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REVIEW ARTICLE

Recent findings on the role of fungal products in the treatment of cancer

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Abstract

In modern medicine, natural products have aided humans against their battles with cancer. Among these products, microorganisms, medicinal herbs and marine organisms are considered to be of great benefit. In recent decades, more than 30 fungal immunity proteins have been identified and proved to be extractable from a wide range of fungi, including mushrooms. Although chemotherapy is used to overcome cancer cells, the side effects of this method are of great concern in clinical practice. Fungal products and their derivatives constitute more than 50% of the clinical drugs currently being used globally. Approximately 60% of the clinically approved drugs for cancer treatment have natural roots. Anti-tumor immunotherapy is prospective with a rapidly growing market worldwide due to its high efficiency, immunity, and profit. Polysaccharide extracts from natural sources are being used in clinical and therapeutic trials on cancer patients. This review aims to present the latest findings in cancer treatment through isolated and extraction of fungal derivatives and other natural biomaterials.

Keywords Anti-tumor · Cancer · Fungi · Immunotherapy · Mushroom · Polysaccharides

Introduction

Among microorganisms, fungi are considered to be a diverse source of secondary fungal metabolites. Secondary metabolites are small organic molecules that are not necessary for the growth, development, and reproduction of fungi cells [1]. Recent studies have suggested varying effects of these compounds. They have shown to be useful as antioxidants, anti-aging, anti-diabetic, anti-inflammatory, anti-viral, and anti-fungal agents; immune system enhancers and efficient wound healers. In recent years, numerous researches have been conducted on the anti-tumor effects of compounds derived from fungi, especially mushrooms—terpenoids, alkaloids, phenyl quinines, ligase, isocoumarin, steroids,

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and polysaccharide propanoids are among these bioactive compounds. In the previous years, due to its unique biological activities, extracted polysaccharides have drawn more attention [2]. In the previous half-century, natural products have helped mankind in their battle against cancer. Microorganisms, medicinal herbs, and marine creatures are important examples of these products. Fungal derivative products constitute more than 50% of clinical drugs that are used globally. Approximately 60% of clinically approved drugs for cancer treatment have natural roots [3].

Cancer is the abnormal growth of cells, considered to life-threatening disease—although influenced by type and clinical stage—and is among the leading factors of mortality around the globe [4]. Cancer can be regarded as one of the most serious threats for human life with 12.7 million new cases and 7.6 million deaths per year [5]. In 2018, new global cancer data suggest that the global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths [6]. At the moment, cancer is the second leading factor endangering human health and the most fatal disease following cardiovascular conditions. Exposure to carcinogenic agents in large quantities can increase the risks of cancer. These agents include tobacco, alcohol, chemical compounds, certain infections, radiotherapy, and mutations—transcriptional, genetic, and epigenetic. Modalities for cancer treatment have been in place for quite some time including surgery, chemotherapy, radiotherapy, immunotherapy, etc. Although chemotherapy is frequently used to treat cancer, the major side effects of this method are of concern to many practitioners [7]. Anti-tumor immunotherapy involves the use of immunomodulatory agents and has a growing market worldwide due to its high efficiency, immunity, and profit. Polysaccharide extracts from natural sources are being used in clinical and therapeutic trials on cancer patients [8]. In recent decades, more than 30 fungal immunity proteins have been found among a variety of fungi such as mushrooms and other species. These compounds can withstand frost, acidity, and dehydration in the human body. Moreover, they can overcome the challenges of stomach acidity and acidic digestion [9]. Bioactive substances produced by fungi can be divided into two major groups: compounds with a low molecular weight such as terpenoids or phenolic compounds, and compounds with high molecular weight like polysaccharides and enzymes. Both of these major groups exhibit similar attributes such as anti-oxidant, anticancer, anti-sclerotic, neuroprotective, anti-inflammatory, anti-allergic, antibacterial, antiviral, and hyperglycemic properties [10]. New methods for polysaccharide extraction have been employed, such as enzyme-assisted extraction (EAE), microwave-assisted extraction (MAE), and supersonic extractions [2]. Recently, different products have been isolated from fungi and this study aims to highlight the potential benefits of such products in cancer treatment.

The most important products with anti-cancer properties

Ganoderma lucidum is a basidiomycete fungus that is routinely used in traditional medicine in China, Japan, and Korea. Bioactive compounds with medicinal properties that can be used to strengthen the immune system have been isolated from this fungus. These compounds are known for their anti-oxidant, anti-cancer, anti-microorganism (fungi, virus, and bacteria), anti-arrhythmic, anti-inflammatory, hypoglycemic properties, and anti-vasogenic properties that protect the heart [11]. Fungal endophytes—all the fungal organisms that colonize internal plant tissue and usually remain asymptomatic—represent an abundant and reliable source of new antioxidant compounds and are considered to have the therapeutic potential [12]. Among various mushroom extracts from the Basidiomycota division, the hexane extract of *Pleurotus pulmonarius* was shown great antimicrobial and anti-hemolytic potential. *Pleurotus species* have high medicinal values. Compounds extracted from these species are vastly active against chronic conditions like hypertension and hypercholesterolemia [13]. Among other well-known polysaccharides, Astragalus polysaccharide (APS) is known to be an active ingredient in the Chinese traditional medicine extracted from the medicinal herb *Astragalus membranaceus*, which inhibits different types of solid tumors. Previous reports suggest that APS has an anti-melanoma potential via the downregulation of CD40 expression. The anti-tumor properties of polysaccharides generally originate from two major pathways. First, by direct inhibition of the malignant cells through the activation of the intrinsic and the acquired defense mechanisms of the host's immune system and second via the activation of the immune cells and mediators such as macrophages and B and T lymphocytes [14].

Ophiololine A is a fungal cytotoxic metabolite that displays anticancer properties by cellular killing; this compound and its medical properties have gained significant attention from researchers. This compound is a secondary metabolite extracted from the filamentous fungi like *Aspergillus*, *Cochliobolus, Drechslera,* and *Cephalosporium*. The compound's biological activity suggests that it has inhibitory effects on the growth of lung cancer, melanoma, glioma, rhabdomyosarcoma, and ovarian cancer cells [15]. Prostate cancer is the third most common cancer type globally. Approximately 70 types of nutrients have been reported to have properties against prostate cancer, especially by triggering apoptosis and the caspase and poly adenosine diphosphate ribose polymerase (PARP) pathway [16]. Compounds with a low molecular weight such as terpenoids or phenolic compounds are classically produced by many of these fungi. Mono-terpenoids have cytotoxic activities against cervical cancer (HeLo) and liver cancer cells (HepG2). Diterpenoids and triterpenoids like ganoboninketalis AG, multiple ganoderic acids, lucidadiol, luciden acids, and some others that can be extracted from *Ganoderma lucidum* and *G.orbiforme* fungal cells have cytotoxic properties on cancer cells besides anti-malarial and anti-tuberculosis properties [17]. Hydroperoxides (R-OOH) represent a small family of natural secondary metabolites that are extracted from higher plants, fungi, and marine organisms. Hydroperoxides that are extracted from plants often tend to exhibit anti-neoplastic and anti-ulcer activities; however, fungal hydroperoxides display anti-neoplastic and anti-hypercholesterolemic activities. Interestingly, side effects of some fungal triterpenoid hydroperoxides have been reported to be effective in the treatment of Dementia symptoms. Norlupane hydroperoxides are arguably the first natural metabolites predicted to exhibit an ability to heal Dementia [18].

Antrodia camphorate, also known as *A. cinnamomea*, is a significant fungus from the Basidiomycota division endemic to Taiwan. Wang and his associates in 2019 reported the recent developments in the medicinal effects of this fungus: anticancer activities against several cancer types such as breast, cervical, ovarian, prostate, bladder, colorectal, pancreatic, liver, and lung cancer. The list expanded to include effects on melanoma, lymphoma leukemia, neuroblastoma, and glioblastoma. Additionally, *A. cinnamomea* was shown to have anti-inflammatory, angiopathic dermatitis, analgesic, immunoregulatory, anti-obesity, anti-diabetes, anti-hypertensive, anti-bacterial, anti-viral, and wound healing properties [19]. *Pholiata nameko,* an edible fungus associated with the decaying-woods, possesses medicinal properties described to be anti-tumor, anti-oxidant, and anti-inflammatory in action [20].

Glucagon receptors on the surface of mammalian immune system cells include the following:

- Complement receptor-3 (CR3)
- Lactosylceramides
- Scavenger receptors
- Dectin-1

Once the fungal derivatives, especially glucagon, bind to their specific receptors on the surface of a cell, messages get transmitted into the cell to activate signaling pathways such as MYD88 and others that eventually induce the activation of NF-kB factor. These pathways ultimately produce cytokines and cause the strengthening of intrinsic and acquired immune system responses and eventually lead to a battle against tumors and pathogens (Fig. 1).

The use of fungal nano-particles in cancer treatment

Since nanomedicine has proven itself in the realm of disease treatment, in the future it will be used to treat various diseases, such as AIDS, diabetes, hepatitis B, and cancer. Nanoparticle biosynthesis using microorganisms is effortless, brisk, satisfactory, efficient, and it does not involve toxic chemical materials. The study of Janakiraman et al. showed that silver nanoparticles produced using *B. ofobomae* and *Psidium guajava* endophytic fungi have significant potential in cancer treatment. In that study, the use of cytotoxicity of AgNPs on human MCF7 breast cancer cell line and A549 lung cancer cell was reviewed. The researchers of the study recommended a new chemotherapeutic agent against breast and lung cancer [22]. Several metal-nanoparticles such as gold, silver, and iron are reported to be antimicrobial (against bacteria and fungi) [23] and anti-tumor agents against cancerous cells such as HT-29, HepG2, MCF-7, and A549 [4]. Substantial studies have been done towards the treatment of breast cancer cells, particularly MCF-7 cell line. According to the studies, silver nanoparticles are mostly extracted from plants (71.27%) and by the same token, fungi are in the second position (14.89%). In line with the above, it is expected that biogenic nanoparticles, whether alone or in combination with other anticancer medicines approved by FDA, could be used sooner [24]. El-kahky et al. in 2019 identified an easy and eco-friendly method for biosynthesis of zinc oxide nanoparticles using the extract of *Aspergillus terreus* and also showed their effectiveness in antibacterial and anti-tumor activities. Zinc oxide was shown to be effective against both Gram-positive and Gram-negative bacteria and also HCT-116 (colorectal cancer cells) cell lines [25]. Also, in vitro studies showed that nano-yam-polysaccharide has an inhibitory property against PG3—one of the human prostate cancer cell lines—by inducing apoptosis in the cancer cells. Nano-yam-polysaccharide utilizes this mechanism through the expression of Caspase 3 protein that inhibits prostate tumor cell proliferation [26]. Saravanakumar et al. evaluated the anticancer photothermal activities of copper oxide nanoparticles with the help of cell-free extracts of *Trichoderma asperellum*. The researchers noted that phototherapy is more beneficial compared to other methods of cancer treatment such as chemotherapy and radiotherapy due to its lesser toxicity, hostility, and specificity to cancer-site. The mechanism of action of photo-thermal agents involves converting UV waves into thermal energy, generating heat, and creating reactive oxygen species (ROS) inside cancerous cells without damaging other cells [4]. Several microorganisms create intercellular and extracellular metallic nanoparticles

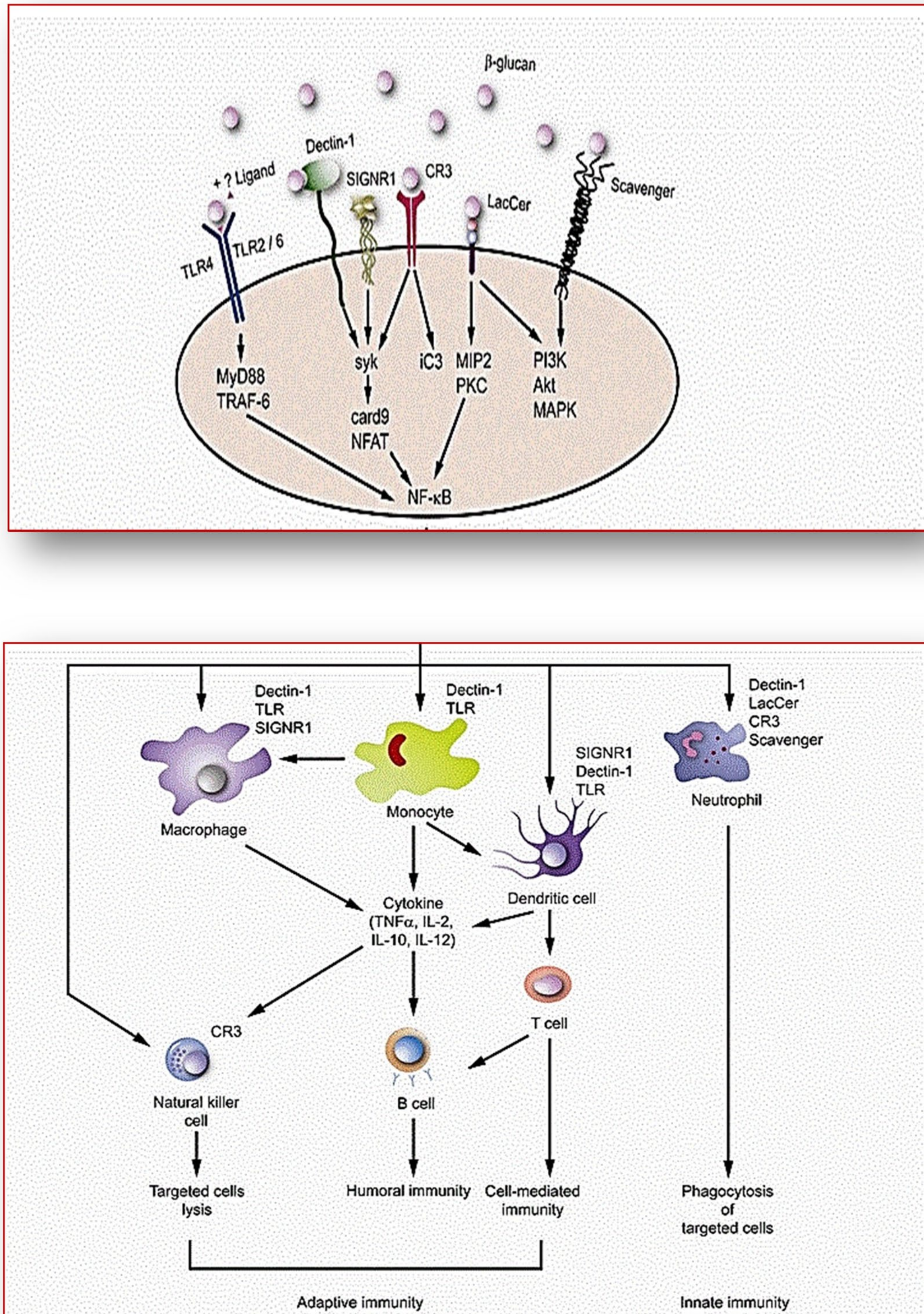

Fig. 1 The activation of signaling pathways and the production and secretion of cytokines in response to tumors and pathogens [21]

with various effects, sizes, and shapes. According to the study of Husseiny, extracellular synthesis of silver nanoparticles from the culture of *Fusarium oxysporum* was performed and antibacterial and anti-tumor properties of the nanoproduct were adequately described [27].

Discussion and conclusion

The study done by Salehi et al. on anti-tumor effects of polysaccharides extracted from different species of *Fusarium* recovered from various samples of dirt used MTT method to study the cellular toxic effects of FK1 strain filamentous fungus against two cell lines of Hela and Lymphoblastoid. The findings of the study showed that mycelial polysaccharides separated from FK1 strains demonstrated the most cytotoxicity against Lymphoblastoid cell line (LCL), whilst their cytotoxicity against HeLa cell line was insignificant [2]. In 2018, Benchamin et al. conducted a study to determine the anti-proliferative property of L-asparaginase enzyme extracted from *Aspergillus fumigatus* in breast cancer treatment. The results of the study showed that L-asparaginase has an anti-proliferative activity against breast cancer cells and can be used to treat breast tumors. L-Asparaginase hydrolyzes asparagine into ammonia and aspartic acid; this is significant when it comes to treating severe lymphoblastic leukemia. Cancerous cells need considerable amounts of asparagine to survive, and for that reason, the enzymatic breakdown deprives and causes the death of tumor cells. Studies have shown that bacterial L-asparaginase leads to allergic reactions in patients, while the fungal L-asparaginase causes minimal adverse or undesirable conditions [28]. In 2018, Erden et al. studied the antimicrobial and anticancer activities of *Aspergillin PZ* and *Terphenyllin* secondary metabolites against human prostate cancer cell line (PC3 and LNCap) and A2780. They found that high density of *Aspergillin PZ* and *Terphenyllin* (50 and 100 micromolar) significantly reduces the survivability of prostate and ovaries cancerous cell lines; however, the antimicrobial properties of the aforesaid were not observed. In another study done on *Aspergillin PZ* extracted from *Trichoderma gamsii*, the cytotoxicity effects of *Aspergillin PZ* against PANC-1, MDA-MB231, and A549 were observed [29].

Oxysophoridine and sophoridine, extracted alkaloids, are noted for their anti-tumor activities in a study done by Meng et al. in 2019. In the same study, a new method was used to prepare OSR naturally from fungal enzyme products [30].

Galiellalactone (GL) is a fungal metabolite that showed anti-inflammatory and anti-tumor activities in vitro and in vivo. Previous studies have displayed that GL targets STAT3 and NF-kB pathways and stops G2/M cell cycle in androgen-insensitive prostate cancer cells. According to Carrido-Rodriguez study in 2019, it was demonstrated that the stoppage of G2/M cell cycle independent of STAT3 and NF-kB pathways happens in DU145 and PG-3 cells [31]. Some studies identified two types of new meroterpenoids named Austalides V, W separated from *Aspergillus ustus* fungus. The two meroterpenoids were capable of stopping the propagation of prostate and bladder cancerous cells. This biologic activity is possibly related to the inhibition of several key pathways for growth adjustment and cell migration of prostate cancer [32]. Medicinal fungi such as *Amauroderma rude*, *Cordyceps, Agaricus bisporus*, *Pleurotus eous,* and *Ganoderma lucidum* have shown anticancer effects, especially against breast cancer. Among all, it seems *Cordyceps* has many favorable features such as high immunity, non-toxicity, and strong effects on the immune system against tumors. Nevertheless, *Cordyceps* is rarely found in nature and their commercialization has been a challenge. Recently Lee et al. have reported the process of cultivating *Cordyceps* in brown rice. The extract of *Cordyceps militaris* can be used in breast cancer treatment. Many compounds such as cordyceps, mannitol, ergosterol, and polysaccharides extracted from *Cordyceps militaris* bear several medicinal properties, particularly antioxidant, anti-inflammatory, anti-virus, anti-diabetes, anti-platelet aggregation, and anticancer property. The study of Lee et al. provides an auspicious plan not only for the isolation of this species from brown rice, but also for using it in traditional medicine, and as an alternative to chemotherapy in breast cancer treatment [33]. In recent studies, chitosan demonstrated excellent antimicrobial activity against pathogenic bacteria. Besides, chitosan has shown average anti-proliferative effects on IMR 32 and HepG2 cells [34]. Choromanska showed for the first time that (1–3, 1–4) β-glucan has anti-tumor activities against skin cancer cells [35]. β-Glucans are mostly used in other treatments, cosmetics manufacturing, and food industry [36].

In the study done by El-Kassem, 48 endophytic fungus species were separated and purified from ten Egyptian medicinal plants, and their extracts were studied for HCV proteinase inhibitory activity and the associated cytotoxicity [37]. Ethyl acetate extracts of *Alternaria alternata* (PGL-3), *Cochlibolus lunatus* (PML-17), *Nigrospora sphaerica* (EPS-38), and *Emerecilla nidulans* (RPL-21) showed the most potent inhibition of HCV NS3/4A protease with IC50 17.0, 20.5, 33.6, and 54.6 µg/ml, respectively, with low cytotoxicity except for the later.

Masuda showed that Maitake α-glucan (YM-2A) that has been extracted from *Grifola frondosa* exhibited significant tumor growth inhibitory properties by strengthening immune system responses. The results of the study prove that YM-2A is edible and can activate dendritic cells and macrophages, and stimulate anti-tumor T cells [8].

Karaman's study describes the anti-oxidant and anti-AChE activities of polysaccharide extracts of *Amanita strobiliformis*. The authors showed that the polysaccharide

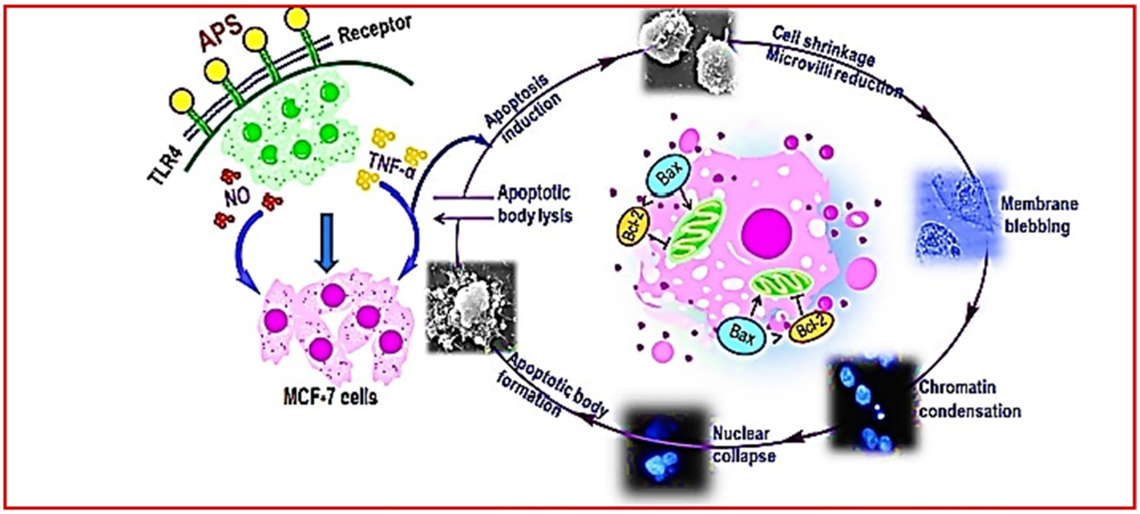

Fig. 2 Schematic illustration of the apoptosis of induced MCF-7 cancerous cells by APS-activated macrophages [14]

extract is a promising bioactive substance [38]. Fungal polysaccharides initiate several different pathways that interfere with cellular proliferation; they were used as versatile scaffolds with anti-tumor potentials [39]. Spectrometric and activity analysis of HPA, a polysaccharide extract from the marine fungus *Hansfordia sinousae*, showed its strong anti-proliferative effect against HeLa and MCF-7 cells. It was proven that HPA can induce the apoptosis of HeLa cells through the mitochondrial pathways [40]. Li et al. studied the effects of APS and macrophages on the growth inhibition of MCF-7 and found that APS can be an ideal activator of RAW264.7 mouse macrophages and can lead to the secretion of TNF-α and NO which can induce apoptosis of MCF-7 cells [14] (Fig. 2).

Liu and associates extracted polysaccharides through liquid fermentation of the fungus *Cordyceps militaris* that showed higher anti-tumor activities in vitro in comparison to the polysaccharides obtained from the fruiting bodies. These results highlighted that the fermentation of *Cordyceps militaris* has numerous benefits such as short cycles, low energy consumption, ease of control, and absence of heavy metals contamination [41].

Pancreatic cancer is the seventh leading cause of cancer deaths and the 11th most common form of cancer among women and the 12th most common type of tumor among men worldwide. Pancreatic duct adenocarcinoma is the most common type of pancreatic cancer and accounts for about 85% of pancreatic cancer cases. In their study, Qi et al. evaluated the anti-tumor properties of Butenolides from a marine-derived fungus called *Aspergillus terreus* in the treatment of adenocarcinoma cells of the pancreatic duct [42]. White rot fungi release a wide range of metabolites with low molecular weight that have interesting characteristics. Colon cancer is the fourth most common cancer and the third deadliest cancer in the world. The study of Matuszewska indicates that LMS fractions isolated from *Cerrena unicolor* induces the apoptosis of HT-29 cells of colon cancerous cells and also prevents metastasis [17]. In Sun's study, structural differences between the polysaccharides extracted from fruiting bodies (FGAP) and the submerged fermentation system (SGAP) of *Ganoderma applanatum* were analyzed using GPC, HPLC, and IR; their anti-tumor activities against sarcoma 180 inside the body were evaluated. These differences include molecular weight, monosaccharide components, and functional groups. Carboxylate groups were present in FGAP but not in SGAP. This structural difference allowed FGAP to exhibit better anti-tumor activity against sarcoma 180 cells in vivo. The results indicated that carboxylate groups could play an important role in the anti-tumor activity of FGAP compounds [43].

Fungal products and their derivatives comprise more than 50% of the world's most commonly used clinical drugs. Approximately 60% of approved drugs for cancer treatment have natural origins. In the field of modern medicine, the anti-tumor immunotherapy—harnesses the use of immunomodulatory agents—is prospective; it is highly effective, profitable with a rapidly growing market worldwide. Presently, natural polysaccharides extracted from natural sources are in use for clinical and therapeutic trials in cancer patients. The majority of these products are fungal derivatives and other natural biomaterials.

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OR provided coordination and oversight; ASM, MM, and MM drafted the manuscript. OR, RA, and MG critically revised the manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare in this work.

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References

1. Vaca I, Chávez R. Bioactive compounds produced by Antarctic filamentous fungi. In: Rosa LH, editor. Fungi of Antarctica. Cham: Springer; 2019. p. 265–83.
2. Salehi B, Bayat M, Dezfulian M, Sabokbar A, Tabaraie B. The assessment of anti-tumoral activity of polysaccharide extracted from terrestrial filamentous fungus. Saudi J Biol Sci. 2018;25(6):1236–41.
3. Stanojković T. Investigations of lichen secondary metabolites with potential anticancer activity. In: Ranković B, editor. Lichen secondary metabolites. Cham: Springer; 2019. p. 155–74.
4. Saravanakumar K, Shanmugam S, Varukattu NB, MubarakAli D, Kathiresan K, Wang M-H. Biosynthesis and characterization of copper oxide nanoparticles from indigenous fungi and its effect of photothermolysis on human lung carcinoma. J Photochem Photobiol B. 2019;190:103–9.
5. Chen L, Zhang Q-Y, Jia M, Ming Q-L, Yue W, Rahman K, et al. Endophytic fungi with antitumor activities: their occurrence and anticancer compounds. Crit Rev Microbiol. 2016;42(3):454–73.
6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. 2018;68(6):394–424.
7. Yan J-K, Pei J-J, Ma H-L, Wang Z-B, Liu Y-S. Advances in antitumor polysaccharides from *Phellinus sensu lato*: production, isolation, structure, antitumor activity, and mechanisms. Crit Rev Food Sci Nutr. 2017;57(6):1256–69.
8. Masuda Y, Nakayama Y, Tanaka A, Naito K, Konishi M. Antitumor activity of orally administered maitake α-glucan by stimulating antitumor immune response in murine tumor. PLoS ONE. 2017;12(3):e0173621.
9. Li Q-Z, Zheng Y-Z, Zhou X-W. Fungal immunomodulatory proteins: characteristic, potential antitumor activities and their molecular mechanisms. Drug Discov Today. 2019;24(1):307–14.
10. Matuszewska A, Stefaniuk D, Jaszek M, Pięt M, Zając A, Matuszewski Ł, et al. Antitumor potential of new low molecular weight antioxidative preparations from the white rot fungus Cerrena unicolor against human colon cancer cells. Sci Rep. 2019;9(1):1–10.
11. Ahmad MF. Ganoderma lucidum: a macro fungus with phytochemicals and their pharmacological properties. In: Ozturk M, Hakeem KR, editors. Plant and human health. vol. 2. Cham: Springer; 2019. pp. 491–515
12. Rajamanikyam M, Vadlapudi V, Upadhyayula SM. Endophytic fungi as novel resources of natural therapeutics. Braz Arch Biol Technol. 2017;60:e17160542.
13. Madhanraj R, Ravikumar K, Maya M, Illuri R, Venkatakrishna K, Rameshkumar K, et al. Evaluation of anti-microbial and anti-haemolytic activity of edible basidiomycetes mushroom fungi. J Drug Deliv Ther. 2019;9(1):132–5.
14. Li W, Song K, Wang S, Zhang C, Zhuang M, Wang Y, et al. Anti-tumor potential of astragalus polysaccharides on breast cancer cell line mediated by macrophage activation. Mater Sci Eng C. 2019;98:685–95.
15. Maehara S, Yamane C, Kitamura C, Hinokuma M, Hata T. High ophiobolin A production in endophytic fungus Bipolaris sp. associated with *Datura metel*. Nat Prod Res. 2019;33:1–3.
16. Noh S, Choi E, Hwang C-H, Jung JH, Kim S-H, Kim B. Dietary compounds for targeting prostate cancer. Nutrients. 2019;11(10):2401.
17. Matuszewska A, Stefaniuk D, Jaszek M, Pięt M, Zając A, Matuszewski Ł, et al. Antitumor potential of new low molecular weight antioxidative preparations from the white rot fungus Cerrena unicolor against human colon cancer cells. Sci Rep. 2019;9:1975.
18. Vil VA, Terent'ev AO, Savidov N, Gloriozova TA, Poroikov VV, Pounina TA, et al. Hydroperoxy steroids and triterpenoids derived from plant and fungi: origin, structures and biological activities. J Steroid Biochem Mol Biol. 2019;190:76–87.
19. Wang C, Zhang W, Wong JH, Ng T, Ye X. Diversity of potentially exploitable pharmacological activities of the highly prized edible medicinal fungus *Antrodia camphorata*. Appl Microbiol Biotechnol. 2019;103(19):7843–67.
20. Yang X-Y, Niu W-R, Li R-T, Cui X-M, Liu J-K. Two new sesquiterpenes from cultures of the higher fungus *Pholiota nameko*. Nat Prod Res. 2019;33(14):1992–6.
21. Vannucci L, Krizan J, Sima P, Stakheev D, Caja F, Rajsiglova L, et al. Immunostimulatory properties and antitumor activities of glucans. Int J Oncol. 2013;43(2):357–64.
22. Janakiraman V, Govindarajan K, Magesh C. Biosynthesis of silver nanoparticles from endophytic fungi, and its cytotoxic activity. BioNanoScience. 2019;9(3):573–9.
23. Mohseni MS, Khalilzadeh MA, Mohseni M, Hargalani FZ, Getso MI, Raissi V, et al. Green synthesis of Ag nanoparticles from pomegranate seeds extract and synthesis of Ag-Starch nanocomposite and characterization of mechanical properties of the films. Biocatal Agric Biotechnol. 2020;25:101569.
24. Barabadi H, Mahjoub MA, Tajani B, Ahmadi A, Junejo Y, Saravanan M. Emerging theranostic biogenic silver nanomaterials for breast cancer: a systematic review. J Clust Sci. 2019;30(2):259–79.
25. El-Kahky D, Attia M, Easa SM, Awad NM, Helmy EA. Biosynthesized of zinc oxide nanoparticles using *Aspergillus terreus* and their application as antitumor and antimicrobial activity. J Ecol Eng. 2019;8(3):90–100.
26. Peng C, Han B, Wang B, Zhao G, Yuan F, Zhao Y, et al. Therapy of prostate cancer by nanoyam polysaccharide. Int J Polym Sci. 2019;2019:1–5.
27. Husseiny SM, Salah TA, Anter HA. Biosynthesis of size controlled silver nanoparticles by *Fusarium oxysporum*, their antibacterial and antitumor activities. Beni-Suef Univ J Basic Appl Sci. 2015;4(3):225–31.
28. Benchamin D, Sreejai R, Sujitha S, Jensy Roshan F, Albert C, Rishad K. Anti-proliferative activity of L-Asparaginase enzyme from fungi on breast cancer. J Pharmacogn Phytochem. 2019;8(1):407–10.
29. Erden Y, Tekin S, Ceylan KBB, Tekin C, Kirbag S. Antioxidant, antimicrobial and anticancer activities of the aspergillin PZ and terphenyllin secondary metabolites: an in vitro study. Gazi Univ J Sci. 2019;32(3):792–800.

30. Meng Q, Zhou X, Ran X, Yan S, Fu S. Microbial synthesis of anti-tumor agent oxysophoridine through one step by filamentous fungus. J Pharm Biopharm Res. 2019;1(2):48–52.
31. Garrido-Rodríguez M, Ortea I, Calzado MA, Muñoz E, García V. SWATH proteomic profiling of prostate cancer cells identifies NUSAP1 as a potential molecular target for Galiellalactone. J Proteom. 2019;193:217–29.
32. Antipova TV, Zaitsev KV, Oprunenko YF, Zherebker AY, Rystsov GK, Zemskova MY, et al. Austalides V and W, new meroterpenoids from the fungus *Aspergillus ustus* and their antitumor activities. Bioorg Med Chem Lett. 2019;29(22):126708.
33. Lee D, Lee W-Y, Jung K, Kwon YS, Kim D, Hwang GS, et al. The inhibitory effect of cordycepin on the proliferation of MCF-7 breast cancer cells, and its mechanism: an investigation using network pharmacology-based analysis. Biomolecules. 2019;9(9):414.
34. Chien R-C, Yen M-T, Mau J-L. Antimicrobial and antitumor activities of chitosan from shiitake stipes, compared to commercial chitosan from crab shells. Carbohyd Polym. 2016;138:259–64.
35. Choromanska A, Kulbacka J, Rembialkowska N, Pilat J, Oledzki R, Harasym J, et al. Anticancer properties of low molecular weight oat beta-glucan—an in vitro study. Int J Biol Macromol. 2015;80:23–8.
36. Choromanska A, Kulbacka J, Harasym J, Oledzki R, Szewczyk A, Saczko J. High-and low-molecular weight oat beta-glucan reveals antitumor activity in human epithelial lung cancer. Pathol Oncol Res. 2018;24(3):583–92.
37. El-Kassem LA, Hawas UW, El-Souda S, Ahmed EF, El-Khateeb W, Fayad W. Anti-HCV protease potential of endophytic fungi and cytotoxic activity. Biocatal Agric Biotechnol. 2019;19:101170.
38. Karaman M, Janjušević L, Jakovljević D, Šibul F, Pejin B. Anti-hydroxyl radical activity, redox potential and anti-AChE activity of *Amanita strobiliformis* polysaccharide extract. Nat Prod Res. 2019;33(10):1522–6.
39. Khan T, Date A, Chawda H, Patel K. Polysaccharides as potential anticancer agents—a review of their progress. Carbohydr Polym. 2019;210:412–28.
40. Li H, Cao K, Cong P, Liu Y, Cui H, Xue C. Structure characterization and antitumor activity of the extracellular polysaccharide from the marine fungus *Hansfordia sinuosae*. Carbohyd Polym. 2018;190:87–94.
41. Liu X-C, Zhu Z-Y, Liu Y-L, Sun H-Q. Comparisons of the antitumor activity of polysaccharides from fermented mycelia and cultivated fruiting bodies of *Cordyceps militaris* in vitro. Int J Biol Macromol. 2019;130:307–14.
42. Qi C, Gao W, Guan D, Wang J, Liu M, Chen C, et al. Butenolides from a marine-derived fungus *Aspergillus terreus* with antitumor activities against pancreatic ductal adenocarcinoma cells. Bioorg Med Chem. 2018;26(22):5903–10.
43. Sun X, Zhao C, Pan W, Wang J, Wang W. Carboxylate groups play a major role in antitumor activity of *Ganoderma applanatum* polysaccharide. Carbohyd Polym. 2015;123:283–7.