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

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 $P \leq 0.05$ 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 ($P = 0.0001$), 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/m^2. 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.** Exp Biol Med 234:53–62, 2009

Key words: hematological; immunological; glycemia; *Agaricus sylvaticus*; cancer

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),

[1] To whom correspondence should be addressed at SHIS- QI 09- conjunto 06- casa 14- Lago Sul, Brasília-DF, Brasil. Cep: 71.625.060. E-mail: renatacfortes@yahoo.com.br

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

DOI: 10.3181/0806-RM-193
1535-3702/09/2341-0053$15.00

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 carcinogenesis 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.** The *A. sylvaticus* fungus (popular name, Sun Mushroom), was obtained from a producer licensed by the Brazilian Agropecuary Company–Embrapa, from the Tapiraí, São Paulo State. The fungus extract was obtained by soaking dehydrated material in hot water for 30 minutes, liquifying, bolting, 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), ergosterol (624 mg/100 g), proteins (4.99 g/100 g), amino acids (arginine 1.14%, lysine 1.23%, histidine 0.51%, phenylalanine 0.92%, tyrosine 0.67%, leucine 1.43%, methionine 0.32%, valine 1.03%, alanine 1.28%, 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: isotone (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

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

Red blood series	Initial	3 months	*P* value[b]	6 months	*P* value[c]	Reference values
Hemoglobin (g/dl)	13.84 ± 1.34	13.44 ± 1.65	0.06	13.74 ± 1.53	0.33	12–17.5 g/dl
Hematocrit (%)	42.09 ± 3.59	41.25 ± 4.58	0.13	42.37 ± 4.14	0.33	35–45%
Erythrocytes (10^6/μl)	4.77 ± 0.43	4.65 ± 0.45	0.13	4.76 ± 0.39	0.45	4.50–6.20 × 10^6/μl
MCV (fL)	88.80 ± 4.19	88.47 ± 5.57	0.33	89.18 ± 6.03	0.32	87 ± 7 fL
MCH (pg)	29.26 ± 1.89	28.81 ± 2.34	0.06	29.01 ± 2.59	0.23	29 ± 2 pg
MCHC (g/dl)	32.85 ± 1.08	32.57 ± 1.15	0.11	32.48 ± 1.13	0.06	35 ± 2 g/dl
Platelets (10^3/mm^3)	225.54 ± 64.38	230.07 ± 76.59	0.34	226.71 ± 64.65	0.47	150–450 × 10^3/mm^3
Iron (μg/dl)	88.51 ± 41.25	80.98 ± 33.24	0.17	72.97 ± 23.87	0.04	50–150 μg/dl

[a] Student's *t*-test and F test used. The values represent average ± SD.
[b] Comparison between initial values and values after 3 months.
[c] Comparison between initial values and values after 6 months.

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 photocolorimeter 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 $P \leq 0.05$.

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 I 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 women in the placebo group at both 3 months (from 13.58 ± 1.35 g/dl to 13.11 ± 1.78 g/dl, $P = 0.17$) and

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

Red blood series	Initial	3 months	*P* value[b]	6 months	*P* value[c]	Reference values
Hemoglobin (g/dl)	13.03 ± 2.54	14.10 ± 1.32	0.0001	14.36 ± 1.40	0.0001	12–17.5 g/dl
Hematocrit (%)	40.00 ± 6.91	42.53 ± 4.39	0.02	44.14 ± 3.73	0.0001	35–45%
Erythrocytes (10^6/μl)	4.63 ± 0.53	4.75 ± 0.48	0.24	5.00 ± 0.52	0.01	4.50–6.20 × 10^6/μl
MCV (fL)	86.26 ± 8.51	89.48 ± 4.86	0.0001	88.44 ± 5.03	0.01	87 ± 7 fL
MCH (pg)	27.79 ± 4.36	29.58 ± 1.90	0.0001	28.91 ± 2.32	0.0001	29 ± 2 pg
MCHC (g/dl)	32.01 ± 2.53	33.00 ± 1.38	0.0001	32.53 ± 1.15	0.0001	35 ± 2 g/dl
Platelets (10^3/mm^3)	244.36 ± 89.48	221.25 ± 51.53	0.01	228.25 ± 58.38	0.03	150–450 × 10^3/mm^3
Iron (μg/dl)	74.03 ± 23.41	90.09 ± 33.20	0.08	86.61 ± 31.70	0.12	50–150 μg/dl

[a] Student's *t*-test and F test used. The values represent average ± SD.
[b] Comparison between initial values and values after 3 months.
[c] Comparison between initial values and values after 6 months.

6 months (from 13.58 ± 1.35 g/dl to 13.24 ± 1.66 g/dl, $P = 0.32$) of the study.

Men treated with *A. sylvaticus* showed a significant increase in hemoglobin levels in the third month (from 13.51 ± 2.98 g/dl to 15.17 ± 0.85 g/dl, $P = 0.0001$) and in the sixth month (from 13.51 ± 2.98 g/dl to 15.28 ± 0.94 g/dl, $P = 0.0001$) of supplementation. Women also demonstrated significant increases of hemoglobin 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 ($P = 0.33$) after 6 months, when compared with the initial results (Table 1). 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 hematocrit 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 43.09 ± 3.27% to 42.31 ± 4.17%, $P = 0.53$) and a nonsignificant increase 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 nonsignificant 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%, $P = 0.86$).

The male group supplemented with *A. sylvaticus* presented initial hematocrit levels of 41.64 ± 7.58%, which were significantly increased to 45.99 ± 2.02% ($P = 0.0001$) within 3 months and to 46.47 ± 2.24% ($P = 0.0001$) after 6 months. The female group also presented a significant increase of hematocrit levels after 6 months (from 38.78 ± 6.32% to 42.4 ± 3.71%, $P = 0.05$), but the increase within 3 months of supplementation in women was nonsignificant (from 38.78 ± 6.32% to 39.95 ± 3.88%, $P = 0.07$).

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 analysis conducted according to sex, 5.40 ± 0.70 × 10^6/μl was used as the reference value for men's erythrocyte levels and 4.80 ± 0.60 × 10^6/μl was used for women's erythrocyte levels. The erythrocyte level was reduced for men in the placebo group within 3 months (from 4.90 ± 0.48 × 10^6/μl to 4.70 ± 0.51 × 10^6/μl, $P = 0.35$) to the end of the study (from 4.90 ± 0.48 × 10^6/μl to 4.81 ± 0.41 × 10^6/μl, $P = 0.59$). Women presented a reduction within 3 months (from 4.67 ± 0.39 × 10^6/μl to 4.62 ± 0.41 × 10^6/μl, $P = 0.53$) and an increase after 6 months (from 4.67 ± 0.39 × 10^6/μl to 4.72 ± 0.37 × 10^6/μl, $P = 0.61$); neither of these results was significant.

Men in the group supplemented with *A. sylvaticus* presented initial erythrocyte levels of 4.74 ± 0.60 × 10^6/μl; significant increases were observed after 3 months (5.11 ± 0.20 × 10^6/μl, $P = 0.0001$) and 6 months (5.15 ± 0.28 × 10^6/μl, $P = 0.02$). The women's group presented a nonsignificant erythrocyte level reduction within 3 months (from 4.55 ± 0.49 × 10^6/μl to 4.49 ± 0.46 × 10^6/μl, $P = 0.52$) and a significant increase after 6 months of supplementation (from 4.55 ± 0.49 × 10^6/μl to 4.90 ± 0.63 × 10^6/μl; $P = 0.01$).

Levels of mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) increased significantly ($P \leq 0.01$) in the group that received *A. sylvaticus* during the entire supplementation period, remaining within normal levels (Table 2). In the placebo group, no statistically significant alterations were found (Table 1).

In the placebo group, there was a significant reduction ($P = 0.04$) of serum iron levels after 6 months and a nonsignificant reduction within 3 months ($P = 0.17$; Table 1). Significance was not demonstrated in the group supplemented with *A. sylvaticus*, with increases of serum iron levels within 3 months ($P = 0.08$) and 6 months ($P = 0.12$) of supplementation (Table 2).

The reference ranges used for serum iron levels were 75.00–150.00 μg/dl for men and 60.00–140.00 μg/dl for women. The following alterations were observed in the placebo group. Men had an initial level of 105.80 ± 48.01 μg/dl; a nonsignificant reduction to 93.39 ± 37.44 μg/dl occurred at 3 months ($P = 0.31$) and, after 6 months, a significant reduction to 72.17 ± 23.41 μg/dl ($P = 0.05$) was noted, when compared with the initial values. Women of the placebo group presented nonsignificant reductions within 3 months (from 77.71 ± 32.74 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 significant increases of serum 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 treatment group presented nonsignificant reductions within 3 months (from 77.57 ± 19.46 μg/dl to 75.67 ± 17.91 μg/dl, $P = 0.77$) and 6 months (from 77.57 ± 19.46 μg/dl to 75.07 ± 27.79 μg/dl, $P = 0.77$) of supplementation. Platelets showed a discrete increase in the placebo group within 3 months and after 6 months of supplementation. The group supplemented with *A. sylvaticus* presented a significant reduction in platelets ($P < 0.05$) during the whole treatment period, remaining at a normal band.

In the placebo group, there were nonsignificant increases ($P > 0.05$) in lymphocyte levels, total lymphocyte count (TLC), monocytes, and eosinophils and nonsignificant reductions ($P > 0.05$) of leukocytes, neutrophils, and

Table 3. Results of the White Blood Series of the Placebo and *A. sylvaticus* Groups[a]

White blood series	Placebo group					*A. sylvaticus* group					Reference values
	Initial	3 months	*P* value[b]	6 months	*P* value[c]	Initial	3 months	*P* value[b]	6 months	*P* value[c]	
Leukocytes (10^3)	5.41 ± 1.66	5.78 ± 2.05	0.17	5.42 ± 1.46	0.48	7.55 ± 7.43	6.46 ± 1.76	0.41	6.04 ± 1.67	0.29	7.8 ± 3 × 10^3
Lymphocytes (%)	28.8 ± 9.78	28.07 ± 8.38	0.31	31.24 ± 11.39	0.08	29.72 ± 10.81	29.28 ± 8.61	0.79	29.06 ± 10.04	0.71	20–35%
TLC (/mm^3)	1550.18 ± 719.51	1580.80 ± 639.23	0.36	1656.11 ± 670.75	0.07	1733.90 ± 613.29	1806.62 ± 420.16	0.49	1647.06 ± 379.85	0.36	1200–2000/mm^3
Neutrophils (%)	57.91 ± 9.34	57.33 ± 12.05	0.36	56.61 ± 13.57	0.26	55.99 ± 11.89	60.62 ± 9.66	0.01	62.99 ± 10.27	0.0001	40–60%
Monocytes (%)	8.24 ± 2.40	7.67 ± 2.14	0.11	9.80 ± 13.65	0.27	7.05 ± 3.32	7.69 ± 2.41	0.26	7.80 ± 2.36	0.08	4–8%
Eosinophils (%)	4.26 ± 3.57	3.97 ± 3.26	0.28	4.28 ± 3.84	0.49	2.17 ± 1.35	2.33 ± 1.38	0.52	2.34 ± 1.49	0.53	2–4%
Basophils (%)	0.21 ± 0.19	0.24 ± 0.30	0.26	0.17 ± 0.20	0.17	0.18 ± 0.18	0.25 ± 0.24	0.22	0.18 ± 0.15	0.21	0–1%

[a] Student's *t*-test and F test used. The values represent average ± SD.
[b] Comparison between initial values and values after 3 months.
[c] Comparison between initial values and values after 6 months.

basophils after 6 months. Leukocytes showed increases within 3 months of supplementation, but this alteration was not statistically significant ($P > 0.05$; Table 3).

The *A. sylvaticus* group developed a significant increase ($P \leq 0.01$) of neutrophil levels and nonsignificant ($P > 0.05$) increases of monocytes and eosinophils after 3 and 6 months. The values of leukocytes, lymphocytes, and TLC presented discrete reductions in 6 months. However, nonsignificant increases ($P > 0.05$) of TLC and basophils were observed within 3 months of supplementation (Table 3).

Regarding the fasting plasma glucose test, the placebo group initially had an average glucose concentration of 94.36 ± 15.34 mg/dl. After 3 months, a significant increase to 98.12 ± 15.54 mg/dl ($P = 0.03$) occurred, with the levels remaining within the normal range (70–110 mg/dl). During the sixth month of supplementation, a significant increase was noted in the plasma glucose concentration, to 98.52 ± 9.03 mg/dl ($P = 0.01$), also with the values remaining within the normal range.

The group supplemented with *A. sylvaticus* initially had an average glucose concentration of 95.92 ± 11.64 mg/dl; after 3 months, a reduction to 94.88 ± 12.24 mg/dl was observed, which was not statistically significant ($P = 0.65$). In the sixth month of supplementation, a more significant reduction of fasting plasma glucose levels occurred, from 94.88 ± 12.24 mg/dl to 92.86 ± 6.82 mg/dl ($P = 0.01$).

The relationship between plasma glucose levels and body mass index (BMI) in the placebo group suggests that eutrophic patients ($n = 14$; BMI $\geq$18.5 and $<$25.0 kg/m^2) had better fasting glucose levels at the beginning of the study (91.93 ± 18.50 mg/dl) when compared with the levels in overweight ($n = 11$; BMI $\geq$25 and $<$30 kg/m^2) and obese ($n = 3$; BMI $\geq$30 kg/m^2) patients at the beginning of the study (97.15 ± 10.70 mg/dl). After 6 months, a statistically significant increase of plasma glucose was observed in eutrophic patients (from 91.93 ± 18.50 mg/dl to 96.31 ± 9.16 mg/dl, $P = 0.02$); the increase was not significant in overweight and obese patients (from 97.15 ± 10.70 mg/dl to 100.92 ± 8.62 mg/dl, $P = 0.25$).

When the groups were analyzed by sex, the women in the eutrophic group ($n = 8$) had lower initial glucose levels, 89.25 ± 12.09 mg/dl, compared with the overweight and obese patients ($n = 6$), 97.38 ± 13.26 mg/dl. After 6 months, an increase of glucose levels was evident in both groups, which was statistically significant in the eutrophic group (from 89.25 ±12.09 mg/dl to 95.29 ± 7.36 mg/dl; $P = 0.05$), but not significant in the overweight and obese group (from 97.38 ± 13.26 mg/dl to 100.14 ± 9.77 mg/dl; $P = 0.62$). Men of the eutrophic group ($n = 6$) and the overweight or obese group ($n = 5$) had practically the same levels of initial fasting plasma glucose (96.33 ± 13.71 mg/dl and 96.8 ± 5.97 mg/dl, respectively). After 6 months, both groups presented increases in glucose levels, but the increase was greater, although not significantly, in the overweight or obese group (from 96.80 ± 5.97 mg/dl to 102.00 ± 7.65 mg/dl; $P = 0.22$) than in the eutrophic group

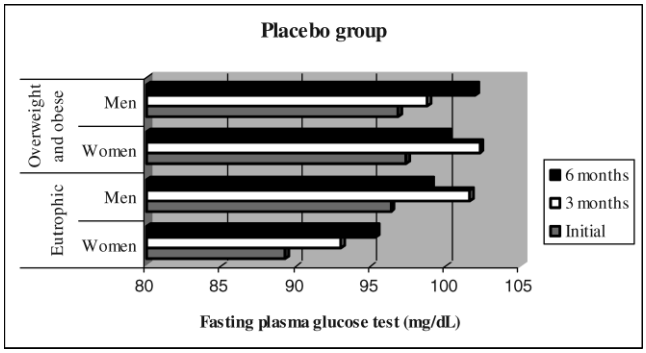

Figure 1. Relationship between sex, fasting plasma glucose test, and BMI in patients of the placebo group.

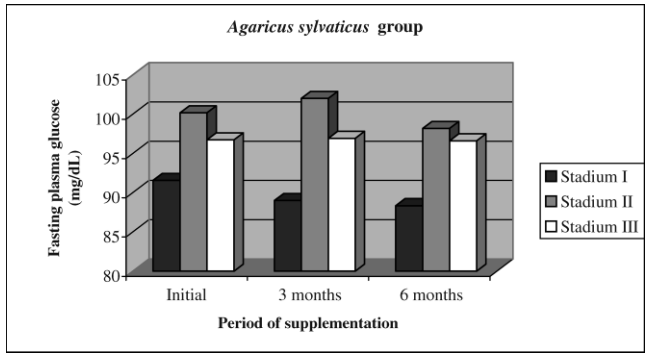

Figure 2. Relationship between stage of colorectal cancer and fasting plasma glucose in the group supplemented with *A. sylvaticus*.

(from 96.33 ± 13.71 mg/dl to 99.00 ± 11.55 mg/dl; $P = 0.74$) (Fig. 1).

In relation to glucose and stage of cancer in the placebo group, patients in stage I ($n = 4$) had lower initial glucose levels than did patients in stages II ($n = 10$) and III ($n = 14$), 87.67 ± 16.80 mg/dl, 95.64 ± 6.76 mg/dl, and 98.00 ± 16.35 mg/dl, respectively. In the sixth month of the study, all 3 groups presented an increase in glucose levels, with patients in stage I colorectal cancer maintaining lower levels (95.33 ± 10.69 mg/dl, $P = 0.16$; vs. 100.73 ± 8.99 mg/dl, $P = 0.09$ of patients with stage II; and 99.45 ± 8.80 mg/dl, $P = 0.06$ of patients with stage III).

In the group treated with *A. sylvaticus*, the relationship between plasma glucose levels and BMI was shown. At the beginning of treatment, fasting glucose levels in eutrophic patients ($n = 11$) were 95.00 ± 12.30 mg/dl and in overweight ($n = 14$) and obese ($n = 3$) patients were 97.67 ± 11.00 mg/dl. After 6 months of supplementation, nonsignificant reductions of plasma glucose levels were observed in both the eutrophic patients (from 95.00 ± 12.30 mg/dl to 91.00 ± 8.70 mg/dl; $P = 0.34$) and in the overweight and obese patients (from 97.67 ± 11.00 mg/dl to 96.93 ± 7.56 mg/dl; $P = 0.09$).

In the evaluation of the group supplemented with *A. sylvaticus* according to sex and BMI, we observed that eutrophic women ($n = 8$) had approximately the same levels of fasting plasma glucose as did patients who were overweight or obese ($n = 6$), 94.67 ± 13.59 mg/dl and 93.75 ± 10.19 mg/dl, respectively. At the end of the supplementation period, the eutrophic patients had a reduction of glucose levels (from 94.67 ± 13.59 mg/dl to 85.60 ± 5.94 mg/dl); however, this reduction was not statistically relevant ($P = 0.34$). In the overweight or obese group, consistent levels of fasting plasma glucose were maintained (from 93.75 ± 10.19 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).

Discussion

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 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 who were receiving

chemotherapy treatment. The supplemented group achieved significant increases of hematocrit and erythrocytes and nonsignificant increases of hemoglobin, MCV, MCH, MCHC, and iron, thus suggesting benefits for the hematological system of these patients. Novaes *et al*. (1), in a prospective, randomized, blinded, placebo-controlled study, evaluated the effects of the administration of *A. sylvaticus* extract in Wistar rats with ascitic Walker 256 tumors. The investigators observed significant improvement in hematological and immune function, with the probable mechanism of action consisting of inhibition of tumor growth and stimulation of the hematopoietic and immunological systems.

When the sexes were analyzed separately in our study, both men and women in the *A. sylvaticus* group presented significant increases of hemoglobin, hematocrit, and erythrocytes after 6 months of supplementation. These alterations were not observed in the placebo group. A significant reduction in the serum iron level occurred in both sexes in the placebo group; 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 physiopathology 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).

Despite the fact that platelet counts remained at normal levels in both groups, the placebo group had a nonsignificant increase during the entire study, while the *A. sylvaticus* group had a significant reduction of platelets during the third and sixth months of supplementation. This finding suggests that *A. sylvaticus* is capable of preventing common thrombocytosis in patients with malignant neoplasia.

The development of a persistent hypercatabolic condition in cancer, caused by protein-calorie malnutrition, threatens the immunological defenses of patients. This condition occurs through alterations in specific and nonspecific immunity components due to a functional deficiency of lymphocytes, granulocytes, and macrophages (7).

Some cytokines, such as interleukin-1, tumor necrosis factor-α (TNF-α), and interleukin-6, play an important role in cancer-associated cachexia. *In vivo* studies have demonstrated that rats with a deficiency of T and NK cells or specific molecules, such as γ-interferon (IFN-γ), interleukin-12, perforin, and TNF-α, have a higher incidence of tumors (7).

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 common. These alterations may be directly linked 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 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 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 produce nonsignificant immunological effects in individuals with normal parameters; however, the extracts are 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% reached complete tumoral remission and 20% did not achieve remission. The levels of erythrocytes, granulocytes, and giant nuclear cells returned to normal during the week 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 *Agaricales* fungus is the polysaccharide β-glucans. β-glucans may act in the human organism through immune function increase; stimulation and activation 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 glucans bind 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/m^2).

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 and *A. sylvaticus* groups in our study. Obesity is associated with hyperinsulinemia and a growing risk of neoplasia at sites such as the breast, prostate, and endometrium, but mainly in the colorectal area (20, 28). Hyperinsulinemia seems to be a determinant factor between colorectal cancer and several other types of cancer (16, 17, 19, 20, 32). Measures can be taken to reduce plasma insulin levels and peripheral resistance to insulin, such as energy restriction, high fiber consumption, and daily physical activities, all having a preventive effect or producing a delay in the growth of specific tumors (12, 20).

In obese individuals, the risk of carcinogenesis is statistically correlated with abdominal fat distribution. Abdominal obesity poses a higher risk of colorectal cancer than does generalized obesity. In adults, weight gain culminates with abdominal obesity, which in turn significantly increases the risk of colonic adenomas and colorectal carcinoma (12, 13, 28). However, in our study, visceral adiposity was not evaluated.

Some hypotheses, such as physical inactivity, high BMI, central adiposity, alcohol consumption, and a typical Western diet, might explain the accruement of colorectal cancer risk. The association of these factors with insulin resistance, hyperinsulinemia, and high levels of IGF may stimulate the growth of colorectal tumors (12–14, 16, 18).

Experimental studies with animals indicate that insulin administration can promote carcinogenesis, since the multiplicity of focus of aberrant epithelial cells in the intestinal cryptas and the production of sialomucin in female rats is augmented by the action of insulin, resulting in growth of the intestinal epithelium (28).

The action of insulin on its receptor can promote mitogenic stimulation for a long period of time. In normal physiological conditions, a reduction in the concentration of the insulin receptor on the cytoplasmic membrane results in an increase of plasma insulin levels. This does not occur in cancerous cells, which maintain a high number of receptors, independent of insulin levels. The insulin receptors of neoplastic cells lose their capacity to underregulate the binding sites of insulin, with a consequent increase of tumoral sensitivity to the stimulatory effects of this hormone. This abnormal subregulation and the dissociation of the biological action of insulin can offer diverse metabolic advantages to the cancerous cells. Additional studies are needed to investigate the role of insulin and IGF-1 in the process of carcinogenesis (28).

The metabolism of oncologic patients may be significantly altered as a consequence of the tumor's presence (33–35). It has been observed that alterations in the metabolism of carbohydrates in patients with cancer is due mainly to elevated glucose turnover, increase of gluconeogenesis (2, 36), and resistance to insulin (36), processes that will most likely culminate in hyperglycemia (36).

In this study, a significant reduction of fasting glucose levels in patients with colorectal cancer was observed after 6 months of dietary 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.

The gravity of the nutritional state of patients with colorectal neoplasia depends on the tumor's type and evolutive stage (37). To establish a correlation between fasting glycemia and stage of cancer, we noted that in both groups, patients with stage I cancer had lower glycemic

levels compared with patients with stages II and III colorectal cancer. These findings are in agreement with those in the literature, with scientific evidence demonstrating that peripheral glucose absorption is deficient in patients with cancer, even after the infusion of high doses of insulin, and that all alterations occurred in patients with more advanced stages of the disease. These findings suggest that there is an increment of glucose turnover as the tumor expands (36). However, after 6 months of supplementation with *A. sylvaticus*, all patients in the different stages of the illness presented a reduction of glycemic levels. These results were not observed in patients in the placebo group; the levels of glycemia in these patients had increased, although not significantly, suggesting once more that the bioactive substances present in *A. sylvaticus* fungus are capable of reducing plasma glucose levels.

Experimental studies carried out with rats with type 1 diabetes have demonstrated that the administration of *Agaricus campestris* fungus has important hypoglycemic action (9) through insulin secretion from the closure of the potassium-ATP canals, leading to membrane depolarization of pancreatic β-cells with consequent influx of calcium (38).

The antihyperglycemic action of *A. bisporus* has also been investigated and attested, demonstrating that this mushroom exerts its effect on insulin secretion and/or action (5).

Other studies have demonstrated that soluble polysaccharides present in the *Auricularia auricula-judae* fungus are capable of promoting significant glycemia reduction, insulinemia and glycosuria, besides increasing intraperitoneal insulin tolerance and the content of hepatic glycogen in rats (39).

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 m*M* in the supplemented group when compared with the placebo group (40).

We identified no studies in the literature that evaluated the effects of *A. sylvaticus* 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, proteoglucans, glucans, and arginine in *Agaricaceae* fungus. Scientific evidence shows that the substance responsible for the pharmacologic and nutritional attribute of mushrooms is β-glucans (2, 6, 7).

The ingestion of moderate amounts of fiber can improve glycidic 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 glycidic 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.

1. Novaes MRG, Garcez LCG, Melo A, Recova V. Effects of administration of *Agaricus sylvaticus* fungi on hematological and immunological systems of rats with walker-256 carcinoma. Fund Clin Pharmacol 18(S1):125–129, 2004.

2. Fortes RC, Novaes MRCG. Efeitos da suplementação dietética com

cogumelos *Agaricales* e outros fungos medicinais na terapia contra o câncer. Rev Bras Cancerologia 52:363–371, 2006.
3. Novaes MRCG, Novaes LCG. Fármaco-nutrientes em cogumelos comestíveis *Agaricales* e outros basidiomicetos. Rev Bras Nutrição Clínica 20:181–187, 2005.
4. Monro JA. Treatment of cancer with mushroom products. Arch Environ Health 58:533–537, 2003.
5. Novaes MRCG, Fortes RC, Garcez LC. Cogumelos comestíveis da família *Agaricaceae*: aspectos nutricionais e atividade farmacológica no câncer. Rev Soc Bras Farm Hosp 2(5):15–20, 2004.
6. Novaes MRCG, Fortes RC. Efeitos antitumorais de cogumelos comestíveis da família *agaricaceae*. Rev Nutr Bras 4:207–217, 2005.
7. Fortes RC, Taveira VC, Novaes MRCG. The immunomodulator role of β–D-glucans as co-adjuvant for cancer therapy. Rev Bras Nutr Clin 21: 163–168, 2006.
8. Sullivan R, Smith JE, Rowan NJ. Medicinal mushrooms and cancer therapy. Perspect Biol Med 49:159–170, 2006.
9. Wasser SP. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. Appl Microbiol Biotechnol 60: 258–274, 2002.
10. Borchers AT, Keen CL, Gershwin ME. Mushrooms, tumors, and immunity: an update. Exp Biol Med (Maywood) 229:393–406, 2004.
11. Toews VD. Power your immunity with mushrooms. Better Nutr 61(4): 58–60, 1999.
12. Campos FG, Waitzberg AGL, Kiss DR, Waitzberg DL, Habr-Gama A. Diet and colorectal cancer: current evidence for etiology and prevention. Nutr Hosp 20:18–25, 2005.
13. Fortes RC, Recôva VL, Melo AL, Novaes MRCG. Hábitos dietéticos de pacientes com câncer colorretal em fase pós-operatória. Rev Bras Cancerol 53:277–289, 2007.
14. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 131:3109–3120, 2001.
15. Kim Y.-I. Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? Nutr Rev 56:275–279, 1998.
16. Hsu IR, Kim SP, Kabir M, Bergman RN. Metabolic syndrome, hyperinsulinemia, and cancer. Am J Clin Nutr 86:867–71, 2007.
17. HagymÃisi K, Tulassay Z. [Role of obesity in colorectal carcinogenesis]. Orv Hetil 148:2411–2416, 2007.
18. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr 86:836–842, 2007.
19. Pierartz CZ, Rozowsky JN. Papel de la nutrición em la prevención del cáncer gastrointestinal. Rev Chil Nutr 33:8–13, 2007.
20. Cavalleira JBC, Saad MJA. Doenças associadas à resistência à insulina/ hiperinsulinemia, não incluídas na síndrome metabólica. Arq Bras Endocrinol Metab 50:360–367, 2006.
21. Recomendações da Sociedade Brasileira de Patologia Clínica/ Medicina Laboratorial para Coleta de Sangue Venoso. 1aedição. São Paulo, pp1–76, 2005.
22. Fortes RC, Novaes MRCG, Recôva V, Melo A. Hematological profile of patients of colorectal cancer submitted to dietary supplementation with *Agaricus sylvaticus* mushroom after six-month treatment. In: Proceedings of the World Congress of Public Health Nutrition/ VII National Congress of the Spanish Society of Community Nutrition. Public Health Nutrition; 2006 September 28–30, Barcelona, Spain, NS 2006.
23. Ouden M, Ubachs JMH, Stoot JEGM, Wersch JWJ. Whole blood cell counts and leucocyte differentials in patients with benign or malignant ovarian tumors. Eur J Obstet Gynecol Reprod Biol 72:73–77, 1997.
24. Leite AB, Silva HF, Nogueira OL. Trombocitemia essencial. Rev Bras Hematol Hemoter 23:49–51, 2001.
25. Chu KKW, Ho SSS, Chow AHL. *Coriolus versicolor*: a medicinal mushroom with promising immunotherapeutic values. J Clin Pharmacol 42:976–984, 2002.
26. Fortes RC, Novaes MRCG, Recôva V, Melo A The impact of dietary supplementation with *Agaricus sylvaticus* on immune function of post-surgical patients with colorectal cancer: a randomized, double blind, placebo-controlled clinical trial. In: Proceedings of the World Congress of Public Health Nutrition/VII National Congress of the Spanish Society of Community Nutrition. Public Health Nutrition, 2006 September 28–30, Barcelona, Spain: NS 2006.
27. Shimizu S, Kitada H, Yokota H, Yamakawa J, Murayama T, Izumi H, Yamaguchi N. Activation of the alternative complement pathway by *Agaricus blazei* Murril. Phytomedicine 9:536–545, 2002.
28. Halpern A, Mancini MC. Obesidade, hiperinsulinismo e câncer. In: Waitzberg DL. Dieta, nutrição e câncer. São Paulo: Atheneu, pp734–738, 2004.
29. Behall AM, Schofield DJ, Hallfrisch JG, Liljeberg-Elmståhl HGM. Consumption of both resistant starch and β-glucan improves postprandial plasma glucose and insulin in women. Diabetes Care 29:976–981, 2006.
30. Anisinov VN. Biology of aging and cancer. Cancer Control J Moffitt Cancer Ctr 14:23–31, 2007.
31. Anisinov VN. Carcinogenesis and aging 20 years after: escaping horizon. Mech Ageing Dev (in press), 2008.
32. Suba Z, UpjÃil M. Disorders of glucose metabolism and risk of oral cancer. Fogorv Sz 100:243–249, 2007.
33. Argilés JM, Busquets S, López-Soriano FJ, Figueras M. Fisiopatología de la caquexia neoplásica. Nutr Hosp 21(Suppl 3):4–9, 2006.
34. Planas M, Puiggrós C, Redecillas S. Contribución del suporte nutritional a combatir la caquexia cancerosa. Nutr Hosp 21(Suppl 3): 27–36, 2006.
35. Cardona D. Tratamiento farmacológico de la anorexia-caquexia cancerosa. Nutr Hosp 21(Suppl 3):17–26, 2006.
36. Rivadeneira DE, Evoy D, Fahey TJ III, Liemberman MD, Daly JM. Nutritional support of the cancer patient. CA Cancer J Clin 48:69–80, 1998.
37. Farriol M, Pons M, Roca N, Martínez M, Delgado G. Quimioterapia pre-operatoria y nutrición parenteral total en la neoplasia de colon. Nutr Hosp 21:303–306, 2006.
38. Gray AM, Flatt PR. Insulin-releasing and insulin-like activity of *Agaricus campestris* (mushroom). J Endocrinol 157:259–266, 1998.
39. Yuan Z, He P, Cui J, Takeuchi H. Hypoglycemic effect of water-soluble polysaccharide from *Auricularia auricula-judae* Quel. on genetically diabetic KK-Ay mice. Biosci Biotechnol Biochem 62: 1898–1903, 1998.
40. Lindequist U, Niedermeyer THJ, Jülich W-D. The pharmacological potential of mushrooms. eCAM 2:285–299, 2005.
41. Bourdon I, Yokoyama W, Davis P, Hudson C, Backus R, Richter D, Knuckles B, Schneeman BO. Postprandial lipid, glucose, insulin, and cholecystokinin responses in men fed barley pasta enriched with β-glucan. Am J Clin Nutr 69:55–63, 1999.
42. Cavallero A, Empillit S, Brighenti F, Stanca AM. High (1→3,1→4)-β-glucan barley fractions in bread making and their effects on human glycemic response. J Cereal Sci 36:59–66, 2002.
43. Catalani LA, Kang EMS, Dias MCG, Maculevicius J. Fibras alimentares. Rev Bras Nutr Clin 18:178–182, 2003.