Dinesh Chandra Agrawal
Muralikrishnan Dhanasekaran *Editors*

Medicinal Mushrooms

Recent Progress in Research and Development

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Editors dedicate this book to their beloved families:
Manju, Somya, Neha, and Mihir (Family Agrawal)
and
Madhu, Rishi (Family Dhanasekaran)

Preface

The present book is the continuation of Professor Agrawal's previous two Springer books: *Medicinal Plants – Recent Advances in Research and Development* (Springer link: http://www.springer.com/in/book/9789811010842) and *Medicinal Plants and Fungi – Recent Advances in Research and Development* (Springer link: https://www.springer.com/gp/book/9789811059773).

In this volume, chapters (mostly review articles) on medicinal mushrooms have been included considering their importance in the human health. Medicinal mushrooms are now gaining worldwide attention because of its pharmacologically bioactive compounds which have demonstrated potent and unique clinical properties. Scientific studies carried out during the last decade have validated evidence of their efficacy in a wide range of diseases. Extracts and bioactive compounds obtained from different mushrooms have been used medicinally as anticancer, immunomodulator, antibacterial, antiviral, anti-inflammatory, anti-atherosclerotic, neuroprotectant, cardioprotectant, antioxidant, and anti-hypoglycemic agents and in stem cell-based therapies. There are ongoing research efforts on various aspects of medicinal mushrooms in different parts of the world. The editors wish to bring their recent research and development works into light in the form of this book.

The book contains chapters, mostly review articles, contributed by eminent researchers working with different disciplines of medicinal mushrooms in different countries across the globe. This book not only extends our knowledge about medicinal mushrooms and confirms the great potential of mushrooms for the development of new drugs but hopefully also inspires the readers to get involved in medicinal mushroom research.

The editors hope that this compendium of review articles will be very useful as a reference book for advanced students, researchers, academics, business houses, and all individuals concerned with medicinal mushrooms.

Taichung, Taiwan
Auburn, AL, USA
24 August 2018

Dinesh Chandra Agrawal
Muralikrishnan Dhanasekaran

Acknowledgments

The editors thank all the invited authors to this book for preparing their valuable manuscripts. Without their contributions, this book would not have been possible.

The coeditor, Dr. Dhanasekaran, wishes to place on record special appreciation and thanks to Professor Agrawal for initiating the book proposal; handling the entire correspondence with Springer and authors; dealing with editing, reviewing, and revision process of manuscripts; and managing them from start to finish. Without his untiring efforts, this book would not have become a reality.

Editor Professor Agrawal thanks Professor Tao-Ming Cheng, President of the Chaoyang University of Technology (CYUT); Professor Wen-Goang Yang, Vice-President, CYUT; Professor Sung-Chi Hsu, Dean, R&D Office, and Assistant Vice-President, CYUT; Professor Chia-Chi Cheng, Dean, College of Science and Engineering, CYUT, and Professor Hsin-Sheng Tsay, Emeritus Chair Professor, CYUT, Taichung, Taiwan, for their constant support and encouragement during the progress of the book. Editor Professor Muralikrishnan thanks Professor Timothy Moore, Head of the Department, Harrison School of Pharmacy; Professor Randall Clark, Harrison School of Pharmacy; and all his beloved students (Ms. Fujihashi, Mr. Majrashi, Mr. Almaghrabi, Dr. Sindhu, Dr. Manoj) for their relentless care and inspiration.

The editors sincerely thank the entire Springer Nature Singapore Pte. Ltd., the team concerned with the publication of this book, and place on record a special appreciation to Ms. Aakanksha Tyagi, Editor, Life Sciences, Springer, for her encouragement and prompt support during the publication of this book.

Editors express profound gratitude toward "God, the Infinite Being" for providing strength to accomplish the arduous task of handling this book.

Contents

About the Editors and Contributors

Editors

Dinesh Chandra Agrawal graduated in 1976 from Aligarh Muslim University (national university) and obtained his Ph.D. in 1982. Professor Agrawal has more than 37 years of research experience in plant biotechnology of diverse species including medicinal plants and medicinal mushrooms. After serving for more than 31 years, in 2013, he superannuated as a chief scientist and professor of biological sciences at the CSIR-National Chemical Laboratory (NCL), Pune, the top-ranking institute in chemical sciences under the umbrella of the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, Government of India. Currently, he is working as a professor in the Department of Applied Chemistry, Chaoyang University of Technology (CYUT), Taiwan. While in CSIR-NCL, Prof. Agrawal worked as a coordinator and project leader of several research projects funded by the Government of India. He has more than 175 publications including 4 books to his credit on the different aspects of plant biotechnology including medicinal plants and medicinal mushrooms. More than 35 M.Tech./M.Sc. and 7 Ph.D. students have completed their thesis work under his guidance. Professor Agrawal has been bestowed several prestigious awards and fellowships such as the Alexander von Humboldt Fellowship (Germany), DBT Overseas Associateship (USA), British Council Scholar (UK), European Research Fellow (UK), and INSA Visiting Scientist. During these fellowships, he had opportunities to work in the USA, Germany, and the UK. Also, he had a research collaboration with UMR Vigne et Vins, INRA,

Centre de Recherché Colmar, France. For more than 10 years, he has been a member of the executive committee of the Humboldt Academy, Pune Chapter, and held the position of treasurer. Professor Agrawal has reviewed a large number of research papers for several SCI journals on plant biotechnology and served as a member of the editorial board of *Medicinal and Aromatic Plants Abstracts*, NISCAIR, Government of India. Presently, he is on the editorial board of the *International Journal of Applied Sciences and Engineering* (Scopus), serving as associate editor in chief of the journal.

Muralikrishnan Dhanasekaran completed his Bachelor of Pharmacy from Annamalai University and Master of Pharmacy from Jadavpur University, West Bengal, India. He obtained his Ph.D. from the Indian Institute of Chemical Biology, Kolkata, India. Following which, he attained his postdoctoral training from renowned scientists Dr. Manuchair Ebadi (Professor at the University of North Dakota, Grand Forks, ND) and Dr. Bala Manyam (Scott & White Clinic/Texas A&M, Temple, TX). Dr. Dhanasekaran joined Auburn University in the year 2005 and is currently working as a full professor at Harrison School of Pharmacy, Auburn University, USA. Dr. Dhanasekaran's area of research and interest focuses on neuropharmacology, toxicology, dietary, and natural products. Dr. Dhanasekaran successfully completed the New Investigator Research Grant from Alzheimer's Association, several Auburn University grants, and several research projects from a pharmaceutical company. He has graduated 6 students (as a mentor) and currently has 3 graduate and 30 undergraduate students in his lab. Dr. Dhanasekaran has received several teaching awards from Auburn University, for teaching Pharm.D. and graduate students. He has published more than 100 scientific abstracts, 70 peer-reviewed publications, and several book chapters. With regard to professional service, he is the current chair of the "Faculty Grievance Committee" and "Teaching Effective Committee." Dr. Dhanasekaran also serves as a reviewer and member of the editorial board in several scientific journals.

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1 Recent Progress in Research on the Pharmacological Potential of Mushrooms and Prospects for Their Clinical Application

Susanna M. Badalyan, Anush Barkhudaryan, and Sylvie Rapior

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Abstract

Fungi are considered one of the most diverse, ecologically significant, and economically important organisms on Earth. The edible and medicinal mushrooms have long been known by humans and were used by ancient civilizations not only as valuable food but also as medicines. Mushrooms are producers of high- and low-molecular-weight bioactive compounds (alkaloids, lectins, lipids, peptidoglycans, phenolics, polyketides, polysaccharides, proteins, polysaccharide-protein/peptides, ribosomal and non-ribosomal peptides, steroids, terpenoids, etc.) possessing more than 130 different therapeutic effects (analgesic, antibacterial, antifungal, anti-inflammatory, antioxidant, antiplatelet, antiviral, cytotoxic, hepatoprotective, hypocholesterolemic, hypoglycemic, hypotensive, immunomodulatory, immunosuppressive, mitogenic/regenerative, etc.).

The early record of *Materia Medica* shows evidence of using mushrooms for treatment of different diseases. Mushrooms were widely used in the traditional medicine of many countries around the world and became great resources for modern clinical and pharmacological research. However, the medicinal and biotechnological potential of mushrooms has not been fully investigated. This review discusses recent advances in research on the pharmacological potential of mushrooms and perspectives for their clinical application.

Keywords

Bioactive compounds · Clinical application · Ethno-mycopharmacology · Medicinal mushrooms · Pharmacological potential

Abbreviations

ACE	Angiotensin-converting enzyme
AIDS	Acquired immune deficiency syndrome
BDNF	Brain-derived neurotrophic factor
CL	Cultural liquid
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CSF	Colony-stimulating factor
CVD	Cardiovascular diseases
DENV-2	Dengue virus type 2
DS	Dietary supplement
EPS	Exopolysaccharides
FIP	Fungal immunomodulatory protein
GLPS	*G. lucidum* polysaccharide

GSK-3	Glycogen synthase kinase 3
HIV	Human immunodeficiency virus
HK2	Hexokinase 2
HMG-CoA	5-Hydroxy-3-methylglutaryl-coenzyme A
HPV-1	Human papillomavirus 1
HSV-2	Herpes simplex virus 2
IC_{50}	The half maximal inhibitory concentration
IFN	Interferon
IL	Interleukin
iNOS	Inducible NO synthase
LPS	Lipopolysaccharide
MDCK	Madin-Darby canine kidney cells
MIC	Minimal inhibitory concentrations
MMDD	Medicinal mushroom-derived drug
MS	Mycosterol
NGF	Nerve growth factor
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drug
OLTT	Oxygenated lanostane-type triterpenoid
PAMP	Pathogen-associated molecular pattern
PPAR	Peroxisome proliferator-activated receptor
PRR	Pattern recognition receptor
PI3K/Akt	Phosphatidylinositol-3-kinase and protein kinase B
PSK	Polysaccharide K
PSP	Polysaccharide-protein
PSPC	Polysaccharide-protein complex
PTP1B	Protein tyrosine phosphatase 1B
QoL	Quality of life
STAT3	Signal transducer and activator of transcription 3
TCM	Traditional Chinese medicine
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor alfa
VDM	Vitamin D-enriched mushroom

1.1 Introduction

Mushrooms have widely been appreciated all over the world for their nutritional and medicinal properties (Moore and Chiu 2001; Chang and Miles 2008; Barros et al. 2008; Wasser 2010, 2011; Bandara et al. 2015, 2017; Valverde et al. 2015; de Mattos-Shipley et al. 2016; Chang and Wasser 2017; Gupta et al. 2018). The early

civilizations of Greek, Egyptian, Roman, Japanese, and Mexican people prized mushrooms for their therapeutic value (Hobbs 1995; Guzmán 2015). Mushrooms have been used in traditional Chinese medicine (TCM) for more than 3000 years for prevention and treatment of different diseases. There are many sources of ethno-mycopharmacological information on wild mushrooms in Eastern and Western countries, but their medicinal and biotechnological potential has not been fully exploited yet (Boa 2004; Chang and Miles 2008; Lindequist 2011; Grienke et al. 2014; Money 2016; Karun and Sridhar 2017).

The ethno-mycological and ethnographic evidence has documented that mushrooms, particularly bracket species (e.g., *Coriolopsis gallica*, *Daedalea quercina*, *Daldinia concentrica*, *Fomes fomentarius*, *Ganoderma adspersum*, *Lenzites warnieri*, *Piptoporus betulinus*, and *Skeletocutis nivea*), could be used by humans not only as food and medicine but also as tinder for fire-lighting (Roussel et al. 2002; Boa 2004; Uzunov and Stoyneva-Gärtner 2015; Berihuete-Azorín et al. 2018).

Mushrooms or macrofungi are widely distributed worldwide. They are taxonomically placed in two phyla, the *Basidiomycota* (class *Agaricomycetes*) and *Ascomycota* (class *Pezizomycetes*) in the subkingdom Dikarya. From overall numbers of fungal species estimated between 0.5-(1.5)-(5.1) million, about 140,000–160,000 species are macrofungi from which around 10% (14,000–16,000) have been identified (Hawksworth 1991, 2012; Kirk et al. 2008; Blackwell 2011; Hibbet and Taylor 2013; Tedersoo et al. 2014; Dai et al. 2015; Peay et al. 2016). From about 7000 known mushroom species, possessing various degrees of edibility, more than 3000 species from 231 genera are considered prime edible mushrooms. About 3% of the known species (at least 170, currently around 500) are poisonous, while around 700 species from 2000 known safe mushroom species have medicinal properties (Boa 2004; Barceloux 2008; Chang and Wasser 2017).

Edible/medicinal wild and cultivated mushroom species produce a broad spectrum of high- and low-molecular-weight bioactive compounds (alkaloids, lectins, lipids, peptidoglycans, phenolics, polyketides, polysaccharides, polysaccharide-proteins/peptides, proteins, ribosomal and non-ribosomal peptides, steroids, terpenoids, etc.) which possess more than 130 therapeutic effects (analgesic, antibacterial, antifungal, anti-inflammatory, antioxidant, antiviral, cytotoxic, hepatoprotective, hypocholesterolemic, hypoglycemic, hypotensive, immunomodulatory, immunosuppressive, mitogenic/regenerative, etc.) (Mizuno et al. 1995; Wasser and Weis 1999; Hawksworth 2001; Wasser 2002, 2010, 2011; Zjawiony 2004; Lindequist et al. 2005; Poucheret et al. 2006; Cerigini et al. 2007; Park et al. 2007; Stanikunaite et al. 2007; Lee et al. 2008; Saltarelli et al. 2009, 2015; Baggio et al. 2010; Ferreira et al. 2010; Xu et al. 2011; Badalyan 2012; Chang and Wasser 2012; De Silva et al. 2012a, b, 2013; Patel et al. 2012; Wang et al. 2012; Grienke et al. 2014; Park 2014; Schueffler and Anke 2014; Bandara et al. 2015, 2017; Duru and Çayan 2015; Stadler and Hoffmeister 2015; Fu et al. 2016; Kosanić et al. 2016; Venkatachalapathi and Paulsamy 2016; Chaiyasut and Sivamaruthi 2017; Chen et al. 2017; Kolundčzić et al. 2017; Kües and Badalyan 2017; Phan et al. 2017a; Sánchez 2017a, b; Shen et al. 2017; Surup et al. 2018).

The medicinal properties and therapeutic potential of mushrooms were revealed in species from different ecological groups, such as xylotrophs (e.g., *F. fomentarius*, *Fomitopsis pinicola*, *Ganoderma lucidum*, *Grifola frondosa*, *Lentinula edodes*, *Pleurotus ostreatus*, *Trametes versicolor*, *Schizophyllum commune*) and mycorrhiza-forming mushrooms (e.g., *Boletus edulis*, *Cantharellus cibarius*, *Tuber borchii*) (Chang 1996; Wasser 2010) (Figs. 1.1 and 1.2). In Asian countries, wild and cultivated mushrooms (fresh or dried) and mushroom-based bio-products are used to prevent and treat different diseases (Wasser 2010; Bandara et al. 2015), while the usage of medicinal mushrooms in Western societies is limited to

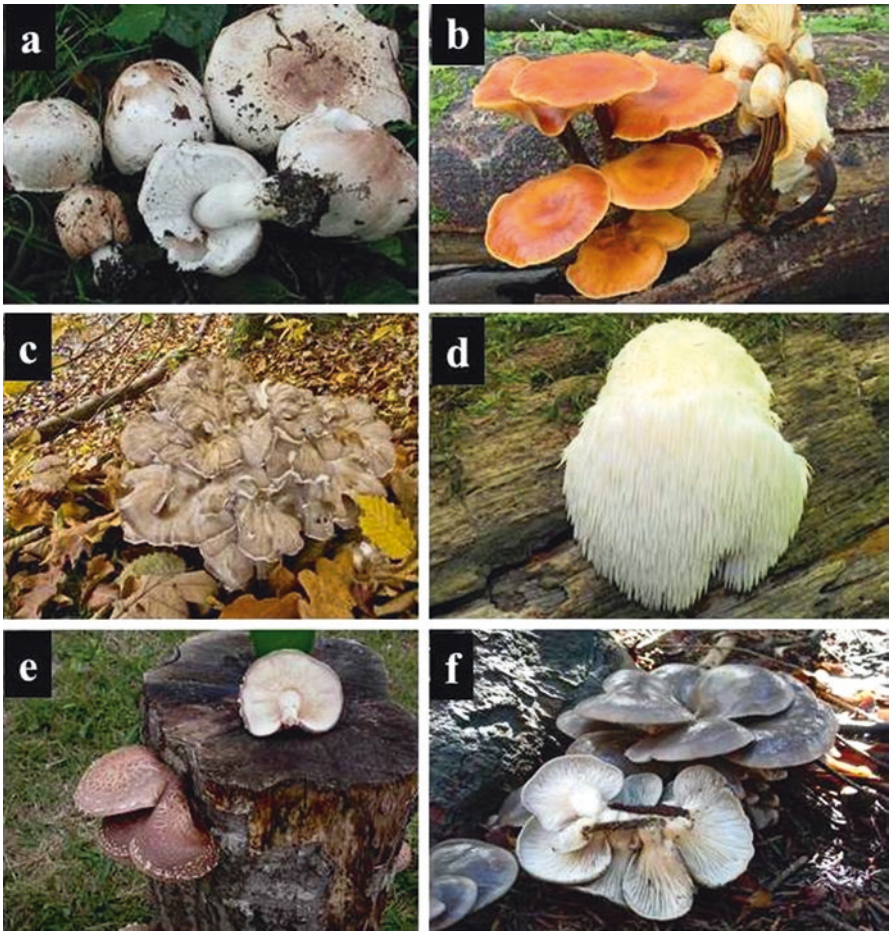

Fig. 1.1 Wild-growing fruiting bodies of edible medicinal mushrooms tested in clinical trials: (**a**) *Agaricus subrufescens* (Photo Courtesy of Guinberteau J), (**b**) *Flammulina velutipes* (Photo Courtesy of Moingeon JM), (**c**) *Grifola frondosa* (Photo Courtesy of Verstraeten P), (**d**) *Hericium erinaceus* (Photo Courtesy of Moingeon JM), (**e**) *Lentinula edodes*. (Photo Courtesy of Fourré G), (**f**) *Pleurotus ostreatus*. (Photo Courtesy of Maurice JP)

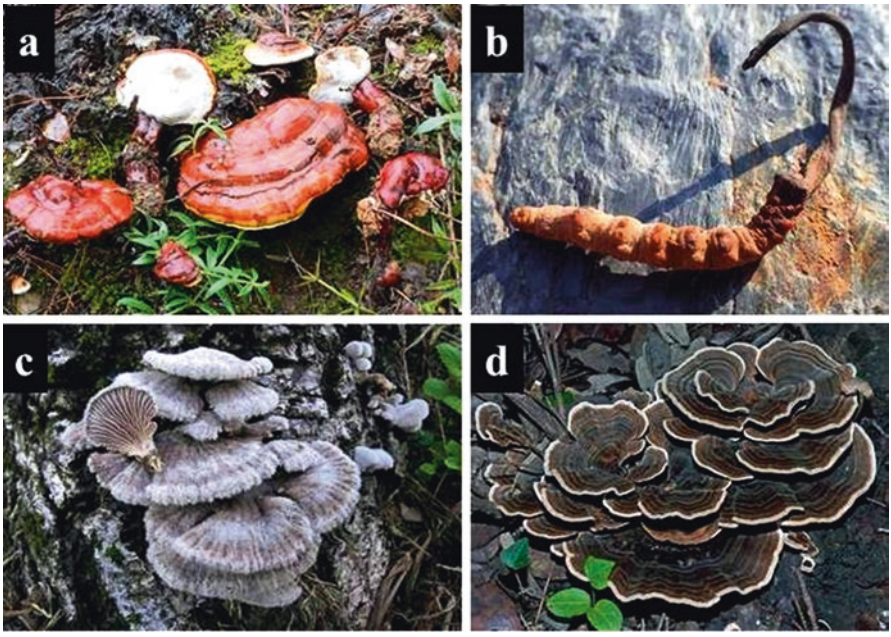

Fig. 1.2 Wild-growing fruiting bodies of inedible medicinal mushrooms tested in clinical trials: (**a**) *Ganoderma lucidum* (Photo Courtesy of Moingeon JM), (**b**) *Ophiocordyceps sinensis* (Photo Courtesy of Rioult JP), (**c**) *S. commune* (Photo Courtesy of Angelini C), (**d**) *T. versicolor*. (Photo Courtesy of Perrone L)

"nutraceuticals" (healthy dietary food) and "nutriceuticals" (functional food or DSs) (Wasser 2002, 2011; Cheung 2008; De Silva et al. 2012a, b; Chen et al. 2017). The cultivation and commercialization of natural mushroom resources will create an opportunity to study their nutraceutical and pharmacological potential for developing health-enhancing mycofood and myco-pharmaceuticals (Badalyan and Zambonelli 2019).

Mushrooms are also widely used in the production of natural cosmetic products ("cosmeceuticals" and "nutricosmetics") (Wisitrassameewong et al. 2012; Bandara et al. 2015; Taofiq et al. 2016a, c, 2017a, b; Wu et al. 2016; Badalyan and Zambonelli 2019).

The pharmacological potential of mushrooms has not been fully investigated yet. Further clinical trials are needed to substantiate the pharmacological properties or side effects of mushroom consumption before they could be recommended as health-enhancing dietary food or myco-pharmaceuticals (Money 2016; Taofiq et al. 2017a; Wasser 2017; Mustonen et al. 2018; Zmitrovich et al. 2019).

We refer our review to recent advances in the study of medicinal properties and pharmacological potential of mushrooms and prospects for their clinical application.

1.2 Biological and Genetic Resources of Medicinal Mushrooms and Their Application

The study and conservation of genetic resources and biodiversity of edible and medicinal agaricoid, polyporoid, and other groups of mushrooms, as valuable biological resources possessing high exploratory potential, including the production of nutraceuticals, nutriceuticals, pharmaceuticals, and cosmeceuticals, are carried out in different countries (Lindequist 2011; Badalyan et al. 2012, 2015; Al-Fatimi et al. 2013; Allen and Lendemer 2015; Bhattacharjee et al. 2015; Degreef et al. 2016; Badalyan and Gharibyan 2017a; Gargano et al. 2017; Badalyan and Zambonelli 2019; Bhatt et al. 2018; Gargano 2018).

Prehistoric artifacts dating back to over 5000 years ago describe the tradition of using agaricomycetous polypore fungi (order *Polyporales*) for various applications, including food and medicinal usage. Several polypores (*F. fomentarius*, *F. pinicola*, *Laetiporus sulphureus*, *Laricifomes officinalis*, and *P. betulinus*) were used in the traditional medicine of central European countries for the treatment of bladder diseases, cancer, dysmenorrhoea, hemorrhoids, pyretic diseases, and rheumatism (Lindequist et al. 2005; Lindequist 2011). Modern chemical studies have reported the presence of several primary and secondary bioactive metabolites in crude extracts of bracket fungi and a wide spectrum of their medicinal activities (anti-inflammatory, antimicrobial, cytotoxic, and others) (Suay et al. 2000; Roussel et al. 2002; Anke and Antelo 2011; Grienke et al. 2014).

Nowadays, the biological resources of edible and medicinal mushrooms are used as *dietary food* (world mushroom production was 33 million tons in 2015), *dietary supplements* (DSs) (the market for mushroom-based products is rapidly expanding and comprises more than the US $20 billion/year), *biocontrol agents* (bactericides, fungicides, herbicides, insecticides, and nematocides), *cosmeceuticals* (activator of epidermal growth factor, stimulator of collagen activity, etc.), and *mushroom-derived pharmaceuticals* or *myco-pharmaceuticals* (Wasser et al. 2000; Lindequist 2013; Kumar 2015; Gargano et al. 2017; Glamočlija and Soković 2017; Carocho et al. 2018).

1.3 Mushroom-Derived Bioactive Compounds

Fungi, including mushrooms, are considered active producers of different primary and secondary bioactive metabolites (alkaloids, fatty acids, lectins, nucleic acids, nucleosides, peptides, phenolics, polyketides, polysaccharides, proteins, statins, steroids, terpenoids, etc.) which are responsible for their pharmacological properties (antibacterial, antifungal, anti-inflammatory, antinociceptive, antioxidant, antiproliferative, antitumor, antiviral, hypocholesterolemic, hypoglycemic, hypotensive, immunomodulatory, etc.) (Badalian et al. 1996, 1997a, b, 1999, 2001; Badalian and Serrano 1999; Badalyan 2001, 2015, 2016; Badalyan and Hambardzumyan 2001;

Fang et al. 2006; Zhang et al. 2007; Wasser 2010, 2014; Lindequist 2011, 2013; Chang and Wasser 2012; De Silva et al. 2013; Khatua et al. 2013, 2017; Grienke et al. 2014; Paterson and Lima 2014; Stojković et al. 2014a, b, 2017; Duru and Çayan 2015; Valverde et al. 2015; Friedman 2016; Tao et al. 2016; Hapuarachchi et al. 2017; Khadhri et al. 2017; Masri et al. 2017; Nielsen and Nielsen 2017; Sánchez 2017a, b; Yang et al. 2017). A wide spectrum of biological activities of mushroom-derived biomolecules could be used to develop health-enhancing mycopharmaceuticals for human and animal use, such as the immunomodulatory β-glucan lentinan from *L. edodes* (Novak and Vetvicka 2008); anti-quorum-sensing agents from *Agaricus brasiliensis* (syn. *Agaricus subrufescens*) (Kerrigan 2005), as potential antibiotics (Soković et al. 2014); the antimalarial alkaloid 4-hydroxymethylquinoline from *T. versicolor* (Liu 2005); pain-suppressive enkephalinase inhibitors from *P. betulinus* (Rathee et al. 2012); and nephroprotective polysaccharides, phenolics, and flavonoids from *Pleurotus tuber-regium* (Okolo et al. 2018). The medicinal species *A. subrufescens*, *Ganoderma* spp., *G. frondosa*, *Hericium erinaceus*, *L. edodes*, *Phellinus linteus*, *P. ostreatus*, and *Polyporus umbellatus* were also reported as producers of different groups of bioactive compounds and have been recommended for a variety of therapeutic applications (Donatini 2011; Thongbai et al. 2015; Hapuarachchi et al. 2017; Thongklang et al. 2017). Among the above-mentioned species, *Ganoderma* mushrooms produce the highest diversity of bioactive compounds with different pharmacological activities (Mizuno et al. 1995; Paterson 2006; Saltarelli et al. 2009, 2015; Welti et al. 2010; Yang et al. 2013; Ma et al. 2014b, 2015; Peng et al. 2015, 2016; Klupp et al. 2015; Wang et al. 2015b, 2017a; Hapuarachchi et al. 2016a, b; Klaus et al. 2016; Meneses et al. 2016; Xu et al. 2016a; Pu et al. 2017; Stojković et al. 2017; Suárez-Arroyo et al. 2017; Subramaniam et al. 2017; Taofiq et al. 2017a; Rubel et al. 2018; Zeng et al. 2018). Alkaloids, fatty acids, nucleosides, polysaccharides, proteins, sterols, triterpenoids, and other compounds were isolated and identified from *Ganoderma* spp. They are responsible for antiaging, antibacterial, anticancer, antidiabetic, antifungal, antihypertensive, anti-inflammatory, antioxidant, antiviral, hepatoprotective, hypoglycemic, immunomodulatory, neuroprotective, wound healing, and other medicinal effects (Paterson 2006; Dai et al. 2009; De Silva et al. 2012a, b, 2013; Cheng et al. 2013; Baby et al. 2015; Bishop et al. 2015; Liu et al. 2015a; Hennicke et al. 2016; Chang et al. 2017; Chen et al. 2017; Sánchez 2017a, b; Wang et al. 2017a).

Anticancer, antimicrobial, antioxidant, antiviral, hypolipidemic, immunomodulatory, and estrogen-like activities were observed in edible oyster mushroom *Pleurotus eryngii* due to the production of diterpenoids, as eryngiolide A, hemolysins, polysaccharides, pentacyclic triterpenoids, ubiquinone-9, and other pharmacologically active biomolecules (Shibata et al. 2010; Ma et al. 2014a; Fu et al. 2016; Zhang et al. 2016; Yen et al. 2018). Recent studies of agaricomycetous species *Suillus bellinii* and *P. eryngii* demonstrated that the mycelium of *S. bellinii* possessed a higher content of ergosterol and phenolic compounds with strong antioxidant effects, while the mycelium of *P. eryngii* showed anti-inflammatory and cytotoxic effects (Souilem et al. 2017).

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) (Yap et al. 2014, 2015).

Nowadays, pharmaceutical companies consider the medicinal mushrooms a rich source of innovative biomedical molecules extracted not only from fruiting bodies but also from cultivated mycelial biomass and cultural broth. Moreover, the mycelia and the cultural broth might be considered 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) (Zhang et al. 2016; Bandara et al. 2017; Souilem et al. 2017). A recent review on 40 mushroom-derived pharmaceuticals available in the markets of Australia and New Zealand has demonstrated that fungal-based natural products have a major role in the future of medicine (Beekman and Barrow 2014).

1.3.1 Polysaccharides

Modern phytochemical and pharmacological studies have shown that polysaccharides are one of the major bioactive compounds in mushrooms (Wasser and Weis 1999; Zhang et al. 2007). Macrofungal β-glucans are mainly represented by β-1,3 and β-1,6 glycosidic bonds and used in the treatment of cancer because of their immunomodulatory and antitumor effects (Aleem 2013; Yoon et al. 2013; Khan et al. 2014; Piotrowski et al. 2015; Meng et al. 2016; Wang et al. 2017b). Moreover, fungal polysaccharides have less toxic side effects, unlike many existing chemotherapeutic drugs, and can be used to develop alternative medicines for supportive healthcare for the treatment of cancer (Ramberg et al. 2010). Mushroom-derived β-glucans also exhibit significant antioxidant, antiviral, and other bioactivities (Wasser and Didukh 2005; Khan et al. 2014; Kozarski et al. 2014; He et al. 2017a, b).

About 80–85% of all the existing medicinal mushroom products are (1–3)-, (1–6)-β-D-glucans, such as lentinan extracted from *L. edodes*, polysaccharide K (PSK) or Krestin derived from fruiting bodies of *T. versicolor*, schizophyllan from *S. commune*, a polysaccharide-protein complex (PSPC) or polysaccharide peptide (PSP) from *Tricholoma laboyense*, pleuran from *P. ostreatus*, as well as polysaccharides from fruiting bodies and mycelium of *H. erinaceus* (Zhu et al. 2015). The polysaccharides extracted from *Auricularia auricula-judae* possess anti-inflammatory, antioxidant, and cardioprotective effects, whereas exopolysaccharides from *P. eryngii* exhibit higher antitumor activity on human hepatoma cells (Jing et al. 2013) and suppress the proliferation of HepG-2 cells (Ma et al. 2014a).

Although there are many reports on the bioactivity and structure of fungal glucans, studies on the quantitative assessment of these compounds are scarce. The overall β-glucan content in the wild-growing mushrooms *A. auricula-judae*, *Boletus pinophilus*, *Craterellus cornucopioides*, *Gyroporus cyanescens*, *Hydnum*

repandum, *Suillus granulatus*, *S. variegatus*, and *Tricholomopsis rutilans* in comparison with edible cultivated mushroom *Agaricus bisporus* has recently been analyzed (Mirończuk-Chodakowska et al. 2017). The highest percentage of 1,3- and 1,6-β-D-glucan content in relation to the total β-glucan content was detected in *G. cyanescens* (54%), *S. granulatus* (49.8%), *A. auricula-judae* (47.9%), and *S. variegatus* (40.6%). It was shown that the average β-D-glucan content was higher in wild-growing mushrooms compared to cultivated specimens. The studied species are recommended as a source of dietary food (Mirończuk-Chodakowska et al. 2017).

The functional properties of polysaccharides obtained from medicinal mushroom *Ganoderma neo-japonicum*, as well as the presence of total phenolics, protein, and sugar in crude extracts, confirm that β-glucan-inhibiting carbohydrate-hydrolyzing enzymes may be used in the treatment of diabetes mellitus (Subramaniam et al. 2017). Biological and chemical characteristics of *Ganoderma* polysaccharides; their antioxidant, antitumor, and antimicrobial activities; as well as the structure-bioactivity relationship were recently discussed by Ferreira et al. (2015). Although *Ganoderma* polysaccharides are suggested as a healthy dietary food supplement, particularly for cancer patients, the authors considered that further clinical trials are required.

1.3.2 Terpenoids, Steroids, and Sterols

Many medicinal mushrooms contain different bioactive triterpenes, steroids, and sterols with antibacterial, antimitotic, antiviral, cytotoxic, immunomodulatory, and apoptosis-inducing effects (Baby et al. 2015; Castellano and Torrens 2015; Duru and Çayan 2015; Hadda et al. 2015a; Zhao et al. 2015, 2016; Corrěa et al. 2017; Wang et al. 2017b; Kovács et al. 2018; Morales et al. 2018). Currently, 431 secondary metabolites, over 380 terpenoids, and 30 steroids (lanostane triterpenes as ganoderic and lucidenic acids, meroterpenoids, pentacyclic triterpenes, prenyl hydroquinone sesquiterpenoids, steroids), as well as alcohols, aldehydes, alkaloids, esters, glycosides, ketones, and lactones with significant bioactivities, were isolated from 22 *Ganoderma* species (*G. amboinense*, *G. annulare*, *G. applanatum*, *G. australe*, *G. boninense*, *G. capense*, *G. carnosum*, *G. cochlear*, *G. colossum*, *G. concinna*, *G. fornicatum*, *G. hainanense*, *G. lipsiense*, *G. mastoporum*, *G. neo-japonicum*, *G. orbiforme*, *G. pfeifferi*, *G. resinaceum*, *G. sinense*, *G. theaecolum*, *G. tropicum*, and *G. tsugae*) (Baby et al. 2015). The structure-activity relationship of 71 triterpenoids and steroids isolated from *Ganoderma* species was revealed (Castellano and Torrens 2015). The chemopreventive agents for cancer, a new lanostanoid tsugaric acid F, and a novel palmitamide with antioxidant and weak cytotoxic activities against PC3 cells were isolated and characterized from the fruiting bodies of *G. tsugae* (Lin et al. 2016). Twelve new highly oxygenated lanostane nor-triterpenoids and 9 known ganoderic acids with moderate inhibitory effects against α-glucosidase were isolated from the fruiting body of *G. lucidum* (Zhao et al. 2015), while 6 new lanostane-type triterpenoids, leucocontextins, and 12 compounds with toxicity

against K562, SMMC-7721, and MCF-7 cells were identified from the fruiting bodies of *Ganoderma leucocontextum* (Zhao et al. 2016). Fourteen lanostane triterpenoids, including nine *Ganoderma* acids and five *Ganoderma* alcohols, were isolated from the fruiting bodies of *Ganoderma hainanense*. Considering that *G. hainanense*, similar to *G. lucidum* and *G. sinense*, contains lanostane triterpenoids, it could also possess a broad spectrum of activities, particularly against HL-60, SMMC-7721, A-549, and MCF-7 cells (Peng et al. 2015). Three new nortriterpenes, ganoboninketals, and highly complex polycyclic systems with antiplasmodial activity against *Plasmodium falciparum*, as well as with weak cytotoxicity against A549 and HeLa cells, and no inhibitory activity against the lipopolysaccharide (LPS)-induced macrophages were detected in other *Ganoderma* species – *G. boninense* (Ma et al. 2014b). Sixteen new lanostane triterpenes (ganoleucoins A-P) together with ten known triterpenes were originally isolated from the cultivated fruiting bodies of *G. leucocontextum* belonging to *G. lucidum* complex (Zhou et al. 2015). These compounds showed inhibitory effects on HMG-CoA reductase and α-glucosidase, as well as cytotoxicity against the K562 and PC-3 cell lines (Wang et al. 2015b). The triterpene lactones (colossolactone G), seven new triterpene lactones (ganodermalactones A–G), five known triterpene lactones (colossolactone B, colossolactone E, colossolactone I, colossolactone IV, and schisanlactone B), and ergosterol have been isolated from mycelial biomass of *Ganoderma* strain KM01 (Lakornwong et al. 2014). Among these biomolecules, several compounds exhibited antimalarial activity against *P. falciparum*.

Fifteen undescribed and five known lanostane-type C31 triterpenoid derivatives (palustrisoic and polyporenic acids) were isolated from the aqueous-ethanolic extract of the fruiting bodies of cultivated *Fomitopsis palustris*. Strong cytotoxicity of polyporenic acid B against HCT116, A549, and HepG2 cell lines and weak cytotoxicity of palustrisolides A, C, and G were revealed (Zhao et al. 2018). Eight undescribed lanostane triterpenoids, pardinols A–H, and one previously reported lanostane triterpenoid saponaceol B were isolated from the fruiting bodies of agaricomycetous species *Tricholoma pardinum* (Zhang et al. 2018). Pardinols B and pardinols E–H exhibited certain inhibitory effects of nitric oxide (NO) production with IC_{50} value ranging from 5.3 to 14.7 mM, as well as cytotoxicity against human cancer cell lines.

It is known that a high rate of aerobic glycolysis which occurs in malignant tumors is one of the most fundamental metabolic alternatives during tumor development and progression (Patra et al. 2013; Ros and Schulze 2013; Tan and Miyamoto 2015). The enzyme hexokinase 2 (HK2) plays a pivotal role in the glycolytic pathway of cancer cells, promotes tumor progression in animal models, and provides a new target for cancer therapy. A new steroid isolated from *Ganoderma sinense* possesses a high binding affinity to HK2 with significant binding free energy. It was identified as an HK2 inhibitor and can be considered as a potential drug targeting the HK2 for cancer therapy (Bao et al. 2018). Highly oxygenated lanostane-type triterpenoids (OLTT) obtained from the fruiting bodies of *Ganoderma gibbosum*, their bioactivity (Pu et al. 2017), and chemotaxonomic significance (Welti et al. 2015) have recently been investigated.

Nine new sesquiterpenoids, clitocybulol derivatives, clitocybulols G–O, and three known sesquiterpenoids, clitocybulols C–E, with moderate inhibitory effects against protein tyrosine phosphatase 1B (PTP1B) were isolated from the solid culture of edible fungus *Pleurotus cystidiosus* (Tao et al. 2016). The piptolinic acid A isolated from a methanolic extract of the fruiting bodies of *P. betulinus* showed cytotoxic activity against human promyelocytic leukemia cell line HL-60 and human acute monocytic leukemia cell line THP-1 (Tohtahon et al. 2017). Fungal bioactive sesquiterpenoid eremophilanes possessing antibacterial, anti-inflammatory, anti-obesity, antiviral, and cytotoxic effects were reported in several mushrooms, particularly belonging to genera *Xylaria* (Yuyama et al. 2017a). Alliacane sesquiterpenoids were isolated from submerged cultures of *Inonotus* sp. (Isaka et al. 2017). The metabolites and multicomponent pharmacokinetics of ergostane and lanostane triterpenoids were identified in the mushroom *Antrodia cinnamomea* (Qiao et al. 2015). Further chemical screening of mushrooms allows discovering new pharmacologically promising terpenoids, steroids, and sterols with therapeutic effects.

1.3.3 Phenolics and Other Compounds

Phenols are a diverse group of biocompounds which include a large number of subclasses, such as flavonoids, phenolic acids, quinones, tocopherols, tannins, etc. Fungal phenolic derivatives are primarily known for their anticarcinogenic, anti-inflammatory, antioxidant, and antimutagenic effects (Palacios et al. 2011; Kozarski et al. 2015; Islam et al. 2016). It has been found that mushroom phenolics are outstanding antioxidants which lack mutagenic properties (Khatua et al. 2013).

The extraction of total phenolics and flavonoids from wild and cultivated edible, medicinal mushrooms by different solvents was reported (Abugri and McElhenney 2013). Phenolic compounds, flavonoids, ascorbic acid, β-carotene, and lycopene were detected in a methanol-soluble extract from fruiting bodies of *G. frondosa* and *Volvariella volvacea* (Acharya et al. 2015, 2016). Five phenolic acids (vanillic acid, *m*-hydroxybenzoic acid, *o*-hydroxybenzene acetic acid, 3-hydroxy-5-methyl benzoic acid, and *p*-hydroxybenzoic acid) with analgesic effects were isolated from *S. commune* (Yao et al. 2016).

The analysis of phenolic constituents, as well as antimicrobial and anti-radical activities of edible mushrooms growing in Poland, have recently been reported (Nowacka et al. 2014). Bioactivities and phenolic contents of 25 wild edible mushrooms from Northeastern Thailand were analyzed for their antioxidant properties, proteins, sugars, β-glucan, and phenolic profiles (Butkhup et al. 2018). The strongest scavenging activity (83.07 and 86.6%) and reductive power (9.79 and 8.42 g Fe^{2+}/kg) were revealed in *Termitomyces clypeatus* and *V. volvacea*, respectively. Both species were identified as sources of healthy compounds (β-glucans and flavonoids) which could be used to mitigate diseases involving free radicals.

The antioxidant capacity and total phenolic contents of wild *T. versicolor* and *T. gibbosa* were evaluated in Romania (Pop et al. 2018). Twenty-eight compounds

were identified as coumarins, flavanols, flavones, flavonols, isoflavonoid derivatives, and phenolic acids. The methanolic extract revealed the highest antioxidant activity, while the highest total polyphenol and flavonoid contents were detected in a water extract of mushrooms. It was suggested that *Trametes* species could be considered a source of bioactive phenolics.

Recent studies of antioxidant activity of cultivated (*A. bisporus*, *P. ostreatus*) and wild-growing (*Agaricus campestris*, *B. edulis*, *C. cibarius*, *Macrolepiota procera*, *P. ostreatus*, *Russula alutacea*, and *R. vesca*) edible mushrooms identified them as sources of bioactive phenolics and flavonoids (Buruleanu et al. 2018).

Fungal alkaloids (N-containing heterocyclic compounds) are known for their toxicological relevance, e.g., ergot alkaloids in *Claviceps purpurea* and psilocybin in *Psilocybe* species (Liu 2005; Streith 2011; Tylš et al. 2014). Eight new alkaloids isolated from the medicinal mushroom *H. erinaceus* with inhibitory effects against protein tyrosine phosphatase-1B (PTP1B), α-glucosidase and moderate cytotoxicity against K562 cells were described (Wang et al. 2015a).

The nucleic acid constituents (purine and pyrimidine nucleobases, uridine, guanosine, adenosine, and cytidine nucleosides) play an important role in the regulation of various physiological processes in the human body. The nucleic acid constituents and other bioactive compounds (alkaloids, polysaccharides, and terpenoids) were recently identified in several edible and nonedible mushrooms (Phan et al. 2017b, 2018).

1.4 Pharmacological Activity of Mushrooms

The scientific research and case studies from a traditional medicine show that mushrooms possess promising pharmacological potential. Bioactive compounds and extracts from medicinal mushrooms showed mainly anti-allergic, antibacterial, antidepressant, antifungal, anti-inflammatory, antioxidant, antiviral, cardioprotective, hepatoprotective, neuroprotective, cytotoxic, hypotensive, and immunomodulatory activities (Badalyan 2003a, b, 2004a, b, 2012; Lindequist et al. 2005; Fan et al. 2006; Wasser 2010, 2014; Chang and Wasser 2012; Roupas et al. 2012; Stachowiak and Reguła 2012; De Silva et al. 2013; Ivanova et al. 2014; Paterson and Lima 2014; Muszynska et al. 2015; Xu et al. 2016a, b; Sharma et al. 2017; Özcan and Ertan 2018). Therefore, mushrooms can be considered as prospective sources of new myco-pharmaceuticals or natural product-derived drugs.

Several mushrooms (*A. brasiliensis*, *Agrocybe cylindracea*, *A. auricula-judae*, *Coprinus comatus*, *G. applanatum*, *G. lucidum*, *G. frondosa*, *Gymnopus confluens*, *H. erinaceus*, *Inonotus obliquus*, *Ophiocordyceps* (syn. *Cordyceps*) *sinensis*, and *Tremella fuciformis*) are used in the production of functional foods for the prevention and treatment of diabetes mellitus (Perera and Li 2011). Triterpenes isolated from the medicinal mushroom *Wolfiporia cocos* also reduce blood glucose levels in mice (Sato et al. 2002).

One of the most valuable medicinal fungi in China is ascomycetous mushroom *O. sinensis* known for its invigorating effects in strengthening the body and

restoring energy. The fungus parasitizes larvae of moths and converts them into sclerotia from which grows the fruiting body of the fungus (Fig. 1.2b). A considerable effort has been devoted to the study of host insects related to the fungus. The information on the management of insect resources and sustainable use of *O. sinensis* has been reported (Wang and Yao 2011). The extract derived from mycelia and ascomata of *Cordyceps sinensis* and *C. militaris* possess anticancer effects by modulating the immune system and inducing cell apoptosis (Khan et al. 2010; Xu et al. 2016b). The availability of laboratory cultures of these entomopathogenic fungi will further expand their pharmacological usage (Wang et al. 2012).

Another well-known medicinal mushroom *A. subrufescens* contains a number of bioactive compounds with immunomodulatory, anticancer, and other pharmacological effects (Ahn et al. 2004; Kim et al. 2005; Ellertsen and Hetland 2009; Johnson et al. 2009; Bouike et al. 2011; Lima et al. 2011; Wang et al. 2013; Da Silva de Souza et al. 2017) (Fig. 1.1a). We recommend following Kerrigan (2005, 2016), Ludwig (2007), Cappelli (2011), Parra (2013), and Thongklang et al. (2014, 2017) for taxonomy and synonymy of *A. subrufescens*. The main synonyms of *A. subrufescens* are *Agaricus blazei* Murrill sensu Heinemann, *A. rufotegulis* Nauta, *A. brasiliensis* Wasser, M. Didukh, Amazonas and Stamets, *A. albopersistens* Zuccher, and *A. bambusae* Beeli var. *bambusae*. Previously, *A. subrufescens* has not only been misidentified as *A. blazei* but also to *A. sylvaticus* Schaeff. (Souza Dias et al. 2004). In other respects, Kerrigan (2005) hybridized between each other strains isolated from North, South America, Brazil, France, and Thailand (Thongklang et al. 2014, 2016).

The compounds extracted from edible medicinal *Pleurotus* mushrooms showed efficacy for treatment of several chronic disease (Gunde-Cimmerman 1999) due to their antibacterial, anti-inflammatory, anti-mitogenic, antitumor, antioxidant, antiviral, hypoglycemic, immunomodulatory, cardioprotective, and other pharmacological activities (Jose et al. 2002; Filipic et al. 2002; Hossain et al. 2003; Hu et al. 2006; Badalyan et al. 2008b; Baggio et al. 2010; Papaspyridi et al. 2011; Patel et al. 2012; Schillaci et al. 2013; Jayasuriya et al. 2015; Khatun et al. 2015; Fu et al. 2016; Venturella et al. 2016; Zhang et al. 2016; Acharya et al. 2017; Adebayo et al. 2018; Baskaran et al. 2017; Debnath et al. 2017; Ebrahimi et al. 2017; Masri et al. 2017; Owaid et al. 2017; Abidin et al. 2018; Finimundy et al. 2018a, b).

Bioactive compounds extracted from inedible bracket fungi also possess pharmacological potential and could be used to develop healthcare products with different formulations (Barros et al. 2008; Dai et al. 2009; Reis et al. 2014; Heleno et al. 2015a, b). The bioactive compounds isolated from *T. versicolor* exhibited health-beneficiary effects, as inhibitors of aflatoxins (Scarpari et al. 2016), while compounds (amino acids, aromatic acids, flavones, polysaccharides, triterpenes, etc.) isolated from *Ph. linteus* showed anticancer, hypoglycemic, anti-inflammatory, antioxidant, and immunoregulatory activities (Chen et al. 2016). The induction of ovulation by the extract of edible Maitake mushroom (*G. frondosa*) in patients with polycystic ovary syndrome (Chen et al. 2010) and medicinal properties of *F. fomentarius* and *F. pinicola* have been reported (Badalyan and Shahbazyan 2015).

A comparative chemical analysis, acute toxicity, and pharmacological activity of fruiting body extracts of several agaricoid mushrooms, particularly of nonedible