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Mini Review

Mushrooms Against Tumors: Are Endofungal Microbes Also Armed?

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Abstract

The medical properties of mushrooms are being actively investigated, but clinical studies are quite rare. The complexity of further progress lies in the fragmentation of the initial data of various studies. A search in the Science Direct, Pub Med Central, and Google Scholar databases on the topic revealed a wide range of physicochemical properties of the investigated mushroom polysaccharides. The discrepancy between the data of different researchers can be caused by various conditions for obtaining preparations, including the likely effect of the fungal microbiota on the production of biologically significant compounds.l plant led to marked regeneration of cardiomyocytes. The toxic cardiac injury induced by CCl_4 was significantly blocked by the phytochemicals.

Keywords: Mushrooms; Medicinal properties; β-glucans; Co-culture; Endofungal microbiota

Introduction

Mushrooms have been used in medicine for many centuries. Macrofungi are a source of a range of bioactive compounds, including polysaccharides, peptides, terpenes, fatty acids, phenols, sterols, glycosides, flavonoids, carotenoids, and others, with a total of more than 130 therapeutic effects (Wasser 2017; Panda and Luyten 2022; Pathak et al. 2022; Rowaiye et al. 2022). Some mushroom compounds have already been clinically tested and therapeutically used in several Asian countries, but the general public knows little about their medicinal properties (Wasser 2011).

The antitumor and immunomodulatory effects of mushrooms are most pronounced (Wasser 2017; Motta et al. 2021). Evidence for the antioxidant activity of various fungal species has also been presented (Mwangi et al. 2022; Sunil and Xu 2022). Active compounds and preparations of mushrooms can prevent oncogenesis and tumor metastasis, both through direct inhibition of tumor cell growth and through effects on the immune system (Jesenak et al. 2013; Garcia et al 2022; Panda and Luyten 2022).

Mushrooms can also be used as adjuvants in chemotherapy (Steimbach et al. 2021; Garcia et al. 2022) and were shown to suppress the production of pro-inflammatory mediators (Rowaiye et al. 2022). There is strong evidence for the influence of mushrooms on macrophages, lymphocytes, T cells, dendritic cells, monocytes, neutrophils, natural killer cells, and hematopoietic stem cells of the immune system (Wasser 2011; Pathak et al. 2022). Fungal compounds also affect chemical messengers of complementary and acute phase responses (Wasser 2011).

However, many authors noted the paucity of clinical trials compared to the abundance of in vitro and cell culture studies and the need for further research to improve the validity and reliability of randomized trials for elucidating the therapeutic value of mushrooms (Markovina et al. 2020; Steimbach et al. 2021; Panda and Luyten 2022).

Discussion

Among the medical compounds of macro-mushrooms, special attention is paid to polysaccharides, namely β-glucans. The ability of bioactive mushroom polysaccharides and polysaccharide-protein complexes to suppress tumors in animals and humans has been shown hitherto. It has been demonstrated that β-glucans are responsible for most mushroom bioactivity manifestations (Wasser 2017; Vetvicka et al., 2021), primarily antitumor and immunomodulatory effects. However, differences in fungal strains, growing conditions, stage of development, and the part of a mushroom give rise to significant differences in the physicochemical properties of β-glucans (Motta et al. 2021; Vetvicka et al. 2021). The use of various extraction methods and storage conditions makes it even more difficult to advance in revealing the mechanisms of action and defining possible clinical effects. A high immunomodulatory effect of soluble β-glucans has been shown (Wasser 2011). For different research, a hot aqueous extract of polysaccharides is commonly used (Khan et al. 2014; Tanaka et al. 2016; Minato et al. 2017). Nowakowski et al. (2021) found a higher efficiency of alcoholic extracts of mushrooms compared to water extracts. At the same time, it is known that fungal β-glucans are usually characterized by a branched structure, and the solubility depends on the structure, while β-glucans with β-1,3 bonds and a high degree of polymerization are completely insoluble in water (Mudgil 2017). As can be seen, the greatest stimulation of immunity was noted in β-glucans with a 1,3 configuration and additional branching in positions 0–6 of 1,3-linked d-glucose residues (Vetvicka et al., 2021). There is also evidence that high molecular weight and water solubility with low branching correlate with higher antitumor activity (Angelis et al. 2013). Available information on the structure of polysaccharides of some fungal species, their toxicological effects, and their pharmacokinetic profiles is limited (Neergheen et al. 2022). The structure of glucans of the same mushroom can significantly vary depending on the cultivation conditions. This may explain the difference in immunomodulatory activity between homemade and commercial lentinan products in the research of Murphy et al. (2020).

The presence of other bioactive compounds in extracts, such as, for example, protein complexes (Zhang et al. 2020), may have an additional effect. One of the unaccounted factors in the study of the impact of various factors on the biological activity of mushroom polysaccharides may be microorganisms. Bacteria, molds, and microalgae that exist inside or on the surface of fruiting bodies and hyphae can make a significant contribution to the production of various biologically active compounds of medicinal mushrooms. The discovery of endophytic microorganisms within plants and data on the internal microbiomes of humans and animals have made a huge breakthrough in our understanding of the interactions of various organisms and the consequences of these interrelations.

Endofungal and endohyphal microorganisms are still very poorly studied. However, in the field of polysaccharide production, it has already been shown that the co-cultivation of mushrooms from the genera Ganoderma, Lentinus, Trametes, Pleurotus, and Agaricus with microalgae and cyanobacteria affects not only the quantitative yield of polysaccharides but also the production of fundamentally new ones, other than those of monocultures (Angelis et al. 2012). Some pseudomonads capable of three-fold increasing the production of the red pigment hypocrellin A, which is used in particular in photodynamic therapy of cancer, have been found in the fruiting bodies of the Shiraia mushroom (Ma et al. 2019). The mechanism of their action is up-regulation of the expression of polyketide synthase (hypocrellin A biosynthesis) and transporter genes including ATP-binding cassette and major facilitator superfamily transporter for hypocrellin A exudation. At the same time, Bacillus cereus, also isolated from the fruiting body of this mushroom can reduce hypocrellin via the down-regulation of biosynthetic genes or possibly biodegradation. Another mushroom, Xylaria flabelliformis, in co-culture with Aspergillus fischeri forms a number of new secondary metabolites, one of which, wheldone, revealed cytotoxicity against breast, ovarian, and melanoma cancer cell lines (Knowles et al. 2019, 2020). And the endophytic bacteria of the fungus Cordyceps cicadae contributed to the production of N6-(2-hydroxyethyl)-adenosine and other compounds of this famous medicinal mushroom (Qu et al. 2019).

Conclusion

Who knows, maybe the main conductors of the orchestra, aimed at the production of bioactive, including antitumor compounds of mushrooms, are actually microorganisms living inside them? It is known that certain functions of plant endophytic fungi are associated with the presence of endohyphal bacteria. They participate in the activation of genes involved in the recognition processes, transcription regulation, and synthesis of primary metabolism proteins, and perform many other functions (Arora and Riyaz-Ul-Hassan 2019). It is possible that the control of the composition of endofungal bacteria can also make progress in the production of medically significant components of macrofungi.

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Conflict of Interest

The authors declare no conflict of interest.

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