Câncer colo retal Efeitos imunológicos, hematológicos e glicêmico do Agaricus sylvaticus

19/05/11

Immunological, hematological, and glycemia effects of dietary supplementation with Agaricus sylvaticus on patients’ colorectal cancer.

Fortes RC, Novaes MR, Recôva VL, Melo AL.

Source
Human Nutrition, Science and Education School, Sena Aires-GO/ University of Brasilia–DF, Brazil. renatacfortes@yahoo.com.br

Abstract
The aim of this study was to evaluate the effects of dietary supplementation with Agaricus sylvaticus fungus on hematological, immunological, and glycemia levels of postsurgical patients with colorectal cancer.

METHODS:
A randomized, placebo-controlled, clinical trial was conducted at the General Hospital of Brazil for 6 months. Fifty-six patients with colorectal cancer (stages I, II, and III) were divided into 2 groups: A. sylvaticus (30 mg/kg/day) and placebo. Complete hemogram, serum iron, and fasting glycemia evaluations were carried out throughout the treatment course. Subjects were divided according to body mass index (BMI), sex, and stage of colorectal cancer. Data were analyzed using SPSS 14.0 programs, Student’s t test, and F statistical test, with P < or = 0.05 considered significant.

RESULTS:
After 6 months of supplementation, the group that received A. sylvaticus showed significant increases in hemoglobin (P = 0.0001), hematocrit (P = 0.0001), and mean cell volume (P = 0.01), mean cell hemoglobin concentration (P = 0.0001), and neutrophil levels (P = 0.0001). The platelet count was significantly reduced (P = 0.03), but remained within normal levels. No significant alterations were observed in the placebo group. The study group was composed of 32 women (57.1%) and 24 men (42.9%). Mean BMI was 24.65 kg/m2. Glycemia levels in the placebo group (average age 59.14 +/- 12.95 years) were: initial, 94.36 +/- 15.34 mg/dl; 3 months, 98.12 +/- 15.54 mg/dl (P = 0.03); and 6 months, 98.52 +/- 9.03 mg/dl (P = 0.01). Glycemia levels in the supplemented group (average age 56.34 +/- 15.53 years) were: initial, 95.92 +/- 11.64 mg/dl, 3 months, 94.88 +/- 12.24 mg/dl (P = 0.65); and 6 months, 92.86 +/- 6.82 mg/dl (P = 0.01).

CONCLUSIONS:
The results of this study suggest that supplementation with A. sylvaticus produces benefits in hematological and immunological parameters and can reduce glycemia levels in patients with colorectal cancer.

PMID:
19997106

Immunological, Hematological, and Glycemia Effects of Dietary Supplementation with Agaricus sylvaticus on Patients’ Colorectal Cancer
Renata C. Fortes*1, Maria Rita C. G. Novaes, Viviane L. Recôva and Andresa L. Melo
* Human Nutrition, Science and Education School, Sena Aires-GO/University of Brasilia–DF, 71.000.000, Brazil; School of Medicine, Institute of Health Science (ESCS/ FEPECS/ SESDF)/ University of Brasilia–DF, 71.625.030, Brazil; and Institute of Health Science (ESCS/ FEPECS/ SESDF), Brasilia–DF, 71.000.000, Brazil
1 SHIS-QI 09- conjunto 06- casa 14- Lago Sul, Brasilia-DF, Brasil. Cep: 71.625.060. E-mail: renatacfortes@yahoo.com.br

Abstract
Objective: The aim of this study was to evaluate the effects of dietary supplementation with Agaricus sylvaticus fungus on hematological, immunological, and glycemia levels of postsurgical patients with colorectal cancer. Methods: A randomized, placebo-controlled, clinical trial was conducted at the General Hospital of Brazil for 6 months. Fifty-six patients with colorectal cancer (stages I, II, and III) were divided into 2 groups: A. sylvaticus (30 mg/kg/day) and placebo. Complete hemogram, serum iron, and fasting glycemia evaluations were carried out throughout the treatment course. Subjects were divided according to body mass index (BMI), sex, and stage of colorectal cancer. Data were analyzed using SPSS 14.0 programs, Student’s t test, and F statistical test, with P 0.05 considered significant. Results: After 6 months of supplementation, the group that received A. sylvaticus showed significant increases in hemoglobin (P = 0.0001), hematocrit (P = 0.0001), erythrocytes (P = 0.01), mean cell volume (P = 0.01), mean cell hemoglobin concentration (P = 0.0001), and neutrophil levels (P = 0.0001). The platelet count was significantly reduced (P = 0.03), but remained within normal levels. No significant alterations were observed in the placebo group. The study group was composed of 32 women (57.1%) and 24 men (42.9%). Mean BMI was 24.65 kg/m2. Glycemia levels in the placebo group (average age 59.14 +/- 12.95 years) were: initial, 94.36 +/- 15.34 mg/dl; 3 months, 98.12 +/- 15.54 mg/dl (P = 0.03); and 6 months, 98.52 +/- 9.03 mg/dl (P = 0.01). Glycemia levels in the supplemented group (average age 56.34 +/- 15.53 years) were: initial, 95.92 +/- 11.64 mg/dl, 3 months, 94.88 +/- 12.24 mg/dl (P = 0.65); and 6 months, 92.86 +/- 6.82 mg/dl (P = 0.01). Conclusions: The results of this study suggest that supplementation with A. sylvaticus produces benefits in hematological and immunological parameters and can reduce glycemia levels in patients with colorectal cancer.

Keywords: hematological, immunological, glycemia, Agaricus sylvaticus, cancer

Introduction
The Agaricus sylvaticus fungus has been used as a dietary supplement in patients with several kinds of cancer (1, 2). Although its mechanisms of action have not yet been completely elucidated (3), researchers have proven that A. sylvaticus acts as an inhibitor of tumor growth as well as a stimulator of both the hematological and immunological systems (1, 4). Diverse substances present in A. sylvaticus are responsible for its pharmacologic and nutritional attributes, especially because of their performance, and include β-glucans polysaccharides, ergosterol, lectin, triterpenes, and arginine, among other immunomodulator amino acids (1, 2).

Experimental studies in animals with neoplastic cell lineage have demonstrated that the administration of solutions containing A.
sylvaticus extract produces beneficial effects on the hematopoietic system (1, 2). Accordingly, clinical studies have shown significant increases in red blood cell counts after patients with cancer are administered the medicinal fungus as a supplement (2, 5–8). Scientific evidence has demonstrated that medicinal fungi may also modify the host’s biological response by stimulating his/her immune system through improvement of function and number of macrophages, neutrophils, monocytes, natural killer (NK) cells, and T cells (2, 7, 9, 10), which prevents the multiplication, metastasis, and recurrence of cancerous cells (11).

Inadequate dietary habits and lifestyle factors are associated with peripheral resistance to insulin and, consequently, to hyperinsulinemia, eventually resulting in high levels of insulin-like growth factor (IGF-1) (12–14). Hyperinsulinemia is related directly to the carcinogenic process since it can stimulate colorectal tumor growth (15–20). Likewise, IGF-1 is responsible for proliferation and apoptosis, being able to influence carcinogenesis significantly (12, 14, 18, 19).

The objective of this study was to evaluate the effects of dietary supplementation with A. sylvaticus fungus on hematological, immunological, and fasting glycemia levels of postsurgical patients with colorectal cancer.

Materials and Methods

Study Design.

The study was designed as a randomized, double-blind, placebo-controlled clinical trial. It was approved by the Research Ethics Committee of the Health Ministry–Federal District–Brazil, under protocol 051/2004. Terms of free consent were obtained from patients, whose participation was voluntary, after they acknowledged the procedures of the study. The work was developed at the ambulatory proctology clinic of the Base Hospital of the Federal District, a public hospital in Brazil, from November 2004 to July 2006.

Patients.

The sample consisted of 56 patients (24 men, 32 women) with colorectal cancer, stages I (n = 12), II (n = 16), and III (n = 28), divided into 2 groups: placebo (n = 28) and supplemented with A. sylvaticus (n = 28). Inclusion criteria were: postsurgery colorectal cancer (3 months to 2 years after surgical intervention) and age 20 years or older. Patients excluded were pregnant women, breastfeeding infants, patients physically disabled, those receiving alternative therapy, patients with any other nontransmissible chronic disease, and those with evidence of metastasis.

Agaricus sylvaticus Extract.

Agaricus sylvaticus fungus (popular name, Sun Mushroom), was obtained from a producer licensed by the Brazilian Agropecuária Company–Embrapa, from the Tapiraí, São Paulo State. The fungus extract was obtained by soaking dehydrated material in hot water for 30 minutes, liquefying, boiling, and drying in a box. The chemical composition of the final solution was analyzed at the Japan Food Research Laboratories Center by high-performance liquid chromatography, and the results showed the presence of carbohydrates (18.51 g/100 g), lipids (0.04 g/100 g), eresol (624 mg/100 g), proteins (4.99 g/100 g), amino acids (arginine 1.14%, lysine 1.23%, histidine 0.51%, phenylalanine 0.93%, methionine 0.33%, valine 1.03%, amino 1.06%, glycine 0.94%, proline 0.95%, glutamic acid 3.93%, serine 0.96%, threonine 0.96%, aspartic acid 1.81%, tryptophan 0.32%, cysteine 0.25%), and micronutrients in trace quantities.

The dried extract was compressed into tablets, according to pharmacotechnical procedures, and the dosage administered to the group was the equivalent of 30 mg/kg/day, divided into 2 daily doses (6 tablets per day, 3 in the morning and 3 in the afternoon, between meals), considering the average weight of the studied population, during a 6-month period. The placebo group received the same number of tablets, with similar ingredients and the same amount of calories, but without A. sylvaticus extract (starch was used instead).

Clinical Evaluation.

Patients were monitored for 6 months. During the first 3 months, consultations were scheduled every 15 days for clinical evaluation and, during the final 3 months, consultations were conducted every 30 days. All patients continued their usual diet, but during the treatment, they received general guidance on how to maintain a healthy diet. After 6 months of supplementation, all patients were prescribed a personal diet and were referred to other health professionals when necessary. The patients underwent 3 fasting plasma glucose tests: one before the beginning of the supplementation, one after 3 months of treatment, and the last one at the end of the treatment (after 6 months).

The researchers contacted all patients by telephone weekly to address the patients’ doubts, determine their adequate use of the mushroom according to orientation, and confirm appointments, guaranteeing major adherence to the treatment and continuity of the study.

Drop outs were identified as patients who presented only for the first appointment, did not come to consultations during the 6-month period, or underwent less than 3 examinations. Patients who died before the end of the treatment were not included in the sample.

Immunological and Hematological Evaluation.

Blood samples were collected after patients had fasted for 12 hours. The samples were placed into vacuum tubes to allow obtainment of serum, according to protocols recommended by the Brazilian Society of Pathology for Collection of Venous Blood (21). Complete hemograms were performed using the Coulter T-540 analyzer, following laboratory procedures of the Base Hospital of the Federal District, Brazil. The analysis followed the principle of flow cytometry, using the following reagents: isoton (diluent), lytic (erythrocyte hemolysis), and Coulter detergent (to clean the device). Test results were analyzed according to standardized reference values of the State Health Secretariat Laboratory–Federal District.

Fasting Glycemia Level Evaluation.

Blood samples were collected after patients had fasted for 12 hours. The samples were placed into vacuum tubes to allow obtainment of serum, according to the protocols recommended by the Brazilian Society of Pathology for Collection of Venous Blood (21). The samples were centrifuged and analyzed in a 3000 Targa device, Random Access Chemistry Analyzer, following laboratory procedures of the Base Hospital of the Federal District, Brazil. Analyses were conducted using the enzymatic method in photo-colorimeter pipes using Wiener kits. The reagents used contained glucose-oxidase, peroxidase, 4-aminofenazone, and drain plugs phosphate.

Statistical Analysis.

Men and women were analyzed separately within the placebo and A. sylvaticus groups for comparison of the results of the serum evaluations. Data were analyzed using SPSS 14.0 programs, with the Student’s t test and the F test. Significance was set at P 0.05.

Results

After 6 months of monitoring at the ambulatory proctology clinic of the Base Hospital–Federal District, 56 patients with colorectal cancer completed the study, with 32 women (57.1%) and 24 men (42.9%) included in the placebo and A. sylvaticus groups. Patients in the placebo group (n = 28) were 59.14 ± 12.95 years of age. Females made up 57.1% (n = 16) of the group; 3 of the women were diagnosed with stage 1 colorectal cancer, 7 with stage II, and 6 with stage III. Males made up 42.9% (n = 12) of the placebo group; 1 of the men was diagnosed with stage I cancer, 3 with stage II, and 8 with stage III.

Patients supplemented with A. sylvaticus (n = 28) were 56.34 ± 15.53 years of age. Females made up 57.1% (n = 16) of the treatment group; 6 women were diagnosed with stage I colorectal cancer, 2 with stage II, and 8 with stage III. In the group’s male population (42.9%; n = 12), 2 patients were diagnosed with stage I cancer, 4 with stage II, and 6 with stage III.

The placebo group presented a nonsignificant reduction of hemoglobin serum levels within 3 months (P = 0.06) and in the sixth month of the study (P = 0.33, Table 1). The group supplemented with A. sylvaticus achieved a significant increase of hemoglobin levels within 3 months and after 6 months of supplementation (P = 0.0001; Table 2).
When the groups were analyzed by sex, the reference values used for hemoglobin levels were 16.00 ± 2.00 g/dl for men and 14.00 ± 2.00 g/dl for women. Men in the placebo group presented a nonsignificant reduction of hemoglobin within 3 months (from 14.18 ± 1.31 g/dl to 13.87 ± 1.41 g/dl; P = 0.49) and a nonsignificant increase within 6 months (from 14.18 ± 1.31 g/dl to 14.40 ± 1.06 g/dl; P = 0.37). Nonsignificant reductions in hemoglobin occurred in the hemoglobin group at both 3 months (from 13.58 ± 1.35 g/dl to 13.11 ± 1.78 g/dl; P = 0.17) and 6 months (from 13.58 ± 1.35 g/dl to 13.24 ± 1.66 g/dl; P = 0.32) of the study.

The group supplemented with A. sylvaticus showed a nonsignificant increase in the third month (P = 0.0001) and in the sixth month (from 13.51 ± 2.98 g/dl to 15.28 ± 9.49 g/dl; P = 0.0001) of supplementation. Women also demonstrated significant increases in fasting plasma glucose levels within 3 months (from 12.68 ± 2.19 g/dl to 13.30 ± 1.02 g/dl; P = 0.01) and after 6 months (from 12.68 ± 2.19 g/dl to 13.66 ± 1.29 g/dl; P = 0.05).

Hematocrit values in the placebo group showed a nonsignificant reduction (P = 0.13) within 3 months and a nonsignificant increase (P = 0.37) within 6 months, when compared to the beginning of the study. The hematocrit levels of the group supplemented with A. sylvaticus significantly increased in the third (P = 0.02) and sixth (P = 0.0001) months of supplementation (Table 2).

When patients in the placebo group were analyzed according to sex, the reference values used for hemoglobin were 47.00 ± 5.00% for men and 42.00 ± 5.00% for women. There was a nonsignificant reduction of hematocrit levels in the men's group within 3 months (from 42.31 ± 3.56% to 42.51 ± 3.56% within 6 months (from 43.09 ± 3.27% to 43.99 ± 3.48%; P = 0.37). The reductions in the women's group were also significant within 3 months (from 41.34 ± 3.74% to 40.46 ± 4.84%; P = 0.36) and 6 months (from 41.34 ± 3.74% to 41.16 ± 4.27%; P = 0.86).

In the placebo group, the erythrocyte values had a discrete reduction after 3 months (P = 0.13) and 6 months (P = 0.45) when compared with initial results (Table 1). The group that received A. sylvaticus showed a statistically nonsignificant increase (P = 0.24) within 3 months and a significant increase (P = 0.01) within 6 months of supplementation (Table 2).

In the placebo group, there was a nonsignificant reduction (P = 0.04) of serum iron levels within 6 months of supplementation (Table 1). Significant increases were observed in the second month of supplementation (from 69.52 ± 27.98 µg/dl to 73.23 ± 28.88 µg/dl; P = 0.55) and 6 months (from 77.71 ± 32.74 µg/dl to 73.46 ± 24.91 µg/dl; P = 0.66).

The male group supplemented with A. sylvaticus showed the following results in iron levels within 3 months (from 69.52 ± 27.98 µg/dl to 108.48 ± 39.56 µg/dl; P = 0.03) and 6 months (from 69.52 ± 27.98 µg/dl to 101.29 ± 31.37 µg/dl; P = 0.03). The female group presented nonsignificant reductions within 3 months (from 5.05 ± 0.47 x 10^6/µl to 4.90 ± 0.63 x 10^6/µl; P = 0.52) and a significant increase after 6 months of supplementation (from 5.05 ± 0.47 x 10^6/µl to 4.81 ± 0.41 x 10^6/µl; P = 0.59). Women presented a nonsignificant increase after 3 months (from 4.67 ± 0.39 x 10^6/µl to 4.72 ± 0.37 x 10^6/µl; P = 0.61) of the study.

In the placebo group, the erythrocyte values had a discrete increase after 3 months (P = 0.55) and 6 months (P = 0.45) of supplementation (Table 2). In the placebo group, the erythrocyte values had a discrete increase after 3 months (P = 0.55) and 6 months (P = 0.45) of supplementation (Table 2).
Hematological and immunological alterations are common in patients with malignant neoplasms (1, 7). Scientific evidence has shown that dietary supplementation with medicinal fungi is capable of significantly improving the physiological condition and prognosis of patients with cancer (1, 8, 10) because of their effects on red blood cells and the immune system (1).

Several immunomodulator substances are found in Agaricales fungus, such as β-glucans, β-proteoglucans, lectin, ergosterol, triterpenes, and arginine, which are capable of modulating the carcinogenesis process (1, 2, 5, 6).

In Fortes et al. (22), who evaluated the effects of supplementation with extracts of A. sylvaticus in postsurgical patients with colorectal cancer, the A. sylvaticus group achieved a significant increase in the immunity of patients with colorectal cancer compared to the placebo group (P = 0.02). In the present study, a significant increase in serum levels of hemoglobin, hematocrit, erythrocytes, MCV, MCH, and MCHC and a nonsignificant increase of iron levels were observed after 6 months of supplementation with A. sylvaticus fungus. These findings were not noted in the placebo group. Similar results were found in a randomized, double-blind, placebo-controlled clinical trial conducted by Fortes et al. (22), who evaluated the effects of supplementation with extracts of A. sylvaticus in postsurgical patients with colorectal cancer. The A. sylvaticus group achieved significant increases of hemoglobin, hematocrit, erythrocytes and nonsignificant increases of iron, and thus, supporting the hematological system of these patients. Novaes et al. (1), in a prospective, randomized, blinded, placebo-controlled study, evaluated the effects of A. sylvaticus in patients with colorectal cancer. The A. sylvaticus group experienced a significant increase in the immunity of patients with colorectal cancer compared to the placebo group (P = 0.02). In the present study, a significant increase in neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation. In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation. In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation. In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation. In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation. In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation. In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of supplementation.

Despite the fact that platelet counts remained at normal levels in both groups, the placebo group had a non-significant increase during the study. Also, in the A. sylvaticus group, there was a significant increase in men and a nonsignificant reduction in women. Again, these findings suggest the presence of bioactive compounds in the A. sylvaticus fungus that are capable of acting beneficially on the hematological system of patients with colorectal cancer.

Reactive thrombocytosis is usually observed in patients with cancer; nevertheless, its pathophysiology is still poorly understood. Humoral factors are believed to be responsible for the increase in platelets in these patients (23). Studies have demonstrated a quantitative and qualitative abnormal production of platelets originating from abnormal megakaryocytic clones (24).

In the present study, a significant increase of neutrophils and a nonsignificant increase of monocytes and eosinophils were observed in the A. sylvaticus group after 6 months of supplementation. The TLC and basophils presented nonsignificant increases after 3 months of treatment. In the placebo group, there was a reduction of neutrophils and basophils and an increase of monocytes and TLC; however, none of these alterations was statistically significant.

Clinical studies have demonstrated that the combination of reduced eosinophil and basophil counts in a heterogeneous group of patients with cancer is significant. These alterations may be due to the presence of a tumor. Furthermore, the reduction of lymphocytes is associated with more aggressive tumoral behavior (23).

Leukopenia, and particularly lymphopenia and neutropenia, are consequences of cachexia and metabolic alterations caused by the tumor and increase the risk of infections (1). In the A. sylvaticus group, there was a nonsignificant reduction of leukocytes and lymphocytes after 6 months of supplementation, with the levels remaining within normal limits. The placebo group experienced a little alteration of leukocytes and an increase of lymphocytes after 6 months of the study; these alterations were not statistically relevant. Several factors, such as dosage, rate, time, and frequency of administration, in addition to the mechanism of action, interfere with the bioactive compounds present in medicinal fungi and their ability to enhance or suppress the host's immune response. Few studies have been carried out regarding the pharmacokinetics of such bioactive substances (8). In vivo studies have revealed that extracts of specific fungi have the potential to modulate the immune system. The extractions in the present study were able to restore the depressed immunological responsiveness caused by tumors, with the parameters reaching normal levels (25). All of these factors may partially explain the results found in the white blood cell counts of patients supplemented with A. sylvaticus in this study.

Fortes et al. (26) evaluated the immunological function of patients with colorectal cancer in the postsurgical phase after supplementation with A. sylvaticus during a 3-month period. The investigators observed significant increases of leukocytes, lymphocytes, TLC, and basophils, as well as a nonsignificant reduction of monocytes, eosinophils, and neutrophils in the supplemented group, reaching reference values. No significant alterations were observed in the placebo group. The authors concluded that dietary supplementation with A. sylvaticus is capable of promoting a significant increase in the immunity of patients with colorectal cancer.

Shimizu et al. (27) conducted a study of 20 patients with acute nonlymphocytic leukemia undergoing chemotherapy treatment, with the patients divided in 2 groups: Agaricus blazei (n = 10) and control (n = 10). Of all patients supplemented with A. blazei, 80% of patients divided in 2 groups: Agaricus blazei (n = 10) and control (n = 10). Of all patients supplemented with A. sylvaticus, 80% of patients had a significant reduction of glucose levels (from 94.67 ± 13.59 mg/dl to 94.13 ± 6.4 mg/dl; P = 0.90). Eutrophic men (n = 5) presented initial glucose concentrations of 95.50 ± 12.01 mg/dl; levels in overweight or obese men (n = 8) were 102.14 ± 10.78 mg/dl. At the end of the treatment, an increase of the glucose levels was observed in the eutrophic group (from 95.50 ± 12.01 mg/dl to 97.75 ± 6.70 mg/dl); however, this also was not statistically relevant (P = 0.46). In the group of overweight or obese subjects, glucose levels decreased from 102.14 ± 10.78 mg/dl to 100.67 ± 5.57 mg/dl; this was not statistically significant (P = 0.97).

In comparing the levels of fasting plasma glucose and stage of cancer in the A. sylvaticus group, we observed that patients in stage I (n = 8) had lower glucose levels (91.56 ± 8.19 mg/dl) than did patients in stages II (n = 6, 100.17 ± 11.48 mg/dl) and III (n = 14, 96.73 ± 14.14 mg/dl). After 6 months of supplementation, patients in all stages of cancer had glucose reductions. In patients with stage III colorectal cancer, glucose reductions from 96.73 ± 14.14 mg/dl to 95.6 ± 5.02 mg/dl were statistically significant (P = 0.05). However, reductions in the final results were not statistically significant in patients with stage I cancer (from 91.56 ± 8.19 mg/dl to 88.33 ± 5.39 mg/dl, P = 0.26) and in those with stage II cancer (from 100.17 ± 11.48 mg/dl to 98.17 ± 9.64 mg/dl, P = 0.66; Fig. 2).
reached complete tumoral remission and 20% did not achieve remission. The levels of erythrocytes, granulocytes, and giant nuclear cells returned to normal after chemotherapy was completed. In the control group, 50% of the patients had reached complete remission, 20% achieved partial remission, and 30% experienced no remission. Plasmatic cells of 80% of the patients returned to normal levels within 14–21 days after chemotherapy; however, 20% of the patients retained abnormal cellular levels. Scientific evidence has shown that the main substance responsible for the pharmacologic and nutritional attributes of Agaricus fungus is the polysaccharide β-glucans. β-glucans may act as an immunomodulatory factor through an increase of NK cells, T lymphocytes, B lymphocytes, and complementary cells; and a consequent increase in the number of macrophages and monocytes. In addition, proliferation and/or production of antibodies and some cytokines, such as interleukins 2 and 6, IFN-γ, and TNF-α, is promoted (2, 3, 5, 6).

The glucose binders to receptors on the cell membranes of macrophages, neutrophils, NK cells, T cells, dendritic cells, fibroblasts, and vascular endothelial cells. The molecular structure of these substances influences their affinity for receptors. These receptors have been described as phagocytic receptors for particular antigens of the alternative pathway of the complement system. Research carried out with β-glucans extracted from fungi has proven that these substances act by stimulating neutrophils, eosinophils, monocytes, macrophages, and NK cells through its specific receptors (7). Nevertheless, the exact mechanism of action of these polysaccharides has not been clarified. The components may regulate some aspects of the humoral and/or cellular components of the immune system (8).

Other bioactive compounds present in Agaricaceae fungus may exert antineoplastic effects. These compounds include ergosterol, oleic acid, and triterpenes, which inhibit neovascularization induced by tumors; and arginine, which promotes increased immunological activity through the release of growth hormone and stimulates the production of nitric oxide, hydroxyproline, cytokine, and polyamines. These actions are beneficial in cancer cachexia (1, 2, 3, 6).

In the present study, patients supplemented with A. sylvaticus were characterized as adult (average age 56.34 ± 15.53 years), eutrophic, and overweight (average BMI 24.76 ± 4.10 kg/m²).

The relationship between cancer, obesity, and hyperinsulinemia is fairly clear in the literature (28). The increased prevalence of abnormal carbohydrate metabolism, especially in relation to high plasma glucose levels and insulin, occurs with aging (29–31) and overweight (17, 29), as observed in the placebo group, and is associated with insulin resistance (32, 33). In obese patients, there is an increment of glucose turnover as the tumor expands (36). However, after 3 months of supplementation with A. sylvaticus fungus, inverse results were found in the placebo group, where a significant increase in glucose levels was observed, suggesting that A. sylvaticus fungus possesses substances capable of reducing glycemia.

In a clinical trial carried out with 71 patients diagnosed with type 2 diabetes and treated with fractions of Ganoderma lucidum polysaccharides (1800 mg 3 times/day for 12 months) showed significant reduction of average values of postprandial glycemia of 11.8 mM in the supplemented group when compared with the placebo group (40). We hypothesized that the increase in the literature that evaluated the effects of polysaccharides on carbohydrate metabolism; nonetheless, results have demonstrated that this fungus is capable of reducing fasting glycemic levels in patients with colorectal cancer. There has been enough evidence to attest the presence of bioactive substances such as lecithin, ergosterol, proteoglycans, glucans, and arginine in Agaricaceae fungus. Scientific evidence shows that the substance responsible for the pharmacologic and nutritional attributes of mushrooms is β-glucans (2, 6, 7).

The ingestion of moderate amounts of fiber can improve glycemic metabolism in eutrophic individuals and overweight individuals (29) and modify postprandial glycemia as well as insulin responses in individuals with or without diabetes (41). Studies have demonstrated that a linear decrease in glycemia levels occurred when the amount of β-glucans was increased (42). The consumption of soluble fibers, particularly of β-glucans present in fungus, lowers the insulin and postprandial glucose peak and its respective curves, promoting beneficial effects on glucose tolerance (29, 42).

According to Bourdon et al. (41), fiber regulates the amount and location of the digestive and absorptive carbohydrate processes, consequently modifying alimentary and physiological responses to a particular food. When fibers containing viscous polysaccharides
such as glucans are included in the meals, reduced glycemic absorption can be observed, which modifies alimentary hormone responses, thus precipitating slower carbohydrate absorption.

Even though the intrinsic mechanisms of alimentary fiber and the improvement of homeostasis of glucose have not been totally detailed in the literature, it is recognized that this property is multifactorial, involving retardation of gastric emptying, absorption reduction of carbohydrates, production of short-chain fatty acids, improvement of insulin sensitivity, and alteration in hormonal secretion (12, 43). These phenomena could be related to liquid retention caused by the presence of soluble fiber in the intestine, reduction of access to pancreatic enzymes in reaching the diet polysaccharides through the increase of chyme viscosity, and reduction of glucose diffusion by enterocytes. In so doing, the fiber acts by liberating the gastrointestinal-inhibiting peptide, cholecystokinin, and enteric glucagons hormones that, together with parasympathetic stimulation, promote retardation of gastric emptying, increasing intestinal motility and the release of insulin by the pancreas (43).

The results of this study suggest that dietary supplementation with A. sylvaticus fungus is capable of significantly reducing fasting glycemia in patients with colorectal cancer in the postoperative phase. This reduction results in beneficial effects on the metabolism of carbohydrates in these patients. Nevertheless, due to the lack of published studies, additional randomized clinical trials are necessary to determine other clinical conditions for which the adjuvant use of A. sylvaticus would be beneficial.

The contributions of each author to this study were as follows: R. C. Fortes, design, collection of data, analysis and interpretation of data, revision of the manuscript, and approval of the final version of the manuscript; V. L. Recôva, collection of data, analysis and interpretation of data, and revision of the manuscript; A. L. Melo, collection of data, analysis and interpretation of data, and revision of the manuscript; and M. R. C. G. Novaes, design, revision of the manuscript, and approval of the final version of the manuscript.

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Table 1. Results of the Hemogram Red Blood Series and the Serum Iron Tests of the Placebo Group

Table 2. Results of the Hemogram Red Blood Series and the Serum Iron Tests of the A. sylvaticus Group

Table 3. Results of the White Blood Series of the Placebo and A. sylvaticus Groups

Figure 1. Relationship between sex, fasting plasma glucose test, and BMI in patients of the placebo group.

Figure 2. Relationship between stage of colorectal cancer and fasting plasma glucose in the group supplemented with A. sylvaticus.

Received for publication June 9, 2008. Accepted for publication September 5, 2008.

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