Journal of Tumor

Online Submissions: http://www.ghrnet.org/index.php/jt
doi:10.17554/j.issn.1819-6187.2016.04.98

Journal of Tumor 2016 December; 4(5-6): 469-473
ISSN 1819-6187

ORIGINAL ARTICLE

Effect of β-glucan Supplementation on Levels of IgM, IgA, IgG and Its Subclasses IgG1, IgG2, IgG3, and IgG4 in Cancer Patients

Richter Josef, Kral Vlastimil, Vetvicka Vaclav, Rajnohova Dobiasova Lucie, Fernandez-Botran Rafael

Richter Josef, Kral Vlastimil, Rajnohova Dobiasova Lucie, Health Institute of Usti nad Labem, Usti nad Labem, Czech Republic
Vetvicka Vaclav, Fernandez-Botran Rafael, University of Louisville, Department of Pathology, Louisville, KY, USA

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Correspondence to: Vaclav Vetvicka, University of Louisville, Department of Pathology, Louisville, KY 40202, USA.
Email: Vaclav.vetvicka@louisville.edu
Telephone: +1-502-852-1612

Received: August 27, 2016
Revised: November 12, 2016
Accepted: November 15, 2016
Published online: December 18, 2016

ABSTRACT

AIM: The role of β-glucan supplementation on cancer development is well established. In this report we focused on the effects of glucan on levels of individual classes and subclasses of immunoglobulins.

MATERIALS AND METHODS: We evaluated the levels of IgM, IgG, IgA, IgG1, IgG2, IgG3 and IgG4 in 39 patients diagnosed with breast or colorectal cancer.

RESULTS: We found a significant decrease of IgG1 levels in the placebo group, which was particularly pronounced in females.

CONCLUSIONS: Short-term glucan supplementation significantly stabilized levels of IgG1 resulting in maintaining anti-infectious immunity. The decrease in IgG1 levels found in the placebo group was clearly caused by a complex therapy of cancer disease.

Key words: Glucan; Immunoglobulins; Cancer; Treatment

Richter J, Kral V, Vetvicka V, Rajnohova Dobiasova L, Fernandez-Botran R. Effect of β-glucan Supplementation on Levels of IgM, IgA, IgG and Its Subclasses IgG1, IgG2, IgG3, and IgG4 in Cancer Patients. *Journal of Tumor* 2016; 4(5-6): 469-473 Available from: URL: http://www.ghrnet.org/index.php/jt/article/view/1830

INTRODUCTION

As part of complex immunological evaluation, a wide spectrum of humoral and cellular response was evaluated in patients who finished cancer treatment (either/or chemotherapy and irradiation). The aim of this study was to find if it is possible to influence some of the problems accompanying cancer treatment. Some of our findings were previously published in papers evaluating important parameters of cellular response[1,2,3]. In this paper we focused on humoral immunity and measured changes in IgM, IgG, and IgA levels. For better understanding of the potential changes and clinical perspective of patients, we also included evaluation of levels of IgG1, IgG2, IgG3 and IgG4 subclasses. We expected that possible changes in subgroups levels might be connected with the risk of development of frequent respiratory diseases. It is known that the decrease in IgG1 levels might result in the risk of loss of a capacity to bind soluble antigens and membrane proteins, to modulate reactivity of polysaccharide antigens, to bind via Fc receptors on macrophages and to activate complement[4].

Out of five isotypes, IgG is the most common protein found in human serum, forming 10-20% of all plasma proteins. It represents the main immunoglobulin class and is further divided into four subclasses, named mostly based on their percentages IgG1, IgG2, IgG3, and IgG4. IgG1 is known for its response to protein antigens and membrane antigens which usually raise very low response of other Ig classes[5]. Abnormal levels of IgG1 are often found in patients with reoccurring respiratory diseases[6] and in patients with risk of atopia or autoimmune diseases. The fact that molecular properties of individual IgG subclasses participated in the treatment of several diseases including infectious diseases is well established[4]. Detailed evaluation of antibody response of individual subclasses together with evaluation of the presence of β-glucan helps in early diagnosis of candidiasis[7]. Regulation of IgG and IgE production is mediated

by IL-4 induction[8]. Detailed ways of induction of different B cell responses involving pleitropic variants of IL-4 are currently being studied[8]. It was suggested that in patients with elevated levels of specific anti-cancer antibodies have a better prognosis of survival[9]. In 40% of patients with mammary cancer, it was shown that the presence of anti-MUC-1 antibodies correlates with better prognosis [10].

Patients recovering from cancer treatment and suffering from stress related fatigue were used in our study for search of possible innovation of immune functions by affecting not only cellular immunity, but also specific and nonspecific humoral immunity. Based on excellent results in supplementing the diet with β-glucan[2,11,12] we decided to evaluate the effects of short term supplementation with β-glucan. β-Glucan is part of the group of biologically active materials and consists of highly conserved structural components of cell wall of yeast, mushroom and seaweed. With over 15,000 published papers, it is not surprising that more and more attention is focused onβ-glucan in medicine. Effects of β-glucan supplementation on cancer growth, allergy, autoimmune diseases, gastrointestinal tract problems, infections and other pathophysiological problems were repeatedly demonstrated[13-16] (for review see Vetvicka[17], Vannucci[18]. Our own experience with the positive effects of the addition of glucan to the diet of patients finishing their cancer treatment on cellular immunity led us to this study evaluating effects of glucan supplementation on humoral immunity and on possible elimination of stress and additional side effects of cancer treatment.

Changes of cognitive functions connected with chemotherapy are significant, particularly due to the high frequency in patients treated for breast cancer[19]. The range of factors playing role in disrupting cognitive functions is clearly defined in Tannock *et al*[20]. Briefly, these factors involve effects of treatment, depression, fatigue, fear, changes in coagulability of microvascular small blood vessels, induction of endogenous hormones and cytokines and also genetical disposition. One cannot forget depressed function of reflux pump (P-glycoprotein), deficit of DNA repair mechanisms and deregulation of immune functions[21]. Some authors even suggested possible correlation between clinical manifestation of insomnia and immune mechanisms[2,3,19]. Studies focusing on the problems mentioned above are currently the focus of numerous laboratories[22-25]. Numerous studies, with respect of our current study, evaluated the neurological effects of exogenous polysaccharides. These studies showed that many plant-based polysaccharides have positive effects on cognitive functions in both healthy population and in cancer patients[26]. In our study, we observed that supplementation with glucan caused some effects on cognitive functions and feelings.

Abnormalities within the immune system appearing during fatigue can play some role in the development and progress of insomnia. Repeated proofs of cognitive deficits in cancer patients (during and after clinical treatment) led to extensive research of possible changes in functions of the central nervous system. In most patients, we can observe a connection between disruption of cognitive functions (memory and attention) and disease. Some hypothesize that inflammation or immune dysfunctions, microvascular damage or genetical predisposition can be involved in these changes[1,27]. Complex cancer treatment, endocrinal changes, mood swings (depression and fear) and pro-inflammatory cytokines can negatively influence neuropsychical function and performance of brain. Subjective problems connected with deterioration of cognitive function are often described as "chemobrain"[20]. These problems are most commonly accompanied with mood swings, but might be influenced by additional factors. With well-established central role of cytokines in neuro-immuno-endocrine axis one can speculate that these bioactive molecules can affect cognition via several various mechanisms[28,29]. The brain is not only independently immunoactive, but performs numerous complex immune interactions with the rest of the body. Peripheral cytokines penetrate blood-brain barrier not only via active mechanisms, but also indirectly via vagal stimulation. In addition, it is known that some cytokines results in negative effects on cognitive functions [30]. Additional factors might be hormonal changes, particularly estrogen and testosterone, and attention fatigue[31].

The fact that the interaction of cytokines with neurons and glial cells leads to a decrease in cognitive functions is well established (for review see Wilson *et al*[28]). The dysregulation of both peripheral and central nervous system cytokine network strongly affects the immune system. It is clear that to ensure optimal treatment of these late consequences, evaluation of patients at the end of oncologic treatment needs to gain more interest from multidisciplinary teams.

MATERIALS AND METHODS

Glucan

Yeast-derived insoluble Glucan #300 (> 85% dry w/w basis) was purchased from Transfer Point (Columbia, SC, USA). This glucan contains 96% carbohydrates and 2.1% proteins. Neutral sugar analysis confirmed 91.3% glucose and 8% mannose.

Protocol

The same protocol described in Richter *et al* [3] was used throughout this study. Briefly, a randomized, double-blind, placebo-controlled trial compared β-glucan #300 and a placebo in people after complex surgical, radiation and/or chemotherapy treatment of cancer. Out of a total of 39 patients, 10 were males and 29 females with a diagnosis of breast or colorectal cancer. All patients underwent basic immunologic screening with evaluation of full spectrum of inflammatory reaction, cancer markers and cellular immunity. In all patients, medical evaluation revealed chronic fatigue syndrome with significant problems in cognitive functions. In addition to evaluations at the Department of Clinical Immunology, all patients were also evaluated by an oncologist.

Out of a total of 39 patients, 23 individuals obtained glucan #300 at a daily dose of 200 mg, 16 patients obtained a placebo which was not distinguishable from the glucan in shape, color or size. All participants were introduced to IMULITE analyzer, treatment program and agreed to proposed treatment in writing. The placebo group consisted of 6 males and 10 females with an average age of 58.4 ± 2.9 years. The glucan supplemented group consisted of 4 males and 19 females with an average age of 58.6 ± 3.8 years. After three months of application, all patients underwent a final evaluation of blood parameters and cognitive functions. This study was performed in full agreement with the Helsinki declaration (revised version 2000.09.01) and was in full compliance with the rules for clinical testing in the Czech Republic.

We measured the levels of IgA, IgG and IgM and subclasses IgG1, IgG2, IgG3 and IgG4 using nephelometer Siemens BM II (Siemens Health Care, Diagnostics, Germany) as suggested by the manufacturer. Relevant antibodies and controls were provided by Siemens. Evaluation employed IMULITE 20 analyzer.

Statistical analysis

Statistical significance was evaluated by a pair t-test using GraphPad Prism 5.04 software (GraphPad Software, USA). An average and standard deviation was evaluated after determination of composition of standard values (D'Agostino, Pearson). In case of non-standard composition, we converted the values into logarithms.

Table 1 Paired t test was used for statistical evaluation (see Methods section). Data are shown as mg/ml. Patient clinical status is given in Methods section.

		IgG		IgA		IgM		IgG1		IgG2		IgG3		IgG4	
		day 1	day 90	day 1	day 90	day 1	day 90	day 1	day 90	day 1	day 90	day 1	day 90	day 1	day 90
Placebo	n	16	16	16	16	16	16	16	16	16	16	16	16	16	16
	mean	10.88	10.85	1.94	1.95	0.91	0.95	7.13	6.01	3.22	3.22	1.52	1.54	0.67	0.71
	SD	1.87	2.14	0.21	0.22	0.21	0.2	1.04	1.31	0.82	0.88	0.22	0.21	0.91	0.88
	Paried-t-test	0.871		0.966		0.359		0.039		0.994		0.864		0.104	
Glukan	n	23	23	23	23	23	23	23	23	23	23	23	23	23	23
	mean	11.39	11.74	2.19	2.22	0.98	0.98	6.67	6.12	3.75	3.76	1.59	1.65	0.51	0.51
	SD	2.8	2.91	0.18	0.18	0.17	0.16	1.35	1.58	1.7	1.51	0.18	0.2	0.33	0.35
	Paried-t-test	0.311		0.788		0.926		0.451		0.982		0.558		0.495	

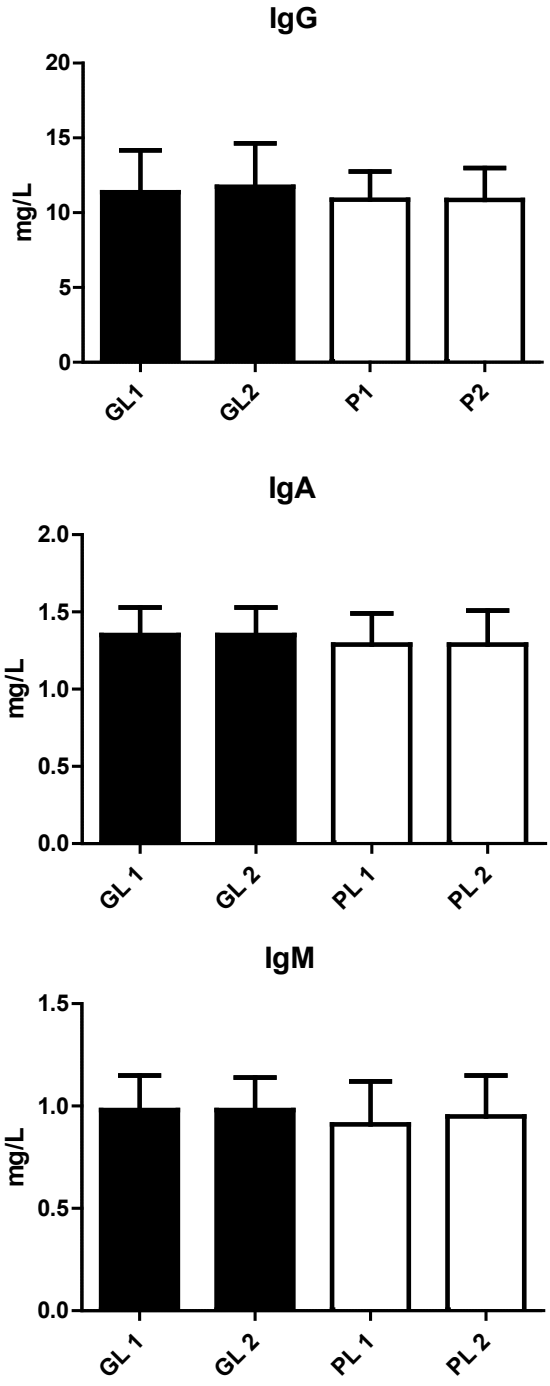

Figure 1 IgG, IgA and IgM levels in the groups of cancer patients supplemented BG and PL.

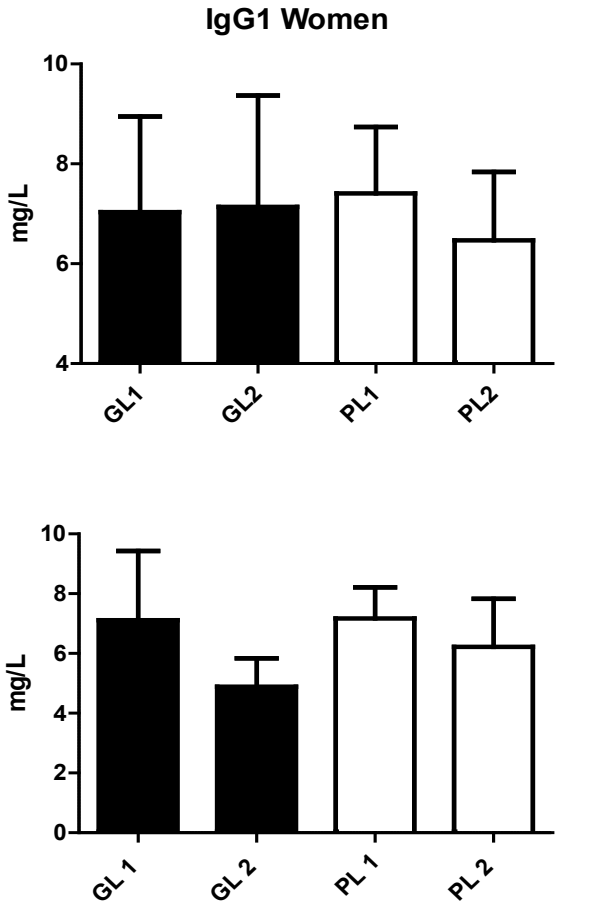

Figure 2 Effect of glucan supplementation on IgG1 levels in female and male patients.

RESULTS

Table 1 and Figure 1 summarize immunoglobulin levels. These data show that three months glucan supplementation did not change the immunoglobulin levels, the changes between original and endpoint levels are not statistically significant. In all classes of immunoglobulins, the levels correspond to control levels at the same geographical region with respect to both sex and age.

A different situation was found when we focused on IgG subclasses. Average levels of IgG1 showed a significant decrease in the placebo group from 7.13 to 6.01 mg/ml ($p < 0.0394$), but no such effects were found in the glucan-supplemented group (6.67 and 6.12 mg/mL with $p < 0.4505$). All other IgG subclasses showed no changes. The only interesting change was found in the case of

IgG4, where neither glucan nor placebo showed any effects, but a significant change between both groups was found. The high average level of IgG4 in the placebo group is caused by one patient with IgG4 levels of 3.82 mg/mL (and 3.68 mg/mL at the end of experiment) corresponds with an IgG4-related disease diagnosis.

Significant differences in IgG1 levels were found when we divided groups according to sex (Figure 2). In the female placebo group the level of IgG1 significantly decreased from 7.41 ± 1.33 to 6.47 ± 1.37 mg/mL ($p < 0.0213$), in the male placebo group we found a small decrease from 7.17 ± 1.04 to 6.22 ± 1.61 mg/mL ($p < 0.1615$). In the female glucan group the IgG1 levels did not change (7.03 ± 1.92 to 7.14 ± 2.23 mg/mL, $p < 0.6634$), in the male glucan group the differences in the IgG1 levels seem to be strong, but due to the limited number of patients they are not statistically significant (7.11 ± 2.32 to 4.89 ± 0.95 mg/mL, $p < 0.1046$).

To evaluate multidimensional markers of fatigue, we used bases gain from several studies[20,24,25,]. Our results clearly showed improvements in both groups - 43.8% improvement in the placebo group and 87.0% improvement in the glucan supplemented group. Improvement in the placebo group can be explained by well-known placebo effects. In a follow-up study, we will use a group of patients with no intervention at all.

DISCUSSION

Together with more successful oncological treatments, the number of patients after systemic oncological treatment in the general population steadily and significantly increases. Another reason for this trend is the wider spectrum of indication of adjuvant treatment. On the other hand, programs which would specifically concentrate on problems of patients in remission are still lacking. Late effects of oncological treatment can significantly lower quality of life and possibility of survival even after long remission. Higher mortality can be caused by late relapse of original cancer, secondary malignity connected with the oncological treatment, individual predisposition to malignant diseases or direct or indirect effects of cancer treatment (either chemotherapy or irradiation). One cannot forget the effects of after-treatment including higher fatigue, loss of sleep and cognitive problems. Fatigue is one of the most common and at the same time most limiting impacts of cancer treatments. Fatigue as a multidimensional syndrome can be influenced by several physiological and biological factors. Sleep problems represent a problem often connected with fatigue. Effects of radiotherapy on induction of cancer-related fatigue (CRF) were described in patients undergoing treatment of oncological diseases, particularly of colon and uterus cancer [22]. These authors suggested a possible connection with induction of systemic inflammation and discuss the possible impact of anemia. In addition, levels of plasmatic citrulline were suggested as an indicator of intestinal damage. We can clearly establish CRF diagnosis in over 80 percent of patients, in one third of patients these problems can last several years[22-24].

Effects of glucan supplementation in cancer patients, both during and after treatment, are already well established. Glucan affects virtually all facets of both cellular and humoral immunity[1,2,3,8,10,32,33]. Together, with other authors Ostrasrahimi *et al*[33], we conclude that glucan is beneficial in complementary and adjuvant therapy of cancer, increases quality of life, and reduces both psychical and pathophysiological impacts of anticancer treatment[26,33]. Glucan supplementation can influence the levels of IgG, interferon gamma and other hematological parameters[34]. In clinical trials, short term glucan supplementation strongly influenced levels of secretory immunoglobulins[11]. In our study, 200 mg/day did not change total levels of individual groups of immunoglobulins, but caused significant changes in levels of IgG1. In the placebo group, a strong decrease of IgG1 levels occurred, whereas glucan supplementation inhibited these changes. When we divided the individual groups into males and females, we found that these changes were significant only in the females group.

Our findings are accompanied by findings of significant improvements in cognitive functions and in the reduction of risk of respiratory tract infections. Among our patients we founda patient after complex treatment of colorectal carcinoma with extreme levels of IgG4. These levels, together with other parameters, fulfilled all conditions for diagnosis of IgG4-related disease[35,36]. This patient was part of the placebo group and no changes of IgG4 levels were found. This particular patient is still evaluated in our Department and the possibility of using glucan supplementation aimed on regulation of his cytokine network, phagocytosis and antibody-dependent cellular cytotoxicity is discussed [36].

CONCLUSIONS

Our results indicate that short-term supplementation with orally-given glucan significantly stabilized levels of IgG1 resulting in maintaining anti-infectious immunity. All other Ig classes and subclasses were not affected.The decrease in IgG1 levels found in the placebo group was clearly caused by a complex therapy of cancer disease. Our study continues by evaluating the activation of dendritic cells via Dectin-1 with a possibility of affecting B-cell immune response[37].

REFERENCES

1 Vetvicka V, Richter J, Král V, Dobiášová Rajnohová L, Stiborova I, Pohorska J. Regulation of hematopoiesis in cancer patients: placebo-driven, double-blind clinical trials of β-glucan. *J Tumor* 2015; **3(1)**: 305-308. [http://www.ghrnet.org/index.php/JT/article/view/1149]

2 Pohorska J, Richter J, Kral V, Dobiášová Rajnohová L, Stiborova I, Vetvicka V. Reconstruction of NK cells during complex cancer treatment. *J Tumor* 2016; **4(2)**: 398-402. [http://www.ghrnet.org/index.php/jt/article/view/1671]

3 Richter J, Kral V, Pohorska J, Dobiášová Rajnohová L, Vetvicka V. Effects of β-glucan on natural killer cells in patients recovering from cancer treatment: clinical trial. *Int J Clinical Experimental Med Sciences* 2016; **2**: 26-30. DOI: 10.11648/j.ijcems.20160202.12

4 Irani V, Guy AJ, Andrew D, Beeson JG, Ramsland PA, Richards JS. Molecular properties of human IgG subclasses and their implications for designing therapeutic monoclonal antibodies against infectious diseases. *Mol Immunol* 2015; **67**: 171-182. [DOI: 10.1016/j.molimm.2015.03.255]

5 Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. *Front Immunol* 2014; **5**: 520. [DOI: 10.3389/fimmu.2014.00520]

6 Barton JC, Bertoli LF, Barton JC, Acton RT. Selective subnormal IgG1 in 54 adult index patients with frequent or severe bacterial respiratory tract infections. *J of Immunol Research* 2016; **2016**: 1405950. [DOI: 10.1155/2016/1405950]

7 Kondori N, Edebo L, Mattsby-Baltzer I. Circulating β (1-3) Glucan and immunoglobulin G subclass antibodies to Candida albicans cell wall antigens in patients with systemic candidiasis. *Clin Diagn Lab Immunol* 2004; **11**: 344-350. [DOI: 10.1128/CDLI.11.2.344-350.2004]

8 Severinson E. Identification of the IgG1 induction factor (interleukin 4). *Front Immunol* 2014; **5**: 628. [DOI: 10.3389/fim-

mu.2014.00628]
9 Fremd C, Stefanovic S, Beckhove P, Pritsch M, Lim H, Wallwiener M, Heil J, Golatta M, Rom J, Sohn C, Schneeweiss A, Schuetz F, Domschke C. Mucin 1-specific B cell immune responses and their impact on overall survival in breast cancer patients. *Onco Immunology* 2015; **5**: e1057387. [DOI: 10.1080/2162402X.2015.1057387]
10 El Khoury D, Cuda C, Luhovyy BL, Anderson GH. Beta glucan: health benefits in obesity and metabolic syndrome. *J Nutr Metabolism* 2012; **2012**: 851362. [DOI: 10.1155/2012/851362]
11 Vetvicka V, Richter J, Svozil V, Rajnohova Dobiasova L, Kral V. Placebo-driven clinical trials of Transfer Point Glucan #300 in children with chronic respiratory problems: Antibody production. *Am J Immunol* 2013; **9**: 43-47. DOI: 10.3844/ajisp.2013.43.47]
12 Vetvicka V, Richter J, Svozil V, Rajnohova Dobiasova L, Kral V. Placebo-driven clinical trials of yeast-derived β-(1,3) glucan in children with chronic respiratory problems. *Ann Transl Med* 2013; 1. [DOI:10.3978/j.issn.2305-5839.2013.07.01]
13 Nosalova V, Bobek P, Cerna S, Galbavy S, Stvrtina S. Effect of pleuran β-glucan isolated from Pleurotus ostreatus on experimental colitis in rats. *Physiol Res* 2001; **50**: 575-581. [DOI: 10.1002/1521-3803(20011001)45:5<360::AID-FOOD360>3.0.CO;2-C]
14 Markova N, Kussovski V, Drandarska I, Nikolaeva S, Georgieva N, Radoucheva T. Protective activity of Lentinan in experimental tuberculosis. *Int. Immunopharmacol* 2003; **3**: 1557-1562. [DOI: 10.1016/s1567-5769(03)00178-4]
15 Yamada J, Hamuro J, Hatanaka H, Hamabata K, Kinoshita S. Alleviation of seasonal allergic symptoms with superfine β-1,3-glucan. A randomized study. *J Allergy Clin Immunol* 2007; **119**: 1119-1126. [DOI: 10.1016/j.jaci.2007.02.005]
16 Vetvicka V, Arriola J, Kaveti A, Dvorak B. Yeast-derived β-glucan reduced intestinal injury in rat model of necrotizing enterocolitis. *Int Clin Pathol J* 2015b; 1. [DOI:10.15406/icpjl.2015.01.00017]
17 Vetvicka V. β-Glucans as Natural Biological Response Modifiers. Biochemistry Research Trends, Nova Biomedical, NY, 2013
18 Vannucci L, Krizan J, Sima P, Stakheev D, Caja F, Rajsiglova L, Horak V, Saieh M. Immunostimulatory properties and antitumor activities of glucans (Review). *Int J Oncol* 201; **43**: 357-364. [DOI: 10.3892/ijo.2013.1974]
19 Standish LJ, Torkelson C, Hamill FA, Yim D, Hill-Force, A, Fitzpatrick A, Olsen M, Schildt S, Sweet E, Wenner CA, Martzen MR. Immune defects in breast cancer patients after radiotherapy. *J Soc Integr Oncol* 2008; **6**: 110-121
20 Tannock IF, Ahles TA, Ganz PA, Van Dam FS. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol* 2004; **22**: 2233-2239. [DOI: 10.1200/jco.2004.08.094]
21 Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer* 2007; **7**: 192-201. [DOI: 10.1038/nrc2073]
22 Jakobsson S, Ahlberg K, Taft C, Ekman T. Exploring a link between fatigue and intestinal injury during pelvic radiotherapy. *Oncologist* 2010; **15**: 1009-1015. [DOI: 10.1634/theoncologist.2010-0097]
23 Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer* 1996; **73**: 241-245. [DOI: 10.1038/bjc.1996.42]
24 Johnson JA, Garland SN, Carlson LE, Savard J, Simpson JS, Ancoli-Israel S, Campbell TS. The LITE study: Rationale and protocol for a randomized controlled trial of light therapy for cancer-related fatigue in cancer survivors. *Contemp Clin Trials* 2016; **49**: 166-173. [DOI: 10.1016/j.cct.2016.07.004]
25 Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: Immunologic effects. *J Clin Oncol* 2005; **23**: 6097-6106. [DOI: 10.1200/JCO.2005.12.513]
26 Nelson ED, Ramberg JE, Best T, Sinnott RA. Neurologic effects of exogenous saccharides: A review of controlled human, animal, and in vitro studies. *Nutr Neurosci* 2012; **15**: 149-162. [DOI: 10.1179/1476830512y.0000000004]
27 Sartori AC, Vance DE, Slater LZ, Crowe M. The impact of inflammation on cognitive function in older adults: Implication for health care practice and research. *J Neurosci Nurs* 2012; **44**: 206-217
28 Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition – The case for a head-to-toe inflammatory paradigm. *JAGS* 2002; **50**: 2041-2056. [DOI: 10.1046/j.1532-5415.2002.50619.x]
29 Menza M, De Fronzo Dobkin R, Marin H, Mark MH, Gara M, Bienfait K, Dicke A, Kusnekov A. The role of inflammatory cytokines in cognition and other non-motor symptoms of Parkinson's disease. *Psychosomatics* 2010; **51**: 474-479. [DOI: 10.1176/appi.psy.51.6.474]
30 Merriman JD, Ah DV, Miaskowski C, Aouizerat BE. Proposed mechanisms for cancer- and treatment-related cognitive changes. *Semin Oncol Nurs* 2013; **29**: 260-269. [DOI: 10.1016/j.soncn.2013.08.006]
31 Cimprich B, Visovatti M, Ronis DL. The attention function index – a self-report cognitive measure. *Psychooncology* 2011; **20**: 194-202. 【DOI: 10.1002/pon.1729]
32 Khalkhane AS, Abbasi K, Zadeh FS, Arian AH. Effects of dietary beta-glucan supplementation on humoral and cellular immunologic factors in lambs. *Global Veterinaria* 2013; **11**: 38-43. [DOI: 10.5829/idosi.gv.2013.11.1.73188]
33 Ostadrahimi A, Esfahani A, Jafarabadi MA, Ziaei JE, Movassaghpourakbari A, Farrin N. Effect of beta glucan on quality of |life in women with breast cancer undergoing chemotherapy: a randomized double-blind placebo-controlled clinical trial. *Adv Pharm Bull* 2014; **4**: 471-477. [DOI: 10.7314/apjcp.2014.15.14.5733]
34 Jung K, Ha Y, Ja SK, Han DU, Kim DW, Moon WK, Chae C. Antiviral effect of Saccharomyces cerevisiae beta-glucan to swine influenza virus by increased production of interferon-gamma and nitric oxide. *J Vet Med B Infect Dis Vet Public Health* 2004; **51**: 72-76. [DOI: 10.1111/j.1439-0450.2004.00732.x]
35 Choi SB, Lim CH, Cha MG, Kang WK. IgG4-related disease of the rectum. *Ann Surg Treat Res*. 2016; **90**: 292-295. [DOI: 10.4174/astr.2016.90.5.292]
36 Crescioli S, Correa I, Karagiannis P, Davies AM, Sutton BJ, Nestle FO, Karagiannis SN. IgG4 characteristics and functions in cancer immunity. *Curr Allergy Asthma Rep* 2016; **16**: 7. [DOI: 10.1007/s11882-015-0580-7]
37 Agrawal S, Gupta S, Agrawal A. Human dendritic cells activated via Dectin-1 are efficient at priming Th17, cytotoxic CD8 T and cell responses. *PLoS ONE* 2010; **5**: e13418. [DOI: 10.1371/journal.pone.0013418]

Peer reviewer: Esin Aktas Cetin, Xiao-Ping Chen.