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Benefits of ß-glucans in patients with breast cancer: systematic literature review

Benefícios das ß-glucanas em pacientes com câncer de mama: revisão sistemática da literatura

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Abstract

Abstract: Breast cancer is the most prevalent cancer, totaling 50 thousand new cases per year, as well as being responsible for a high annual mortality rate. Some preventive measures are simple and easy to carry out, such as practicing physical activities, eating a healthy diet, not smoking, avoiding drinking alcohol, carrying out self-examinations and mammograms frequently. Several recent studies have demonstrated that the consumption of nutraceuticals rich in beta-glucans (ß-glucans) can have a positive impact on both the prevention and treatment of breast cancer. ß-glucans are natural polysaccharides found in the cell walls of fungi and yeast that promote the stimulation of cells that make up the immune system and modulation of tumor cells.

Keywords: ß-glucans; Breast cancer; benefits of ß-glucans; modulation of the immune system; nutraceutical.

Resumo

O câncer de mama é o cancer de maior incidência, totalizando 50 mil novos casos por ano, assim como é responsável por uma elevada mortalidade anual. Algumas medidas preventivas são simples e de fácil realização como, por exemplo, praticar atividades físicas, ter uma alimentação saudável, não fumar, evitar a ingestão de bebidas alcoólicas, realizar autoexames e exames mamográficos frequentemente. Diversos estudos recentes demonstraram que o consume de nutracêuticos ricos em betaglucanas (ß-glucanas) pode produzir um impacto positivo tanto na prevenção quanto no tratamento do câncer de mama. As ß-glucanas são polissacarídeos naturais encontrados nas paredes celulares de fungos e leveduras que promovem a estimulação das células constituintes do sistema imunológico e modulação das células tumorais.

Palavras-chave: ß-glucanas; Câncer de mama; benefícios dos ß-glucanas; modulação do sistema imunológico; nutracêutico.

Introduction

Currently, cancer ranks among the leading causes of morbidity and death worldwide. It also drives up the cost of diagnosis and appropriate treatment, which is administered using a variety of therapeutic modalities, the most notable of which are immunotherapy, chemotherapy, radiation, and surgery [1-3]. Since these biochemical activities are linked to cellular signaling cascades and are unquestionably crucial for normal cellular functioning, they are mostly responsible for the malignancy and invasiveness of many malignancies, also for the exchange of vital events that enable the existence of basal cellular activity and the interaction of the cell with its surroundings. Thus, these molecular events govern the existence and upkeep of the state of cellular dynamic balance, which permits the cell to accomplish tissue repair, whether by regeneration or scarring, as well as preventing or lowering the risk of neoplastic cell emergence and growth [4,5], since mistakes in cell signaling cascades or intercellular interactions can result in diseases like, for instance, a variety of cancer types.

Breast cancer is the most common cancer among women, according to published data from the World Health Organization, with approximately 1.6 million new cases diagnosed worldwide each year

[6]. Nowadays, mammography has become the most efficient method for detecting this deadly illness. Moreover, in 2006, in the southeast of Brazil, breast cancer emerged as the tumor with the highest incidence, totaling 73 new cases per 100,000 women [7]. Due to these circumstances, it is a matter of public health concern. Even though the major development in breast cancer treatment, drug resistance has been one of the main causes of relapses and death. Studies have shown that various natural components have a huge variety of biological proprieties that represent promising options in the discovery of new treatments [8].

Development in the research field has evidence that ß-glucans, a natural polysaccharide from monomers of D-glucose, is found in the cellular walls of vegetables, fungi, and bacteria. When it encounters a human organism, it activates an immunologic receptor that triggers the immune cells, increasing phagocytosis and activating the adaptative and innate responses. The analysis of nonclinical models of breast cancer revealed that the mechanisms of the polysaccharides involve apoptosis, inhibition of the proliferation of the cells and angiogenesis, and antimetastatic by multiple's vias, in this matter ß-glucans and fucoidan are the most popular polysaccharides in the studies and their mechanism [8].

The anticancer effects caused by ß-glucans include inhibiting tumor growth in the promotion phase, the initial stage of transformation to malignant cells. Moreover, anti-angiogenesis prevents the formation of new blood vessels, reducing tumor metastasis. Likewise, ß-glucans can be used as an adjuvant in aggressive treatments such as chemotherapy, radiotherapy, and monoclonal therapy, because the antibody monoclonal that activates the complement system and opsonization of tumoral cells is induced by the presence of polysaccharides [2].

The human organism is not capable of producing ß-glucans, in this matter, their immune system does not recognize this component. Therefore, there is a response of the innate system through the pattern recognition receptor (PPR), expressed by immune cells but also found on other types of cells. The most important PPRs for ß-glucans are dectin-1, complement 3 receptors (CR3), and toll-like receptors (TLR) distributed in different cells e.g. macrophages, monocytes, dendritic cells, neutrophils, eosinophils, and natural killer cells, as well as intestinal epithelial cells (enterocytes). The connection between ß-glucans and dectin-1 induces an immune response, activating the production of cytokines by the macrophage, dendritic cells, and oxidative pathways. This bond induces a cascade of adaptative and innate immune responses, such as phagocytosis, activation of oxidative pathways, and cytokine production in dendritic cells and macrophages, both antigen-presenting cells [9].

ß-glucans solubility is classified as a portion being soluble and other as insoluble, both stimulate the immune system but in different ways. Studies have shown *in vivo* and *in vitro* that the insoluble portion, also known as particulate, is engulfed by the macrophages and dendritic cells through dectin-1, which is an essential receptor for the activation of the dendritic cells that consequently will mediate the differentiation of Th into Th1 and elevate the cytotoxicity of the lymphocytes TCD8. On the other hand, the soluble portion has the capacity to connect directly to the receptor CR3, stimulating an immunological response coordinated by the complement system depending in specific antibodies [9].

Objective

To analyze the available evidence in the recent literature on the ß-glucans use in breast cancer.

Materials and Methods

The primary search was conducted on the PubMed database. The articles included were published between 2010 and 2023 in Portuguese, English, or Spanish, identified through searches using the following terms: 'ß-glucans,' 'breast cancer,' and 'ß-glucans and breast cancer,'. A total of 78 research publications were identified. Thirty-two potentially relevant papers were initially screened based on their titles. Of these, 29 were further assessed based on their abstracts, resulting in the exclusion of 8 papers deemed unreachable. After a thorough review, 21 relevant articles were selected to form the final sample for this investigation.

The objective of this literature review is to examine the role of ß-glucans in patients with breast cancer, focusing specifically on the female gender. Selected articles met the research objectives by analyzing the efficacy and usage of ß-glucans as a new medication, with a focus on understanding their benefits as a medication and adjuvant therapy in the treatment of breast cancer in women.

Eligibility criteria

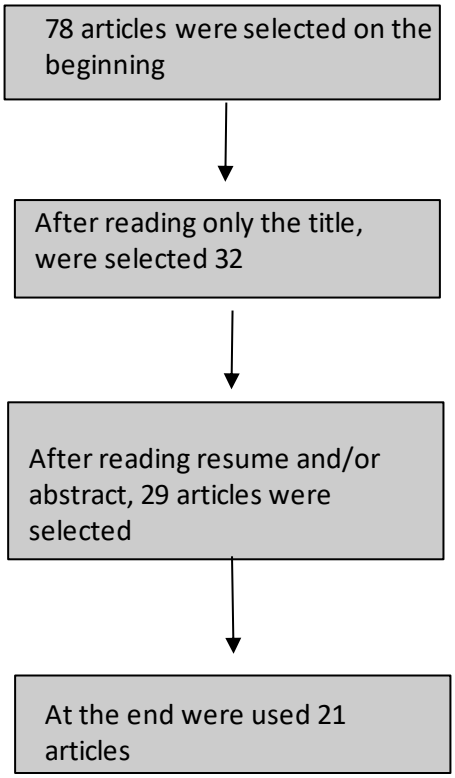
The selected articles described the benefit and effectiveness of the use of ß-glucans, from the perspective of the efficiency of the treatment in female patients diagnosed with breast cancer.

In this matter, bibliography review, systematic review, journal articles, and monograph of the product were selected. Articles that used animals in their trials were only selected if they followed the ethics and bioethical norms. Articles that were not found in the complete version were excluded.

Selection process

The study was conducted by two reviewers who analyzed the initial sample separately, applying the same inclusion and exclusion criteria, and both reached the same final sample. For the analysis, Microsoft Excel was used to organize the articles to generate a table from the databases by applying the filters selected descriptors and articles published in the last 13 years. All selection was performed manually by the reviewers without associated tools, and under this circumstance were used the criteria already mentioned before, therefore selecting 21 articles (Figure 1).

Figure 1. Flowchart of the research method used.



Source: Data collected by the authors.

Results

A total of 21 articles were included in the analysis aiming to understand if the use of ß-glucans is or isn't beneficial in patients with breast cancer. One study made in Germany, by Auinger, focused on showing the relation between the supplementary use of ß-glucans and the incidence of the flu. On this matter, 162 healthy individuals were selected and then separated into two groups. The first group had 81 patients that received one dose of 900mg of ß-glucans for 16 weeks, the second group had the same number of patients that received 900mg of placebo for 16 weeks. Results evidenced that the use of ß-glucans decreased in 25% the incidence of the flu (p=0,041), having positive effects on health and the patient's immunity [9].

The University of Southampton in England collected information on 100 individuals between the ages of 50 to 75 years old; those members were divided into two different groups, one half receiving the placebo and the other ß-glucans. The study occurred for 90 days at the peak of the flu outbreak.

The results showed that the daily use of this medication increases the immunity against respiratory infection and decreases the durability of the symptoms [9]. Moreover, other research pointed out that ß-glucans increase apoptosis in MCF-7 and LCC 9 cells. Thus, trials were made aiming to study and confirm cellular death through the intracellular activity of the esterase and integrity of the plasmatic membrane. The results of this trial were positive, once it was confirmed that beta-D-glucan increases the cellular death of MCF-7 and LCC9 [10].

In the same trial, a PCR array of 84 genes was conducted to investigate the broad impact of ß-glucans. This process aimed to identify additional genes potentially involved in breast cancer that could be regulated by ß-glucans. During the experiment, MCF-7 or LCC9 cells were deprived of serum for 48 hours in a phenol-free environment and then treated with DMSO (vehicle control). The ß-glucans altered the expression of 17 genes in MCF-7 cells: 9 were upregulated, 8 were downregulated, and some genes showed a dose-dependent relationship [10].

According to another study that is being conducted by the nutritionist Clisia Mara Carreira in the State University of Londrina (UEL), Laboratory of Genetics and Toxicology, women with the diagnosis of breast carcinoma will be gathered and, in this population, will be analyzed the efficiency of the ß-glucans. Will be selected 250 women who are going to be evaluated for about 2 years. Half of the group will be using ß-glucans and the other will be using a placebo [3].

Another study researched the medical mushroom of "tiger milk", *Lignosus rhinocerus*. This fungus has the capacity to heal various diseases and anticancer activity that is being explored. The "white rot" fungus is of the Basidiomycetes class and Polyporacea family [9]. Once analyzed, the chemical composition of the "tiger milk" was found to be 46-68% glucan (beta-D-glucan) [9]. It is the most present polysaccharide in the cellular wall of this fungus [1].

Furthermore, during the study, it was evidenced that a fraction of the cytotoxic protein purified named F5 of the extract from sclerotia cold water extraction of the mushrooms consists mainly of serine proteases by LC-MS/MS which have selective cytotoxicity against the breast adenocarcinoma MCF-7. The F5 fraction was purified and showed a high selectivity cytotoxic against MCR7 cells with IC 50 184B5 a 7,60ug/ml. The substance was classified as a serine protease and was identified as having proteolytic and cytotoxic activities [6].

Regarding various types of ß-glucans, a study [11] compared the different origins with their action on the cancer cells, based on clinical trials, as evidenced in table 1.

Table 1 - Origin, effects, and disadvantages of each ß-glucan studied.

Letninus edodes	***Sparassis crispa***	***Agaricus ablazei***	***Pleurotus osteatus***
Cell proliferation of macrophages, lymphocytes and induce the production of TNF-a, but poorly absorbed in the gastrointestinal tract	Inhibited the suppression of B-10F16, therefore suppressing tumor metastasis when orally administrated in mice	Anticancer activity *in vivo* and *in vitro* studies	Was observed to be more effective in suppressing proliferation of breast cancer (MCF-7 and MDA-MB-23), than other ß-glucan derived from other mushrooms

Source: Data collected by the authors.

Most of the articles analyzed evidenced that the use of ß-glucans had an immunomodulatory effect, through the receptor Dectin-1 and PPR. Therefore, the polysaccharide can "train" the immune system by various mechanisms explained in table 2. In the same table, was described the mechanism involving metastasis and inhibition of growth, in which different types of biological origin had the same or different pathway.

Table 2 - Authorship, article title, and key findings.

Title	Authorship	ß-glucan studied	Mechanisms	Results
In-depth spectral characterization of antioxidative (1,3)-ß-D-glucan from the mycelium of an identified tiger milk mushroom *Lignosus rhinocerus* strain ABI in a stirred-tank bioreactor	Usuldin et al.	*Lignosus rhinocerus*	ß-D-glucan represented 90% of the total glucan in the aqueous extracts of mycelium *L. rhinocerus* strain ABI (LRSA). LRSA was morphologically identified through biomolecular characterization.	The evaluation of antioxidant activity showed that LRSA has effective antioxidant properties with high free radical scavenging activity.
Effects of beta-glucans on the immune system	Akramiene et al.	*Gaporderma lucidum*	*Ganoderma lucidum* and *Tricholoma lobayense* mushrooms tested against chemically induced tumors showed polysaccharide inhibition of cell transformation, requiring the presence of healthy cells. ß-glucan inhibits tumor growth by activating natural killer cells, observed in MM-46 carcinoma-bearing mice treated with Maitake mushroom D-Fraction, which also increased interleukin-12 to activate NK cells and inhibited angiogenesis to prevent tumor growth and metastasis.	Increase IL-12 and activates NK cells, plays a role in inhibition angiogenesis, decreasing the tumor growth.
Beta-glucan offers hope for cancer sufferers: studies conducted in the laboratory and on animals point to promising results of the substance, found in high concentrations on the "sun mushroom" and oats	Vetvicka et al.	Maitake, Basidiomycetes class and *Agaricus blazei*	Mushrooms with significant anti-cancer activity are the ones of the Basidiomycetes class. *Schizophyllum commune* can reduce the number of metastasis and increase lifespan. *Agaricus blazei* can inhibit pulmonary and peritoneal metastasis. It was also found that the use of ß-glucan modulates the tumor microenvironment by changing the phenotype of immunosuppressive cells to an immunostimulatory one, leading that ß-glucan can "train immunity".	The fact that the ß-glucan can penetrate the wall easily helps the recognition by immunologic cells. The most important receptors for ß-glucans are dectin-1, CR3 receptor and Tol-like receptor. ß-glucan modulate the microenvironment of the tumor and train immune innate cells, leading to the suppression of the tumor.
The effects of beta-glucan on human immune and cancer cells	Chan et al.	*Ganoderma lucidum*, *Grifola frondose* and others	ß-glucan was administered in 3 different ways, revealing no systemic absorption of the agent. However, the immunoglobulin A concentration increased, suggesting a systemic immune effect.	The ß-glucan is quickly captured in the proximal small intestine by macrophages.
Polysaccharides with antitumor effect in breast cancer: a systematic review of non-clinical studies	Corso et al.	*Botryosphaeria rhodian*, *Lasiodiplodia theobromae*, *S. cerevisiae*	A study analyzed by the authors mentioned the use of 1,3-D-glucan isolated from *S. cerevisiae* and compared its effects in endocrine-sensitive MCF-7 to LCC9 endocrine-resistant and LY2 breast cancer cell lines. It was concluded that B-D-glucan inhibited cell proliferation and increased Bax/Bcl-2 ratio. Other study evidenced the glucan form *Botryosphaeria rhodian* had anti proliferative activities.	B-D-glucan inhibited cell proliferation and increased Bax/Bcl-2 ratio.
ß-D-glucan inhibits endocrine-resistant breast cancer cell proliferation and alters gene expression	Jafaar et al.	1,3- ß-D-glucan	The study aimed to assess the influence of purified 1,3-ß-D-glucan on the growth of MCF-7 cells, which are responsive to hormonal treatments and express estrogen receptor α (ERα), in comparison to MCF-10A cells, which are normal breast epithelial cells lacking ERα. The study also investigated how 1,3-ß-D-glucan affected the expression of genes associated with breast cancer in MCF-7 and LCC9	The inconsistency between batches of ß-glucan extracts has caused problems due to variations in their effects, leading to debates about their potential as anticancer agents. To address this concern, the authors acquired barley-derived ß-D-glucan from Sigma and evaluated its impact on

			cells using a PCR array. The results demonstrated that 1,3-ß-D-glucan hinders the growth of breast cancer cells and alters gene expression independently of Erα activity, indication its potential for inhibiting the proliferation of endocrine-resistant breast cancer cells.	breast cancer cells. When treated with ß-glucan dissolved in boiling water, MCF-7 cell proliferation was unaffected. However, when dissolved in DMSO, ß-glucan inhibited cell growth.
Novel medicinal mushroom blend suppresses growth and invasiveness of human breast cancer cells	Jiang & Silva	Branched polysaccharides, triterpenes, ß-1,3-glucan, Cordycepin, protein-bound polysaccharide-K, polysaccharopeptide	In this study, researchers examined if MC could inhibit the growth of highly invasive MDA-MB-231 breast cancer cells in a dose and time-dependent manner. They evaluated whether MC's impact on cancer cells was cytotoxic or cytostatic by studying cell viability after 24, 48 and 72 hours of MC treatment. Impressively, MC treatment did not harm the viability of MDA-MB-231 cells, indicating that MC restricts the growth of breast cancer cells through its cytostatic mechanism.	This suggests that the combination of medicinal mushrooms in MC may counteract the cytotoxic or pro-apoptotic effects of individual mushrooms. Alternatively, MC's cytostatic effect may result from the synergistic of additive effects of low, non-cytotoxic doses of these individual mushrooms.
Fighting secondary triple-negative breast cancer in cerebellum: a powerful aid from a medicinal mushrooms blend	De Luca et al.	Extracts mycelia and sporophores	The triple-negative breast cancer (TNBC) is the most aggressive breast cancer, with high proliferation and metastasis. Medicinal mushrooms are approved to be used as adjuvant in cancer treatments, because of its results regarding: antimutagenic, oncoimmunological and immunomodulator effects. The ß-1,3 and ß-1,6 glucans as a biological response modifier and stimulate immune system by biological.	Medicinal mushroom showed direct effect on apoptosis of cancer cells, improved the survival and quality of life.
Effect of ß-glucan on quality of life in women with breast cancer undergoing chemotherapy: a randomized double-blind placebo-controlled clinical trial	Ostadrahimi et al.	*Saccharomyces cerevisiae*	ß-glucan can protect against tumor by immunostimulation. In this study, patients from the intervention group received 2 capsules between the chemotherapy course, 10 mg of double 1-3,1-6-D-glucan from *S. cerevisiae* while the control received only placebo treatment.	ß-glucan improved quality of life regarding symptom/scale and global health status, enhance immunity in chemotherapy, effectiveness of the treatment.
1-6-D-glucan induce M1 phenotype on macrophages and increases sensitivity to doxorubicin of triple negative breast cells	Corso et al.	*Agaricus bisporus*	The glucan extracted from the *A. bisporus* have already demonstrated immunostimulatory activity and was tested in breast cancer, while being combined to THP-1 macrophages and chemotherapy.	It was proven that the use of polysaccharides induces a disbalance in the oxidative status of the cancer, making them more vulnerable do cell death.
ß-glucan from *Aureobasidium pullulans* augments the anti-tumor immune responses through activated tumor-associated dendritic cells	Shui et al.	*Aureobasidium pullulan*	The mechanism mentioned for ß-glucan (AP-BG) in this text is that, following the administration of AP-BG, it demonstrated the ability to promote the production of cytolytic granules and the secretion of inflammatory cytokines by tumor-infiltrating CTLs (cytotoxic T lymphocytes). Furthermore, AP=BG conferred immune stimulatory potential to TADCs (tumor-associated dendritic cells).	The presence of AP-BG resulted in a significant increase in the proliferation of antigen-specific T cells, as well as a substantial enhancement of CTL functions. Therefore, the mechanism involves the activation of cytotoxic T cells and the enhancement of dendritic cell functions, suggesting potential immune-potentiating adjuvant properties.
Combination of glucan, resveratrol and vitamin C demonstrates strong antitumor potential	Vetvicka and Vetvickovaa		Vitamin C causes a stronger effect of beta glucan. It was measured substances present in the development of cancer, such as Ptas64 in breast	The use of beta glucan, Resveratrol and vitamin C caused a reduction of 86% in tumor metastasis and tumor growth.

			cancer, and results showed strong growth inhibition.	
ß-glucan: a dual regulator of apoptosis and cell proliferation	Wani et al.	*Lentinan erode*, *Schiphyllum commune*, *Sparassis crispa* and others	Orally administered ß-glucan is recognized by pattern recognition receptors (PPR's), especially dectin-1. The molecule is fragmented and circulate through endothelial system, where it intersects with immune cells.	Isolated ß-1,3-glucan from *Lentinan erodes* promoted cell proliferation and induced TNF-α production in peritoneal macrophages, suggesting that this compound can cell-mediate cytotoxicity. Macrophages treated with substances derived from *Schiphyllum commune* showed antitumoral activity on non-allogenic and allogenic tumors in mice. The polysaccharides from substances from *Sparassis crispa* inhibited the expression of B-10G16 cells and induced angiogenesis by vesicular endothelial growth factor.
Molecular attributes and apoptosis inducing activities of a putative serine protease isolated from Tiger Milk mushroom (*Lignosus rhinocerus*) sclerotium against breast cancer cells in vitro	Yap et al.	*Lignosus rhinocerus*	The cytotoxic effects of F5 on MCF7 cells were investigated. This was done by analyzing apoptosis using flow cytometry, measuring caspase activity, and studying the expression of apoptosis-related markers through western blotting. Additionally, molecular characteristics of F5 were explored using data from the published genome and transcriptome of *L. rhinocerus* for future research.	The process of apoptosis activation in MCF7 cells by F5 appears to result from interactions between intrinsic and extrinsic apoptotic pathways. This involves an increase in caspase-8 and 9 activity and a significant reduction in Bcl-2 levels. Additionally, proapoptotic factors like Bax, BID, and cleaved BID are elevated, along with noticeable actin cleavage. At the genetic level, F5 contains three predicted non-synonymous single nucleotide polymorphisms and an alternative 5' splice site.
ß-glucan from *Lentinus edodes* inhibits breast cancer progression via the Nur77/HIF-1α axis	Zhang et al.	*Lentinus edodes*	Immunohistochemistry, immunofluorescence, and hematoxylin-eosin staining techniques were employed to examine tumor growth and metastasis in MMTV-PyMT transgenic mice. Western blotting and reverse transcription-quantitative PCR were used to identify molecules associated with proliferation and metastasis. A hypoxic cellular model was created by exposing cells to $CoCl_2$. Small interfering RNA was introduced using Lipofectamine reagent. The ubiquitin proteasome pathway was inhibited by adding the proteasome inhibitor MG132.	LNT effectively inhibited the growth of breast tumors and the formation of lung metastasis in breast cancer, which coincided with a reduction in HIF-1α and Nur77. However, when LNT was introduced in an oxygen-deprived environment, it reduced HIF-1α expression, and this process was dependent on Nur77. Furthermore, a strong positive association between Nur77 and HIF-1α expression was observed in human breast cancer samples.

Source: Data collected by the authors.

Discussion

The use of ß-glucans has been shown to be beneficial in increasing immunity as a supplement, such as helping in the treatment of breast carcinoma. This use causes a higher immunological response because it triggers immunological receptors, activating cells of the immune system and causing more phagocytosis and cellular death [12].

Another effect of this polysaccharide is its anticancer activity, which inhibits the growth of cancer cells and their transformation into malignant cells. Additionally, a study has evidenced its antiangiogenic effects, which are responsible for reducing the risks of metastasis. Moreover, ß-glucans have been found to be efficient when used as an adjuvant in immunotherapy. This is because monoclonal antibodies are activated by the complement system and opsonize tumor cells, a process induced in the presence of the polysaccharide [13-15].

When ß-glucans bind to biological receptors, the immune response via dectin-1 begins and phagocytosis is induced. Oxidation via is activated, and dendritic cells and macrophages produce cytosine. Dectin-1 is extremely important for the activation of dendritic cells, which consequently induces the differentiation of T cells into Th1 and Th2, thereby elevating the cytotoxicity of TCD8 lymphocytes [16,17].

The use of ß-glucans as a supplement was shown to be beneficial when it comes to increasing immunity, and the use of a dose of 900mg for 16 weeks evidenced a decrease of 25% in the incidence of the flu. However, it was concluded that the daily use of ß-glucans auxiliaries on immunity against respiratory infections [18-20].

Studies also found that the use of ß-glucans increases the apoptosis of MCF-7 and LCC9 cells that are present in breast adenocarcinoma, concluding that there is a relation between the use of ß-glucans and patients with breast cancer of MCF-7 or LCC, which results in the increased cytotoxicity of those cells [21,22].

This polysaccharide can be used as an adjuvant on antitumoral treatment, helping patients to have a better response to treatment such as chemotherapy, radiotherapy, and monoclonal antibodies [23].

Conclusions

It was possible to confirm that the use of ß-glucans has positive effects on health once they improve the immunity of healthy individuals. Moreover, it also presented extraordinary results in patients with breast cancer because there are mechanisms that increase apoptosis and anti-angiogenesis and can be used as an adjuvant.

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