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POTENTIAL CLINICAL BENEFITS AND PROBABLE MECHANISMS OF ACTION PROMOTED BY A NUTRACEUTICAL OBTAINED BY FERMENTATION AND RICH IN B-GLUCANS AND AMINO ACIDS FOR ONCOLOGIC PATIENTS

Potenciais benefícios clínicos e prováveis mecanismos de ação promovidos por um nutracêutico obtido por fermentação e rico em β-glucanas e aminoácidos para pacientes oncológicos

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Abstract

Cancer patients are generally submitted to chemotherapy and radiotherapy, which tend to cause problems related to intense inflammatory processes, malnutrition, nausea, and emesis. Therefore, performing supplementation in these patients is important and necessary, as it favors cancer patients from a nutritional point of view. Amino acids and β-glucans obtained from fermentation processes proved to be important in the care of cancer patients because they improve the nutritional parameters and general condition of the patient. We aim to discuss the benefits obtained by cancer patients undergoing chemotherapy and radiotherapy who received supplementation with a fermented nutraceutical rich in β-glucans and amino acids. A literature review was carried out through an active search for scientific articles by the following descriptors in Portuguese: “nutraceutical”, “β-glucans”, “oncological patients”. In addition, we also discuss the benefits caused using the product called BionutriAR1®, a nutraceutical that contributes to the recovery of nutritional status. We conclude that the use of products capable of promoting supplementation of β-glucans and amino acids is beneficial to cancer patients, especially those undergoing chemotherapy and radiotherapy and, therefore, there is an indication of supplementation for these patients with the fermented product BionutriAR1®.
Keywords: Nutraceutical, β-glucans, Aminoacids, Oncological Patients, Immune System, BionutriAR1®.

Resumo

Pacientes com câncer geralmente são submetidos à quimioterapia e radioterapia, que tendem a causar problemas relacionados a processos inflamatórios intensos, desnutrição, náuseas e êmese. Portanto, realizar suplementação nesses pacientes é importante e necessária, pois favorece os pacientes oncológicos do ponto de vista nutricional. Os aminoácidos e β-glucanos obtidos a partir de processos de fermentação se mostraram importantes no cuidado de pacientes com câncer, pois melhoram os parâmetros nutricionais e o estado geral do paciente. Nosso objetivo é discutir os benefícios obtidos por pacientes oncológicos submetidos à quimioterapia e radioterapia que receberam suplementação com um nutracêutico fermentado rico em β-glucanos e aminoácidos. Foi realizada uma revisão de literatura por meio de busca ativa de artigos científicos pelos seguintes descritores em português: “nutracêuticos”, “β-glucanos”, “pacientes oncológicos”. Além disso, discutimos também os benefícios causados pelo uso do produto chamado BionutriAR1®, um nutracêutico que contribui para a recuperação do estado nutricional. Concluímos que a utilização de produtos capazes de promover a suplementação de β-glucanas e aminoácidos é benéfica aos pacientes oncológicos, principalmente aqueles em tratamento quimioterápico e radioterápico e, portanto, há indicação de suplementação para esses pacientes com o produto fermentado BionutriAR1®.
Palavras-chave: Nutracêutico, β-glucanos, Aminoácidos, Pacientes Oncológicos, Sistema Imunológico, BionutriAR1®.

Introduction

Cancer ranks among the leading causes of morbidity and death worldwide. It also drives up the expense of diagnosing and treating the disease, which can be accomplished by combining various therapeutic modalities like immunotherapy, chemotherapy, radiotherapy, and surgery [1-3].

The majority of the time, biochemical events that are characteristic of different tumors can be blamed for the malignancy and invasiveness of different cancers. These events, which are connected to the cascade of cellular signalization, unquestionably play a significant role in proper cellular functioning as well as the communication of essential phenomena that enable basic cellular activity to exist and permit the cell to interact with its microenvironment. These molecular processes ascertain the presence and sustenance of the dynamic equilibrium state of the cell, permitting it to perform tissue restoration via cicatrization or regeneration, as well as prevent or lessen the likelihood of the development and manifestation of malignant cells [4,5] because diseases like many forms of cancer can develop as a result of mistakes that occur in the cascade of cellular signaling or in the contact between cells. Furthermore, four gene groups are associated with the growth and development of cancerous cells: protooncogenes, which stimulate cell growth; tumor suppressor genes; genes that control the process of apoptosis; and genes involved in deoxyribonucleic acid or DNA repair [4-6].

The mistakes that lead to detrimental cellular processes that cause aberrant cell division and the appearance of a cancerous cell (a process called carcinogenesis) are frequently aided by the cell's exposure to chemicals (like benzopyrene), microorganisms (like viruses), and radiation (like ultraviolet radiation) [7-9]. In addition to giving cancers a significant ability to invade, grow, and metastasize, it is important to emphasize that the process of carcinogenesis is caused by genetic mutations that persist and accumulate regardless of the type of cell. These mutations can also give cancers a relevant and detrimental ability to resist the action mechanisms of the various classes of antineoplastic drugs [10,11].

It is possible for several regular metabolic processes to change, which can result in the development of malignant cells. These modified pathways lead to modifications in the intracellular Ca^{2+} influx and efflux behavior as well as in the signaling stages mediated by second messengers, such as cyclic AMP (cAMP). Changes in this signaling are essential for the survival and proliferation of the malignant cells. The intracellular signaling mediated by calcium and cAMP is a canonical event [5,11,12]. Therefore, understanding the physiology of cancer is essential to creating novel tactics that regulate its growth, spread, and metastasis. Ca^{2+} influx occurs through receptor-operated channels in alveolar macrophages (AMs) upon stimulation of ß-(1-3)-glucan receptors; nevertheless, the mechanism(s) controlling Ca^{2+} inflow remains unclear. Using the particulate (1-3)-b-glucan receptor agonist zymosan, the scientists showed the function of protein kinase C (PKC) modulation of Ca^{2+} influx in the NR8383 AM cell line. While PKC activation with phorbol-12-myristate 13-acetate (PMA) or 1,2-dioctanoyl-sn-glycerol (DOG) imitated zymosan and generated a concentration-dependent Ca^{2+} influx, PKC inhibition with calphostin C (CC) or bisindolylmaleimide I (BSM) greatly reduced zymosan-induced Ca^{2+} influx. The receptor operated Ca^{2+} channel blocker SK&F96365 blocked this influx, which was dependent on extracellular Ca^{2+} and suggests that PKC and zymosan activate Ca^{2+} inflow via a comparable mechanism. One novel PKC isoform (d) and two atypical PKC isoforms were expressed by NR8383 AMs. Zymosan and PKC trigger Ca^{2+} inflow via a comparable route, as this influx was dependent on extracellular Ca^{2+} and blocked by the receptor operated Ca^{2+} channel blocker SK&F96365. Conventional PKC isoforms were absent from NR8383 AMs, while two atypical PKC isoforms (i and l) and one unique PKC isoform (d) were expressed.

PKC-d was found to translocate from the cytosol to the membrane fraction upon zymosan stimulation. Moreover, PKC-d translocation and zymosan-stimulated Ca^{2+} influx was inhibited by genistein-mediated protein tyrosine kinases (PTKs). Recently published data led us to believe that the use of the BionutriAR1® nutraceuticals, rich in ß-glucans and amino acids, can contribute to the treatment of oncological patients, decreasing problems related to emesis, loss of appetite, pain, and response to treatments with radiotherapy and chemotherapy. Reducing adverse reactions, and consequently reducing the rate of non-compliance with the treatment by the patients [13], by having in mind, that many discontinue treatment caused by the toxic effects caused by antineoplastic drugs, which in turn can lead to the progression of cancer, resulting in therapeutic failure, decreasing the quality of life, and finally causing early death of the patients [11-13].

Objective

This article's goal is to review the research to assess the benefits of employing a highly bioavailable nutraceutical made by fermentation that is rich in amino acids and ß-glucans for cancer patients undergoing radiation and chemotherapy.

Method

The research approach based on scientific and clinical data is elaborately described in this article, which aims to integrate the findings of the study into a cohesive whole pertaining to the topic under discussion. Using the computational tool Publish or Perish, which chooses publications based on the quantity of citations obtained by other papers, a search for the articles was conducted between July and October of 2023. Since they had distinct diagnoses even though the disease was linked, two searches were conducted. The following descriptors were used in the search for the scientific articles: "nutraceutical, ß-glucans, oncological patients" in the databases of SciELO and PubMed.

Results

Table 1 presents the main information regarding review findings from the database search.

Table 1. Authorship, article title, and key findings.

Authorship	Title	Type of study	Key findings
Behall et al., 2006 [13]	Consumption of both resistant starch and beta-glucan improves postprandial plasma glucose and insulin in women.	Clinical trial	The objective was to determine whether the effects of soluble fiber and resistant starch on glycemic variables are additive. Authors concluded that soluble fiber may have a greater effect on postprandial insulin response while glucose reduction is greater after resistant starch from high-amylose cornstarch. Consumption foods containing moderate amounts of these fibers may improve glucose metabolism in both normal and overweight women.
Maiuolo et al., 2021 [14]	Nutraceuticals and cancer: potential for natural polyphenols	Literature review	The authors established that nutraceutical supplementation, along with current anticancer drug treatment, may be considered for better responses and compliance in patients with cancer.
Argilés, 2005 [16]	Cancer-associated malnutrition	Literature review	Cancer-associated malnutrition is a multifactorial condition. Early intervention by providing nutritional support can delay or prevent the onset of malnutrition and improve patient outcomes, despite adequate nutritional intake alone may not be sufficient to halt or reverse weight loss.
Muscaritoli et al., 2017 [17]	Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study.	Prospective observational study	Of patients enrolled (N=1,952), 51% had nutritional impairment, 9% were overly malnourished, 43% were at risk for malnutrition, and over 40% were experiencing anorexia. Therefore, authors concluded that malnutrition, anorexia, and weight loss are common in cancer patients, even at their first visit to a medical oncology center.
Vetvicka et al., 2019 [18]	Beta glucan: supplement or drug? From laboratory to clinical trials	Literature review	Despite glucans are relatively inexpensive and possess extremely low risk of negative side effects, they are still criticized. Authors established that, in the last 15 years, research has finally reached the stage where the basic mechanisms of glucan effects are well established.
Tartari et al., 2010 [19]	Nutritional profile of patients submitted to chemotherapy in a tertiary outpatient clinic	Descriptive study	The authors observed that the majority of patients presented protein depletion and did not worsen their energy and calcium needs. Furthermore, some medications used in conjunction with chemotherapy,

			such as glucocorticoids and hormonal therapy, can mask malnutrition in these patients.
Cencioni et al., 2022 [20]	Gastrointestinal cancer patient nutritional management: from specific needs to novel epigenetic dietary approaches	Literature review	Studies established that diet composition impinges on gastrointestinal cancer onset, progression, and therapy response. Nutritional interventions influence the quality of life of these patients and their tolerability to antineoplastic treatment.
Prado & Campos, 2007 [21]	Nutritional status of oncology patients	Literature review	Cancer-related cachexia contributes to the catabolic state, with anorexia and significant loss of muscle mass. The nutritional assessment of cancer patients must occur as early as possible and must be individualized.
Van Cutsem & Arends, 2005 [22]	The causes and consequences of cancer-associated malnutrition	Literature review	Cancer-associated malnutrition is the result of a combination of factors, including local tumour effects, the host response to the tumour, and the effects of anticancer therapies. The main consequences of progressive weight loss and nutritional deterioration is reduced survival, or debilitating morbidities such as depression, fatigue, and malaise. Authors concluded that prophylactic nutritional interventions should be an integral part of cancer therapy in order to improve clinical outcomes.
Carvalho et al., 2018 [25]	Nutritional parameters in patients with cancer attended at a reference center in the south of Minas Gerais state, Brazil	Cross-sectional study	The objective was to evaluate the nutritional profile of oncological patients. Authors observed that there was a predominance of female sex and the group age of > 50 years, systemic arterial hypertension was the most reported comorbidity and motion sickness the most common adverse event. In addition, 48% of the patients evaluated used nutritional supplements. They concluded that nutritional counseling should be developed together with oncological patients.
Boligon & Huth, 2011 [26]	The impact of use of glutamine on patients with head and neck tumors in radiotherapy and chemotherapy treatment	Cross-sectional study	The objective was to verify the impact of using the amino acid glutamine in patients with head and neck cancer and undergoing chemotherapy and radiotherapy treatment. After observation, the authors concluded that the use of glutamine in these patients helps during treatment in maintaining nutritional status and preventing mucositis.
Yun et al., 2008 [27]	Beta-glucan, extracted from oat, enhances disease resistance against bacterial and parasitic infections	*In vitro* and *in vivo* assays	The objective was to examine the immunostimulating activities of oat beta-glucan in vitro and in vivo and to assess the potential of oat beta-glucan as an alternative means of disease prevention or treatment. In conclusion, the study suggests that immune functions may be up-regulated by both oral and parenteral administration of oat beta-(1,3)(1,4)-linked glucan, and these enhanced responses may play an important role in providing resistance to bacterial and parasitic infections.
Magnani & Castro-Gómez, 2008 [28]	ß-glucana from *Saccharomyces cerevisiae*: constitution, bioactivity and obtaining	Literature review	The antitumor action mechanism of ß-glucans acts by activating and expanding the host's various immunological functions, improving the host's immunosurvival against the tumor through the activation of leukocytes by stimulating phagocytic activity and cytokine production, in addition to enhancing the effects of chemotherapy.

Ko & Lin., 2004 [29]	1,3-beta-glucan quantification by a fluorescence microassay and analysis of its distribution in foods	*In vitro* assays	The authors applied a systematic method to quantify 1,3-beta-glucan (1,3-ß-G) and analyze its distribution in foods. Food items that possess high 1,3-ß-G contents are candidates as functional 1,3-ß-G sources, but absolute values cannot be used as reference since variation should exist when they are grown in different geographical areas and in various soil conditions.
Kim et al., 2006 [30]	Biomedical issues of dietary fiber beta-glucan	Literature review	Many studies have examined the efficacy of ß-glucan in terms of the lipid lowering effects, blood sugar reduction, weight reduction, immune modulator and anticarcinogenic effect. In addition, the result of several clinical experiments shows that the increased intake of ß-glucan through oat or barley generally reduces the cholesterol level.
Kogan et al., 2002 [31]	Increased efficiency of Lewis lung carcinoma chemotherapy with a macrophage stimulator--yeast carboxymethyl glucan	*In vivo* assays	The authors stated that although the precise mechanism by which the immunomodulator ß-D-glucan affects activity of cysteine proteases and level of their inhibitors is not yet known, the presented data suggest that administration of ß-D-glucan with cyclophosphamide resulted in enhanced antitumor efficiency.
Lin et al., 2004 [32]	Maitake beta-glucan MD-fraction enhances bone marrow colony formation and reduces doxorubicin toxicity in vitro	*In vitro* assays	The data presented suggest that beta-glucan MD-fraction enhancement of granulocyte-macrophages colonies is mediated directly through inducing both proliferation and differentiation of progenitor myeloid stem cells.
Moon et al., 2005 [36]	BRD-glucan exhibits potent immunochemotherapeutic activity in vitro and in vivo	*In vitro* and *in vivo* assays	The objective was to investigate the immunomodulatory and immunochemotherapeutic action mechanism of BRD-glucan. *In vivo*, BRD-glucan/adriamycin co-treatment effectively reduced the number and size of metastatic colonies. Authors proposed that BRD-glucan is a promising immunochemotherapeutic antitumor agent.
Demir et al., 2007 [37]	Beta glucan induces proliferation and activation of monocytes in peripheral blood of patients with advanced breast cancer.	Prospective clinical trial	Authors concluded that oral beta glucan administration seems to stimulate proliferation and activation of peripheral blood monocytes *in vivo* in patients with advanced breast cancer.
Vetvicka et al., 2015 [38]	Glucan supplementation has strong anti-melanoma effects: role of NK cells	*In vivo* and *in vitro* assays	Glucan supplementation had a strong-positive effect in both reducing tumor weight, lung colonies and overall survival rate of tested animals. In addition, glucan inhibited the damage to blood cells and potentiated the effects of regular chemotherapy.
Fuller et al., 2017 [40]	Yeast-derived ß-1,3/1,6 glucan, upper respiratory tract infection and innate immunity in older adults.	Randomized clinical trial	Daily oral ß-1,3/1,6 glucan may protect against upper respiratory tract infection (URTIs) and reduce the duration of URTIs symptoms once infected in older people.
Mörk et al., 1998 [48]	Effects if particulate and soluble (1-3)-beta-glucans on Ca2+ influx in NR8383 alveolar macrophages	*In vitro* assays	The authors stated that literature have demonstrated differential responses in the ability of particulate and soluble (1,3)- ß-glucans to induce Ca^{2+} influx in NR8383 alveolar macrophages despite their apparent interaction with common (1,3)- ß-glucan receptors.
Mörk et al., 2000 [59]	Regulation of (1,3)-betta-glucan-stimulated Ca(2+)	*In vitro* assays	The data presented established that PKC-D plays a critical role in regulating (1,3)- ß-glucan receptor

	influx by protein kinase C in NR8383 alveolar macrophages		activated Ca^{2+} influx in NR8383 alveolar macrophages and PKC-D translocation is possibly dependent on PTK activity.
Noss et al., 2015 [60]	Cellular and molecular mechanisms of fungal ß-(1→6)-glucan in macrophages	*In vivo* assays	The authors demonstrated that macrophages specifically bind and internalize ß-(1→6)-glucans followed by activation of intracellular signaling and modulation of anti-fungal immune response-related gene regulation. The interaction between innate immunity and ß-(1→6)-glucans may play an important role in shaping the anti-fungal immune response.
Xue et al., 2009 [63]	Single and combined supplementation of glutamine and n-3 polyunsaturated fatty acids on host tolerance and tumour response to 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11)/5-fluorouracil chemotherapy in rats bearing Ward colon tumour	*In vivo* assays	Prior to initiating chemotherapy, diets enriched either with glutamine or n-3 PUFA alone, inhibited Ward colon tumour growth. These diets also completely or partially normalized the changes in peripheral leucocyte counts associated with the tumour-bearing state. During chemotherapy, either glutamine- or n-3 PUFA-enriched diet enhanced tumour chemo-sensitivity, and reduced body weight loss, anorexia and muscle wasting. Providing both glutamine and n-3 PUFA together did not confer a greater benefit on tumour inhibition either in the presence or absence of chemotherapy.
Dillon et al., 2007 [64]	Amino acid metabolism and inflammatory burden in ovarian cancer patients undergoing intense oncological therapy	Clinical trial	The authors concluded that despite advanced cancer, ongoing therapy, and an enhanced inflammatory burden, amino acids were capable of acutely stimulating muscle protein synthesis.

Discussion

The presence of an intense or chronic inflammatory process, caused by inflammatory cytokines (tumor necrosis factors, interleukins, bradykinins etc.) is common and harmful in oncological patients, and can be associated with their state of malnutrition. In this sense, the use of nutraceuticals can cause benefits due to the presence of nutrients that can improve the nutritional parameters and modulate inflammatory responses in these patients [14]. Since oncological patients commonly develop a clinical picture known as cancer cachexia, characterized by anorexia, which is promoted by the production of tumorous substances that lead to the resistance of antineoplastic treatments and infections, it is important to promote early nutritional intervention, avoiding a progressive deterioration of the patient's general conditions [15].

Such measures of nutritional intervention are necessary because of the metabolic alterations induced by the tumor, oncological treatment, protein calorie malnutrition (PCM), alterations that can be aggravated by the increase of energy expenditure and by the patient's deficient food intake [16,17]. Therefore, the use of beneficiary substances to the well-functioning of the body, such as amino acids and ß-glucans, have been shown to be efficient in the supplementation of cancer patients, especially those submitted to chemotherapy and radiotherapy. In the case of ß-glucans, this happens due to their capacity to act on various receptors located on the membrane of leukocytes (e.g., macrophages, dendritic cells, and natural killer cells). When these receptors are activated, these components stimulate various action mechanisms in the cells, which can promote the synthesis of cytokines, antibody response, amongst other reactions [18].

Data collected from literature highlights that malnutrition in oncological patients is related to various parameters, for instance, the location of the tumor, the stage of which the cancer is the type of treatment adopted. Furthermore, studies show that patients with cancers that affect the gastrointestinal tract (60% of patients with esophageal cancer and 85% to 90% of patients with pancreatic and gastric cancer) show important cases of malnutrition [19,20]. These cases are related to the increased risk of infection, the decrease of tolerance to the treatment and consequently a reduction in the quality of life [21].

In this regard, nutritional orientation is essential for oncological patients, since it prevents nutritional deficiencies that may generate serious complications [22,23]. Miola et al., 2016 [24], evaluated 1222 patients in the first day of chemotherapy and identified that 13,8% of the patients were malnourished, a result which demonstrates the importance of carrying out a nutritional triage and consequently the supplementation with the use of nutraceuticals in these patients with cancer which were submitted to chemotherapy.

Data published by Carvalho et al., 2018 [25], with the participation of fifty-two oncological patients treated with chemotherapy and radiotherapy, demonstrates that the nutritional parameters of the patients that already previously carried out a food supplementation did not show significant alterations during the treatment. The previous results led the authors to conclude that the nutritional orientation of these patients must be developed and widely discussed with them, since those patients that did not have a nutritional supplementation presented less favorable outcomes.

Nutritional Supplementation in Patients with Cancer

Oncological patients undergoing chemotherapy and radiotherapy tend to present difficulties feeding themselves, which can lead to nutritional complications with different grades of severity. Additionally, important signs and symptoms may appear because of these difficulties, like mucositis, odynophagia, xerostomia, weight loss and malnutrition [26]. In this sense nutritional supplementation rich in ß-glucans is indicated, especially for patients that present continuous and intense adverse reactions caused by chemotherapy and radiotherapy. ß-glucans are polysaccharides which are part of the cell wall of yeast, fungi, and some cereals (present in algae, bacteria, higher plants, fungi, and yeast). They present different structures and are differentiated according to the types of chemical bonds between the units of glucose in the main chain and ramifications of the molecule [27,28]. Currently, these polymers are being studied thoroughly attributable to their biological actions, especially their immunomodulatory effects [29,30].

Data published shows that ß-glucans promote immunostimulant action in immunocompromised patients, causing various beneficial effects for those undergoing oncological treatment, such as anti-inflammatory, hypoglycemic, antimutagenic, hypolipidemic, antimicrobial and antitumor effects [13,30-32]. In relation to its antitumor effect, ß-glucans prevent, slow down or reduce the emergence or development of neoplasms [33]. Consequently, the association of nutritional therapy with ß-glucans becomes interesting, due to their capacity of promoting biomodulation in the oncological patient submitted to chemotherapy and radiotherapy [34].

Di Luzio et al., 1979 [35], demonstrated the preparations rich in ß-glucans produced from fermentation carried out by Saccharomyces cerevisiae significantly reduced the growth of breast carcinomas and melanomas. Diverse studies corroborate the findings, showing that ß-glucans promote modulation of immunological functions of the host, cause patient survival and in some cases present clinical cure even in patients undergoing chemotherapy and radiotherapy [36].

Kim et al., 2006 [30], demonstrated that the process of fermentation utilized not only influences but determines the quality and type of ß-glucans. These are relevant factors that must be observed as water soluble ß-glucans have been shown to help in cancer prevention and therapy [34]. Demir et al., 2007 [37], showed that ß-glucans produced by S. cerevisiae, when administered orally for two weeks to twenty-three women with advanced stage breast cancer, resulted in the proliferation of monocytes in peripheral blood without side effects directly caused by ß-glucans.

Vetvicka et al., 2015 [38], highlighted that the addition of ß-glucans in food increased serum IgG levels of cancer patients undergoing treatment. In cases where the supplementation was done for three months, hematopoiesis improved significantly, causing an improvement in the physical and psychological condition of patients. Pohorska et al., 2016 [39], exemplified that the supplementation with ß-glucans increased considerably both quantity and activity of NK cells, suggesting that the continuous supplementation with ß-glucans can help in preventing cancer recurrence.

Fuller et al., 2017 [40], demonstrated in a study with the participation of 49 women, aged between 50 and 70 years, that supplementation with ß-glucans of yeast (Wellmune®) was capable of significantly decreasing the duration of signs and symptoms caused by respiratory tract infections, an effect that was partly attributed to increased production of the interferon-ϒ. Souza et al., 2017 [41], showed that the administration of an immunomodulatory diet promoted an attenuation of the inflammatory process associated with cancer, promoting physical and mental benefits to the oncological patients studied.

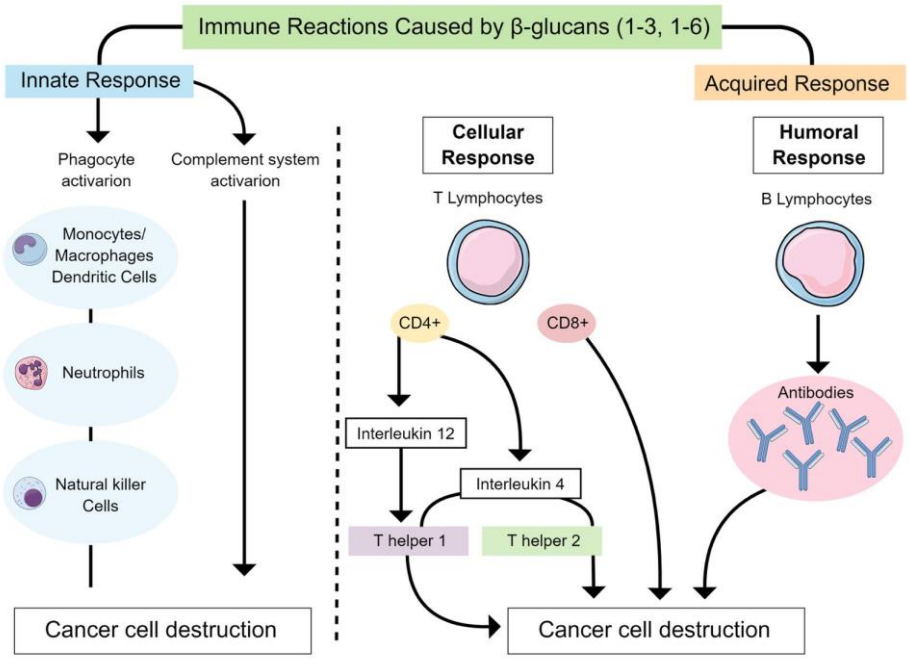

Figure 1. This figure addresses potential mechanisms through which ß-glucans 1,3-1-6 modulate the functioning of the immune system and increase the activity of this system in combating cancer cells and pathological microorganisms.

ß-glucans act in various manners to modulate the functioning of the immune system (Fig. 1), they are recognized by various receptors present in the membranes of diverse cells (monocytes, macrophages, dendritic cells, and natural killer cells). Out of the receptors with greater importance, those of dectin-1, Toll-2 and those of the scavenger receptor family stand out [18]. After binding ß-glucans do their receptors, many processes are activated (e.g., pleiotropic effects that trigger the production of cytokines and the activation of antibody mediated responses. Numerous studies show that ß-glucans can stimulate B cells, that after being activated promote the secretion of pro-inflammatory cytokines such as interleukin-8. Process which occurs with the participation of receptors of dectin-1, mitogen-activated protein kinase (MAPK) and NFkB transcription factors. In addition to the evidence of the existence of mechanisms involving the regulation of ERK1/2 and the transcription of interleukin-10 (IL-10) [18].

ß-glucans promote immunomodulatory effects that depend on their origin and structure, which explains why ß-glucans can be utilized in the treatment of patients diagnosed with various diseases that relate to the deficiency of the immune system, like in cancers. Activation of cytoplasmic by controlling the release of inflammatory mediators, Ca2+ is a crucial signaling mechanism linked to macrophages' capacity to respond to infections and environmental stressors [42-46]. As evidenced by other studies [47-49], exposure to particulate (1-3)-b-glucan agonists, such as zymosan, causes a rise in [Ca2+]i in NR8383 AMs.

Since the rise was eliminated by removing extracellular Ca2+ or by SK&F96365, a selective inhibitor of receptor-operated Ca2+ channels, the (1-3)-b-glucan receptor-mediated increase in i[Ca2+] was caused by Ca2+ inflow via receptor-operated channels [47-49]. The intracellular signaling cascade controlling the receptor-operated Ca2+ influx in AMs is currently poorly understood.

According to several studies [50-55], PKC is implicated in Ca2+ mobilization and the functional regulation of phagocytosis in leukocytes. In neutrophils and the murine macrophage cell line PU5-1.8, PKC activation reduced intracellular Ca2+ release, which in turn decreased Ca2+ influx and increased Ca2+ efflux [56,57].

Additionally, PKC increases the activity of the Ca2+ pump, which modifies the amounts of cytosolic free Ca2+ in Jurkat T cells [58]. In NR8383 AMs, activation of the ß-(1-3)-glucan receptor and Ca2+ influx is independent of phospholipase C, IP3 production, and DAG synthesis [47]. PKC is

linked to the phosphoinositide signaling pathway; hence, it is unclear whether β-(1,3)-glucan receptors are activated [59].

According to recent research, β-(1-6)-glucan may have even greater immunological modulating power than β-(1-3)-glucan. It is uncertain how β-(1-6)-glucan are identified and how they affect immunity. In this work, we investigated the cellular and molecular effects of pure water-soluble β-(1-6)-glucan on primary peritoneal macrophages and macrophage cell lines. According to this work, there is a particular β-(1-6)-glucan receptor that internalizes the glucan ligand through a clathrin-dependent process. We demonstrate that the identification and interaction of b-(1-6)-glucans are not mediated by the known β-(1-3)-glucan receptors. The apparent dissociation constant (KD) of the receptor-ligand interaction is approximately 4 mM, and it has been linked to the phosphorylation of JNK and ERK but not of IkB-α or p38. According to our findings, the interaction between macrophages and β-(1-6)-glucans may modify genes linked to anti-fungal immunity and activate/recruit neutrophils [59,60].

Supplementation with Amino Acids

Glutamine is considered an essential amino acid during hypermetabolism associated with major surgeries, extensive burns, sepsis, inflammation (where there is a negative nitrogen balance and increased proteolysis rates), and immunodeficiency states, frequently found in patients with neoplasms [61,62]. The use of glutamine in the nutritional supplementation of patients with cancer has shown to be a viable option, especially for the prophylaxis of severe forms of oral mucositis of patients submitted to chemotherapy and radiotherapy. Consequently, this helps enable the ingestion of food and maintenance of an adequate nutritional state of patients [62].

The supplementation of glutamine reduced the incidence and severity of peripheral neuropathies in patients treated with chemotherapy, being observed various advantages: reduction of hospitalization time, attenuation of adverse effects caused by chemotherapy, improvement in nutritional status and lymphocyte recovery, and increased patient survival [63].

Boligon and Huth, 2010 [26], evaluated the benefits promoted by the supplementation of glutamine in sixteen patients (13 males and 3 females), divided in control and test groups. The control group was composed of patients with clinical diagnosis of head and neck cancer, undergoing oncological treatment, without the use of any nutritional supplementation. The test group was composed of patients that received supplementation. The patients in the control group presented grades I to IV of mucositis, meanwhile patients that received glutamine presented only grades I to II. Furthermore, patients in the control group presented a reduced nutritional risk index, something that was not observed in patients that received supplementation with glutamine.

Leucine is another amino acid utilized in the supplementation of patients with cancer, with the objective of minimizing the loss of muscular mass, commonly observed in these patients [64].

BionutriAR1®

BionutriAR1® is a nutraceutical produced by Pharnutri, demonstrating a capacity to promote an important improvement in the nutritional state of a patient with cancer. It contributes significantly by reducing damage, especially that related to the loss of body mass induced by chemotherapy, radiotherapy, and cancer itself.

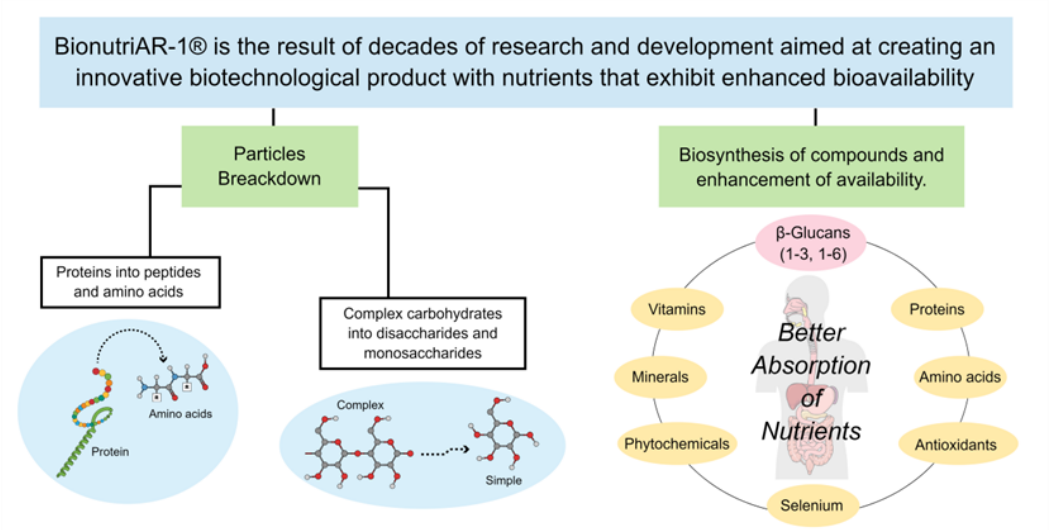

Figure 2- Chemical composition of BionutriAR1®

BionutriAR1® consists of a nutraceutical in the form of powder, obtained through an exclusive biotechnological process, with a unique procedure of fermentation carried out without adding any additives. It is also nutritionally balanced, intended for oral and enteral use, valid for 24 months. In Fig. 2, the important characteristics of BionutriAR1® are illustrated, such as active substances, probable biological actions and high bioavailability of components, something that increases and guarantees benefits to cancer patients.

Conclusions

The use of the nutraceutical produced from BionutriAR1® fermentation, rich in fermented amino acids and ß-glucan, can be considered an excellent alternative for supplementation in cancer patients undergoing chemotherapy and/or radiotherapy. This nutraceutical provides nutrition to the patient and is associated with a substance capable of modulating the immune system and reducing the inflammatory condition found in oncology patients.

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