

Perspectives of Biomedical Application of Macrofungi



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Submission: March 13, 2020; **Published:** July 29, 2020

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Abstract

Macrofungi (mushrooms) have widely been appreciated all over the world for their nutritional values and medicinal properties. They have been used in traditional medicine for more than 3000 years for prevention and treatment of different diseases. Modern scientific research shows that macrofungi are producers of a broad spectrum of high- and low-molecular-weight bioactive compounds, i.e., alkaloids, polysaccharides, proteins, phenolics, terpenoids, polyketides, cyclic peptides, lectins and ribosome-inactivating proteins. They have various therapeutic effects as antidiabetic, anti-inflammatory, antimicrobial, antioxidant, antitumor, antiviral, cardioprotective, hepatoprotective, hypocholesterolemic, hypotensive, immunomodulatory, neuroprotective and regenerative, and possess promising pharmacological potential. Development of fungal biotechnological cultivation industry will support production of macrofungi-derived biotech products, healthy food and mycopharmaceuticals pharmaceuticals. Further advances in fungal biology and biotechnology, genomics and proteomics will assist biomedical research and application of macrofungi.

Keywords: Medicinal macrofungi; Basidiomycota; Ascomycota; Bioactive compounds; Pharmacological effect; Biomedicine

Abbreviations: BAC: Bioactive Compounds; FIP: Fungal Immunomodulatory Protein; MM: Medicinal Macrofungi

Introduction

Fungi are very diverse organisms distributed worldwide and found in almost all habitats. From estimated 1.5-3 million species of fungi about 150,000 species are macrofungi (mushrooms) taxonomically placed in two phyla, the Basidiomycota (class *Agaricomycetes*) and *Ascomycota* (class *Pezizomycetes*) in the subkingdom Dikarya [1]. Among them about 10% (14,000-16,000) are scientifically well-known including, about 7000 edible species and 500 poisonous species [2,3]. There may be as many as 700 medicinal macrofungi (MM) which are regarded safe and possess around 130 different pharmacological activities [4,5].

Macrofungi have widely been appreciated all over the world not only for their nutritional values but also medicinal properties [5-12]. They have been used in traditional medicine for more than 3000 years for prevention and treatment of different diseases [13,14]. Despite available ethno-mycopharmacological information and scientific data the extensive pharmacological and biotechnological potential offered by Macrofungi is certainly not yet fully exploited [15-20].

Bioactive Compounds and Pharmacological Activity of Macrofungi

Modern scientific data shows that agaricoid, polyporoid, and other taxonomic groups of Macrofungi are producers of a broad spectrum of high- and low-molecular-weight bioactive compounds (BAC), i.e., alkaloids, polysaccharides, proteins, phenolics, terpenoids, polyketides, cyclic peptides, lectins, ribosome-inactivating proteins [21-27]. These BAC means Bioactive Compounds were investigated for their various therapeutic effects as analgesic, antimicrobial, antiviral, antioxidant, immunomodulatory, anti-inflammatory, antitumor, mitogenic/regenerative, hypotensive, hepatoprotective, antidiabetic/hypoglycemic, hypocholesterolemic, cardio- and neuroprotective activities [28-45].

Wild and cultivable edible, and non-edible MM (e.g. *Agaricus brasiliensis*, *Agrocybe cylindracea*, *Auricularia auricula-judae*, *Coprinus comatus*, *Ganoderma applanatum*, *G. lucidum*, *Grifola frondosa*, *Hericium erinaceus*, *Flammulina velutipes*, *Inonotus*

obliquus, *Lentinula edodes*, *Ophiocordyceps* (syn. *Cordyceps*) *sinensis*, *Phellinus linteus*, *Pleurotus ostreatus*, *Polyporus umbellatus*, *Trametes versicolor*, *Tremella fuciformis*, *Wolfiporia cocos*, etc.) are considered as valuable sources to develop health enhancing functional food (nutraceuticals, nutraceuticals), macrofungi-derived drugs (mycopharmaceuticals), and cosmetic products (cosmeceuticals, nutricosmetics) which are perspective for biomedical application [12,18-20,46].

A wide spectrum of bioactive molecules with macrofungi origin has been recommended for a variety of therapeutic applications, such as the immunomodulatory β -glucan lentinan from *L. edodes* [27], the antimalarial alkaloid 4-hydroxymethylquinoline from *T. versicolor* [47]; pain-suppressive enkephalinase inhibitors from *Piptoporus betulinus* [48]; nephroprotective polysaccharides, phenolics, and flavonoids from *Pleurotus tuber-regium* [37].

The extract derived from well-known medicinal species *Cordyceps sinensis* and *Agaricus subrufescens* possess anticancer effects by modulating the immune system and inducing cell apoptosis [25,38]. The edible medicinal oyster mushroom *P. ostreatus* has significant hypocholesterolemic properties and other pharmacological effects [30,39,40,43]. Anticancer, antimicrobial, antioxidant, antiviral, hypolipidemic, immunomodulatory, and estrogen-like activities were observed in *Pleurotus eryngii* due to the production of diterpenoids, as eryngiolide A, hemolysins, polysaccharides, pentacyclic triterpenoids, ubiquinone-9, and other pharmacologically active biomolecules [43,49,50]. Genome sequencing, comparative genomics, and phylogenetic analysis of medicinal polypore mushroom *Lignosus rhinocerotis* revealed sesquiterpenoid biosynthesis genes. Moreover, the genome of *L. rhinocerotis* encodes for 1,3- β - and 1,6- β -glucans, as well as for laccase, lectin, and other fungal immunomodulatory proteins (FIP) [51,52].

The *Ganoderma* species produce the highest diversity of bioactive compounds (alkaloids, fatty acids, nucleosides, polysaccharides, proteins, sterols, triterpenoids, etc.) with antiaging, antibacterial, anticancer, antidiabetic, antifungal, antihypertensive, anti-inflammatory, antioxidant, antiviral, hepatoprotective, hypoglycemic, immunomodulatory, neuroprotective, wound-healing, and other pharmacological effects [22,23,32-34,41,42].

Conclusion and Future Perspectives

Nowadays, pharmaceutical companies consider the medicinal macrofungi as a rich source of innovative biomedical molecules extracted not only from fruiting bodies but also from both cultivated mycelial biomass and cultural broth. Moreover, the mycelium and the cultural broth might be considered as safe potential sources of bioactive compounds, due to their shorter incubation time and affordable culture conditions (e.g., requiring less space, low probability of contamination, and higher production of biomass) [12,36,43].

The advances in multidimensional biotechnological cultivation industry of macrofungi will further support development and application of myco-biotech products biotech products and pharmaceuticals in biomedicine [7,19,20].

Currently, *in vitro* assays, animal studies, and clinical trials justify the experience of traditional medicine and suggest a great potential of macrofungi-derived compounds and pharmaceuticals for both the prevention and treatment of various diseases. However, development of high-quality and safe biotech products under controlled conditions with standardized procedures for further clinical trials are needed to substantiate the pharmacological properties or side effects of mushroom consumption before their clinical recommendation as myco-pharmaceutical drugs [36,53-56]. Compared to available extensive lists of bioactive compounds of macrofungi and their therapeutic effects and therapeutic effects, the pathways of their biosynthesis and the genes behind are largely understudied [19]. Therefore, advances in fungal biology and biotechnology, genomics and proteomics are required for further biomedical research and application of macrofungi.

Acknowledgments

This review arises from a long-standing cooperation between two authors (S.M.B. and S.R.) on fungal biomedical research directed to the identification of bioactive compounds and medicinal properties of macrofungi supported by the collaboration between the Institute of Pharmacy; Yerevan State University, Armenia; and Faculty of Pharmacy of the University of Montpellier/UMR 5175 CNRS, France. The research project on medicinal mushrooms was partially sponsored by MES SCS Republic of Armenia (grant number #18T-1F115).

References

- Hibbett DS, Taylor JW (2013) Fungal systematics: is a new age of enlightenment at hand? *Nat Rev Microbiol* 11: 129-133.
- Hawksworth DL (2001) Mushrooms: the extent of the unexplored potential. *Int J Med Mushrooms* 3: 333-337.
- Hawksworth DL (2012) Global species numbers of fungi: are tropical studies and molecular approaches contributing to a more robust estimate? *Biodivers Conserv* 21: 2425-2433.
- Boa ER (2004) Wild edible fungi a global overview of their use and importance to people. Food and Agriculture Organization of the United Nations, Roma.
- Chang ST, Wasser SP (2017) The cultivation and environmental impact of mushrooms. In: *Oxford research encyclopedia of environmental science - Agriculture and the environment*.
- Chang ST, Miles PG (2004) *Mushrooms: Cultivation, nutritional value, medicinal effect, and environmental impact*, 2nd edn. CRC Press, Boca Raton.
- Chang ST, Buswell JA (1996) Mushroom nutraceuticals. *World J Microbiol Biotechnol* 12(5): 473-476.
- Wasser SP (2014) Medicinal mushroom science: current perspectives, advances, evidences, and challenges. *Biomed J* 37(6): 345-356.
- Valverde ME, Hernández-Pérez T, Paredes-López O (2015) Edible mushrooms: improving human health and promoting quality life.

- Intern J Microbiol ID 376387, 14 p.
10. Gupta S, Summuna B, Gupta M, et al. (2018) Edible mushrooms: cultivation, bioactive molecules, and health benefits. In: Mérillon JM, Ramawat KG (Eds) Bioactive molecules in food, reference series in Phytochemistry. Springer, pp. 1-33.
 11. Bandara AR, Rapior S, Bhat DJ, Pattana K, Sunita C, et al. (2015) *Polyporus umbellatus*, an edible-medicinal cultivated mushroom with multiple developed health-care products as food, medicine and cosmetics: a review. *Cryptogam Mycol* 36(1): 3-42.
 12. Bandara AR, Rapior S, Mortimer PE, Kakumyan P, Hyde KD, et al. (2019) A review of the polysaccharide, protein and selected nutrient content of *Auricularia*, and their potential pharmacological value. *Mycosphere* 10(1): 579-607.
 13. Hobbs CR (1995) Medicinal mushrooms: an exploration of traditions, healing, and culture. Botanica Press, Santa Cruz.
 14. Chen H, Tian T, Miao H, Zhao YY (2016) Traditional uses, fermentation, phytochemistry and pharmacology of *Phellinus linteus*: a review. *Fitoterapia* 113: 6-26.
 15. Lindequist U (2013) The merit of medicinal mushrooms from a pharmaceutical point of view. *Int J Med Mushrooms* 15(6): 517-523.
 16. Grienke U, Zöll M, Peintner U, et al. (2014) European medicinal polypores - a modern view on traditional uses. *J Ethnopharmacol* 154(3): 564-583.
 17. De Silva DD, Rapior S, Sudarman E, Marc S, Jianchu X, et al. (2013) Bioactive metabolites from macrofungi: ethnopharmacology, biological activities and chemistry. *Fungal Divers* 62: 1-40.
 18. Badalyan SM (2012) Medicinal aspects of edible ectomycorrhizal mushrooms. In: Zambonelli A & Bonito G (Eds) Edible ectomycorrhizal mushrooms, current knowledge and future prospects. Vol. 34. Springer/Heidelberg, pp. 317-334.
 19. Kues U, Badalyan SM (2017) Making use of genomic information to explore the biotechnological potential of medicinal mushrooms. In: Agrawal DC, et al. (Eds). Medicinal plants and fungi: recent advances in research and development. In book series Medicinal and aromatic plants of the world Vol. 4. Springer Nature Singapore, pp 397-458.
 20. Badalyan SM, Zambonelli A (2019) Biotechnological exploitation of macrofungi for the production of food, pharmaceuticals and cosmeceuticals. In: Sridhar KR, Deshmukh SK (Eds) Advances in macrofungi: diversity, ecology and biotechnology. Boca Raton, CRC Press, pp. 199-230.
 21. Xu X, Yan H, Chen J, Zang X (2011) Bioactive proteins from mushrooms. *Biotechnol Adv* 29(6): 667-674.
 22. Sánchez C (2017) Bioactives from mushrooms and their application. In: Puri M (Ed) Food bioactives. Springer-Verlag, pp. 23-57.
 23. Yang YL, Tao QQ, Han JJ, et al. (2017) Recent advance on bioactive compounds from the edible and medicinal fungi in China. In: Agrawal DC, et al. (Eds) Medicinal plants and fungi: recent advances in research and development, Medicinal and aromatic plants of the world. Springer Nature Singapore, pp. 253-313.
 24. Pandya U, Dhuldhaj U, Sahay NS (2018) Bioactive mushroom polysaccharides as antitumor: an overview. *Nat Prod Res* 4: 1-13.
 25. Da Silva de Souza AC, Corrêa VG, Goncalves GA, et al. (2017) *Agaricus blazei* bioactive compounds and their effects on human health: benefits and controversies. *Curr Pharm Des* 23(19): 2807-2834.
 26. Wang Q, Wang F, Xu Z, Ding Z (2017) Bioactive mushroom polysaccharides: a review on monosaccharide composition, biosynthesis and regulation. *Molecules* 22: 955.
 27. Novak M, Vetricka V (2008) β -Glucans, history, and the present: immunomodulatory aspects and mechanisms of action. *J Immunotoxicol* 5(1): 47-57.
 28. Morel S, Arnould S, Vitou M, Boudard F, et al. (2018). Antiproliferative and antioxidant activities of wild Boletales mushrooms from France. *Int J Med Mushrooms*, 20(1): 13-29.
 29. Diallo I, Boudard F, Morel S, Vitou M, et al. (2020) Antioxidant and anti-inflammatory potential of *Lentinula edodes* (Shiitake) sporophores from various culture conditions. *Int J Med Mushrooms* 22 22(6): 535-546.
 30. Thongbai B, Rapior S, Hyde KD, Wittstein K, Stadler M (2015) *Hericium erinaceus*, an amazing medicinal mushroom. *Mycological Progress* 14(10), Article 91.
 31. Chen CC, Shiao YJ, Lin RD, et al. (2006) Neuroprotective diterpenes from the fruiting body of *Antrodia camphorata*. *J Nat Prod* 69: 689-691
 32. De Silva DD, Rapior S, Fons F, et al. Medicinal mushrooms in supportive cancer therapies: an approach (2012a) to anti-cancer effects and putative mechanisms of action. *Fungal Divers* 55: 1-35.
 33. De Silva DD, Rapior S, Hyde KD, et al. (2012b) Medicinal mushrooms in prevention and control of diabetes mellitus. *Fungal Divers* 56: 1-29.
 34. Perera PK, Li Y (2011) Mushrooms as a functional food mediator in preventing and ameliorating diabetes. *Funct Food Health Dis* 4: 161-171.
 35. Xu H, Kong YY, Chen X, et al. (2016) Recombinant FIP-gat, a fungal immunomodulatory protein from *Ganoderma atrum*, induces growth inhibition and cell death in breast cancer cells. *J Agric Food Chem* 64:2690-2698.
 36. Hyde KD, Jianchu Xu, Rapior S, Lumyong S, et al. (2019) The amazing potential of fungi, 50 ways we can exploit fungi industrially. *Fungal Diversity* 97:1-136, 1-136.
 37. Okolo KO, Orisakwe OE, Siminialayi IM (2018) Nephroprotective and antioxidant effects of king tuber oyster medicinal mushroom, *Pleurotus tuber-regium* (Agaricomycetes), on carbon tetrachloride-induced nephrotoxicity in male Sprague dawley rats. *Int J Med Mushrooms* 20(5): 419-429.
 38. Xu J, Huang Y, Chen XX, et al. (2016) The mechanisms of pharmacological activities of *Ophiocordyceps sinensis* fungi. *Phytother Res* 30:1572-1583.
 39. Patel Y, Naraian R, Singh VK (2012) Medicinal properties of *Pleurotus* species (oyster mushroom): a review. *World J Fungal Plant Biol* 3:1-12.
 40. Schillaci D, Cusimano MG, Cascioferro SM, et al. (2017) Antibacterial activity of desert truffles from Saudi Arabia against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *Int J Med Mushrooms* 19(2): 121-125.
 41. Saltarelli R, Ceccaroli P, Buffalini M, et al. (2015) Biochemical characterization, antioxidant and antiproliferative activities of different *Ganoderma* collections. *J Mol Microbiol Biotechnol* 25(1): 16-25.
 42. Wang XL, Ding ZY, Zhao Y, et al. (2017) Efficient accumulation and in vitro antitumor activities of triterpene acids from submerged batch-cultured *Lingzhi* or *Reishi* medicinal mushroom, *Ganoderma lucidum* (Agaricomycetes). *Int J Med Mushrooms* 19(5): 419-431.
 43. Zhang C, Li S, Zhang J, et al. (2016) Antioxidant and hepatoprotective activities of intracellular polysaccharide from *Pleurotus eryngii* SI-04. *Int J Biol Macromol* 91: 568-577.
 44. Taofiq O, Martins A, Barreiro MF, et al. (2016) Anti-inflammatory potential of mushroom extracts and isolated metabolites. *Trends Food Sci Technol* 50: 193-210.

45. Souilem F, Fernandes Â, Calhelha RC, et al. (2017). Wild mushrooms and RC, et al. their mycelia as sources of bioactive compounds: antioxidant, anti-inflammatory and cytotoxic properties. *Food Chem* 230: 40-48.
46. Taofiq O, González-Paramás AM, Martins A, et al. (2016) Mushrooms extracts and compounds in cosmetics, cosmeceuticals and nutricosmetics - a review. *Ind Crop Prod* 90: 38-48.
47. Liu JK (2005) N-containing compounds of macromycetes. *Chem Rev* 105(7): 2723-2744.
48. Rathee S, Rathee D, Vikash K, Permender R, et al. (2011) Mushrooms as therapeutic agents. *Bras J Pharmacognosy* 22(2): 459-474.
49. Ma G, Yang W, Mariga AM, Yong F, Ning M, et al. (2014) Purification, characterization and antitumor activity of polysaccharides from *Pleurotus eryngii* residue. *Carbohydr Polym* 114: 297-305.
50. Yen MT, Chang YH, Huang SJ, Ming-Ching C, Jeng-Leun M, et al. (2018) Extraction of ergothioneine from *Pleurotus eryngii* and *P. citrinopileatus* (Agaricomycetes) and preparation of its product. *Int J Med Mushrooms* 20(4): 381-392.
51. Yap HY, Chooi YH, Firdaus-Raih M, Fung SY, Ng ST, et al. (2014) The genome of the tiger milk mushroom, *Lignosus rhinocerotis*, provides insights into the genetic basis of its medicinal properties. *BMC Genomics* 15(1): 635.
52. Yap HY, Fung SY, Ng ST, Tan CS, Tan NH (2015) Genome-based proteomic analysis of *Lignosus rhinocerotis* (Cooke) Ryvarden sclerotium. *Int J Med Sci* 12(1): 23-31.
53. Money NP (2016) Are mushrooms medicinal? *Fungal Biol* 120(4): 449-453.
54. Wasser SP (2017) Medicinal mushrooms in human clinical studies. Part I. Anticancer, oncoimmunological, and immunomodulatory activities: a review. *Int J Med Mushrooms* 19(4): 279-317.
55. Badalyan SM, Barkhudaryan A, Rapior S (2019) Recent progress in research on the pharmacological potential of mushrooms and prospects for their clinical application. In: Agrawal DC & Dhanasekaran M. (eds) *Medicinal Mushrooms: Recent Progress in Research and Development*. Springer Nature Singapore, pp 1-70.
56. Zmitrovich IV, Belova NV, Balandaykin ME, Bondartseva MA, Wasser SP (2019) Cancer without pharmacological illusions and a niche for Mycotherapy (review). *Int J Med Mushrooms* 21(2): 105-119.



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DOI: [10.19080/CTBEB.2020.19.556024](https://doi.org/10.19080/CTBEB.2020.19.556024)

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