

Fungi a source with huge potential for “mushroom pharmaceuticals”

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Mushrooms for ages have been used by humans, not only as a source of food but as medicinal resources as well. They were used as a part of traditional medicine, first of all in the civilizations of the East and recently in Western civilizations. The mushrooms constitute 16,000 species worldwide with more than 2000 species identified as safe. Among these mushrooms, 1000 are edible, while others have been used as a source of biofuel, in medicinal formulation, as biochemicals, and for other purposes. Mushrooms have also huge potential, such as a “mushroom pharmaceuticals” with 130 medicinal functions. Therefore, they have been considered as potential source of antioxidant, antitumor, antiviral, antimicrobial, and immunomodulatory agents. This review focuses on the antimicrobial and analgetic activities of some medicinal mushrooms.

Key words: *fungi, medicinal mushrooms, edible mushrooms, antibacterial, antifungal, analgetic activities*

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1. INTRODUCTION

Fungi are group of organisms belonging to separate kingdom according to Whittaker (1969) classification. The fungi are most diverse groups of organisms on Earth assumed that total of more than 1,5 million species. Currently, 100,000 species of fungi of all kinds have been described (Blackwell, 2011). The mushrooms constitute 16,000 species, calculated from the Dictionary of Fungi (Kirk et al., 2008) with approximately 700 species, with the pharmacological properties of 2000 known, safe species (Wasser, 2010).

The term mushroom will be used for a distinctive fruiting body (epigeous or hypogeous) of higher fungi. Mushrooms are (mostly higher Basidiomycetes and some Ascomycetes) macrofungi within fruiting bodies large enough to be seen with the naked eye and to be picked up by hand (Chang and Miles, 2004). Usage of medicinal mushrooms has a long history in different folk's medicines and in prevention and treatment of many diseases, especially in countries such as China, India, Japan and Korea, but also in of eastern European countries, Mesoamerica, Africa, Algeria, and Egypt (Wasser, 2014).

Medicinal mushrooms (MM) can be defined as macroscopic fungi, which are used in the form of extracts or powder for prevention, alleviation or healing multiple diseases, and/or in balancing a healthy diet. There is a total more than 130 medicinal functions produced by MMs and fungi (Gargano

et al., 2017).

The mushrooms possessed high content of proteins (20–30% of dry matter), and all the essential amino acids are presented. They are rich in chitin as a source of dietary fiber and have high vitamin B content. The mushrooms are low in total fat but with a high proportion of unsaturated fatty acids, and have no cholesterol. They have been used not only as a source of delicious foodstuff and also as a source of food flavoring substances but medicinal resource as well. The medicinal properties of mushrooms have been confirmed through an intensive research conducted worldwide (Valverde et al., 2015). Mushrooms possess immense nutritional and medicinal bio-components that substantiate their usage in maintaining global public health. It was shown that they constitute a rich source of bioactive compounds exhibiting antitumor, hypcholesterolemic, immunosuppressive, antioxidant, antimicrobial and anti-inflammatory properties. These compounds are polysaccharides, complexes (polysaccharide–protein and polysaccharide–peptide), ribonucleases, proteases, and lectins. Other mushroom compounds of therapeutic interest are the secondary metabolites, especially some low molecular weight compounds such as lactones, terpenoids, and alkaloids, antibiotics with different chemical groups, and metal chelating agents (Cheung, 2010; Wasser, 2011). Many species of mushrooms are used in traditional medicine, but the following are the most valuable: *Ganoderma lucidum*, *Lentinus edodes*, *Trametes versicolor*, *Schizophyllum commune*, *Flammulina velu-*

tipes, *Pleurotus ostreatus*, *Agaricus bisporus*, *A. brasiliensis*, *Tricholoma matsutake*, *Auricularia auricula*, *Grifola frondosa*, *Cordyceps sinensis*, *Coprinus comatus*, *Inonotus obliquus*, *Phellinus linteus*, *Laetiporus sulphureus*, and *Hericium erinaceus*. These and other species are referred as "medicinal mushrooms" due to their long history of medical use. The biologically active compounds and extracts from this species exhibit a broad spectrum of pharmacological activities (Chang and Wasser, 2012; Fan et al., 2006; Lindequist et al., 2005; Muszynska et al., 2015; Paterson and Lima, 2014; Roupas et al., 2012; De Silva et al., 2013; Stachowiak and Regula, 2012; Wasser, 2010; 2014).

In this review, the special attention is paid on antimicrobial activities of selected mushrooms and their positive analgetics effect of in the treatment of pain.

2. ANTIMICROBIAL ACTIVITY OF EDIBLE AND MEDICINAL MUSHROOMS

Antimicrobial agents are substances used to treat infections caused by pathogenic microorganisms. These compounds achieve activity through several mechanisms, which specifically acts on the specific processes in the bacterial cell (DNA replication and transcription, inhibition of certain enzymes) or their structures (ribosomes, cell wall and membrane) in the bacterial and fungal cells in order to enable their growth (Madigan and Martinko, 2006). The antifungal agents can form a complex with ergosterol compromising the cell membrane fluidity or other antifungals inhibit the synthesis of enzyme that catalyzes a critical reaction of the sterol biosynthetic pathway, leading to the depletion of ergosterol in the membrane or other antifungal classes inhibit glucan biosynthesis. The development of new antimicrobials, both natural and synthetic, is critical due to the increasing number of isolated multi-drug resistant microorganisms on the environment, human and veterinary medicine. Antimicrobial compounds with more or less strong activities could be isolated from many mushrooms and that they could be of benefit for human (Sokovic et al., 2017). There are many literature data concerning *in vitro* studies of antimicrobial potential of mushroom extracts, where tested extracts demonstrated activities against gram-positive and gram-negative bacteria as well as foodborne pathogenic bacterial strains, yeasts and micromycetes: phytopathogens and dermatomycetes (Soboleva et al., 2006; Hearst et al., 2009; Jagdish et al., 2009; Venturini et al., 2008).

1. Antibacterial activity of extracts and compounds isolated from mushrooms

According to the World Health Organization (WHO, 2001) despite the wide variety of existing antibiotics and antimycotics treating of bacterial and fungal infections has become an increasingly complicated task due to the development of microbial resistance to existing antimicrobial drugs. For example, some of the microorganisms that have developed resistance to antibiotics are penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococci*, methicillin-resistant *Staphylococcus aureus* (MRSA), and multi-resistant *Salmonellae* and *Mycobacterium tuberculosis*. Many infections are multidrug resistant, with a mortality rate of nearly 400 deaths per year (Ventola, 2015).

The antimicrobial potential of mushroom species depends on samples origin, type of extract, assays applied and bacterial and fungal species investigated, as well as the numerical values of the results are presented (Alves et al., 2012a; Barros et al., 2007; Harikrishnan et al., 2011; 2012). A large number of species from phylum Basidiomycota are known to be prolific producers of antibacterial bioactive metabolites. Some mushroom extracts, particularly obtained from *Lentinus edodes* and *Phellinus linteus*, have been reported as effective even

against highly resistant bacteria, such as MRSA (Hearst et al., 2009; Hur et al., 2004). *L. edodes* ethyl acetate extract showed inhibitory activity against *Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus* and *S. epidermidis*. *Streptococcus pyogenes* was very sensitive to the chloroform extract of *Lentinus edodes*, while aqueous extract demonstrated good activity against MRSA. *L. edodes* extracts showed a strong bactericidal effect against *Streptococcus mutans* (Alves et al., 2012a).

Agaricus genus represents the most important cultivated edible mushroom. Antimicrobial activity of three *Agaricus* species was published by Ozturk et al. (2011), who described effects of methanolic extracts against six species of Gram-positive bacteria, seven species of Gram-negative bacteria. Giri et al. (2012) described that a methanolic extract of *A. campestris* from India showed antimicrobial activity against seven bacterial species. Glamoclija et al. (2015) investigated biological activity of methanolic and ethanolic extracts of *A. bisporus*, *A. bitorquis*, *A. campestris* and *A. macrosporus*. All extracts showed antibacterial potential. The biofilm forming capability of *P. aeruginosa* was also reduced in a concentration-dependent manner. Furthermore, ethanolic extracts demonstrated statistically significant reduction of virulence factors such as AQ inhibition zones, twitching and swimming motility of the tested bacteria. Petrovic et al. (2014a) showed good antibacterial activity of different extracts (aqueous and methanolic) of *Laetiporus sulphureus* fruiting body against tested bacteria, being in some cases stronger than the used antibiotics.

In a recent screening of antibacterial activity of water and methanol crude extracts of the species, *Meripilus giganteus* against nine species of Gram-positive and four species of Gram-negative bacteria, the most active extract was methanolic, inhibiting all the Gram-positive bacteria and only two Gram-negative ones (Karaman et al., 2009). Stojkovic et al. (2017) demonstrated the activity of the methanolic extract of *M. giganteus* decreased in the order: *S. aureus* = *B. cereus* > *S. typhimurium* > *E. coli* > *L. monocytogenes* > *M. flavus* = *P. aeruginosa* > *E. cloacae*. Karaman et al. (2010), even though applying different method, also found *S. aureus* strain as the most sensitive to the antimicrobial action of *M. giganteus*.

Antimicrobial activities and the antitumor effect on *Pseudomonas aeruginosa* of *Agrocybe aegerita* methanolic extract were investigated. The *A. aegerita* methanolic extract regulated the virulence factors in the quorum sensing (QS) test, as well as biofilm formation on *P. aeruginosa* (Petrovic et al., 2014b). Extracts from the fruit bodies of the medicinal mushroom *Hericium erinaceus* inhibited the adverse *in vivo* effects of *Salmonella* in mice via stimulation of the immune system (Kim et al., 2012). The high antibacterial activity was observed for *Ganoderma lucidum* and *Coprinus* species. Numerous studies on the potential of *G. lucidum* are well documented. Heleno et al. (2013a) present is a good activity of methanol extract of *G. lucidum* on *S. aureus*, *B. cereus*, *M. flavus*, *L. monocytogenes*, *E. coli*, *S. typhimurium*, *P. aeruginosa*, and *E. cloacae*. Antimicrobial activities of *Ganoderma lucidum*, *G. praelongum* and *G. resinaceum* were evaluated against 30 strains of clinical isolates of methicillin-resistant and -sensitive *Staphylococcus aureus* (Ameri et al., 2011). Coprinol, a new antibacterial cuparane-type terpenoid from cultures of a *Coprinus* sp. exhibited activity against multidrug-resistant Gram-positive bacteria Johansson et al. (2001). Micaceol, a sterol and (Z,Z)-4-oxo-2,5-heptadienedioic acid were isolated from *Coprinus* (*Coprinopsis*) *micaceus* with activities against *Corynebacterium xerosis* and *S. aureus* (Zahid et al., 2006).

Ramariolides A–D, isolated from the fruiting bodies of the coral mushroom *Ramaria cystidiophora*, showed *in vitro* antimicrobial activity against *Mycobacterium smegmatis* and *M. tuberculosis* (Centko et al., 2012). The *Armillaria mellea*, which

produces antibiotic, melleolides, unusual sesquiterpene ester (Baumgartner et al., 2010; Bohnert et al., 2014), showed high antibacterial potential. The capacity of methanolic extract of *A. mellea* indicates the possible presence of compounds with a broad spectrum of activity to interfere with quorum-sensing regulated functions (biofilm formation, pyocyanin production, bacterial motility), which might have great potential in the near future (Kostic et al., 2017).

Some of the tested Ascomycetes, as *Morchella esculenta* and *Tirmania pinoyi*, as well showed excellent antibacterial activity. The methanolic extracts of *M. esculenta* exhibited very good activity against five bacteria (Heleno et al., 2013b). It was noticed that *T. pinoyi* methanolic extract dissolved in different solvents, showed antibacterial activities against food poisoning and food spoilage bacteria demonstrated *in vitro* and *in situ*. Activities of *Tirmania pinoyi* methanolic extract successfully inhibited the growth of *S. aureus* in chicken soup (Stojkovic et al., 2013a).

2. Antifungal activity of extracts and compounds isolated from mushrooms

Pathogenic fungi are capable to induce infections of humans, animals, crops, and other living organisms. The main pathogens responsible for fungal infections are yeasts, moulds and dermatomycetes. Fungal infections contribute substantially to human morbidity and mortality. *Candida spp.*, the yeast-like fungi, is one of the most common infectious agents. This genus as the 5th most common pathogen associated with bloodstream infections, while skin mycosis affects approximately 25% of the world's population (Havlickova et al., 2008). In agriculture, fungal invasion brings about serious reduction in the quality and yield of crops and incurs enormous economic losses. After fungal attack, the crops may be contaminated with toxic secondary metabolites produced by fungi, mycotoxins. This contamination of food and feed crops may occur in various stages of the food chain. The species from genera *Penicillium*, *Aspergillus* and *Fusarium* are among the best known and widely studied moulds that mostly contaminate agricultural products and produce mycotoxins (Bryden, 2012; Zain, 2011). Just because of that in recent years there has been an increased use of antifungal agents and has resulted in the development of resistance and toxicity, low efficacy rates. This has given rise to a search for new natural antifungal agents.

Macrofungi seem greatly promising in terms of compounds with potential biological activities (Alves et al., 2013). Mushroom extracts, primary and secondary metabolites from mushrooms have been associated with their antimicrobial properties, such as oxalic acids, peptides or proteins, and terpenes, steroids or benzoic acids derivatives (Alves et al., 2012b). The compounds of different biogenetic origins have been isolated from Basidiomycota and were found to have antifungal activity. A total of 103 isolates of basidiomycetes, representing 84 species from different Brazilian ecosystems, were used in a bioassay panel (Rosa et al., 2003).

The diversity and abundance of mushrooms in Serbia is large (between 10,000 and 20,000 different species) and can be attributed to favorable climatic and geographic conditions, as well as plant diversity, however, is the lack of data on the bioactive properties of mushrooms increased interest in domestic scientific community about these properties (Karaman et al., 2014). Until recently, macromycetes in Serbia are primarily considered a delicacy high nutritional value and organoleptic properties, while their potential medical application was in the background. Considering a large number of new data indicate that macromycetes says pharmacodynamic agents, there is a perspective to change

these facts. Moreover, our research group has an extensive work in the antifungal characterization of wild and cultivated mushroom species from Serbia and other countries. The antifungal potential of extracts of different macromycetes (*Agaricus bisporus*, *A. bitorquis*, *A. campestris*, *A. macrosporus* (syn. *A. albertii*), *A. bohussii*, *A. brasiliensis* (syn. *A. blazei*), *Agrocybe aegerita*, *Armillaria mellea*, *Boletus aereus*, *Coprinus comatus*, *Coprinopsis atramentaria*, *Clitocybe subconnexa*, *Ganoderma lucidum*, *Laetiporus sulphureus*, *Macrolepiota procera*, *M. mastoidea*, *M. rachodes*, *Meripilus giganteus*, *Morchella esculenta*, *M. conica*, *Pleurotus ostreatoroseus*, *Polyporus squamosus*, *Suillus granulatus*, *Inonotus obliquus*, *Cordyceps militaris*, *Phellinus linteus*, *Tirmania pinoyi*, *Volvopluteus gloiocephalus*) have been evaluated *in vitro* and *in situ*.

The *in vitro* antimicrobial activity of mushroom extracts obtained from different extraction solvents has been investigated by the microdilution method on panel of pathogenic microfungi (Petrovic et al., 2014b; 2013; 2014a;c; Reis et al., 2014a; 2013; 2014b; 2012; Stojkovic et al., 2013b;a; 2014a;b). *Laetiporus sulphureus* proved to be a very successful biocontrol agent *in situ* food system (tomato paste and chicken patè), having dose-dependent and time-dependent influence on food borne pathogen *Aspergillus flavus* (Petrovic et al., 2013; 2014c).

Armillaria mellea methanolic extracts exhibited great anticandidal potential. Four strains of *Candida albicans* (clinical isolates from human) were tested for their susceptibility to the methanolic extract, and the results indicate very good antifungal effect of tested extract (Kostic et al., 2017).

Extract of *Cordyceps militaris* showed very good antifungal activity against *Penicillium ochrochloron*, *P. funiculosum* and *Trichoderma viride* (Wang et al., 2012). This study proved that extracts of *C. militaris* could be used as a good alternative to synthetic antimicrobial agents in prevention and treatment of different plant, animal, human pathogenic species, and food-borne pathogens. Another bioactive compound from *C. militaris* is cordymin. This peptide was studied for its antifungal properties and found to inhibit mycelial growth of *Bipolaris maydis*, *Mycosphaerella arachidicola*, *Rhizoctonia solani* and *Candida albicans* (Reis et al., 2013).

Eryngin, an antifungal peptide isolated from *Pleurotus eryngii* fruiting bodies, also gave activity against *F. oxysporum* and *M. arachidicola*. Another peptide, pleurostrin, isolated from *Pleurotus ostreatus* showed antifungal activity against *F. oxysporum*, *M. arachidicola* and *P. piriicola* (Chu et al., 2005). Agrocybin, an antifungal peptide isolated from *Agrocybe cylindracea* showed activity against *M. arachidicola* (Ngai et al., 2005).

In fact, there is a gap in the identification of the individual compounds responsible for antifungal properties. Among identified single compounds from mushrooms extracts, a few low-molecular-weight compounds, some peptides, and proteins have been described. In the study Alves et al. (2013) and Sokovic et al. (2017) different extracts and some low molecular weight (LMW) and high molecular weight (HMW) compounds isolated from mushroom with antifungal activity are reported. The sesquiterpenes, enokipodim F, G and I, isolated from *Flammulina velutipes* mycelium presented low activity against *Aspergillus fumigatus* (Wang et al., 2012).

Phenolic acids and related compounds such as p-hydroxybenzoic and cinnamic acids identified in *Ganoderma lucidum* also revealed activity against different fungi species, such as *Aspergillus fumigatus*, *A. versicolor*, *A. ochraceus*, *A. niger*, *Trichoderma viride*, *Penicillium funiculosum*, *P. ochrochloron* and *P. verrucosum*. The mentioned compounds gave higher activity than antimycotics (Heleno et al., 2013a).

Some studies suggested that mushrooms could be used also

as inhibitors of mycotoxins production. Culture filtrates from *Lentinula edodes* and *Trametes versicolor* have revealed promising aflatoxin-inhibiting effects (Reverberi et al., 2005; Zjalic et al., 2006).

3. ANALGETICS EFFECT OF MEDICINAL MUSHROOMS

There has been an increasing interest in the health-enhancing role of functional foods or physiologically-active food compounds. One of the most important traits of some functional food ingredients, in addition to their nutritional values, is their physiological benefit. Many recent studies have reported that components from mushrooms play a very important role in health promotion (Morris et al., 2017). The term “functional foods” has been described as foods that “should have a relevant effect on well-being and health or result in a reduction in disease risk” (Roberfroid, 1999). Mushrooms are attractive as a source of functional food and medicines to treat cancer and as therapeutic approach for inflammation-associated disorders such as rheumatoid arthritis, psoriasis, and other autoimmune afflictions. Pain is an unpleasant sensation usually associated with these and other diseases.

Many edible mushrooms such as species from genus *Pleurotus*, *Agaricus* and *Lactarius* exhibited analgetic effect (Wang et al., 2013). *Pleurotus* spp., mainly *P. ostreatus*, *P. pulmonarius*, *P. eryngii* and *P. djamor* are known as “oyster” mushrooms. There have been some reports showing that *P. pulmonarius* have analgetic effects (Baggio et al., 2012; 2010; Smiderle et al., 2008). Smiderle et al. (2008) isolated β -glucan from *P. pulmonarius* and found the glucan had potent anti-inflammatory and antinociceptive activities in mice. Animals treated with β -glucan showed a reduction of neurogenic pain and inflammatory pain.

Fucogalactans from *Agaricus brasiliensis* (EPF-Ab) and *A. bisporus* var. *hortensis* (EPF-Ah) have a positive role in antinociceptive, anti-inflammatory, and anti-sepsis (Komura et al., 2010). *Agaricus macrosporus* is another species which has obvious analgetic effect by inhibiting neurolysin with agaricoglycerides, a new class of fungal secondary metabolites that constitute esters of chlorinated 4-hydroxy benzoic acid and glycerol produced in cultures (Stadler et al., 2005).

Ruthes et al. (2013) studied and found that *Lactarius rufus* had the anti-inflammatory and antinociceptive potential of their polysaccharides evaluated using the formalin model. Soluble β -d-glucan isolated from fruiting bodies of *L. rufus* produced potent inhibition of inflammatory pain caused by formalin.

Not only genera described above, but also many others have the effect of analgesia. Van Griensven et al. (2017) concluded that the different *Inonotus obliquus* extracts consist mostly of lignin derivatives. Their application (intra-peritoneal in mice) suppressed the nociception of the inflammatory phase induced by formalin. The phenolic acid isolated from *Schizophyllum commune* has been found as an analgetic in rat's neurons. Smiderle et al. (2013) demonstrated suppression of formalin-induced nociceptive response of mice by glucan purified from cultivated *Cordyceps militaris* fruiting bodies.

The active components with analgetic effects are identified from many mushrooms (Van Griensven et al., 2017). However, further research is required prior to clinical trials and applications to humans. The main interest of research is now to find a drug that provides excellent analgetics effect, with little or no harmful effect on the organism. Also, many research efforts are focused on finding new compounds or formulations which could reduce or prevent the negative effects of drugs which are used in the treatment of pain. Particularly it is desired the discovery of novel prototype therapeutic agents representing

new chemical classes, operating by different modes of action compared to the existing agents and, consequently, lack cross-resistance to chemicals currently used.

CONCLUSION

Most evidence regarding the beneficial antimicrobial effects of a large number of mushroom varieties and mushroom extracts and components on bacteria, yeast, and pathogenic micromycetes have been confirmed via *in vitro* studies. Numerous of animal studies have been undertaken and the data suggest that the antimicrobial effects *in vivo* may be mediated by effects on the immune system (De Silva et al., 2013) Clinical studies investigating the influence of mushroom preparations on pathological disorders are very rare. Mushroom extracts and fungal compounds are being investigated in clinical trials by National Institutes of Health in the US; Hospital Clinic of Barcelona and others hospital (Morris et al., 2017). In the future, we expect more numerous clinical trials that will accelerate the commercial production „mushroom pharmaceuticals”.

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