Research Article **Open Access**

BCHD
Bioactive Compounds in Health and Disease

Antitumor activity of chitin-glucan complex of basidiomycetes

Razin A.N.[1], Vorobeychikov E.V.[1], Konusova V.G.[1], Shamtsyan M.M.[1], Murzina E.V.[2], Volkov M.Yu.[3]

[1] Saint-Petersburg State Institute of Technology, Russia; [2]S.M. Kirov Military Medical Academy of the Ministry of Defense of Russian Federation, Saint Petersburg, Russia; [3]Moscow State Academy of Veterinary Medicine and Biotechnology named after K.I. Skrjabin, Russia

***Corresponding Author:** Razin Aleksandr N., Ph.D., Saint-Petersburg State Institute of Technology, 26, Moskovskiave., Saint-Petersburg, 190013, Russia

Submission Date: September 5th, 2023; **Acceptance Date:** November 20th, 2023; **Publication Date:** November 22nd, 2023

Please cite this article as Razin A. N., Vorobeychikov E. V., Konusova V. G., Shamtsyan M. M., Murzina E.V., Volkov M. Y. Antitumor activity of the chitin-glucan complex of basidiomycetes. *Bioactive Compounds in Health and Disease* 2023; 6(11): 292-302. DOI: https://www.doi.org/10.31989/bchd.v6i11.1224

ABSTRACT

Background: High-molecular β-D-glucans of basidiomycetes modify the immune response and indirectly affect antitumor mechanisms by stimulating the activity of various immune cells and signaling pathways. However, the severity of the immune activity of β-D-glucans depends on many factors, which indicates the need to study them to obtain standardized agents of various pathogenetic directions.

Objective: Evaluation of the antitumor activity of the chitin-glucan complex in the form of aqueous suspensions obtained from the fungi Ganoderma lucidum, Grifola frondosa, and Phallus impudicus using the Ehrlich adenocarcinoma (ACE) model.

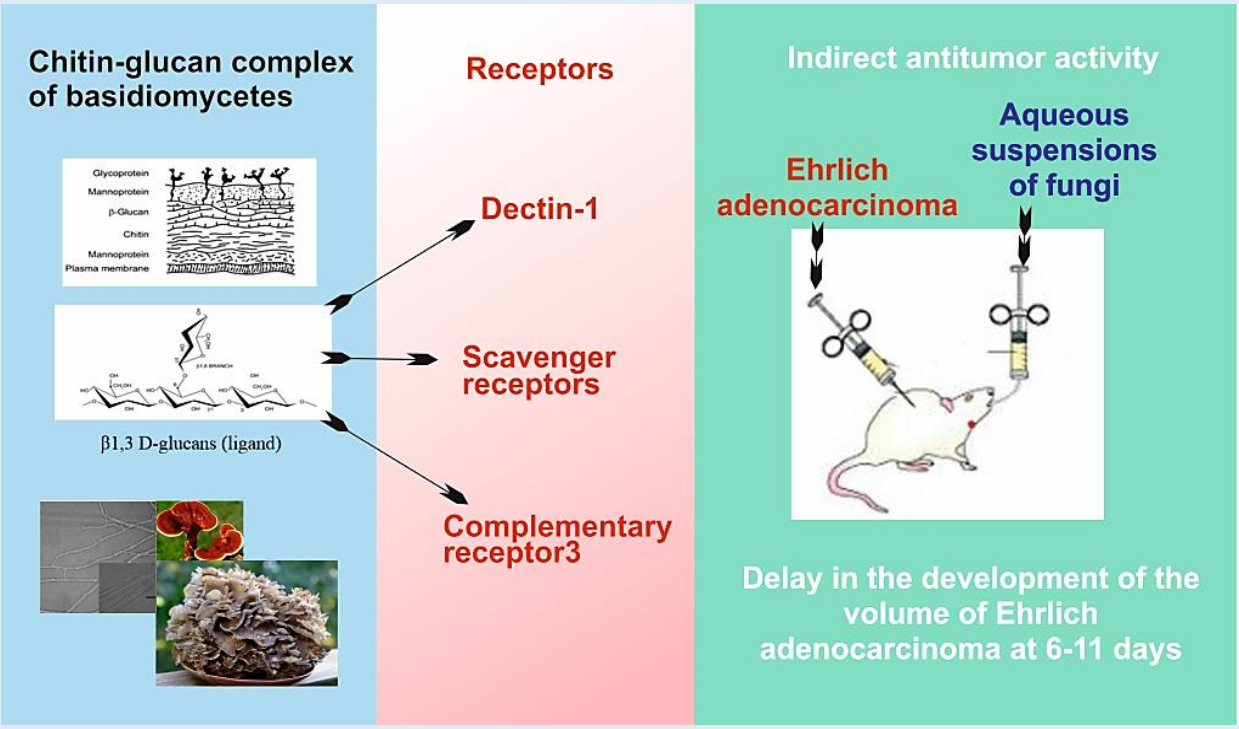
Methods: The work was carried out on male F1(C57Bl×CBA) hybrid mice. Animals were transplanted subcutaneously with ACE at a dose of 106 cells in 0.5 ml of Hank's solution. Animals were given prophylactic oral administration of suspensions of fungi for 10 days before inoculation with ACE. After inoculation with ACE, suspensions of fungi were orally administered to animals of these groups for 28 days for therapeutic purposes. From the 6th day after transplantation of the tumor, its volume was recorded in mm3 according to three linear dimensions.

Results: Survival in all groups of animals within 28 days after inoculation with ACE was 100%. Administration of aqueous suspensions of Phallus impudicus, Ganoderma lucidum, and Grifola frondosa fungi to animals with ACE compensated for metabolic disturbances in the body, which increased the dynamics of their weight gain. However, the weight of these animals on the 28th day of the experiment did not reach the weight of animals that were not transplanted with ACE. Against the background of the introduction of suspensions of these fungi to animals from 6 to 11 days, a statistically

significant ($p<0.05$) effect of inhibition of the development of the ECA volume was obtained, which did not depend on the type of fungi studied.

Conclusion: Aqueous suspensions of these fungi have a similar effect of inhibiting the development of ACE. This allows us to consider the chitin-glucan components of the studied mushrooms as substances with indirect antitumor activity for their standardization and optimization of their use for prophylactic or therapeutic purposes.

Keywords: β-D-glucans, chitin-glucan complex, basidiomycetes, Ehrlich's adenocarcinoma.



INTRODUCTION

The immunomodulatory and antitumor activity of basidiomycetes is associated with the polysaccharide components of their cell wall containing high molecular weight β-D-glucans. These biopolymers consist of D-glucose residues linked by 1→3 β-glycosidic bonds; the core of the glycosidic chain has 1→6 side branches specific for fungal glucans [1-2]. Mushroom β-D-glucans are studied and considered biological response modifiers since their interaction with immune cell receptors causes an effective immune response not only against antigens of pathogenic microorganisms, but also against tumor cells [3].

There are three main mechanisms of action of β-D-glucans that enhance antitumor immunity based on immunomodulatory, antiangiogenic, and cytotoxic effects [4-6]. The biological activity of β-D-glucans depends both on the structure, size of the polysaccharide chain, the presence and number of branches from the main chain, molecular weight, and charge [7-9], but also on their activation of innate immunity receptors [10-11]. There have been multiple studies on receptors that recognize β-D-glucans.

The first receptor is dectin-1, which belongs to the signal type of pattern-recognition receptors, or PRR receptors. This receptor is expressed on dendritic cells (DC), monocytes, macrophages, and, to a lesser extent, on neutrophils [12-13]. Biological effects caused by β-D-glucans through the dectin-1 receptor are associated with maturation of dendritic cells (DC), activation of phagocytosis and endocytosis, respiratory burst, formation of nitric oxide, synthesis of various cytokines and chemokines, and enhanced adaptive immune responses that inhibit growth tumor cells and metastasis [14-15]. These effects are realized in various ways: via the classical NF-κB pathway involving Src- and Syk-kinases and signal adapter protein CARD9 involving Bcl-10 and MALT1 [16] or signal transmission occurs with the involvement of ERK and MAPK proteins instead of CARD9 [17].

The second receptor, through which the immunomodulatory effect of β-D-glucan is realized, is the complementary receptor 3 (CR3), known as Mac-1 or CD11b/CD18 integrin [18-19]. This receptor is localized predominantly on neutrophils, EK, and to a lesser extent on monocytes, B cells (CD5 subpopulation), and T cells (CD8 subpopulation). Mature macrophages lack CR3. The ligands for this receptor are ICAM-1 adhesion molecules, fibrinogen, and β-D-glucans. Through CR3, such important functions as cell migration through the endothelium of the vascular wall to the site of inflammation, phagocytosis by neutrophils, oxygen burst, degranulation, as well as cytotoxicity of natural killers (NK), which ensure the recognition and destruction of tumor cells, are carried out.

The third group of receptors interacting with β-D-glucans includes scavenger receptors (SR) or scavenger receptors [20]. These receptors are divided into 12 classes (A, B, C, D et al) and are expressed on myeloid cells, phagocytic cells, macrophages, DCs, neutrophils, monocytes, T and B lymphocytes, and on some tumor cells [21]. In addition, they perform various functions in cancer: they inhibit the production of NO, IFN-β and IFN-γ TAMs necessary for tumor cell invasion, DC activation, and antigen cross-presentation, induction of tolerogenic DCs, regulation of tumor angiogenesis, suppression of leukemic stem cells [2-24].

Stimulation of these receptors by fungal β-D-glucans leads to various antitumor defense reactions. Several studies have shown that polysaccharides isolated from the higher fungi Agaricusblazei, Agaricusbisporus, Grifola frondosa, Ganoderma lucidum, and Tricholoma matsutake increase cytotoxicity and EK population size [25-27]. The polysaccharide lentinan, isolated from the fruiting body of the fungus Lentinus edodes, has been approved in Japan as an adjuvant in the treatment of gastric cancer [28]. The paper [29] reports on polysaccharide products isolated from Poriacocos, Ganoderma lucidum, and Grifola frondosa, which are used in China for radiation and chemotherapy of various types of cancer. Thus, the antitumor activity of fungal polysaccharides is confirmed by experimental and clinical studies.

Additionally, these substances can inhibit the growth and development of tumor cells by stopping the cell cycle, inducing apoptosis, antiangiogenesis, and regulating the tumor microenvironment. Furthermore, they are able to modify the body's immune response and indirectly affect its antitumor mechanisms, while simultaneously stimulating various immune cells and signaling pathways. However, fungal β-D-glucans have different immune activity. The activity depends on many factors, which indicates the need for their detailed study, including for obtaining standardized agents and their further use.

The study aims to evaluate the antitumor activity of the chitin-glucan complex in the form of aqueous suspensions containing β-D-glucans obtained from Phallus impudicus, Ganoderma lucidum and Grifola frondosa on an experimental model of Ehrlich's adenocarcinoma (ACE).

METHODS

The study was carried out on 75 male F1(C57BlxCBA) hybrid mice aged 6 weeks, weighing 18.0–20.0 g. The animals were obtained from the Stolbovaya specialized nursery (Moscow region). The animals were kept in a well-ventilated room under standard vivarium conditions. There were 4-6 individuals each at 22-24°C humidity between 45% and 65%, with a 12/12-hour light regimen on a standard laboratory diet of 26% protein, 63% carbohydrate, and 11% fat, and free access to water and food. For their feeding, complete granular feed and drinking water were used, and the animals were cared for in the first half of the day. Before the start of the study, the animals were quarantined for 14 days. Animals with signs of disease or visible damage were excluded from the experiment. All necessary manipulations were performed in compliance with the rules of humane treatment of laboratory animals used for scientific purposes.

After quarantine, the mice were divided into groups: the animals of group 1 (n=15) were not transplanted subcutaneously with ACE and were not administered orally with aqueous suspensions of fungi - intact group; animals of groups 2 (n=15), 3 (n=15), 4 (n=15), and 5 (n=15) were subcutaneously transplanted with ACE at a dose of 10^6 cells in 0.5 ml of Hank's solution.

Oral administration of aqueous suspensions of fungi: animals of group 2 were not injected with fungal preparations - the group for the control of the development of ACE; animals of groups 3, 4, and 5 were given prophylactic administration of suspensions of fungi for 10 days before inoculation with ACE, and after inoculation with ACE, animals of these groups received therapeutic administration of suspensions of fungi for 28 days. Group 3 animals received an aqueous suspension of Phallus impudicus. Group 4 animals received an aqueous suspension of Ganoderma lucidum. Group 5 animals received an aqueous suspension of Grifolafrondosa. The oral dose of Ganoderma lucidum and Phallus impudicus was 1.2 mg/mouse, and the oral dose of Grifolafrondosa was 1.8 mg/mouse. From the 6th day after transplantation of the tumor, its volume was recorded in mm3 according to three linear dimensions. Measurements of tumor volumes and control of the weight of the animals were performed every 3 days. The weight of the animals was recorded in grams (g).

To obtain aqueous suspensions of Ganoderma lucidum and Grifolafrondosa, dry fruiting bodies were used, which were crushed to particles <100 μm in size and then placed in distilled water. Before the introduction, aqueous suspensions were kept in a water bath at a temperature of +90.0^{0}C for 15 minutes. Then, aqueous suspensions of these fungi were cooled to a temperature of +21.0^{0}C and injected into the animals. For an aqueous suspension of Phallus impudicus, mycelium was used, which was obtained by deep cultivation. Next, the mycelium was freeze-dried, crushed to particles <100 μm in size, and placed in distilled water. Before administration, the suspension of this fungus was kept in a water bath at a temperature of +90.0^{0}C for 15 minutes, cooled to a temperature of +21.0^{0}C, and administered to the animals. Aqueous suspensions of these fungi differed in the method of preparation but had a similar active component: a chitin-glucan complex containing β-D-glucan. Using the method of enzyme analysis [36], the amount of β-D-glucan in the chitin-glucan complex of Ganoderma lucidum was 26.8 wt%, in the chitin-glucan complex of Grifola frondosa - 32.5 wt%, in the chitin-glucan complex of Phallus impudicus - 28.0 wt%.

For statistical processing of the study results, the SPSS 13.0 for Windows and Microsoft Excel software packages were used. The software contains descriptive statistics methods, as well as analysis of variance and the nonparametric Mann-Whitney test to compare the significance of differences in parameters in independent groups [30, 31]. The probability $p<0.05$ was assessed as sufficient to conclude that there were statistically significant differences in the results of the study.

RESULTS

Table 1 presents the results of changes in the weight of mice in groups 1 and 2, as well as the significance of differences in the average values of the weight of animals between these groups. The results in Table 1 show that in the animals of control group 1 (animals without ECE transplantation), there is a fairly rapid dynamics of weight gain, which indicates their normal physiological development. During the experiment, the weight of the animals increased from 18.12±0.002 g to 29.11±0.331 g. d, which is associated with the development of a tumor process that changes the normal metabolic activity of the body. Differences in mean animal weights between groups 1 and 2 are statistically significant ($p<0.01$), which allows these values to be used as control parameters.

Table 2 shows the changes in the weight of animals between group 2 and group 3. Animals of group 3, who received an oral aqueous suspension of the fungus Phallus impudicus against the background of the development of ACE, showed a statistically significant ($p<0.01$) increase in weight from 19.19±0.002 g to 25.89 ± 0.048 g relative to the weight of animals in group 2. The results demonstrate that the administration of an aqueous suspension of Phallus impudicus to animals activates antitumor defense mechanisms that compensate for metabolic disorders in the body. However, the weight gain of animals in this group does not reach the weight of animals in group 1 (control).

Tables 3 and 4 show the changes in animal weight between groups 2 and groups 4 and 5, respectively. The results show a similar direction of changes in the weight of animals between group 2 and groups 4 and 5. Against the background of the development of ACE and oral administration of aqueous suspensions of fungi from Ganoderma lucidum (Table 4) and Grifola frondosa (Table 5) to these animals, similar values of weight gain are also noted. These changes in weight are relative to the weight of mice of group 2. The obtained changes in the values of the weight of animals are statistically significant ($p<0.01$). This means that the introduction of aqueous suspensions of these types of basidiomycetes to animals against the background of the development of ACE increases their weight, which is associated with compensation for the toxic manifestations of the tumor process.

Figure 1 shows the results of changes in the size of the ECE (V, mm^3) in groups of animals 2, 3, 4 and 5. The results in Figure 1 demonstrate a slowdown in the dynamics of growth in the volume of ECE from days 6 to 11 in groups of animals 3, 4 and 5, treated with water suspensions from fungi Phallus impudicus, Ganoderma lucidum, Grifola frondosa, respectively. In the group of animals 2, which were not injected with suspensions of fungi, there was a pronounced increase in the volume of ACE from 6 to 11 days and, further, the dynamics of this process persisted until the 28th day of the experiment. The survival rate of animals in all groups from 6 to 28 days of observation was 100%.

Table 5 shows the significance of differences in the median values of the volumes of ACE in mice between groups 2–3, 2–4, and 2–5. The results in Table 5 show that in these groups of animals from 6 to 11 days of the experiment, a statistically significant ($p<0.01$) decrease in the values of ACE volumes relative to the volumes of ACE in animals of group 2 is noted. This indicates the presence of an effect of delaying the development of ACE when administered to animals with suspensions of basidiomycetes. However, from the 14th to the 28th day of the experiment in these groups, a statistically significant effect of the delay in the volume of ACE relative to the volume of ACE in animals of group 2 was not detected ($p>0.05$). This means that the effect of inhibition of the development of ACE is noted only in the early stages of the tumor process, i.e. within 11-12 days after its inoculation with animals. The slowdown in the dynamics of ACE development in animals may be associated with the prophylactic administration of aqueous suspensions of the studied fungi. The treatment regimen for their oral administration needs further detailing.

Table 1. Statistical significance of differences in mean animal weights between groups 1 and 2.

Study time, days	Average weight of animals, dispersion (A ± D)		F-criterion	F-critical meaning	Level significance, p
	Group 1	Group 2			
6	18.12 ± 0.002	18.58 ± 0.004	542.20	4.19	<0.01
8	21.11 ± 0.005	19.12 ± 0.004	6429.40	4.19	<0.01
11	22.16 ± 0.008	19.65 ± 0.016	4029.34	4.19	<0.01
14	24.16 ± 0.004	20.15 ± 0.008	19441.27	4.19	<0.01
18	25.15 ± 0.011	20.46 ± 0.007	17805.67	4.19	<0.01
21	26.25 ± 0.008	20.58 ± 0.013	2200.47	4.19	<0.01
25	27.59 ± 0.104	21.68 ± 0.237	1536.42	4.19	<0.01
28	29.11 ± 0.331	21.77 ± 0.334	1213.89	4.19	<0.01

Table 2. Statistical significance of differences in mean animal weights between groups 2 and 3.

Study time, days	Average weight of animals, dispersion (A ± D)		F-criterion	F-critical meaning	Level significance, p
	Group 2	Group 3			
6	18.58 ± 0.004	19.19 ± 0.002	854.00	4.19	<0.01
8	19.12 ± 0.004	20.13 ± 0.004	1818.17	4.19	<0.01
11	19.65 ± 0.016	20.67 ± 0.011	572.61	4.19	<0.01
14	20.15 ± 0.008	21.12 ± 0.006	1015.23	4.19	<0.01
18	20.46 ± 0.007	22.15 ± 0.006	3224.20	4.19	<0.01
21	20.58 ± 0.013	23.17 ± 0.013	3704.12	4.19	<0.01
25	21.68 ± 0.237	24.48 ± 0.110	332.55	4.19	<0.01
28	21.77 ± 0.334	25.89 ± 0.048	315.69	4.19	<0.01

Table 3. Statistical significance of differences in mean animal weights between groups 2 and 4.

Study time, days	Average weight of animals, dispersion (A ± D)		F-criterion	F-critical meaning	Level significance, p
	Group 2	Group 4			
6	18.58 ± 0.003	18.81 ± 0.002	122.14	4.19	<0.01
8	19.12 ± 0.004	19.61 ± 0.003	485.75	4.19	<0.01
11	19.65 ± 0.016	20.23 ± 0.009	250.37	4.19	<0.01
14	20.14 ± 0.008	21.00 ± 0.009	624.10	4.19	<0.01
18	20.46 ± 0.007	21.67 ± 0.012	1120.99	4.19	<0.01
21	20.58 ± 0.014	23.19 ± 0.008	4680.45	4.19	<0.01
25	21.68 ± 0.237	23.27± 0.174	92.79	4.19	<0.01
28	21.77 ± 0.334	24.97± 0.655	155.95	4.19	<0.01

Table 4. Statistical significance of differences in mean animal weights between groups 2 and 5.

Study time, days	Average weight of animals, dispersion (A ± D)		F-criterion	F-critical meaning	Level significance, p
	Group 2	Group 5			
6	18.58 ± 0.003	18.10 ± 0.003	579.44	4.19	<0.01
8	19.12 ± 0.004	19.49 ± 0.003	279.05	4.19	<0.01
11	19.65 ± 0.016	20.02 ± 0.009	81.22	4.19	<0.01
14	20.14 ± 0.008	20.64 ± 0.004	278.89	4.19	<0.01
18	20.46 ± 0.007	21.30 ± 0.019	410.65	4.19	<0.01
21	20.58 ± 0.014	22.47 ± 0.008	2526.21	4.19	<0.01
25	21.68 ± 0.237	23.60 ± 0.142	146.29	4.19	<0.01
28	21.77 ± 0.334	24.43 ± 0.479	130.07	4.19	<0.01

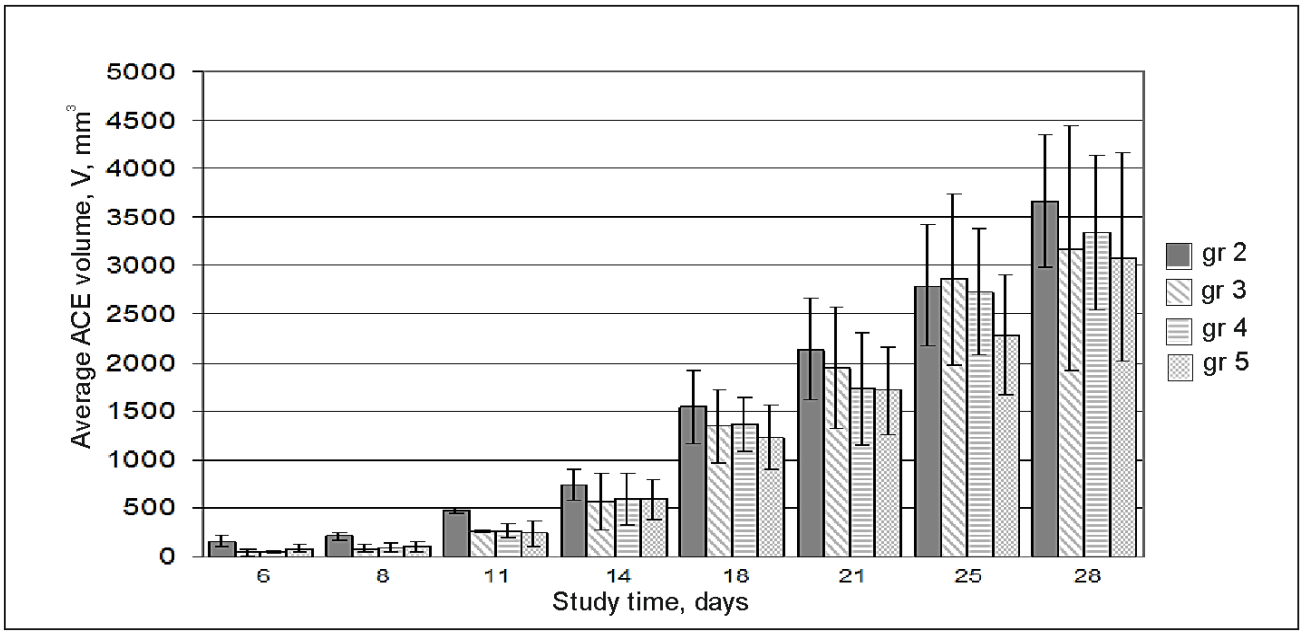


Fig.1. Mean values and standard deviations of ACE volumes in groups of mice 2, 3, 4, 5. The ordinates axis is the average ACE volume, V, mm^3. The abscissa axis is the study time, in days. The animal group numbers are gr2, gr 3, gr 4, gr 5.

Table 5. Statistical significance of differences in median values of ACE volumes of mice between groups 2-3, 2-4 and 2-5 from days 6 to 28 of the experiment.

Observation time, days	Animal Group Numbers	Median ACE values, V, mm3	Average Rank Values	U values (MU)	Z values	Level significance, p
6	2-3	152; 47	22.77;8.23	3.50	-4.52	<0.01
6	2-4	152; 51	21.03; 9.97	29.50	-3.44	<0.01
6	2-5	152; 81	22.83; 8.17	2.50	-4.56	<0.01
8	2-3	207; 76	22.87; 8.13	2.00	-4.58	<0.01
8	2-4	207; 94	22.33; 8.67	10.00	-4.25	<0.01
8	2-5	207; 103	22.53; 8.47	7.00	-4.38	<0.01
11	2-3	475; 255	21.10; 9.90	28.50	-3.48	<0.01

11	2-4	475; 272	21.57; 9.43	21.50	-3.78	<0.01
11	2-5	475; 245	21.93; 9.07	16.00	-4.00	<0.01
14	2-3	742; 582	18.40; 12.60	69.00	-1.80	>0.05
14	2-4	742; 588	18.47; 12.53	68.00	-1.85	>0.05
14	2-5	742; 599	17.93; 13.07	76.00	-1.51	>0.05
18	2-3	1543; 1343	17.53; 13.47	82.00	-1.27	>0.05
18	2-4	1543; 1389	19.13; 11.87	58.00	-2.26	<0.05
18	2-5	1543; 1269	17.77; 13.23	78.50	-1.41	>0.05
21	2-3	2134; 1938	16.80; 14.20	93.00	-0.82	>0.05
21	2-4	2134; 1938	18.73; 12.27	64.00	-2.01	<0.05
21	2-5	2134; 1269	18.53; 12.47	67.00	-1.89	>0.05
25	2-3	2797; 2836	15.33; 15.67	110.00	-0.10	>0.05
25	2-4	2797; 2725	18.73; 12.27	64.00	-2.01	<0.05
25	2-5	2797; 2333	15.83; 15.17	107.50	-0.21	>0.05
28	2-3	3671; 3357	17.10; 13.90	88.50	-0.99	>0.05
28	2-4	3671; 3356	18.03; 12.97	74.50	-1.58	>0.05
28	2-5	3671; 3087	17.40; 13.60	84.00	-1.18	>0.05

Note: MU is the Mann-Whitney test.

DISCUSSION

The results of the experiment showed that, on the one hand, aqueous suspensions of the fungi Ganoderma lucidum, Grifola frondosa and Phallus impudicus, when administered orally, delay the development of ACE in animals after inoculation at the early stages (first 6-11 days) of the tumor process. The presence of this effect confirms the antitumor activity of β-D-glucans of basidiomycetes, the mechanisms of which have been intensively studied over the past decades [32, 33]. Moreover, in Japan, the polysaccharide lentinan from Lentinula edodes has been approved as a biological response modifier in the treatment of gastric cancer [34]. On the other hand, the results of our study showed that the effect of inhibiting the development of ACE does not depend on the type of these fungi and the method of obtaining the chitin-glucan complex. This means that both the fruiting bodies of Ganoderma lucidum and Grifola frondosa and the mycelium of Phallus impudicus can be used to obtain aqueous suspensions of these fungi; their common active ingredient is β-D-glucans.

Notably, basidiomycetes from different geographical regions may differ, both in component composition and in the quality and quantity of β-D-glucans [35]. This makes it difficult to standardize such biological substances and limits their use in the form of drugs.

In our study, we used the fruiting bodies of Ganoderma lucidum and Grifola frondosa growing under natural conditions in the Altai Territory, and the mycelium of Phallus impudicus was obtained from the collection of mushrooms of the Komarov Botanical Institute (St. Petersburg, Russia). Using the method of enzyme analysis [36], we determined that the amount of β-D-glucan in the chitin-glucan complex of Ganoderma lucidum was 26.8 wt%, in the chitin-glucan complex of Grifola frondosa - 32.5 wt%, in the chitin-glucan complex Phallus impudicus - 28.0 mass%. These differences in the content of β-D-glucan in these complexes are minimal (4-6 wt%), and the obtained effect of inhibition of the development of ACE in animals has a similar direction and

severity. β-D-glucans of these fungi have a common structure and physicochemical properties, which showed comparable biological effectiveness associated with the indirect antitumor activity of aqueous suspensions of the studied fungi.

Bioactive compounds have gained popularity in the fight against cancer in recent years [37]. Therefore, the creation of functional food products containing mushroom beta-glucans for patients suffering from cancer is a relevant direction. For example, it is necessary to conduct additional studies determining the mechanisms of anticancer activity of these biopolymers. The structure and functional activity of β-D-glucans of these and other species of basidial fungi also require detailed study, which will allow identification of promising biopolymers for further clinical trials and their subsequent application. A possible technological solution to this problem is the application of the method of deep cultivation of mushroom mycelium to obtain a standardized form of the substance with known physicochemical and functional characteristics.

CONCLUSIONS

1. Oral administration of aqueous suspensions of fungi from Ganoderma lucidum, Grifola frondosa and Phallus impudicus to animals causes a delay in the development of the volume of ACE at 6-11 days after inoculation.
2. Aqueous suspensions of the fungi Ganoderma lucidum, Grifola frondosa and Phallus impudicus have a similar effect of inhibiting the development of ACE in the early stages of the development of the tumor process - 6-11 days.
3. Chitin-glucan components of the studied mushrooms can be considered substances with indirect antitumor activity for their further standardization and optimization of use for preventive or therapeutic purposes.

List of Abbreviations: ACE – Ehrlich adenocarcinoma, MU – Mann-Whitney test, DC – dendritic cells, PRR – pattern-recognition receptors.

Authors' Contributions: All authors made a significant contribution to the development of the concept of the study, its conduct, analysis and discussion of the results, and preparation of the article for its final version before publication.

Competing Interests: All authors have no financial interests or conflicts of interest. The present study was funded by Fungotherapy Center Irina Filippova, Ltd, Saint-Petersburg, Russia, which produced test supplements used in this study; however, the company had no input on the design and conduct of the study, subject recruitment, collection, management, or analysis of the data.

Acknowledgements and Funding: The authors are grateful to the management of the Research Institute of Carcinogenesis, Moscow, Russia, scientific consultants Ph.D. Daryagina V.P. and Ph.D. Ryzhova N.I. for the opportunity to conduct the study.

REFERENCES

1. Abolanle A. A. Kayode, Grace F. Okumede, Great O. Alabi Bioactive Compounds in Health and Disease 2022; 5(3):67-83. DOI: https://doi.org/10.31989/bchd.v5i2.901.
2. Alquraini A, El Khoury J. Scavenger receptors. Curr Biol. 2020 Jul 20;30(14):790-795. DOI: https://doi.org/10.1016/j.cub.2020.05.051.
3. Bao X., Fang J., Li X. Structural characterization and immunomodulating activity of a complex glucan from spores of Ganoderma lucidum // Biosci. Biotechnol. Biochem. 2001. Vol. 65. № 11. P. 2384–2391. DOI: https://doi.org/10.1271/bbb.65.2384
4. Bohn J.A., BeMiller J.N. (1→3)-β-D-Glucans as biological response modifiers are view of structure-functional activity relationships // Carbohydr. Polym.1995. Vol. 28. № 1. P. 3–14. DOI: https://doi.org/10.1016/0144-8617%2895%2900076-3.

5. Borchers A.T., Gershwin M.E. Immunobiology of mushrooms // Exp. Biol. Med. 2008. Vol. 233. № 3. P. 259–276. DOI: https://doi.org/10.3181/0708-mr-227.
6. Borovikov V.P. Populyarnoe vvedenie v sovremennyy analiz dannykh v sisteme STATISTICA. Moscow: Goryachaya liniya – Telekom; 2013. (InRuss.)
7. Borovikov V. STATISTIKA: the art of data analysis on a computer. For professionals. St.Petersburg: Peter, 2001. 656 p. (In Russ.).
8. Camilli G, Tabouret G, Quintin J. The Complexity of Fungal β-Glucan in Health and Disease: Effects on the Mononuclear Phagocyte System. Front Immunol. 2018 Apr 16;9:673. DOI: https://doi.org/10.3389/fimmu.2018.00673.
9. Cerletti C, Esposito S, Iacoviello L. Edible Mushrooms and Beta-Glucans: Impact on Human Health. Nutrients. 2021 Jun 25;13(7):2195. DOI: https://doi.org/10.3390/nu13072195.
10. Chan GC, Chan WK, Sze DM. The effects of beta-glucan on human immune and cancer cells. J Hematol Oncol. 2009 Jun 10;2:25 DOI: https://doi.org/10.1186/1756-8722-2-25.
11. Chen J, Seviour R. Medicinal importance of fungal β-(1→3), (1→6)-glucans. Mycol Res. 2007; 111:635-652. DOI: https://doi.org/10.1016/j.mycres.2007.02.011.
12. Dai Y.C., Zhou L.W., Cui B.K., Chen Y.Q., Decock C. Current advances in Phellinus sensu lato: medical species, functions, metabolites and mechanisms // Appl. Microbiol. Biotechnol. 2010. Vol. 87. № 5. P. 1587–1593. DOI: https://doi.org/10.1007/s00253-010-2711-3.
13. Danielson ME, Dauth R, Elmasry NA, Langeslay RR, Magee AS, Will PM. Enzymatic method to measure β-1,3-β-1,6-glucan content in extracts and formulated products (GEM assay). J Agric Food Chem. 2010 Oct 13;58(19):10305-8. DOI: https://doi.org/10.1021/jf102003m.
14. De Marco Castro E, Calder PC, Roche HM. β-1,3/1,6-Glucans and Immunity: State of the Art and Future Directions. Mol Nutr Food Res. 2021 Jan;65(1):e1901071. DOI: https://doi.org/10.1002/mnfr.201901071.
15. Ellefsen CF, Wold CW, Wilkins AL, Rise F, Samuelsen ABC. Water-soluble polysaccharides from Pleurotus eryngii fruiting bodies, their activity and affinity for Toll-like receptor 2 and dectin-1.CarbohydrPolym. 2021 Jul 15; 264: 117991. DOI: https://doi.org/10.1016/j.carbpol.2021.117991.
16. El Sheikha AF. Nutritional Profile and Health Benefits of Ganoderma lucidum "Lingzhi, Reishi, or Mannentake" as Functional Foods: Current Scenario and Future Perspectives. Foods. 2022 Apr 1; 11(7):1030. DOI: https://doi.org/10.3390/foods11071030.
17. Guo C, Yi H, Yu X, Hu F, Zuo D, Subjeck JR, et al. Absence of scavenger receptor A promotes dendritic cell-mediated cross-presentation of cell-associated antigen and antitumor immune response. Immunology and Cell Biology. 2012; 90:101–108. DOI: https://doi.org/10.1038/icb.2011.10.
18. Hale JS, Otvos B, Sinyuk M, Alvarado AG, Hitomi M, Stoltz K, et al. Cancer stem cell-specific scavenger receptor 36 drives glioblastoma progression. Stem Cells. 2014; 32:1746–1758. DOI: https://doi.org/10.1002/stem.1716.
19. Ina K., Kataoka T., Ando T. The Use of Lentinan for Treating Gastric Cancer. ACAMC. 2013; 13: 681–688. DOI: https://doi.org/10.2174/18715206113130500002.
20. Lee DH, Kim HW. Innate immunity induced by fungal beta-glucans via dectin-1 signaling pathway. International Journal of Medicinal Mushrooms. 2014; 16:1–16. DOI: https://doi.org/10.1615/intjmedmushr.v16.i1.10.
21. McCleary BV, Draga A. Measurement of β-Glucan in Mushrooms and Mycelial Products. J AOAC Int. 2016 Mar-Apr; 99(2):364-73. DOI: https://doi.org/10.5740/jaoacint.15-0289.
22. Muta T. Molecular basis for invertebrate innate immune recognition of (1→3)-β-D-glucans as a pathogen-associated molecular pattern // Curr.Pharm. Des. 2006. Vol. 12. № 32. P. 4155–4161. DOI: https://doi.org/10.2174/138161206778743529.
23. Neyen C, Pluddemann A, Mukhopadhyay S, Maniati E, Bossard M, Gordon S, et al. Macrophage scavenger receptor promotes tumor progression in murine models of ovarian and pancreatic cancer. Journal of Immunology. 2013; 190:3798–3805. DOI: https://doi.org/10.4049/jimmunol.1203194.
24. Reid D.M., Gow N.A., Brown G.D. Pattern recognition: recent insights from Dectin-1 // Curr. Opin. Immunology. 2009. Vol. 21. № 1. P. 30–37. DOI: https://doi.org/10.1016/j.coi.2009.01.003.
25. Ross G.D., Cain J.A., Myones B.L., Newman S.L., Lachmann P.J. Specificity of membrane complement receptor type three (CR3) for beta-glucans //Complement. 1987. Vol. 4. № 2. P. 61–74. DOI: https://doi.org/10.1159/000463010.
26. Schweighoffer E., Tybulewicz V.L., Reis e Sousa C. Syk-dependent ERK activation regulates IL-2 and IL-10 production by DC stimulated with zymosan // Eur. J. Immunol. 2007. Vol. 37. № 6. P. 1600–1612. DOI: https://doi.org/10.1002/eji.200636830.