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Medicinal mushrooms: Valuable biological resources of high exploitation potential

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Abstract

Higher *Basidiomycetes* and *Ascomycetes* mushrooms possess various immunological and anticancer properties. They also offer important health benefits and exhibit a broad spectrum of pharmacological activities including antibacterial, antifungal, antiviral, cytotoxic, immunomodulating, anti-inflammatory, antioxidative, antiallergic, antidepressive, antihyperlipidemic, antidiabetic, digestive, hepatoprotective, neuroprotective, nephroprotective, osteoprotective, and hypotensive activities. This minireview summarizes the perspectives, recent advances, and major challenges of medicinal mushrooms with reference to their nutraceutical properties and dietary value, the production of mushroom biomass on various substrates, and the purification, characterization, and pharmaceutical effects of biologically active compounds from medicinal mushrooms.

Keywords: *Medicinal mushrooms, nutraceutical properties, dietary value, mushrooms cultivation, fungal biomass, active compounds*

Introduction

The use of mushrooms in traditional ancient therapies dates back at least to the Neolithic age. For millennia, mushrooms have been valued as edible and medical provisions for humankind. Contemporary research has validated and documented much of the ancient knowledge on medicinal mushrooms (MM). The interdisciplinary field of science that studies MMs has been developed and increasingly demonstrates potent and unique properties of compounds extracted from a range of mushroom species in the last three decades.

Nowadays, MMs are used as: (a) dietary food (world mushroom production was 33 million tons in 2014); (b) dietary supplement (DS) products (the market of MM DS products is rapidly growing); (c) a new class of drugs called "Mushroom Pharmaceuticals"; (d) natural biocontrol agents in plant protection demonstrating insecticidal, fungicidal, bactericidal, herbicidal, nematocidal, and antiphytoviral activities; and (e) cosmeceuticals – different compounds of MMs including polysaccharides, such as soluble β-glucans, GXM, sacchachitin, tyrosinase, and other enzymes are used by cosmetic companies for their film-forming capability, activation of epidermal growth factor, antioxidative, antiallergic, antibacterial and anti-inflammatory activities, stimulation of collagen activity, inhibition of autoimmune vitiligo, and treating acne.

Medicinal mushrooms are comparable to "medicinal plants" and can be defined as macroscopic fungi, mostly higher *Basidiomycetes* and some *Ascomycetes*, which are used in the form of extracts or powder for prevention, alleviation or healing multiple diseases, and/or in balancing a healthy diet. According to the definition of "herbal drugs", dried fruit bodies, mycelia, or spores are considered "mushroom drugs" or "fungal drugs". Analogous to "phytopharmaceuticals" or "herbal preparations", the resulting mushrooms preparations should be considered as "mushroom pharmaceuticals" or "mushroom preparations". The clear advantages

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of using mushroom-based products with regard to safety (as opposed to herbal preparations) are the following:

(1) The overwhelming majority of mushrooms used for production are cultivated commercially, and not gathered in the wild. This guarantees proper identification and pure, unadulterated products. In many cases, it also means genetic uniformity.
(2) Mushrooms are easily propagated vegetatively and thus keep to one clone. The mycelium can be stored for a long time, and the genetic and biochemical consistency may be checked after considerable time.
(3) The main advantage might be the fact that many mushrooms are capable of growing in the form of mycelial biomass in submerged cultures.

Mushrooms are currently evaluated for their nutritional value. They are rich in proteins, chitin (dietary fibers), vitamins, and minerals, low in total fat but with a high proportion of unsaturated fatty acids, and have no cholesterols. As for the characteristics of taste, mushrooms serve as a delicious foodstuff and also as a source of food flavoring substances (because of their unique flavors). In addition to the volatile eight-carbon compounds, the typical mushroom flavor consists of water-soluble taste components such as soluble sugars, polyols, organic acids, free amino acids, and five nucleotides.

Regarding the beneficial nutritional effects of mushrooms, the following facts should be noted:

(1) Mushrooms are low in calories, which is beneficial for weight reduction.
(2) Mushrooms have a significant level of purine, which is beneficial for the diet of people suffering from metabolic diseases.
(3) Mushrooms have a low glucose level, and more mannitol, which makes them highly suitable for diabetics.
(4) Mushrooms have a very low sodium concentration, which is beneficial for the diet of people suffering from high blood pressure.
(5) Mushrooms have a high content of several key vitamins, which is an important orthomolecular aspect. This means that a significant part of the daily requirement in different essential vitamins can be covered by consuming mushrooms.
(6) Mushrooms have a high content of potassium and phosphorus, which is an important orthomolecular aspect as well.
(7) Finally, mushrooms have a high content of selenium, which is regarded as an excellent antioxidant.

Pharmacological properties of mushrooms are currently widely recognized. They make up a vast and yet largely untapped source of powerfully new pharmaceutical products. In particular, and most importantly for modern medicine, MMs present an unlimited source of polysaccharides (especially β-glucans) and polysaccharide–protein complexes with anticancer and immunostimulating properties. Many, if not all, higher *Basidiomycetes* mushrooms contain different types of biologically active high-molecular weight and low-molecular weight compounds (triterpens, lectins, steroids, phenols, polyphenols, lactones, statins, alkaloids, and antibiotics) in fruit bodies, cultured mycelia, and cultured broth (Wasser 2010, 2014; Lindequist, 2011, 2013; Chang & Wasser 2012; De Silva et al. 2013).

There are a total more than 130 medicinal functions produced by MMs and fungi. Recently studied medicinal actions of mushrooms included antitumor, immunomodulating, antioxidant, radical scavenging, cardiovascular, cholesterol-lowering, antiviral, antibacterial, antiparasitic, antifungal, detoxicative, hepatoprotective, antidiabetic, antiobesity, neuroprotective, neuroregenerative, and some others effects. Also, substances derived from MMs can be used as painkillers and analgetics. The best implementation of MMs drugs and MM DSs has been in preventing immune disorders and maintaining good quality of life, especially in immunodeficient and immunodepressed patients, patients under chemotherapy or radiotherapy, patients with different types of cancers, chronic blood-borne viral infections of Hepatitis B, C, and D, different types of anemia, the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), Herpes simplex virus (HSV), chronic fatigue syndrome, Epstein Bar virus, patients with chronic gastritis and gastric ulcers caused by *Helicobacter pylori*, and people suffering from dementia (especially, Alzheimer's disease) (Wasser 2010, 2014; Chang & Wasser 2012).

Production of medicinal mushroom biomass on various substrates with emphasis on materials rich in lignocellulosics

Mushrooms are fungi belonging to the phyla *Basidiomycota* and *Ascomycota*, which form conspicuous fruit bodies that are ubiquitous in nature. Many of them are major players in the degradation and recycling of various wastes and complex biopolymers deriving from either natural sources or anthropogenic activities. They are usually saprotrophs excreting enzymes in their environment in order to degrade their substrate before using it as a source of nutrients for their growth and development. A large number of these mushrooms are white-rot fungi, a significant group of wood-decaying organisms, whose highly potent enzymatic arsenal is extensively exploited for the bioconversion

of lignocellulosic biomass into various value-added products.

The understanding of such biotechnological processes has resulted in the mass production of edible mushrooms on various plant residues and agro-industrial wastes. In the USA alone, which represents a rather small part of the world mushroom production (largely dominated by China), the total value of mushrooms produced and sold during 2015–2016 is estimated at about US$800 million. Mushrooms and their use as food or supplements and nutraceutical products (the latter started flourishing at about the end of the last century) are estimated to reach a value of US$18 billion. The following paragraphs summarize the degradation/bioconversion of lignocellulosic biomass into mushrooms through solid-state fermentation (SSF), as well as mycelium production in submerged (liquid-state) fermentations.

Degradation of lignocellulosic biomass and complex organic substrates by mushroom fungi

Lignocellulosic biomass has received intensive attention over the past decade since it is a highly valuable raw material, which offers great potential to be used as a renewable feedstock for the production of fuels and fine chemicals with net zero carbon emission (Fava et al. 2015; Khan et al. 2015). Currently, many different biorefinery concepts are being developed and implemented. Some of these concepts are simple, using one feedstock (e.g. vegetable oil) and producing two or three products (e.g. biodiesel, animal feed, and glycerol) with current available commercial technologies. Other concepts are sometimes very complex using many different feedstock to coproduce a broad spectrum of different products which makes it difficult for industry, decision-makers, and investors to decide, which of these concepts are the most promising options on the short, medium, and long terms, and to judge on the technological and economic risks (de Jong & Jungmeier 2015).

Undoubtedly, biorefinery is already a commercial reality and it demonstrates immense potential for the nearby future. However, the development of the processes to convert lignocellulosic biomass to fuels and value-added chemicals remains a big challenge. In particular, most utilization of organic wastes is still being performed in a lab scale. In the case, for example, of enzymes and antibiotics, high productivity with stable quality of product has to be proved in pilot-scale before industrial application. However, pilot and demo initiatives require high investment capital. Another bottleneck is a sustainable availability of biomass feedstock due to seasonal processing of crops and some foods. In addition, the biorefinery process development and improvement are also necessary to significantly decrease processing cost.

Vegetable and fruit processing biowastes from food industry normally consist of proteins, sugars, fibers and lipids along with vitamins and other bioactive agents and, therefore, they might be cheap and abundant sources of chemicals, biomaterials, and substrates for tailored biotechnological production. Indeed, given origin, biodegradability, and non-toxicity of these biowastes and using microbial fermentation followed by specific recovery procedures, several value-added products of special interest (food, feed, biofuels, enzymes and organic acids, pharmaceutical compounds and dietary supplements, etc.) can be obtained from them (de Jong & Jungmeier 2015; Fava et al. 2015; Khan et al. 2015).

Cellulose and hemicellulose are polysaccharides, which together with the complex lignin polymer synthesized from phenylpropanoid precursors, are present in the cell walls of plants in varying composition and proportions (Zhao et al. 2012). Biodegradation of lignin, cellulose, and hemicellulose in wood is a multi-enzymatic process with the mediation of small molecules and radicals working in concert with enzymes excreted by fungi. White-rot fungi (WRF) penetrate wood to access the carbohydrate constituents of the lignocellulose complex; they can degrade lignin selectively (sequential decay) or simultaneously with cellulose (simultaneous rot) (Blanchette 1991; Eriksson et al. 1990). The suite of enzymes WRF employ for attacking the lignin barrier allow them to transform lignin, cellulose, hemicellulose, and other components of plant biomass into simpler compounds. In fact, WRF possess two types of extracellular enzymatic systems to degrade lignocellulosics; a hydrolytic, in which hydrolases are produced to degrade polysaccharides, and a unique oxidative/ligninolytic, which degrades lignin and cleaves phenyl rings (Kirk & Farrell 1987). Among the ligninolytic enzymes produced by WRF, laccases present a low-redox potential, which allows direct oxidation of phenolic units (Martínez et al. 2005). On the other hand, lignin peroxidase (LiP) and manganese peroxidase (MnP) can degrade over 90% of the lignin polymer, thanks to their high-redox potential (Gold et al. 2000; Martínez 2002). While LiP degrades non-phenolic lignin units, MnP generates Mn^{3+} acting as a diffusible oxidizer on phenolic (or non-phenolic lignin) units via lipid peroxidation reactions (Jensen et al. 1996; Martínez et al. 2005). Versatile peroxidase detected in *Pleurotus* (Ruiz-Dueñas et al. 1999) and other fungi, is a third type of ligninolytic peroxidases combining

the catalytic properties of LiP, MnP, and plant/microbial peroxidases oxidizing phenolic compounds (Heinfling et al. 1998). Oxidases like aryl-alcohol oxidase, fungal aryl-alcohol dehydrogenases, and quinone reductases are also considered to be involved in lignin degradation (Gutiérrez et al. 1994; Guillén et al. 1997).

White-rot *Basidiomycetes* synthesize a variety of cellulases and hemicellulases that catalyze the hydrolysis of the plant polysaccharides to sugars in order to ensure micro-organisms with carbon and energy sources for sustainable growth. These hydrolytic enzymes are of fundamental importance for the efficient bioconversion of plant raw materials and for various biotechnological applications (Bhat 2000; Kobakhidze et al. 2016).

Mushrooms have evolved as among the best degraders of cellulose, and they utilize a set of hydrolytic enzymes typically composed of endoglucanases, cellobiohydrolases, and β-glucosidases (Pérez et al. 2002; Banfi et al. 2015). Multiple endo-1,4-β-glucanase (EC 3.2.1.4, endocellulase) systems are common in *Basidiomycota* (Valaskova et al. 2007; Isikhuemhen et al. 2014) and are involved in the breakdown of internal bonds of cellulose macromolecules. Studies with synthetic cellulose have shown that most endoglucanase activity is mainly directed toward amorphous regions in the cellulose molecule; however, some WRF possess what is referred to as "processive endoglucanases", which show significant activity toward crystalline cellulose, and they act as a combination of endoglucanase and cellobiohydrolase (Valaskova & Baldrian 2006). Cellobiohydrolase (EC 3.2.1.91, exocellulase) activity has been detected and isolated from several WRF, litter decomposing, and ectomycorrhizal fungi (Cao & Crawford 1993; Valaskova et al. 2007; Mikiashvili et al. 2011). Cellobiohydrolase removes monomers and dimers from the end of the macromolecule chains. On the other hand, β-glucosidase hydrolyzes glucose dimers and, in some cases, cellulose oligosaccharides to glucose. Hemicellulose biodegradation is performed through the concerted action of a variety of hydrolytic enzymes including endo-1,4-β-xylanase (EC 3.2.1.8), which generates oligosaccharides from the cleavage of xylan, and 1,4-β- xylosidase (EC 3.2.1.37), which produces xylose from oligosaccharides (Pérez et al. 2002; Liu et al. 2017).

SSF – cultivation of mushrooms on lignocellulosic substrates

SSF is a process taking place in the absence (or near absence) of free liquid employing natural (organic) or inert (synthetic/mineral) substrates as a solid support (Pandey et al. 2000; Petre et al. 2016). The cultivation of mushrooms represents a case of sustainable exploitation of plant residues and agro-industrial byproducts rich in lignocellulosics through a controlled SSF, which converts them to fungal biomass (fruit bodies). The latter could be consumed either directly as food or after processing to isolate biologically active metabolites, which are further used as supplements in functional foods or for medicinal purposes. Moreover, the spent substrates colonized by the mushroom mycelium could be used as fodder, soil conditioner/fertilizer, bioremediation agent, etc. (Philippoussis et al. 2004; Chiu et al. 2009; Oh et al. 2010; de Mattos-Shipley et al. 2016). The main growth/substrate requirements for the most noteworthy cultivated mushrooms are summarized below.

Agaricus bisporus (J.E. Lange) Imbach (white or button mushroom or champignon) is the most widely consumed mushroom worldwide. In nature, it grows as a saprotroph in humus-rich soils, while its cultivation is typically performed on previously composted and pasteurized mixtures of chicken/horse manure and cereal straw. Following spawn-run, an organic ("casing") layer usually consisting of peat moss is placed on top of the substrate to promote primordia formation. Several materials have been tested for substituting/supplementing the previously mentioned media, e.g. tea waste, defatted pistachio meal, anaerobically digested food waste, spent mushroom compost, grapeseed meal, and olive mill waste (Gülser & Pekşen 2003; Altieri et al. 2009; Gea et al. 2012; Pardo-Giménez et al. 2012, 2016; Stoknes et al. 2013). Moreover, the cultivation of *Agaricus brasiliensis* Wasser et al. (known also as *A. subrufescens* Peck or *A. blazei* Murrill) is widespread in Brazil, Japan, and in certain regions of South-East Asia where it thrives thanks to its preference for higher (than *A. bisporus*) fructification temperatures, 22–25°C (Largeteau et al. 2011).

Pleurotus spp., mainly *P. ostreatus* (Jacq.) P. Kumm., *P. pulmonarius* (Fr.) Quél., *P. eryngii* (DC.) Quél., and *P. djamor* (Rumph. ex Fr.) Boedijn (known as "oyster" mushrooms) can successfully colonize and produce fruit bodies on a very large spectrum of (most often) pasteurized substrates, which extend from cereal straw, wood sawdust, and sugarcane bagasse to olive mill, palm oil, corn cobs, grape marc, cotton and coffee wastes, as well as many other (Zervakis et al. 1996, 2013; Philippoussis et al. 2001; Salmones et al. 2005; Rodriguez Estrada & Royse 2007; Isikhuemhen et al. 2009; Mikiashvili & Isikhuemhen 2009; Koutrotsios et al. 2014).

Lentinula edodes (Berk.) Pegler (shiitake) grows on dead wood of various deciduous trees (*Castanopsis*, *Quercus*, *Castanea*, *Fagus*, *Acer*, *Liquidambar*, *Populus*, etc.) in tropical–subtropical climates and is widespread in South-East Asia. Its cultivation

started in China 1000 years ago, in woods, using cut logs naturally inoculated by the fungus. Nowadays, it is the third most popular mushroom in the global market and is widely cultivated in artificial substrates typically consisting of hardwood sawdust placed in sterilizable polypropylene bags to form "synthetic logs" (Stamets 1993; Royse 1997). In addition, several agro-industrial byproducts such as wheat straw, ground corn cobs, sugarcane bagasse and leaves, coffee husks, sunflower seed hulls, peanut shells, cotton stalks, and hazelnut husks have been used alone or in combination with other wastes in shiitake cultivation (Curvetto et al. 2002; Philippoussis et al. 2003; Rossi et al. 2003; Mata & Gaitán-Hernández 2004; Elisashvili et al. 2015).

Auricularia auricula-judae (Bull.) Quél. (Jew's ear or jelly ear or wood ear mushroom) and *A. nigricans* (Sw.) Birkebak et al. [syn. *A. polytricha* (Mont.) Sacc.] have been cultivated since 600 AD in China (Luo 1993). Nowadays, they are mainly produced on substrates in the form of artificial logs made of sterilized hardwood sawdust and are usually supplemented with wheat bran. Nevertheless, many other plant byproducts are also in use, e.g. palm oil waste, cottonseed shell, sugarcane bagasse, maize residues, wheat, rice straw, and rapeseed straw (Luo 1993; Kushwaha et al. 2006; Abd Razak et al. 2013).

Flammulina velutipes (Curtis) Singer (winter mushroom, enokitake, or golden needle mushroom) grows naturally on broadleaved trees in Europe, South-East Asia, and America. Its production is mainly based on substrates consisting of sawdust or ground corncobs supplemented with bran, which are placed in polypropylene bottles and are sterilized prior to inoculation (Royse 1997). More recently, several other byproducts rich in lignocellulosics have been used as cultivation media with satisfactory results, e.g. coffee husk and coffee spent-ground, rubber wood sawdust, paddy straw, palm empty fruit bunches and palm-pressed fiber, two-phase olive-mill wastes (Leifa et al. 2001; Harith et al. 2014; Rugolo et al. 2016).

Volvariella volvacea (Bull.) Singer (paddy straw mushroom) is widely cultivated in East Asia and Africa and was traditionally grown on rice straw; however, in the early 1970s cotton waste was introduced as a substrate with notable improvements in mushroom yields (Chang 1977). From then on, these two waste streams as well as banana leaves and pseudo-stems, oil palm waste, wheat straw, sawdust, and sugarcane bagasse have been used after being fermented and pasteurized with varying yields (Philippoussis et al. 2001; Belewu & Belewu 2005; Biswas & Layak 2014).

Ganoderma lucidum (Curtis) P. Karst. and *G. sichuanense* J.D. Zhao & X.Q. Zhang (reishi or mannentake or lingzhi) have been cultivated for more than 40 years either outdoors (in logs; usually basswood, *Tilia* spp.) or indoors in substrates prepared in bags or bottles (Zhou et al. 2012). The latter is principally based on sawdust from broadleaved trees supplemented by various amendments such as wheat and rice bran, corn powder, tea waste, urea (Erkel 2009; Peksen & Yakupoglu 2009; Zhou et al. 2012). However, several other plant residues and agro-industrial byproducts have been also used for commercial or lab-scale production of *Ganoderma* fruit bodies, e.g. cotton seed husks, sunflower seed hulls, cereal straw, corn cobs, and soy waste of tofu manufacturing (González Matute et al. 2002; Hsieh & Yang 2004; Zhou et al. 2012).

Grifola frondosa (Dicks.) Gray (maitake or hen-of-the-woods) naturally grows on hardwood (mainly *Fagus* and *Quercus* spp.) in Europe, Asia, and North America. Its commercial cultivation started in the early 1980s in Japan and has expanded ever since by adopting three main techniques: bottle culture, bag culture, and outdoor bed culture (Mayuzumi & Mizuno 1997). The former two are mainly based on the use of supplemented (with rice, corn, oat and/or wheat bran, soybean cake, or corn meal) sawdust deriving from oak, beech, and larch trees (Mayuzumi & Mizuno 1997; Shen & Royse 2001). However, reasonable yields during indoor cultivation depend on substrate supplementation at high rates (ca. 40%), which is the highest among all exotic mushrooms. Moreover, pinning and fructification has to be managed carefully since more than 30% of primordia do not usually develop into mature fruit bodies.

Hericium erinaceus (Bull.) Pers. (lion's mane or yamabushitake) is traditionally cultivated in East Asia on sawdust-based substrates although corncobs and cottonseed hulls (supplemented with rice or wheat bran) have been also used with success (Oei 1996; Ko et al. 2005). More recently, additional plant residues were examined, and the results showed the suitability of sunflower seed hulls, rice hull and straw, sugarcane bagasse, soybean dregs, and olive pruning for supporting *H. erinaceus* mushroom production (Figlas et al. 2007; Hu et al. 2008; Koutrotsios et al. 2016).

Cyclocybe cylindracea (DC.) Vizzini & Angelini (syn. *Agrocybe cylindracea* (DC.) Maire) is a rather overlooked edible mushroom of high quality and is relative easy to cultivate. It presents a widespread distribution and grows on a large range of broadleaved trees, e.g. *Populus*, *Quercus*, *Ulmus,* and *Salix* spp. (Uhart et al. 2008). It is commercially produced in several countries of Europe and Asia mainly on supplemented sawdust substrates. Still, several other media have been examined including cereal (wheat and barley) straw amended or not with oats or soybean flour, rice husks, sunflower and

cotton residues, solid waste from anaerobic digestion of poultry litter, olive-mill byproducts, grape marc, etc. (Philippoussis et al. 2001; Uhart et al. 2008; Isikhuemhen et al. 2009; Koutrotsios et al. 2014).

Production of mycelium biomass in liquid media or submerged fermentation systems

Traditionally, mushroom biomass is produced through SSF, aimed at the formation of fruit bodies, which are then processed for the extraction of bioactive compounds. However, this approach is generally time-consuming (from 3 to 4 weeks up to a few months) and cannot guarantee constant biomass production in terms of yield and quality. Submerged fermentation is a promising alternative for the efficient and large-scale production of fungal mycelia and extracellular metabolites within a well-specified time, and different strategies have been adopted for implementing it, e.g. batch cultivation in shake-flasks or laboratory fermenters, operation of fed-batch systems, and immobilized cultures. Such processes depend on the accurate regulation of various interrelated parameters including temperature, agitation, pH, carbon source, nutrients, and oxygen concentration; their correct setting is of paramount importance for the best mycelium and metabolite(s) production (Anike et al. 2015; Elisashvili 2012).

Several extracellular metabolites and intracellular compounds of macrofungi have been produced through submerged fermentation under various conditions as they are indicatively presented in Annex I. When shake-flasks or stirred-tank fermenters (5–20 L) were used, optimal temperatures were within the range of 22–30°C, agitation mostly varied between 120 and 150 rpm, pH values were initially set at 5.0–6.5, and cultures were usually removed after 7–15 days. The far most common carbon source utilized was glucose followed by sucrose, maltose, lactose, xylose, and other carbohydrates, while, in several cases, complex compounds (e.g. agricultural residues) were also examined. Yeast extract and peptone were present in most of the culture media as well as various salts such as ammonium sulfate, magnesium sulfate, monopotassium, and dipotassium phosphates, calcium chloride. As a result, biomass yields ranging from a few grams up to ca. 39 g per liter have been reported mainly depending on the fungal species and the duration and scale of cultivation. Accordingly, extracellular polysaccharides production varied between 0.1 and 7.1 g per liter, while intracellular polysaccharides, lectins, phenolics, flavonoids, terpenoids, ergotheionine were also obtained in varying yields (Annex I).

Nutraceutical properties and dietary value of mushrooms

It is estimated that a large number of wild and cultivated edible mushrooms (more than 700 taxa with pharmacological properties out from 2,000 known safe species) contain functional "nutraceutical" or medicinal properties (Chang 1996; Wasser 2010) and are a very important source of some novel dietary fibers with various health benefits to humans (Cheung 2013). The "mushroom nutriceuticals" (*sensu* Chang & Buswell 1996) are extractable, for example, from fungal mycelium, sclerotia, spores powder, basidiomata (fruit bodies of *Basidiomycetes*), or ascomata (fruit bodies of *Ascomycetes*) and represent an important component of the mushroom biotechnology industry.

It is well known that an increasing number of consumers consider the culinary mushrooms as functional food with high vitamin and protein contents as well bioactive activities, including antioxidant activities (Wasser 2010; Chang & Wasser 2012). In comparison with vascular plants (Colombo 2016), fungi are considered a good source of novel product (Varese et al. 2011; Donnini et al. 2013; Zotti et al. 2013), mineral salts and vitamins such as B_1, B_2, B_6, B_{12}, D, H, niacin, and pantothenic acid (Kalač 2016). Crisan and Sands (1978) reported the proximate composition of some common mushroom species and underlined the high-crude protein content (30.1% of dry weight) in *V. volvacea*, a considerable crude fat content (4.9–8.0 g/100 g dry weight) in *L. edodes*, a high content of carbohydrates (81–94.8 g/100 g dry weight) in *A. auricula-judae*, *P. ostreatus*, and *Tremella fuciformis* Berk. A higher value of crude fiber (27.9) is found in *Tuber melanosporum* Vittad. (Crisan & Sands 1978). The total dietary fiber content of mushroom sclerotia of *Lentinus tuber-regium* (Fr.) Fr., *Lignosus rhinoceros* (Cooke) Ryvarden, and *Wolfiporia cocos* (F.A. Wolf) Ryvarden & Gilb. was analyzed by Wong et al. (2003). These sclerotia were carbohydrate-rich (90.5–98.1% dry matter) with a low amount of crude lipid content (0.02–0.14% dry matter). The macrolepiotoid mushrooms *Macrolepiota dolichaula* (Berk. & Broome) Pegler & R.W. Rayner, *M. procera* (Scop.) Singer, and *M. rachodes* (Vittad.) Singer possesses relatively high-protein and carbohydrate content and appreciable quantities of phenolics, flavonoids, and carotenoids (Babita & Narender 2014). An investigation carried out in Nigeria (Adejumo et al. 2015) demonstrated that *V. volvacea* is rich in protein (42.63%), *P. ostreatus* in fat (15.38%), calcium (87.50 mg/g), sodium (6.52 mg/g), and magnesium (51.27 mg/g). Also, *Termitomyces microcarpus* (Berk. & Broome)

R. Heim is rich in ash (8.16%), while *P. pulmonarius* is rich in crude fiber (8.16%), carbohydrate (37.64%), potassium (7.25 mg/g), and vitamin C (14.10 mg/g). *Fistulina hepatica* (Schaeff.) With., *Infundibulicybe geotropa* (Bull.) Harmaja, *Laetiporus sulphureus* (Bull.) Murrill, *M. procera*, and *Suillus granulatus* (L.) Roussel are considered valuable natural products well worth including in many types of diet (Palazzolo et al. 2012). In particular, the protein and calcium content of *L. sulphureus* is higher than other wild and cultivated mushrooms and the vitamin D and B_{12} content is similar to *P. eryngii* and *P. eryngii* var. *thapsiae* Venturella, Zervakis & Saitta. A high vitamin B_{12} and riboflavin content is also reported for *Pleurotus nebrodensis* (Inzenga) Quél. (La Guardia et al. 2005; Venturella et al. 2016).

Some cultivated mushroom species from Ethiopia are considered to be richer in protein than carbohydrate and show a very small amount of fat (as in the case of *Pleurotus floridanus* Singer). A high fiber and ash content is found in *Lyophyllum decastes* (Fr.) Singer and *Russula delica* Fr. (Teklit 2015). Cultivated varieties of edible mushrooms are also low in calories and calcium, while they possess a high content of polyunsaturated fatty acids (Chang & Buswell 1996). At least 72% of the total fatty acids are unsaturated and are considered essential, significant, and healthy components of the human diet. The potential of many edible mushrooms' sporocarps and mycelia to be used as foods or food-flavoring materials or in the formulation of health foods were highlighted by Ulziijargal and Mau (2011). Due to the high amount of dietary fiber present in different mushrooms species, the energy provided by 100 g of basidiomata and mycelia is 47–292 kcal and 196–373 kcal, respectively.

Phenols are the major antioxidant components found in the extracts of *Cantharellus cibarius* Fr. (49.8 mg g^{-1}), followed by flavonoids (86% of the total phenol content) (Kozarski et al. 2015b).

Barros et al. (2008) compared nutrients and nutraceuticals from commercial dried samples of *Boletus edulis* Bull., *Calocybe gambosa* (Fr.) Donk, *C. cibarius*, *Craterellus cornucopioides* (L.) Pers, and *Marasmius oreades* (Bolton) Fr. with wild species of *A. bisporus*, *A. silvaticus* Schaeff., and *A. silvicola* (Vittad.) Peck. The wild mushroom species showed higher contents of protein, polyunsaturated fatty acids, α-tocopherol, and phenols. The commercial species seem to have higher concentrations of sugars, ascorbic acid, fats, and monounsaturated fatty acids. The antimicrobial properties of wild and commercial species are similar. In addition, wild culinary species of *Lentinus* Fr. are significant in their nutraceutical composition as other edible commercially grown mushrooms (Sharma & Atri 2014). In India, water containing Mg, Cr, and HCO_{3-} (Cardio Protective Drinking Water) mixed with medicinal mushrooms is used to produce a "nutraceutical tea" able to reduce deaths due to heart disease and help in glucose metabolism and diabetes (Pandey 2014).

The inclusion of whole mushrooms into the diet may have efficacy as potential dietary supplements. The "Seri Pagi" mushroom variety of *Pleurotus giganteus* (Berk.) Karun. & K.D. Hyde, cultivated in Malaysia, has a nutritional profile that would make it potentially useful in human diets (Phan et al. 2012; Valverde et al. 2015). The dry basidiomata contain 67.2 g/100 g of carbohydrates, 15.4 g/100 g of protein, and 33.3 g/100 g of dietary fiber and are rich in minerals like magnesium (67.64 mg/100 g) and potassium (1345.7 mg/100 g). *Russula vesca* Fr., *R. delica*, and *Termitomyces eurrhizus* (Berk.) R. Heim from India are rich sources of nutrients with high amounts of proteins (22.82–35.17 g/100 g), carbohydrates (45.68–63.27 g/100 g), and low in fats (2.03–4.62 g/100 g). They also are a good source of micronutrients (vitamins and carotenoids) and minerals (P, K, Mn, Co, Ni, Cd, and Fe) with promising bioactive properties (antioxidant and antibacterial potentials) (Singdevsachan et al. 2014). In Turkey, assays of dried samples of *A. bisporus* (white and brown varieties), *L. edodes*, and *P. ostreatus* have demonstrated that dried shiitake samples have the highest dietary fiber and raw fiber content (23.23 +/− 0.018 and 9.71 +/− 0.039 microg/100 g, respectively), while all tested mushrooms are valuable sources of vitamins such as retinol, thiamine, riboflavin, pyridoxine, and niacin (Gağlarirmak 2011). *A. auricula-judae* is a good source of almost all essential amino acids (34.7% of total) as compared to plant proteins (Kadnikova et al. 2015).

L. edodes and *P. pulmonarius* are perhaps the richest source of fungal β-glucans (Manzi & Pizzoferrato 2000). The dried powder and aqueous/ethanol extracts of *G. lucidum* are used worldwide as dietary supplements,while fresh and/or canned basidiomata of *F. velutipes* contain biologically active components such as dietary fiber, polysaccharides, and antioxidants, which reduce blood sugar, blood pressure, and cholesterol (Yeh et al. 2014).

In vitro antioxidant properties and antioxidant enzyme activities were investigated in a white variety of *Auricularia fuscosuccinea* (Mont.) Henn, from Taiwan (Lin et al. 2013). When compared with *A. nigricans* and *T. fuciformis*, *A. fuscosuccinea* possesses the highest content of total phenolic [7.88 mg gallic acid equivalents (GAE)/g], total flavonoid [1.60 mg quercetin equivalents (QE)/g], high superoxide dismutase activity (2.10 U/mg), and total antioxidant capacity (2.26 mM/g).

Some edible mushrooms [i.e. *Agaricus campestris* L., *A. auricula-judae*, *G. lucidum*, *Ophiocordyceps*

sinensis (Berk.) G.H. Sung et al., and *Sanghuang porusbaumii* (Pilát) L.W. Zhou & Y.C. Dai] have been recognized as the ideal food for dietetic prevention of hyperglycemia (Zuomin et al. 1998). Johnson (1991) and Jong and Birmingham (1992) observed that a water-soluble dietary fiber increases the gastric emptying time, as well as suppresses and/or delays the absorption of carbohydrates to prevent rapid blood glucose increase. Glucuronoxylomannan and exopolysaccharides in *T. fuciformis* give this mushroom a potential oral hypoglycemic effect as a functional food for the management of diabetes mellitus (Perera & Li 2011). *W. cocos* extract and its triterpenes reduce postprandial blood glucose levels in mice via enhanced insulin sensitivity irrespective of the peroxisome proliferator-activated receptor-γ (Sato et al. 2002). *G. lucidum*, *G. applanatum* (Pers.) Pat., *Gymnopus confluens* (Pers.) Antonín, Halling & Noordel., *A. auricula-judae*, *A. brasiliensis*, *Inonotus obliquus* (Ach. ex Pers.) Pilát, *H. erinaceus*, *C. cylindracea*, *Coprinus comatus* (O.F. Müll.) Pers., *G. frondosa*, and *O. sinensis* are used as functional foods and ingredients in the traditional medical system and have demonstrated a more significant potential for the prevention or cure of diabetes than components found in plant species (Perera & Li 2011).

Extracts from both mycelium and ascomata of different species of *Cordyceps* Fr. showed anticancer activities by various mechanisms, such as modulating the immune system and inducing cell apoptosis (Khan et al. 2010). *A. brasiliensis* (=*A. blazei*) is considered a mushroom of biomedical importance. This mushroom contains a number of bioactive components (response modifiers), which activate the immune systems for a multitude of defensive functions (Wang et al. 2013).

Papaspyridi et al. (2011) isolated a number of compounds that exhibit valuable biological properties derived from the edible mushroom *P. ostreatus* biomass, produced by submerged fermentation in a batch-stirred tank bioreactor. Bioactive compounds present in some fungi such as *T. versicolor*, have indirect beneficial effects on human health by acting as inhibitors of aflatoxins (Scarpari et al. 2016).

Compounds extracted from *Pleurotus* species exhibit activity against various chronic diseases (Gunde-Cimmerman 1999; Wasser 2002). The extracts of some *Pleurotus* species have been shown to possess antibacterial (Schillaci et al. 2013) and antitumor activities (Venturella et al. 2015), and the polysaccharides contained in their extracts are well documented as potent antitumor and immunomodulating substances (Zhang et al. 2007). *Pleurotus* species also show immunomodulatory and antimitogenic activities (Wang et al. 2005), antioxidant and gene protective activities (Filipic et al. 2002), anti-inflammatory activity (Jose et al. 2002), antiviral, antihyperglycaemic, and antihypercholesterolaemic activities (Hossain et al. 2003), and they also perform protective activity against cardiovascular disease (Hu et al. 2006).

Culinary–medicinal mushrooms such as *H. erinaceus*, *G. lucidum*, *Taiwanofungus camphorates* (M. Zang & C.H. Su) Sheng H. Wu et al., *G. frondosa*, and many others have been investigated for their important role in the prevention of many age-associated neurological dysfunctions, including Alzheimer's and Parkinson's diseases (Phan et al. 2015). Sabaratnam et al. (2013) investigated the potential of *L. rhinocerotis*, *Ganoderma neojaponicum* Imazeki, and *P. giganteus* as nutraceuticals to help in the reduction or even prevention of age-related neurodegenerative diseases.

Many bioactive compounds of several *Basidiomycetes* have been proved to possess antimicrobial and anticancer properties (Lindequist et al. 2005): velutin and flammulin from *F. velutipes*, applanoxidic acid, ganodermadiol, ganomycin, and ganoderiol from *G. lucidum*, lentinin from *L. edodes*, schizophyllan from *Schizophyllum commune* Fr., etc. Nutraceutical potential and active constituents were also reported by Prasad et al. (2015) for *A. bisporus* (lectins), *A. auricula-judae* (acidic polysaccharides), *O. sinensis* (cordycepin), *G. frondosa* (grifloan, lectin), and *Lentinus sajor-caju* (Fr.) Fr. (lovastatin).

Dietary supplements from medicinal mushrooms made from *L. edodes*, *G. lucidum*, *A. brasiliensis*, *G. frondosa*, and *P. ostreatus* were recently approved in Croatia, and they are intended as an important element in the prevention and fighting against serious viral infections (Jakopovich 2011).

Characterization and pharmacological effects of biologically active compounds from medicinal mushrooms

Similar to plants, mushrooms produce many biologically active secondary metabolites, e.g. phenols, terpenes, and alkaloids to ensure their survival in a microbially strongly contaminated environment, to fight against invaders, and for other purposes. Polysaccharides, sterols, proteins, and other compounds are synthesized to build cell walls and improve cellular structures. For human and animal use, fungal metabolites could become highly important as pharmaceuticals, e.g. the immunomodulatory β-glucan lentinan from *L. edodes*, as components of extracts and powder from medicinal mushrooms, e.g. *G. lucidum*, and as lead compounds for drug development, e.g. pleuromutilins from *Clitopilus passeckerianus* (Pilát) Singer, which served as a lead component for the antibiotic retapamulin®. Other candidates for drug development are antiquorum sensing

agents from *A. brasiliensis* as potential antibiotics (Sokovic et al. 2014), the antimalarial alkaloid 4-hydroxymethylquinoline from *Trametes versicolor* (L.) Lloyd (Liu 2005), and pain-suppressive enkephalinase inhibitors from *Piptoporus betulinus* (Bull.) P. Karst. (Rathee et al. 2012).

This part will focus on the pharmacology and chemistry of selected biologically active compounds and extracts from medicinal mushrooms. They exhibit a broad spectrum of pharmacological activities including antibacterial, antifungal, antiviral, cytotoxic, immunomodulating, anti-inflammatory, antioxidative, antiallergic, antidepressive, antihyperlipidemic, antidiabetic, digestive, hepatoprotective, neuroprotective, nephroprotective, osteoprotective, and hypotensive activities (Lindequist et al. 2005; Fan et al. 2006; Wasser 2010, 2014; Chang & Wasser 2012; Roupas et al. 2012; Stachowiak & Reguła 2012; De Silva et al. 2013; Paterson & Lima 2014; Muszynska et al. 2015). Most information about biological effects arises from experiences in traditional medicine, mainly in East Asian countries, but also from Eastern Europe and South America (Lindequist 2011). Meanwhile, numerous *in vitro* and animal studies confirm the ethnomedicinal knowledge. But systematic clinical studies and detailed investigations for mode of action are needed to fully explore the pharmacological potential of medicinal mushrooms and their components.

Chemical characterization of bioactive compounds from medicinal mushrooms

The bioactive compounds responsible for the observed activities belong to different chemical groups, mainly to polysaccharides (β-glucans), polysaccharide–protein complexes, terpenes (triterpenes, diterpenes, and sesquiterpenes), phenolic compounds, alkaloids, peptides, lectins, and nucleosides (Fan et al. 2006; De Silva et al. 2013; Paterson & Lima 2014; Valverde et al. 2015). In the following list, some groups of compounds are briefly characterized.

Polysaccharides are carbohydrates composed of monosaccharide units. Depending on the type of monosaccharides, molecular weight, solubility, linkages, configuration, and connection with other molecules like proteins, many different polysaccharides are found in mushrooms. β-glucans are the most important group of biologically active polysaccharides in mushrooms. They consist mainly of β (1,3) glucose units with side chains bound by 1,6 glycosidic linkages. Nevertheless, considerable structural differences exist between different β-glucans. β-glucans can be isolated by hot water extraction and ethanol precipitation from fruit bodies, mycelium, spores, or culture medium. The commercially available products are not really pure and are usually contaminated by other compounds. Structure elucidation of polysaccharides is very challenging and requires sophisticated equipment. Fungal β-glucans are mostly used because of their immunomodulating activities in adjunct tumor therapy. Regarding the relationships between structure and biological activity, many questions still exist (Villares et al. 2012; Synytsya & Novak 2013; Ruthes et al. 2015; Barrientos et al. 2016).

The next important group of bioactive compounds in mushrooms is **terpenes**. According to the number of building isoprene units, terpenes are classified into mono-, sesqui-, di-, triterpenes, etc. Many medicinal mushrooms contain bioactive triterpenes (Duru & Cayan 2015). Except for *G. lucidum*, about 200 different triterpenes are described (Baby et al. 2015). Triterpenes consist of three isoprene units (30 C atoms) that are head-to-tail coupled. When chemically modified, they are referred to as terpenoids. Steroids are closely related to triterpenes. They possess a steranecore structure, a side chain at C17, and different functional groups. Steroids with a hydroxyl group at C3 are named sterols. Ergosterol is the most important sterol in fungi and determines not only the fluidity of the fungal cell membrane, but can also be converted into Vitamin D_2 under UV exposure. Other triterpenoids and steroids in fungi, e.g. ergosterol peroxide, betulinic acid, and ganoderic acids exhibit cytotoxic, immunomodulatory, antiviral, antibacterial, antimitotic, or apoptosis-inducing activities. Extraction and isolation of these compounds are usually done with ethanol or methanol and followed by chromatographic purification.

Phenols are a very diverse group of compounds that are characterized by one or more aromatic rings with one or more hydroxyl groups. They include a large number of subclasses such as quinones, flavonoids, phenolic acids, including hydroxybenzoic acids and salicylic acid, stilbenes, tocopherols, lignans and lignins, tannins, curcuminoids, coumarins, and oxidized polyphenols displaying a great variety of structures. Phenols are primarily known for their antioxidant properties. Depending on their redox status and the ambient pH value, they can become pro-oxidative and contribute to the generation of reactive oxygen species (ROS). ROS play an important role in the defense against infections. Furthermore, phenols exhibit, e.g. anticarcinogenic, antimutagenic, and anti-inflammatory effects (Islam et al. 2016; Kozarski et al. 2015a). Phenols are usually extracted by mixtures of water and organic solvents.

Alkaloids are N-containing heterocyclic compounds. Till now, fungal alkaloids are mostly known because of their toxicological relevance, e.g.

ergot alkaloids in *Claviceps purpurea* and psilocybin in *Psilocybe* sp. (Liu 2005). An increasing importance of beneficial substances from mushrooms can be expected. Extraction of alkaloids is usually done in methanol or ethanol, respectively, in water when the alkaloids are converted into salts. Separation can be done by HPLC (high-performance liquid chromatography).

Immunomodulating activities

Until now, immunomodulating activity has been the most prominent pharmacological property of medicinal mushrooms. The activity is mainly caused by β-glucans, the main components of the fungal cell wall. These molecules are glucose polymers of a linear ß(1,3) -glucan backbone with ß(1,6)-linked side chains (Mizuno & Nishitani 2013). They are unknown to the human body and belong to the so-called PAMPs (pathogen associated molecular pattern). Following peroral administration, the β-glucans are recognized by PRR (pattern recognition receptors) on the surface of dendritic cells and macrophages in the gastrointestinal tract (M cells of Peyer's spatches). After recognition by PRR, i.e. dectin-1-receptors and TLR 2/6 (toll like receptors 2/6), the glucan molecules are internalized into the cells and fragmented within. The fragments are taken up by the lymph and transported to other parts of the immune system in the body. They bind to specific receptors of the complement system (CR3 receptors) on the surface of immune cells, e.g. neutrophil granulocytes and NK (natural killer) cells, and activate them. The immune cells are then primed. This is followed by the secretion of cytokines, such as TNFα (tumor necrosis factor α), IFN-γ (interferon-gamma), and several interleukins (IL-6, IL-8, IL-12), and leads to the activation of cytotoxic T lymphocytes, T helper cells, and B cells. Increased phagocytic activity, production of nitrite monooxide (NO), and antibody formation occur. Altogether, innate and adaptive immunity are activated reacting fast and strongly against invading micro-organisms and abnormal cells, e.g. tumor cells (Brown & Gordon 2003; Chen & Seviour 2007; Chan et al. 2009; Barsanti et al. 2011; Batbayar et al. 2012; Ren et al. 2012; Giavasis 2014; Guggenheim et al. 2014).

The effects depend strongly on the basic conditions of the organism. An immuno-compromised organism will react much stronger on an immunomodulating drug than an organism with an intact immune system. Therefore, it is recommended to use the term "immunomodulator" or "biological response modifier (BRM)" instead of "immunostimulator". Of course, the extent of activity is also influenced by dosage, mode of application, time of application, and pharmaceutical formulation.

The stimulation of a patient's immune defense against tumor cells by fungal β-glucans can be used in the adjunct treatment of cancer patients in an integrative concept with surgery, chemotherapy, and radiation (Oba et al. 2007; Ramberg et al. 2010; Zong et al. 2012; Guggenheim et al. 2014; Twardowski et al. 2015).

Besides immunomodulation, further activities of β-glucans contribute to the positive effects against cancer. It could be shown that β-glucans have direct tumoricidal effects by inhibiting the expression of aromatase, an enzyme responsible for the conversion of androgens to estrogens, which is often upregulated in breast cancer cells. It is thought that the enzyme downregulates estrogen-dependent cell proliferation and thereby limits or prevents breast cancer (Adams et al. 2008). Furthermore, β-glucans may modify cell cycle-regulating genes, arrest the cell cycle and induce apoptosis (Jiang & Sliva 2010). Maitake mushroom *G. frondosa* β-glucan stimulates hematopoietic progenitor cell differentiation, granulocyte colony-stimulating factor production, and recovery of peripheral blood leukocytes after bone marrow injury. This was tested in a phase 2 study with good results involving patients with preleukemic myelodysplastic syndromes (Wesa et al. 2015). A very interesting observation is that the compounds change adhesion molecules on the surface of cancer cells, inhibit migration, invasion, and adhesion of the cells, and therefore possibly affect the formation of metastases (Masuda et al. 2008; Jiang & Sliva 2010). Moreover, a suppression of angiogenesis by aqueous mushroom extracts could be demonstrated (Lee et al. 2008).

The positive effects of β-glucans against tumor diseases are supported by low-molecular weight compounds of medicinal mushrooms. Some of these exemplary triterpenes are from *G. lucidum*, other *Ganoderma* species, *I. obliquus*, and *W. cocos*. They exhibit cytotoxic and apoptosis-inducing effects by arresting the cell cycle, increasing the level of p53 and *Bax*, inhibiting the phosphorylation of *Erk1/2*, upregulating NF-κB and AP-1, or reducing the activity of topoisomerase II (Ríos et al. 2012).

Clinical observations and studies demonstrate that medicinal mushrooms provide a useful treatment option in adjunct tumor therapy. The purified β-glucan lentinan, isolated from *L. edodes*, is a well-established drug for the combined treatment of cancer diseases in Japan. Formulations for intravenous and peroral administration are available. A meta-analysis of five studies, including 650 patients with non-resectable or recurrent stomach tumors, by Oba et al. (2009), demonstrated that the patients treated by chemotherapy and lentinan (immunochemotherapy group) had a significantly longer survival time in comparison to patients treated

only with chemotherapy. Another big study analyzed eight randomized controlled clinical trials, including 8,009 patients with gastric cancer. The patients were treated with PSK, a polysaccharide–protein complex purified from *T. versicolor* [=*Coriolus versicolor* (L.) Quél.] in combination with chemotherapy. The results of this study indicate that adjuvant immunochemotherapy improved the survival of patients after curative gastric cancer resection in comparison to chemotherapy alone (Oba et al. 2007). Another meta-analysis of *T. versicolor* effects demonstrated an increased rate of survival, especially for patients with breast, gastric, and colorectal cancers (Eliza et al. 2012). The Cochrane foundation confirms that patients receiving *G. lucidum* in addition to chemotherapy/radiation responded stronger to the conventional treatment than patients with conventional treatment alone and that they had a better quality of life. However, the quality of the studies was found unsatisfactory according Cochrane's Systematic Review, and the results of the studies were reported inadequately in many aspects. It was concluded that *G. lucidum* could be administered as an adjunct to conventional treatment in consideration of its potential of enhancing tumor response and stimulating host immunity (Jin et al. 2016). An increase in immunological parameters, improvement in life quality, and in single cases prolongation of survival time could be demonstrated also after treatment with *A. brasiliensis* (Ahn et al. 2004; Talcott et al. 2007) and *G. frondosa* (Kodama et al. 2002; Konno 2009; Rajamahanty et al. 2009). It should be noted that several mushrooms appear to increase the effects of chemotherapy (Guggenheim et al. 2014).

The immunomodulating effects of β-glucans are also useful for the prevention of viral infections. A two-week feeding of influenza virus-infected mice with a mixture of glucans from fruit bodies of *G. frondosa* and mycelium from *L. edodes*, *A. brasiliensis,* and *I. obliquus* significantly reduced the symptoms of infection (Vetvicka & Vetvickova 2015).

Antiallergic activities

The influence of medicinal mushrooms and β-glucans on the immune system can result in antiallergic effects. Such activities have been shown *in vitro* and in animal assays for *A. brasiliensis* (syn: *A. blazei*), *Ganoderma* sp., *G. frondosa*, *Phellinus* ssp., and various others. They are explained by an influence on the balance between Th1/Th2 cells in the immune system (Ellertsen & Hetland 2009; Bouike et al. 2011). A randomized, double-blind, placebo-controlled study in children with recurrent respiratory tract infections showed that treatment with pleuran, an β-glucan isolated from *P. ostreatus*, reduced symptoms of atopy related to such infections (Jesenak et al. 2014). Sesquiterpenes from *Armillaria ostoyae* (Romagn.) Herink are responsible for the degranulation inhibiting activity of this mushroom species (Merdivan et al. 2017).

Antidiabetic and antihyperlipidemic activities

In vitro assays in diabetic rodent investigations and several human studies suggest that several medicinal mushrooms, e.g. *A. bisporus* (Yamac et al. 2010), *A. brasiliensis* (Kim et al. 2005), *G. lucidum* (Ma et al. 2015), *G. frondosa* (Hong et al. 2007), *H. erinaceus* (Thongbai et al. 2015), *Phellinus linteus* (Berk. & M.A. Curtis) Teng (Yamac et al. 2016) and, *Pleurotus* ssp. (Jayasuriya et al. 2015) are able to normalize blood glucose levels. Furthermore, beneficial effects on blood lipids and blood pressure have been observed for several medicinal mushrooms (De Silva et al. 2013). *L. edodes* lowers blood cholesterol level in animals (Yang, Hwang, Kim, Hong, et al. 2013) and humans (Sezuki & Ohshima 1976) and has preventive effects against homocysteinemia (Yang, Hwang, Kim, Ahn, et al. 2013). The adenosine derivative eritadenine has been identified as the responsible compound. It influences not only lipid metabolism but inhibits the activity of angiotensin converting enzyme (ACE) *in vitro* also (Afrin et al. 2016).

Hyperglycemia, obesity, high blood pressure, and hyperlipidemia are important components of metabolic syndrome, pre-stage of diabetes type 2 and cardiovascular diseases. Mushrooms and mushroom-rich nutrition seem to be valuable tools for prophylaxis and in the treatment of such widespread diseases (Guillamón et al. 2010).

However, a recently published double-blind, randomized, placebo-controlled trial found no significant effect of 3 g/d *G. lucidum* (2,240 mg extract 10:1 and 740 mg spores) or a combination of *G. lucidum* with *O. sinensis* (in addition to *G. lucidum* 1,000 mg and *O. sinensis* extract), for 16 weeks on HbA1c and fasting plasma glucose values of a small number of patients with type 2 diabetes (n = 48 for both groups together, Klupp et al. 2016).

Neuroprotective acitivities

H. erinaceus, *G. lucidum*, *Antrodia camphorata* (M. Zang & C.H. Su) Sheng H. Wu, Ryvarden & T.T. Chang, and some other mushrooms are considered as useful therapeutic agents in the management and/or treatment of neurodegenerative diseases, such as Alzheimer's dementia (De Silva et al. 2013; Phan et al. 2015). Experimental studies

have shown that terpenes and polysaccharides from *H. erinaceus* stimulate the synthesis of nerve growth factor (NGF), promote the growth and differentiation of nerve cells, and protect the cells against oxidative stress. In a double-blind, placebo-controlled clinical study oral administration of *H. erinaceus* (250 mg tablets with 96% mushroom powder, three times a day, for 16 weeks) improved cognitive abilities of patients (50-–80-years old) with mild cognitive impairment (Mori et al. 2009). Another human study demonstrated antidepressive effects of *H. erinaceus* (Nagano et al. 2010), which may be caused by its high 5-hydroxytryptamine content (Muszynska et al. 2015).

Conclusions

Mushrooms can be used as food, tonics, medicines, as cosmeceuticals, and natural biocontrol agents in plant protection with insecticidal, fungicidal, bactericidal, herbicidal, nematoticidal, and antiphytoviral activities. The multidimensional nature of the global mushroom cultivation industry, its role in addressing critical issues faced by humankind and its positive contributions are noteworthy. Furthermore, mushrooms can serve as agents for promoting equitable economic growth in society. Since the lignocelluloses wastes are available in every corner of the world, they can be properly used in the cultivation of mushrooms, and therefore could pilot a so-called white agricultural revolution in less developed countries and in the world at large. Mushrooms demonstrate a great impact on agriculture and the environment and also have great potential for generating a great socioeconomic impact in human welfare on local, national, and global levels.

Mushrooms produce many chemically diverse compounds with a broad spectrum of biological activities. *In vitro* assays, animal studies, and a few clinical trials justify the traditional experience and suggest a great potential of medicinal mushrooms and mushroom compounds for the prophylaxis and treatment of several diseases. In view of promising results, more efforts are necessary to explore the potential of medicinal mushrooms and to promote the development to regular drugs. Important tasks are realization and publication of high-quality clinical studies, manufacturing high-quality products with standardized quality, and ensurement of sustainable production under controlled conditions.

Disclosure statement

No potential conflict of interest was reported by the authors.

Supplemental data

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