielo, and Pubmed. Articles written in English, Spanish, and Portuguese were reviewed. We used the following descriptors: Agaricales, medicinal mushroom/fungus, breast cancer, dietary supplementation, synonyms, and related terms. The pharmacological effects of nutritional and medicinal mushrooms have been reported in several experimental clinical studies and have shown promising results in the adjuvant treatment of breast cancer. Adjuvant treatment with mushrooms is associated with improvements in the immunological and hematologic parameters of breast cancer, as well as in the quality of life of these patients. Randomized clinical studies are needed to elucidate the possible mechanisms of action and clinical benefits of these fungi with respect to survival time, disease progression, and metastasis in breast cancer.

KEYWORDS: Nutritional supplement; Agaricus sylvaticus; Medicinal mushroom; Adjuvant treatment; Basidiomycetes.

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INTRODUCTION

Breast cancer is highly prevalent in women. In 2008, the IARC/OMS estimated that breast cancer was the second biggest incidence of cancer in the world (1.29 million cases). In Brazil, it would be responsible for 49,000 new cases in women from 2010 to 2011 and the mortality rate for this type of cancer remains high, on one side, due to the fact that this disease continues to be diagnosed at advanced stages.1,2

Treatment for breast cancer is complex and varies according to the histological diagnosis of the patient, the patient’s age, the disease stage and the therapeutic approaches taken.3

Factors associated with tumor growth and the conventional treatments used to treat cancer often result in malnutrition in breast cancer patients. Side effects caused by conventional treatments, significantly reduced caloric intake and decreased absorption of nutrients can all complicate cancer treatment and reduce the quality of life of cancer patients.4

Previous studies have sought to identify ways to improve the quality of life and nutritional status of cancer patients using adjuvant therapy with mushrooms.4-10

The most recent studies have shown that dietary supplementation with Agaricales mushrooms and other medicinal fungi in breast cancer patients can provide benefits, such as antiproliferative and immunomodulatory effects on tumor cells.11-15

The aim of this study is to analyze the effects of mushrooms and other basidiomycetous Agaricales as adjuvant treatments in breast cancer.

MATERIALS AND METHODS

A critical review of articles published in refereed journals between January, 1990 to March, 2011 was performed. Articles were identified in the Medline, Lilacs, Scielo, and Pubmed, Health Science Descriptors (DeCS) and Medical Subject Heading (MeSH) databases by searching for the following terms: in English (Agaricales, Agaricus, medicinal mushroom/fungus, breast cancer, dietary supplementation, edible mushroom effects, lectin), in Portuguese (câncer de mama, cogumelo medicinal), in Spanish (cáncer de mama, suplementación nutricional/dietética, cogumelos, hongos medicinales).
## Table 1 - Mechanisms of action of various modulating substances present in mushrooms.

| References | Substances | Benefits | Mechanism of Action |
|------------|------------|----------|---------------------|
| Wang et al. (1996) | 20 Lectin | Inhibits the growth of tumor cells | Two lectins (TML-1 and TML-2) were isolated from the mushroom *Tricholoma mongolicum*. Both stimulated the production of nitrite ions and activated macrophages in mice. |
| Novaes et al. (2005a), Novaes et al. (2005b), Fortes & Novaes et al. (2006), Fortes et al. (2008), Fortes & Novaes (2011) | 20 Lectin | Cytotoxic activity against human tumor cells, breast cancer and sarcoma 180 cells; inhibited proliferation of mastocytoma cells in vitro and sarcoma 180 cells in mice | Inhibits cell proliferation by blocking the import of protein into the nucleus |
| Zhang et al. (2009) | 17 Lectin | Antiproliferative activity toward hepatoma and breast cancer cells | Showed antiproliferative activity toward hepatoma Hep G2 cells and breast cancer MCF7 cells with an IC(50) of 2.1 µM and approximately 3.2 µM, respectively |
| Yang et al. (2009) | 18 Lectin | Tumor-suppressing function via apoptosis-inducing activity in cancer cells | Dimerization of AAL is a prerequisite for tumor cell apoptosis-inducing activity and requires galactose and glucose as basic moieties of functional carbohydrate ligands for lectin bioactivity |
| Sendra et al. (2010) | 16 Lectin | Induces an immune response with tumor-associated glycan specificity and biological activity similar to that of ABL | Shows high-affinity binding to T antigen and reversible noncytotoxic inhibitory effects on epithelial tumor cell proliferation |
| Fujimya et al. (1998) | 11 β-Glucan | Tumoricidal activity | Directly inhibits tumor cell growth in vitro by inducing apoptotic processing, increasing expression of the Apo2.7 antigen on the mitochondrial membranes of tumor cells and selective cytotoxicity toward tumor cells |
| Kodama et al. (2003) | 22 β-Glucan | Represses cancer progression, hinders metastatic progress, lessens the expression of tumor markers and increases NK cell activity in all patients | Antitumor effect in tumor-bearing mice due to enhancement of the immune system through the activation of macrophages, T cells, and natural killer (NK) cells |
| Novaes et al. (2005a), Novaes et al. (2005b), Fortes & Novaes (2006), Fortes et al. (2008), Fortes & Novaes (2011) | 31 β-Glucan | Enhances the immune system effects | Increases cellular and humoral immunity, the number and size of the phagocytic cells, stimulates cytokine production by T cells and increases the number of NK cells |
| Zhang et al. (2006) | 24 β-Glucan | Dose-dependently reduces proliferation and viability of MCF-7 breast cancer cells (cancer-cell growth was decreased by 50%) | Time-dependently induces cell cycle G1 arrest in approximately 90% of the cells by down-regulating the cyclin D1 and cyclin E expression in MCF-7 breast cancer cells; induces apoptosis through DNA alterations in subG1 cells; induces depletion of the anti-apoptotic Bcl-2 protein |
| Demir et al. (2007) | 23 β-Glucan | Stimulates proliferation and activation of peripheral blood monocytes in vivo in patients with advanced breast cancer | Stimulates innate immunity by activating monocytes/macrophages (CD95, CD45RA, CD14+) |
| Vetvicka et al. (2008) | 25 β-Glucan | Inhibits growth of tumor cells in vivo and affects expression of several important genes in breast cancer cells | Yeast-derived β-Glucan causes significant stimulation of phagocytic activity as well as potentiation of synthesis and release of interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, IL-13, and tumor necrosis factor-alpha. |
| Jiang et al. (2010) | 16 β-Glucan | Inhibits cell proliferation and suppresses the metastatic behavior of MDA-MB-231 breast cancer cells | Inhibition of cell proliferation and cell cycle arrest at G2/M phase in highly invasive MDA-MB-231 human breast cancer cells; linked to the suppression of secretion of the urokinase plasminogen activator (uPA) from these cells; inhibition of cell adhesion, cell migration and cell invasion |
Table 1 - Cont.

| References                  | Substances | Benefits                                                                 | Mechanism of Action                                                                 |
|-----------------------------|------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Takaku et al. (2001)        | Ergosterol | Direct inhibition of angiogenesis induced by solid tumors                | Tumor growth was retarded by the oral administration of the lipid fraction extracted from A. blazei in sarcoma 180-bearing mice. |
| Novaes et al. (2005a),      |            | Inhibition of tumor growth without causing collateral damage             | Inhibition of neovascularization induced by tumor growth                             |
| Novaes et al. (2005b),      |            |                                                                         |                                                                                      |
| Fortes & Novaes (2006),     |            |                                                                         |                                                                                      |
| Fortes et al. (2008),       |            |                                                                         |                                                                                      |
| Fortes & Novaes (2011)     | Arginine   | Inhibits tumor growth, reduces nitrogen losses and contributes to a positive nitrogen balance | Increases the number of NK cells and T-helper lymphocytes, stimulates the synthesis of cytokines, promotes the increase of immunity through the release of growth hormone and produces nitric oxide, hydroxyproline and polyamines |
| Wu et al. (2007)            |            | Strong antitumor activity                                               | Decrease of tumor size (60%) by cytotoxicity – exhibits a significant inhibitory effect on B16-induced melanoma in C57BL/6 mice. |
| Lee et al. (2009)           |            | Strong anti-migratory effect on human cancer cells                      | Ergosterol peroxide and daucosterol inhibited the migration of MDA-MB-231 cells.     |
| Thohinung et al. (2010)     |            | Anti-proliferation effect.                                              | Cytotoxicity against the human breast cancer and cholangiocarcinoma cell lines.     |
| Novaes et al. (2005a),      |            |                                                                         |                                                                                      |
| Novaes et al. (2005b),      |            |                                                                         |                                                                                      |
| Fortes & Novaes (2006),     |            |                                                                         |                                                                                      |
| Fortes et al. (2008),       |            |                                                                         |                                                                                      |
| Fortes & Novaes (2011)     | Arginine   |                                                                         |                                                                                      |
| Zhang et al. (2011)         |            | Anti-proliferation effect                                               | Depletion of ARGLU1 significantly impairs the growth, as well as anchoragedependent and -independent colony formation of breast cancer cells. |
| Tada et al. (2011)          |            | Improved anticancer activity                                            | Mutated arginine on EGFR-lytic peptide produces higher binding ability to EGFR on cancer cells. |

Articles identified in the indexing databases mentioned above, including both original articles and reviews of the bioactive effects of edible mushrooms on cancer, were selected for inclusion in this study. Experimental trials in animals evaluating the efficacy of medicinal fungi treatments in breast cancer and randomized clinical trials with Agaricales mushrooms (and other medicinal fungi) in humans with breast cancer were also included.

RESULTS AND DISCUSSION

Bioactive substances found in mushrooms and other Agaricales medicinal fungi

The therapeutic effects of medicinal mushrooms are due to the presence of lectin, β-glucan, ergosterol, arginine, and other bioactive substances in mushrooms.5-9 The benefits and possible mechanisms of action of these substances are described in Table 1.

Lectins have been shown to be therapeutic agents with anticancer properties in animals and in clinical studies. They cause cytotoxicity and apoptosis and inhibition of tumor growth by preferentially binding to cancer cell membranes. Lectins function by sequestering the body’s polyamines, thereby inhibiting cancer cell growth. Lectins also alter the production of many interleukins, activate protein kinases, bind to ribosomes, and inhibit protein synthesis. In addition, lectins modify the cell cycle by inducing cell cycle arrest at the G2/M phase, promoting apoptosis, and stimulating non-apoptotic G1-phase accumulation mechanisms. Finally, lectins can also down-regulate telomerase activity and inhibit angiogenesis.16-20

β-glucan is a glucose polymer present in medicinal mushrooms. It exhibits immunomodulatory effects as well as tumoricidal and antiproliferative activities in cancer patients through the stimulation of natural killer cells, neutrophils, monocytes, macrophages, and T-cells.21-27

Ergosterol (or provitamin D2) is a precursor of ergocalciferol, an important substrate in vitamin D biosynthesis and is found in the lipid fraction of Agaricales extracts. This substance has antitumor, antiproliferation, and antimigratory effects on human cancer cells.28-30 It has also been shown to inhibit angiogenesis. In a study on sarcoma 180 cells, patients treated with ergosterol demonstrated delayed tumor growth with minimal side effects. For example, the decrease in lymphocyte count that is commonly caused by chemotherapy was not observed in these patients. Ergosterol appears to have no direct in vitro cytotoxic effects on tumor cells, although it inhibits tumor-induced neovascularization.31

Arginine is a semi-essential amino acid used as a dietary supplement in cancer patients. It has been associated with a reduction of tumor growth and metastasis progression, and it is reported to have beneficial effects on the immune system, weight gain, and the time of survival of cancer patients.32,33

A complete understanding of the actions of these fungi and their bioactive molecules in the prevention and treatment of cancer will require further investigation. However, research shows that many of these substances exert anticarcinogenic, antiviral, antithrombotic, antibiotic,
Experimental studies with mushrooms and other Agaricales medicinal fungi

Promising results have been reported in animals and in vitro using medicinal mushrooms in the treatment of breast cancer and several other cancers. Table 2 provides a summary of the studies mentioned below.

Takimoto et al.35 demonstrated that rats administered Agaricus blazei extract orally exhibited increased cytotoxic T lymphocyte growth, increased levels of interferon-gamma and an increase in NK cells when compared to water-treated controls. This study indicates that mushroom extracts stimulate cytotoxic activity on both, innate and adaptive immunological systems.

Immunomodulatory, antitumor, and antiproliferative effects of lectin isolated from various types of Agaricales mushrooms have been demonstrated by Zhao et al.34 The lectin contained in Agaricus bisporus has been shown to exhibit an antiproliferative effect on breast cancer cells, and the lectin contained in Tricholoma mongolicum has been shown to have an inhibitory effect on mastocytoma cells (P815) in vitro.

In an in vitro study, extracts of Coriolus versicolor promoted significant tumor reductions in mice inoculated with mastocytoma tumor cells and mammary tumors.35

Chen et al.36 showed that the extract decreased proliferation and tumor growth without affecting apoptosis in rats. In experiments with breast cancer cells (MDA-MB-231), Grube et al.37 showed that Agaricus bisporus extract suppresses the activity of aromatase, resulting in a reduction of estrogen production, which is a major contributor to postmenopausal breast cancer in women.

In experiments with breast cancer cells (MDA-MB-231), Thyagarajan et al.38 showed that Ganoderma lucidum extract inhibits cell proliferation and the formation of new cell

Table 2 - The effects of Agaricales mushrooms and other medicinal fungi on breast cancer: experimental studies in animals, in vivo and in vitro.

| References | Mushroom Species | Target Group/Tumor | Results |
|------------|------------------|--------------------|---------|
| Grube et al. (2001)37 | Agaricus bisporus | Breast cancer cells | ↓ aromatase enzyme activity, tumor cell proliferation and estrogen production |
| Zhao et al. (2003)34 | Breast cancer cells (MCF-7) | ↓ proliferation of tumor cells (via DNase) |
| Chen et al. (2006)36 | Breast cancer cells (MCF-7) inoculated in mice | ↓ tumor cell proliferation and tumor growth |
| Talorete et al. (2002)44 | Agaricus blazei | Breast cancer cells (MCF-7) | ↓ cell proliferation |
| Takimoto et al. (2004)33 | Naive BALB/c and meth A-bearing BALB/c mice | ↑ natural killer activity of spleen cells in naive BALB/c Potentiated cytotoxic activity in innate and adaptive immunity in meth A-bearing BALB/c mice |
| Chu et al. (2002)35 | Coriolus versicolor | Mice inoculated with mastocytoma cells and mammary tumor | ↓ tumor cells growth |
| Jiang et al. (2004)43 | Ganoderma lucidum | Breast cancer cells (MDA-MB-231) | ↓ tumor cell proliferation Inhibited NF-κβ messenger activity |
| Thyagarajan et al. (2007)38 | Breast cancer cells (MDA-MB-231) | ↓ tumor growth and metastasis |
| Fang et al. (2006)41 | Lentinus edodes | Breast carcinoma cells (MDA-MB-453 and MCF-7) | ↑ antiproliferative activity |
| Israilides et al. (2006)46 | Breast carcinoma cells (MCF-7) | ↓ tumor cell proliferation ↑ immune response |
| Sliva et al. (2008)47 | Phellinus linteus | Breast cancer cells (MDA-MB-231) | ↓ tumor cell proliferation ↓ angiogenesis |
| Jedink et al. (2008)42 | Pleurotus ostreatus | Breast cancer cells (MCF-7 and MDA-MB-231) | Suppressed tumor cell proliferation |
| Gu & Leonard (2006)40 | Several types of mushrooms | Breast cancer cells (MCF-7, MDA-MB-231 and BT-20) | Inhibited tumor growth |
| Petrova et al. (2007)39 | Several types of mushrooms | Breast cancer cells (MCF-7) | Inhibited messenger activity of NF-Kβ |
| Vetvicka et al. (2008)45 | Breast cancer cells | Breast cancer cells | ↓ tumor cell proliferation |
| Zhao et al. (2003)34 | Tricholoma mongolicum | Mastocytoma cells (P815) | Inhibited tumor growth (via apoptosis-inducing) |

and anti-inflammatory effects in addition to many other activities that provide health benefits.3,6,9,31-32
A study by Jiang et al.⁴³ revealed that *Ganoderma lucidum* inhibits proliferation of MDA-MB-231 breast cancer cells. By inhibiting Akt and NF-kappaB activity in MDA-MB-231 cells, *Ganoderma lucidum* reduced their growth.

Talorete et al.⁴⁴ isolated breast cancer cells (MCF-7) and exposed them to an aqueous extract of *Agaricus blazei*. The results indicated that this extract was able to reduce cell proliferation in 26% compared to the control group, by significantly enhancing the expression of an API gene regulatory complex in the human breast cancer cell line MCF7. This, again, highlights the anticarcinogenic potential of mushrooms.

In a study of rats inoculated with breast cancer cells, Vetvicka et al.⁴⁵ observed a reduction in cell proliferation after oral supplementation of β-Glucan extracted from medicinal mushrooms. Likewise, a decrease in the proliferation of cancer cells has been reported in studies carried out by Israilides et al.⁴⁶ with breast cancer cells (MCF-7) and by Sliva et al.⁴⁷ using the MDA-MB-231 cell line.

**Clinical studies with breast cancer patients using** *Agaricales* **mushrooms and other medicinal fungi**

Although there are some inconsistencies in the results of clinical studies regarding the use of medicinal mushrooms as an adjuvant therapy in breast cancer treatment, the majority of studies suggest a beneficial effect (Table 3).

A study in patients with breast cancer who received four daily doses (1.6 g each) of *Agaricus syilicus* revealed that *Agaricus syilicus* supplementation resulted in an increased number of natural killer (NK) cells in 75.7% of the patients. More than half of the patients were receiving chemotherapy or radiotherapy, which typically reduces the numbers of NK cells in the body.⁴⁵,¹¹

In a clinical study of various cancers, including breast cancer (stage IV), Sliva et al.⁴⁷ provided patients with a complex of immunomodulatory components, including *Agaricus blazei* tea (10 mg/day). After six months of treatment, some patients had increased NK cell activity, as well as increased levels of TNF-α (tumor necrosis factor),

| References | Mushroom Species | Active Principle | Target Group | Results |
|-----------|------------------|-----------------|--------------|---------|
| Dolby (1997)¹² | *Grifola frondosa* | D-fraction-β-Glucan and total mushroom | 15 women with breast cancer | ↓ tumor size improvement in clinical and biochemical parameters ↓ of vomiting and anorexia |
| Kodama et al. (2002)¹³ | *Grifola frondosa* | Mushroom powder | Liver, lung and breast cancer patients | increasing immune-competent cell activity cancer regression or significant symptom improvement |
| Gennari et al. (2002)⁴⁸ | *Agaricus sylvaticus* | Mushroom capsule | 1 patient with breast cancer and lung metastasis | ↑ the number of NK cells and CD 56 total remission of lung metastasis |
| See et al. (2002)⁴⁹ | *Agaricus blazei* | Mushroom tea | 5 stage VI breast cancer patients | ↑ the number of NK cells stimulate macrophages and other immunomodulatory effects |
| Hong et al. (2008)⁷ | Several types of mushroom | Mushroom total | 362 women with breast cancer in menopause | the consumption of dietary mushrooms may decrease breast cancer risk in postmenopausal women |
| Shin et al. (2010)¹⁴ | Several types of mushroom | Mushroom total | 358 women with breast cancer | ↑ mushroom consumption ↓ risk of breast cancer in premenopausal women (stronger with hormone receptor positive tumors) |

Table 3 - The results of clinical studies using *Agaricales* and other medicinal fungi for dietary supplementation and adjuvant treatment in patients with breast cancer.
eripheral blood cells, erythrocytes, hemoglobin, and glutathione. In contrast, the number of TNF-α receptors was reduced. Diarrhea and occasional nausea were reported, but the quality of life had improved. The combination of immune-active components was effective in increasing NK cell function and other immunological parameters in patients with advanced stages of cancer, thus providing an effective nutritional combination for the treatment of the late stages of cancer.

Gennari et al. reported that the D-fraction of Agaricus sylvaticus increased the number of CD56 NK cells in the blood and caused a total regression of lung metastases. Dolby reported that the D-fraction of D-Glucan (extracted from Maitake) and mushroom tablets of Grifola frondosa had a positive effect on the health status of the 15 breast cancer patients included in the study. This study reported an improvement in the clinical parameters and laboratory test results of patients as well as improvements in their hematological parameters, reductions in the amount of vomiting and nausea, which can be a side effect of conventional treatments.

Dolby et al. reported that the D-fraction of D-Glucan had a positive effect on the health status of the 15 breast cancer patients included in the study. This study reported an improvement in the clinical parameters and laboratory test results of patients as well as improvements in their hematological parameters, reductions in the amount of vomiting and nausea, which can be a side effect of conventional treatments.

Gennari et al. conducted a case study of a patient with breast cancer and showed that dietary supplementation with Agaricus sylvaticus increased the number of CD56 NK cells in the blood and caused a total regression of lung metastases. Dolby reported that the D-fraction of D-Glucan (extracted from Maitake) and mushroom tablets of Grifola frondosa had a positive effect on the health status of the 15 breast cancer patients included in the study. This study reported an improvement in the clinical parameters and laboratory test results of patients as well as improvements in their hematological parameters, reductions in the amount of vomiting and nausea, which can be a side effect of conventional treatments.

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