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Life quality of postsurgical patients with colorectal cancer after supplemented diet with *Agaricus sylvaticus* fungus

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**Abstract**

**Introduction:** Therapeutical alternatives, directed to improve life quality and reduce adverse effects of cancer treatment, have been the purpose of studies that try to prove the immunomodulator efficacy of medicinal fungi as coadjuvant for conventional therapies.

**Objective:** The objective of this study was to evaluate the impact on the life quality of post-surgical patients with colorectal cancer after supplemented diet with *Agaricus sylvaticus* fungus cultivated in Brazil.

**Methods:** Randomized, double-blind, placebo-controlled clinical trial carried out at the Federal District Base Hospital-Brazil, for six months. Samples of 56 enrolled patients (24 men and 32 women), stadium phases I, II and III, separated as placebo and *Agaricus sylvaticus* (30 mg/kg/day) supplemented groups. Form-standard and direct anamnesis-standard were used to evaluate indicators for life quality. The method of analysis was qualitative and descriptive, processed with Microsoft Excel 2003 and Epi Info 2004 programs. The protocol was approved by the Ethics Research Committee-Health Department-Federal District.

**Results:** After six months of treatment, the supplemented group had increased adhesion to physical activity; improved disposition and good mood; reduced complaints of pains and alterations of sleep such as insomnia and restless sleep; presenting more appetite, reduced complaining of pains and alterations of sleep such as insomnia and restless sleep; presented more appetite, reduced constipation, diarrhoea, alternate diarrhoea/constipation, flatulence, flatus retention, pyrosis, postprandial fullness, nausea, abdominal distention and abdominal pain, facts not observed in the placebo group.

**Conclusions:** The results suggest that a dietary supplemented with *Agaricus sylvaticus* fungus is capable of improving the life quality of patients with colorectal cancer in post-surgical phase.

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**Resumen**

**Introducción:** Alternativas terapéuticas para mejorar la calidad de vida y reducir los efectos adversos de los medicamentos, han sido la propuesta de estudios que intentan probar los efectos de hongos medicinales en las terapias coadyuvantes de pacientes con cáncer.

**Objetivos:** El objetivo de este estudio fue evaluar el impacto en la calidad de vida de pacientes con cáncer colorrectal, en fase post-quirúrgica, que recibieron suplementación dietética de hongos *Agaricus sylvaticus* cultivados en Brasil.

**Métodos:** Estudio clínico, aleatorizado, ciego, placebo-controlado desarrollado en el Hospital de Base del Distrito Federal, Brasil, durante el periodo de seis meses. Una muestra de 56 pacientes (24 varones y 32 mujeres), estadios I, II y III, separados en 2 grupos: placebo y con hongos *Agaricus sylvaticus* (30 mg/kg/día). Patrones de presentación y anamnesis fueron empleados para evaluar los indicadores de calidad de vida. El método de evaluación fue cualitativo y descriptivo, procesado en los programas: Microsoft Excel 2003 y Epi Info 2004. El protocolo fue aprobado por el Comité de Ética en Investigación de la Secretaria de Salud de Distrito Federal, Brasil.

**Resultados:** Después de seis meses de tratamiento, el grupo con suplementación ha experimentado mayor adhesión a la actividad física, disposición, reducción de los dolores y disminución en las alteraciones en el sueño como el insomnio, mejora en el apetito, reducción en la constipación, flatulencia, pirosis, alteraciones gastrointestinales, náusea, disestesia y dolores abdominales, resultados no observados en el grupo placebo.

**Conclusiones:** Los resultados sugieren que la suplementación con hongos *Agaricus sylvaticus* fueron beneficiosos en la mejora de la calidad de vida en enfermos con cáncer colorrectal en el periodo post-quirúrgico.

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Introduction

In the United States, colorectal cancer represents, in both sex, the third leading cause of incidence and mortality and, in Brazil, the fifth most diagnosed neoplasia ranking as the fourth cause of cancer related death.1

The incidence of colorectal malignant tumor has increased in past years, particularly in people between 50 and 70 years-old, and the possibilities of development start by the fourth decade of life.2

Delay in diagnosis, stadium of illness and tumour aggression markers are some explanations for the favorable evolution of colorectal cancer in patients, greatly contributing for the decrease in life quality.3

Life quality may be defined as "the perception of the individual about his/her position in life according to cultural context, system of values in which he/she lives and, in relation to objectives, expectations, standards and concerns".4

The search for therapies to promote life quality in cancer patients with minimum collateral effects has encouraged researchers to regard phytotherapy as a safe co-adjuvant medicine. This is essentially true with the fungus from the Agaricaceae family, which presents stimulatory results on the immune system.5-11

The objective of this study was to evaluate the impact on the life quality of post-surgical patients with colorectal cancer after supplemented diet with fungus of the Agaricaceae family cultivated in Brazil.

Methods

Study design

The study consists of a randomized, double-blind placebo-controlled clinical trial. This was approved by the Health Ministry Research Ethics Committee-Federal District-Brazil, under protocol 051/2004. Terms of free consent were obtained from patients, who voluntarily participated after acknowledging the procedures of the study. The work was developed at the Ambulatory of Proctology in a Tertiary-Level Base Hospital of the Federal District in Brazil. The study was carried out from November 2004 to July 2006.

The sample

The sample consisted of 56 patients (24 men and 32 women), with colorectal cancer, stages I (n = 12), II (n = 16) and III (n = 28), divided in two groups: placebo and one supplemented with Agaricus sylvaticus fungus. Patients, aged twenty or older, with colorectal cancer in post-surgery phase, from three months to two years of surgical intervention, were included in the study; pregnant women, breast feeding infants, physically disabled patients, patients submitted to alternative therapy, patients with any other non transmissible chronic disease or undergoing metastasis processes were excluded.

Agaricus sylvaticus extract

The Agaricus sylvaticus was first described in Switzerland and has wide geographical distribution, occurring naturally in Brazil. Its identification was confirmed by fungus expert Dr. David N. Pegler of Royal Botanic Gardens of London whose paper was provided by the Botany Institute of the State Environment Secretariat, São Paulo on 10/11/1995.

The Agaricus sylvaticus fungus, family Agaricaceae, popularly known as “Sun Mushroom or Cogumelo do Sol”, was obtained from a producer from the Tapirai area in the countryside of São Paulo State. The fungus extract was obtained by soaking dehydrated material in hot water for 30 minutes, liquefied, bolted and dried in a drying box. The chemical composition of the final solution was analyzed by the Japan Food Research Laboratories Center by HPLC method and the results attested 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%, glicine-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, following pharmacotechnical procedures and the dosage supplemented to the group was the equivalent of 30 mg/kg/day, divided into two daily intakes (six tablets per day, three in the morning and three in the afternoon, between meals), considering the average weight of the studied population, during a six month period. The placebo group received the same number of tablets with resembling ingredients and the same amount of calories, but without Agaricus sylvaticus extract (received starch).

Clinical evaluation

Patients were monitored for six months. During the first three months consultations were scheduled every 15 days for clinical evaluation and towards the final months, every 30 days.

At first all patients remained on their usual diet, but throughout the treatment received general orientation on how to keep a healthy diet. After six months of accompaniment, all patients were prescribed a personal diet and were sent to other health professionals when necessary.

All patients were contacted by researchers weekly by telephone for clarifying any doubts, checking the adequate use of the mushroom according to orienta-
Life quality assessment indicators

To evaluate some life quality indicators, a form-standard and direct anamneses-standard method of analysis were used. The form-standard was applied on the first day of the consultation and anamneses-standard was applied during the following consultations. Both consisted on a questionnaire to assess quality of life, from the World Health Organization, the WHO-QOL-brief, adapted for study. All collection of data was carried through by researchers previously trained.

Habits considered as components of lifestyle were: sedentary activity, smoking, alcoholism, sleep and disposition alterations, mood, pain, gastrointestinal and appetite alterations.

In relation to sedentary activity, sedentary patients were considered as those who did not present any type of physical activity, at least once a week for at least 30 minutes.

Tobaccoism was defined as the smoking of cigarettes, cigars and the like, regardless of amount or type of consumption. Patients were classified as smokers (those who had been smoking for more than a year), ex-smokers (those who had quit smoking for at least a year) and non-smokers (patients who had never smoked).

Alcoholism was defined as the regular consumption of alcoholic beverage regardless of type, amount and/or frequency. Patients were characterized as alcoholics (patients who ingested some type of alcoholic beverage) and non-alcoholics (those who had quit drinking alcohol for at least one year or those who had never drunk).

In relation to alterations in sleep and disposition, patients were evaluated according to complaints of insomnia, restless sleep and classified as good-disposition and tiredness/fatigue respectively.

All patients were evaluated by means of symbolic images as happy/satisfied, not happy/nor sad, unfortunate/unsatisfied for the classification of mood. In relation to complaints about pains, the classifications were: cephalaea, rectal pain, abdominal pain, pain in post-surgery areas and others.

The gastrointestinal alterations evaluated were: constipation, diarrhea, alternate diarrhea/constipation, flatulence, flatus retention, abdominal distention, pyrosis, postprandial fullness, nausea, dysphasia, odynophagia, eructation, regurgitation, vomiting and abdominal pain.

Alterations in appetite (increased, decreased or unaltered) were investigated too.

Life quality indicators were assessed at three distinct occasions: before the beginning of treatment, within three months and after six months, with the exception of mood whose data was analyzed upon beginning and concluding research.

Statistical analysis

Patients were separated in placebo and *Agaricus sylvaticus* groups for the comparison of results. All results were analyzed in qualitative and descriptive form, using the Microsoft® Excel 2003 and Epi Info 2004 for Windows, version 3.3.2 programs.

Results

After six months of monitoring at the Ambulatory of Proctology of the Base Hospital-Federal District-Brazil, 56 patients with colorectal cancer had concluded the study, composing 32 women (57.1%) and 24 men (42.9%) divided in placebo and *Agaricus sylvaticus* groups (table I).

In the placebo group (n = 28), the average age was 59.14 ± 12.95 years. In relation to sex, 57.1% (n = 16) were female and 42.9% (n = 12) were male. The patients supplemented with *Agaricus sylvaticus* (n = 28) were between 56.34 ± 15.53 years of age. In relation to sex, female represented 57.1% (n = 16) and male 42.9% (n = 12).

In the placebo group, observations concluded that, 46.43% (n = 13) of patients were between the age of 45 and 60; 42.86% (n = 12) were between the age of 60 and 80 and only 10.71% (n = 3) were between 30 and 45 years old, and there were no individuals younger than 30 (table I). In the supplemented group, 46.43% (n = 13) of patients were between the age of 60 and 80; 35.71% (n = 10) were between 45 and 60 years old; 10.71% (n = 3) were younger than 30 and only 7.14% (n = 2) were aged between 30 and 45 (table I).

As for the stadium, 50.00% (n = 14) of patients in both groups belonged to stadium III. In stadium II, 35.71% (n = 10) of patients belonged to the placebo group and 21.43% (n = 6) belonged to the group which received *Agaricus sylvaticus*. In stadium I, 14.29% (n = 4) of patients belonged to the placebo group and 28.57% (n = 8) to the supplemented group (table I).

In both groups, observations concluded that 7.14% (n = 2) of patients were smokers. In the placebo group, 17.86% (n = 5) were ex-smokers and 75.00% (n = 21) non-smokers. In the supplemented group, 28.57% (n = 8) were ex-smokers and 64.29% (n = 18) had never smoked (table I).

Regarding alcoholism, 17.86% (n = 5) of patients supplemented with *Agaricus sylvaticus* related alco-
holic beverage consumption, while in the placebo group this number reached 10.71% (n = 3) (table I).

In both groups 7.14% (n = 2) of patients practiced some physical activity (table I). After six months of treatment, an increased number of patients were observed to have adhered to physical activity, 21.43% (n = 6) and 35.71% (n = 10) in the placebo and *Agaricus sylvaticus* groups, respectively (table II).

Throughout treatment, the placebo group showed decreased disposition from 85.71% (n = 24) to 78.57% (n = 22) and 64.29% (n = 18), after three and six months respectively, with consequent increase in tiredness/fatigue (table II). The group supplemented with *Agaricus sylvaticus*, showed opposite results with increased disposition, from 67.86% (n = 19) to 85.71% (n = 24) after three months, which remained stable until the end of treatment (table II).

Among patients of the placebo group, 14.29% (n = 4) related restless sleep at the beginning of treatment and 10.71% (n = 3) related the same after six months (table II). In the *Agaricus sylvaticus* supplemented group, 7.14% (n = 2) presented this complaint at the beginning of treatment, while 3.57% (n = 1) presented such at the end of supplementation (table II).

Insomnia was related by 7.14% (n = 2) of patients belonging to the placebo group and by 10.71% (n = 3) of the supplemented group at the beginning of accompaniment (table II). After six months, 28.57% (n = 8) and 7.14% (n = 2) of patients in the placebo and *Agaricus sylvaticus* groups remained with insomnia respectively (table II).

In relation to mood, it was observed in the placebo group that 64.29% (n = 18) of all patients initiated the study feeling happy/satisfied and 35.71% (n = 10) not happy/nor sad. In the *Agaricus sylvaticus* group, 60.71% (n = 17) initiated the study as happy/satisfied and 39.29% (n = 11) not happy/nor sad. In both groups no patient related the initial feeling of unfortunate/unsatisfied (table II).

After six months of treatment, the observed results were as follows: from the 64.29% (n = 18) of all patients in the placebo group that presented the initial feeling of happiness/satisfaction, 16.67% (n = 3) evolved to unfortunate/unsatisfied, 27.78% (n = 5) to indifference (neither happy/nor sad) and 55.55% (n = 10) remained in the same initial mood. In the *Agaricus sylvaticus* group, from 60.71% (n = 17) of all patients happy/satisfied, 88.24% (n = 15) remained in the same initial mood and only 11.76% (n = 2) evolved to indifference (table II).

With regard to 35.71% (n = 10) of all patients in the placebo group that initiated the study feeling neither happy/nor sad, 30.00% (n = 3) evolved to unfortunate/unsatisfied, 50.00% (n = 5) to indifference (neither happy/nor sad) and 20.00% (n = 2) evolved to

Table I

<table>
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<th>Placebo (n = 28)</th>
<th>Agaricus sylvaticus (n = 28)</th>
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<td>13</td>
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</table>

Fp = percentual frequency.
happy/satisfied. In the *Agaricus sylvaticus* group, 39.29% (n = 11) of those patients who had initiated the study with a feeling of indifference, 81.82% (n = 9) evolved to happiness/satisfaction and only 18.18% (n = 10) did not change mood (Table II).

With reference to pain, at the beginning of treatment, 64.29% (n = 18) of patients in the placebo group and 42.86% (n = 12) of patients in the *Agaricus sylvaticus* group complained about some type of pain. After six months, complaints increased to 71.43% (n = 20) among patients in the placebo group and were reduced to 32.14% (n = 9) in the supplemented group.

When complaints of pains were analyzed separately, observation saw reduced rectal pain in the *Agaricus sylvaticus* group, from 7.14% (n = 2) to 3.57% (n = 1), abdominal pain, from 14.29% (n = 4) to 7.14% (n = 2), and others, from 21.43% (n = 6) to 14.29% (n = 4), after six months of supplementation. On the other hand, in the placebo group, observation recorded an aggravation of the same pains instead, except for rectal pain which remained unchanged. In relation to cephalae, an increase was observed in both groups: from 3.57% (n = 1) to 17.86% (n = 5) after six months, in the placebo group and, from

<table>
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<th>Alterations</th>
<th>Placebo (n = 28)</th>
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<tr>
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<td>Initial Three months Six months</td>
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<tr>
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<td>n Fp n Fp n Fp</td>
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<tr>
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<td>19 67.86% 24 85.71% 24 85.71%</td>
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<td>Practical of physical activity</td>
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</tr>
<tr>
<td>Not-sedentary</td>
<td>2 7.14% 5 17.86% 6 21.43%</td>
<td>2 7.14% 4 21.43% 10 35.71%</td>
</tr>
</tbody>
</table>

Fp = percentual frequency.
3.57% (n = 1) to 10.71% (n = 3), in the Agaricus sylvaticus group (fig. I).

At the beginning of treatment, appetite was reported to have increased by 17.86% (n = 5) and by 10.71% (n = 3) in patients of the placebo and Agaricus sylvaticus groups respectively. In the third month of accompaniment, appetite increase was reported by a larger number of individuals: 32.14% (n = 9) in the placebo group and 28.57% (n = 8) in the Agaricus sylvaticus group (table II). After six months, only 7.14% (n = 2) of patients in the placebo group reported a steady improvement in appetite, while such event was reported by a larger number (32.14%, n = 9) of patients in the supplemented group (table II).

Appetite reduction was reported by a growing number of patients in the placebo group: 10.71% (n = 3), 21.43% (n = 6) and 35.71% (n = 10) at the beginning of treatment, within three months and after six months, respectively (table II). Apparently this reduction was milder in the Agaricus sylvaticus group, considering that at the beginning of supplementation, 7.14% (n = 2) complained about appetite reduction, within three months 17.86% (n = 5) and after six months 14.29% (n = 4) (table II). In the sixth month, 57.14% (n = 16) of patients in the placebo group denied any appetite alteration, while the same was reported by 53.57% (n = 15) of patients pertaining to the Agaricus sylvaticus group (table II).

At the beginning of the treatment, 28.57% (n = 8) of patients in the placebo group and 39.29% (n = 11) in the Agaricus sylvaticus group complained of constipation. Within three months, 35.71% (n = 10) of patients that belonged to the placebo group and 17.86% (n = 5) to the supplemented group with Agaricus sylvaticus continued this complaint. At the end of treatment, observation concluded that 25.00% (n = 7) in the placebo group remained constipated, while there were only 14.29% (n = 4) in the Agaricus sylvaticus group, evidencing apparent bowel system improvement in the supplemented group (table II).

Diarrhea was reported by 21.43% (n = 6) and 32.14% (n = 9) of patients in the placebo and Agaricus sylvaticus groups at the beginning of accompaniment respectively. After the periods of three months and six months, observation verified an increase of as much as 25.00% (n = 7) and a reduction to 17.86% (n = 5) respectively, in the placebo group and a reduction to 7.14% (n = 2) and 3.57% (n = 1) respectively, in the supplemented group (table II).

In the placebo group 7.14% (n = 2) of patients presented alternate diarrhea/constipation at the beginning of accompaniment, increasing to 10.71% (n = 3) after six months. In the Agaricus sylvaticus group, there were 3.57% (n = 1) of all patients with similar symptoms, a fact which discontinued after six months of supplementation (table II).

In relation to complaints of flatulence, the following results were observed after six months of accompaniment: 50.00% (n = 14) of patients in the placebo group presented no alterations in flatulence and 60.71% (n = 17) in the supplemented group. The other 50.00% (n = 14) belonged to the placebo group and reported an increase of flatulence from 39.29% (n = 11) to 46.43% (n = 13) after six months, while in the Agaricus sylvaticus group there was a reduction of 39.29% (n = 11) to 21.43% (n = 6) (table II).

Among patients of the placebo group, 85.71% (n = 24) had no alterations such as retention of flatus during the entire accompaniment period. Of the remaining patients, half reported an increase and the other half related a reduction of this retention after six months. In the Agaricus sylvaticus group, observation concluded that this complaint reduced from 10.71% (n = 3) upon the beginning of treatment to 3.57% (n = 1) upon completing the same (table II).

Abdominal distention was related by 25.00% (n = 7) of patients from the placebo group and 21.43% (n = 6) from the supplemented group. In three months of accompaniment, this number was reduced to 21.43%
(n = 6) in the placebo group and to 7.14% (n = 2) in the Agaricus sylvaticus group. Towards the end of treatment, the placebo group reported the same number of patients with this complaint as had been reported in the third month, while the Agaricus sylvaticus group reported only 3.57% (n = 1) of patients with this complaint (fig. 2).

As for the symptoms of pyrosis, postprandial fullness and nausea, no observation was made as to a reduction of these complaints in the placebo group after six months of accompaniment. In the Agaricus sylvaticus group, apparent improvement was observed in all aspects towards the end of supplementation (fig. 3).

During the entire accompaniment period, both in the placebo and Agaricus sylvaticus groups, no patients related dysphasia, odynophagia, excessive eructation, regurgitation or vomiting.

Discussion

In the present study, 57.1% of all patients belong to the female sex and 42.9% to the male sex. Such data corroborates with the estimates of the National Cancer Institute that indicate a predominance of colorectal cancer among women when compared with men.2

In the placebo and Agaricus sylvaticus groups, the average age was 59.14 ± 12.95 years old and 56.34 ± 15.53 years old, respectively. Such results are confirmed by literature, which indicates the highest incidence of colorectal cancer as being between 50 and 70 years of age showing increased risks for the development of this disease apart from the fourth decade of life.2

In respect of stadium, 50.00% of patients in the placebo and Agaricus sylvaticus groups belonged to
individuals. Malignant neoplasia when compared to non-alcoholic groups stated regular use of the substance. Ex-smokers, respectively. As for biliary acid metabolism and a boosted reduction of contact of carcinogens with intestinal this effect includes: reduction of intestinal transit time, improvement on prostaglandin levels, modification of the biliary acid metabolism and a boosted immune system. In reference to the life quality, among others aspects, fatigue is included as lack of motivation. Fatigue is highly prevalent and is a debilitating and chronic symptom in patients with cancer, diagnosed in this population during and after adjuvant treatment. Patients with cancer often suffer from nausea, vomiting, diarrhea, reduced appetite and unwanted weight loss, accrued by symptoms such as pain and fatigue. These symptoms generally interfere in the performance of daily activities such as work, household chores, leisure activities, and the physical disposition to socially interact, all of which affect life quality indicators. Decline in disposition was also observed in the placebo group with consequent increase in tiredness/fatigue throughout accompaniment. Inverse results were found in the Agaricus sylvaticus group, which contrarily showed better disposition and reduction of tiredness/fatigue after three months of supplementation, and remained until the end of treatment. Scientific evidence demonstrates that fatigue may persist for months or years after completing treatment, being efficient with a minority of patients only. Fatigue in cancer is a multifactor and some promising mechanisms have been identified including disturbed sleep, psychological stress, pain, among others symptoms, involving severe mental, physical and emotional settings.

This study also showed that in the Agaricus sylvaticus group insomnia and restless sleep were reduced after six months of supplementation. Such results were not found in the placebo group. Cancer development and associated symptoms are in direct relation with clinical depression, deepening functional damage with consequent deterioration in life quality. Sadness, anger, anxiety and anguish are negative emotional responses often observed in cancer patients that, once intense and long lasting, may culminate in the diagnosis of depression.

Scientific research has shown that depressed patients present triple the risk of non-adhesion to treatment when compared with patients exempt of depressive symptoms. The diagnosis of depression in oncolgical patients is based on symptoms such as downhearted, insomnia, difficulty to cooperate with treatment procedures, low self-esteem, guilt- and death-related feelings, lost hope, lack of pleasure and goals in life, which should be detected as early as possible.

In the present study, observation noted, in the Agaricus sylvaticus group, an improvement in moods of happiness/satisfaction with consequent reduction of indifference after six months of supplementation. These results were not found in the placebo group, which presented a reduction of happiness/satisfaction and an increase of unfortunate/unsatisfied patients.

Studies have evidenced that in patients with cancer, depressive symptoms may occur owing to different factors such as a lack of regulation of the hypothalamus-pituitary-adrenal and thyroidene axes, oscillations of the immune function of Natural Killer (NK) cells, reduction of the growth hormone secretion, alteration of circadian rhythm, presence of metabolic alterations further to the use of specific medications such as corticoids, tamoxifen and interferon-alpha (INF-α). The activation of pro-inflammatory cytokines as interleukins 1 and 6 (IL-1 and IL-6) is also capable of inducing modifications in neuronal function as well as promoting activation of the hypothalamus-pituitary-adrenal axle. Cancer is frequently associated with pain, which, in turn, alters affectivity, function, appetite, sleep, causes depression, in addition to increasing the risk of suicide. Patients with cancer may present association between chronic pains and emotional distress. Of hospitalized oncological adult patients, 58% to 80% suffered pain, whereas moderate and intense pains are present in 30% to 40% in intermediate stages and about 87% in more advanced phases of the disease.

Of all patients belonging to placebo and Agaricus sylvaticus groups, respectively, 64.29% and 42.86% complained about pains before the beginning of treatment.
After six months, observation noted an increase of up to 71.43% of such complaints in the placebo group and a reduction of 32.14% in the supplemented group.

Upon analyzing complaints of pains separately, observation noted, in the Agaricus sylvaticus group, a reduction of rectal, abdominal and other pains after six months of supplementation. On the other hand, in the placebo group, observation noted an increase of these symptoms, with the exclusion of rectal pain, which remained unchanged during this period. Cephalgia was aggravated in both groups during the entire accompaniment period, worsening in the placebo group.

A study has proven that parenteral administration of proteoglycans extract of medicinal fungus allied to chemotherapy is capable of extending survival time, restoring immunological parameters and improving life quality of colorectal cancer patients and others carcinomas in comparison to patients treated with chemotherapy only.23

Other studies showed that a supplemented diet with Agaricus sylvaticus fungus in colorectal cancer patients during chemotherapy treatment for three months was capable of improving disposition in 55% of the subjects, absence of alterations in 36% and only 9% related loss of heart. These alterations were not observed in the placebo group, which felt dizziness (28%), pains (27%), insomnia (18%), weakness (9%) and absence of alterations (18%).9

In the beginning of treatment, an increase of appetite was related by 17.86% of all patients in the placebo group and by 10.71% of all patients in the Agaricus sylvaticus supplemented group. After six months, only 7.14% of patients in the placebo group related a steady increase of appetite, while in the supplemented group, this had increased by 32.14%. Simultaneously, appetite was decreasing in patients of both groups, though less severe in the supplemented group, evidencing again a possible bioactive effect of Agaricus sylvaticus fungus.

One of the most common symptoms that affect oncological patients is a lack of appetite, which can culminate in anorexia. Anorexia affects about 40% of cancer patients at diagnosis, and more than 2/3 in advanced stadiums of the disease. This constitutes the main cause of alimentary deficit as a result of tumoral and/or mechanical effects, inducing progressive inanition with consequent alteration of nutritional state and immunological status likely to culminate in cachexia26. The main cytokines involved in the geneses of cachexia include: TNF-α (tumor necrosis factor-alpha), IL-1 (interleukin-1), IL-2 (interleukin-2), IL-6 (interleukin-6), IFN-γ (interferon-gamma), leukemia inhibitory factor (LIF) and prostaglandin E (PGE).26

Oncological patients complain about reduced feeding capacity mainly due to slow digestion and gastric emptying resultant of reduced production of digestive secretions, gastric mucosal and gastric muscular atrophy.24 Other factors commonly presented by patients with malignant neoplasia are also able to significantly influence the appearance of anorexia such as: dyspha-sia, odynophagia, nausea, anxiety, fear of vomiting, depression, dehydration, constipation, postprandial fullness, amongst others.18,21,22,24

Other studies have demonstrated that the administration of extracted polysaccharides from medicinal fungus can improve appetite, reduce fatigue and stabilize hematopoietic parameters.25 Scientific evidences show that the substance mainly responsible for the immunomodulator effects of mushrooms is the polysaccharide β-D-glucan. The β-D-glucan act in the human organism through the increase of immunological functions, stimulation of NK cells, lymphocytes T, lymphocytes B and complementary cells, increase the number of macrophages and monocytes, promoting the proliferation and/or production of antibodies and some cytokines as IL-2 e IL-6, IFN-γ, TNF-α and, likewise, preventing regeneration and metastasis of cancer.27

In the beginning of the study, 28.57% of patients from the placebo and 39.29% from the Agaricus sylvaticus groups related constipation. After six months, only 14.29% of patients in the supplemented group remained constipated. These results were not observed in the placebo group, once more an inferring bioactive effect of Agaricus sylvaticus fungus.

Constipation is a common symptom in oncological patients as a consequence of anorexia-cachexia syndrome and its frequency is higher in patients with advanced illness and patients using medication for pain suppression.26 Several factors, other than pain and drug therapy, contribute to the delay of intestinal motility such as: reduction of intestinal content due to routine exams, surgeries, dietary inadequacy, metabolic and emotional disorders. When prolonged, constipation may culminate in diverse manifestations, such as: colic, nausea, vomiting, respiratory failure caused by the rise of the diaphragm, cephalgia, dehiscence of sutures etc.25 The difficulties and discomfort succeeding constipation are associated to a sensation of incomplete rectal emptying followed by abdominal pain, flatulence, abdominal distention and anorexia.26

Patients belonging to the placebo and Agaricus sylvaticus groups, 21.43% and 32.14% respectively, related diarrhea at the beginning of the accompaniment. Throughout the treatment, observation noted a reduction in episodes of diarrhea in the Agaricus sylvaticus group. These results were not found in the placebo group.

Patients with malignant neoplasia suffer constant periods of anxiety and anguish followed by appetite reduction and diverse symptoms of stressful and traumatic events. Amongst the main symptoms of anxiety are: excessive worry and fatigue, pains, dizziness, nausea, abdominal discomfort and, mainly, diarrhea.22

In the placebo group a greater number of patients related alternate diarrhea/constipation after six months of accompaniment. These results were not observed in the Agaricus sylvaticus group, since these symptoms did not appear after six months of supplementation.
A randomized, placebo-controlled, double-blind clinical trial has demonstrated that supplemented diet with *Agaricus sylvaticus* fungus in postoperative patients of colorectal cancer undergoing chemotherapy, significantly improved gastrointestinal function such as episodes of diarrhea and constipation when compared with the placebo group.8

Besides β-D-glucans, medicinal fungus possess high amounts of other fibers.5,7 The gastrointestinal benefits obtained from the use of dietary fibers are evident, since fibers do not undergo any action of digestive enzymes and, through fermentation of colonic bacteria, produce short-chain fatty acids that exert trophic effects on the intestinal mucosa, creating more bulk, reducing intestinal transit time thus protecting the effects on the intestinal microbiota, creating more bulk, reducing intestinal transit time thus protecting the colon of cytotoxic substances. Likewise, this reduces intraluminal pressure as a result of softer stools, increases bacterial proliferation having a modulator effect on intestinal microbiota, stimulates a laxative effect made possible by insoluble fibers.26,27

In the present study, observation noted a reduction of flatulence, flatus retention and abdominal distention complaints in the supplemented group after six months. These results were not observed in the placebo group, demonstrating an important immunomodulator role of the *Agaricus sylvaticus* fungus. Flatulence, flatus retention and abdominal distention may be the consequence of constipation.24,26 Medicinal fungi are capable of bringing relief from these symptoms through the beneficial effects provided by fibers on intestinal microbiota.

At the end of treatment, observation noted an apparent improvement on the pyrosis, postprandial fullness and nausea symptoms in the *Agaricus sylvaticus* group, results not observed in the placebo group, again evidencing bioactive effects of *Agaricus sylvaticus* fungus.

Other manifestations can also be triggered by intestinal disorders such as constipation, nausea, colic and vomits among others.22 Alterations of the emotional state may also culminate in diverse epigastric related conditions, and might persist for days and/or last almost an entire day.21

Discomfort owing to constipation may be associated with abdominal pain,24,26 a symptom commonly found in colorectal cancer patients, partially explaining the effects observed in the supplemented group.

Clinical studies have demonstrated that polysaccharides present in medicinal fungus are capable of alleviating toxic reactions caused by antineoplastic medication, inhibit proteic synthesis of neoplastic cells, normalize the bowel system, act favorably in lipidic metabolism, promote relief from symptoms suffered by oncological patients, stimulate the immunological and hematological systems, enhance life quality and prolong the survival of individuals bearing cancer.5,10,29

In the present study, observation noted an improvement of practically all indicators evaluated in the supplemented group mainly when compared with the placebo group, demonstrating possible presence of bioactive substance in *Agaricus sylvaticus* fungus which is able to improve the life quality of these patients.

Studies demonstrate the capacity of extracted proteoglycans of medicinal fungus to increase the survival of patients with diverse types of malignant neoplasia, including colorectal cancer, besides improving life quality and promoting relief from symptoms in 70% to 97% of patients with cancer.3,25,29 It is believed to be the probable active mechanism related to the stimulation of the immunological functions, macrophages fagocitary activity and the improvement of the reticulum-endothelial system functions.6

In addition to proteoglycans, several other bioactive substances are present in medicinal fungus such as glucans, lectin, ergosterol, triterpenes, arginine and glutamine. The active mechanism of these substances has not been completely elucidated in literature, but scientific evidence suggests that these bioactive components may modulate the carcinogenesis process at the stages of initiation, promotion and progression and, therefore, promote additional benefits to patients with diverse types of cancer.6

It should be emphasized that no evidence has been found in the literature reporting adverse, side effects and toxicity in pharmacology and nutrition studies conducted in animals and clinical trials related to commercialized fungus species for human consumption11. In vivo studies of acute toxicity of *Agaricus sylvaticus* have shown that this species presents no toxicity, since there were no clinical, hematological and/or hystopathological alterations in the animals studied.12

Promising results suggest that supplemental dietary administration with *Agaricus sylvaticus* fungus is capable of improving the life quality of patients with colorectal cancer in post-surgical phase. Nevertheless, further studies should be carried out so as to indicate the safe dosage needed by different diseases in order to obtain its thorough benefits and effectiveness.

References


