Medicinal Mushrooms with Antiallergic Activities

4

Simon Merdivan and Ulrike Lindequist

Abstract

Allergies are an increasing problem worldwide, and new strategies for prophylaxis and therapy are urgently needed. Medicinal mushrooms present such an opportunity. Antiallergic activities have been found for *Agaricus subrufescens*, *Armillaria ostoyae*, *Flammulina velutipes*, *Ganoderma lucidum* and *G. tsugae*, *Inonotus obliquus*, *Phellinus linteus*, *Pleurotus ostreatus* and *P. pulmonarius*, *Tricholoma populinum*, and some further mushroom species. Nevertheless, most effects have been detected only in vitro and/or in animal assays, and responsible bioactive compounds have not yet been identified. Besides, only a limited number of mushroom species has been investigated for antiallergic activities until now. The chapter gives an overview about mushrooms with antiallergic activities and describes the challenges for the exploration of the antiallergic potential of mushrooms.

Keywords

Agaricus subrufescens • Antiallergy • *Armillaria ostoyae* • *Flammulina velutipes* • *Ganoderma lucidum* and *G. tsugae* • Mushrooms • *Inonotus obliquus* • *Phellinus linteus* • *Pleurotus* sp.

Contents

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Abbreviations

ACE	Angiotensin-converting enzyme
cAMP	Cyclic adenosine monophosphate
CD	Cluster of differentiation
ConA	Concanavalin A
DNP	Dinitrophenyl
ED_{50}	Median effective dose
ERK	Extracellular-signal regulated kinase
FIP-*fve*	Fungal immunomodulatory protein *fve*
i.p.	Intraperitoneal
IC_{50}	Half maximal inhibitory concentration
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
JNK	C-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
OVA	Ovalbumin
p.e.	Parenteral
p.o.	Per os (oral administration)
p38	Protein 38
PMA	Phorbol-12-myristate-13-acetate
RPMC	Rat peritoneal mast cells
RRTI	Recurrent respiratory tract infections SLIGRL-NH_2 Agonist peptide derived from the *N*-terminus of protease-activated receptor 2
Syk	Spleen tyrosine kinase
Th1/2 cells	T helper cell subpopulations
TNFα	Tumor necrosis factor α

4.1 Introduction

4.1.1 Importance of Medicinal Mushrooms

The medicinal use of so-called "medicinal" mushrooms has a very long tradition, especially in East Asian countries. Since some decades, their use is strongly increasing also in the Western hemisphere, and numerous scientific studies confirm the pharmacological potential of mushrooms. Some species, e.g., *Lentinula edodes* (Berk.) Pegler, *Ganoderma lucidum* (W.Curt.:Fr.) P. Karst, and *Trametes versicolor* (L.:Fr.) Pilát are well-known for their immunostimulating properties and applied, e.g. in the complementary tumor therapy. These activities are mostly attributed to ß-glucans, heteropolysaccharides, or complexes of polysaccharides and proteins (Lindequist et al. 2005; Wasser 2014; Guthmann 2017). In opposite, immunosuppressive and antiallergic activities are less well documented. Nevertheless, the example of fingolimod underlines that mushrooms are able to produce compounds with immunosuppressive activities. Fingolimod is a chemical modification of myriocin from the ascomycete *Isaria sinclairii* (Berk.) Lloyd and was the first registered drug for p.o. treatment of multiple sclerosis, an autoimmune disease.

4.1.2 Allergic Reactions

Allergic reactions are hypersensitive and harmful reactions of the human immune system to normally harmless antigens, also called allergens. The situation, which arises as the result of such a reaction, is called allergy (Ferenčík et al. 2006). Allergies can be subdivided into type I–VI. Type I allergy, the most frequent type of a pathogenic immune reaction, is caused by IgE-mediated reactions, which result in the release of vasoactive substances, e.g. histamine from mast cells. The necessary stimulus is the bridging of two allergen-specific IgE molecules on the surface of mast cells or basophils. Allergic rhinitis, allergic bronchial asthma, urticaria, angioedema, and anaphylaxis are all type I allergic reactions. Type II allergic reactions are caused by cytotoxic antibodies against surface molecules of cells. The production of such antibodies can be a consequence of the reaction of a hapten, e.g. a drug to structures on the surface of blood cells, resulting in agranulocytosis or thrombocytopenia. Type III allergic reactions are mainly induced by immune complexes, which activate the complement system or neutrophils and platelets. Type IV allergies are produced by lymphocytes, which react against certain structures. This mechanism is a cause of atopic eczema and drug-induced exanthema. Type V reactions are the reason of granuloma development, e.g. after the injection of xenografts. Type VI reactions can be found in the case of autoimmune diseases such as thyreoiditis or myasthenia gravis, where antibodies exhibit stimulating or inhibiting activity. From the aforementioned classification, type I and IV allergies have the greatest practical importance (Ring 2005).

The pharmacological treatment of allergy consists mainly of administration of immunosuppressants, antiphlogistic, and/or antiallergic drugs. Immunosuppressive agents are effective primarily in the case of type II, III, and IV allergies. Antiphlogistic drugs, e.g. glucocorticoids, can be used in all types of allergy. Antiallergic drugs are degranulation inhibitors (e.g. cromoglicin, nedocromil), anti-IgE antibody omalizumab, and H1-antihistaminic substances like azelastine and loratadine (Freissmuth et al. 2012).

The best option besides avoiding the allergen is a hyposensibilization with specific allergens. It leads to a 50% drop in symptoms and blocks the progression of allergic reactions to other antigens or the switch from allergic rhinitis to allergic bronchial asthma (Ledford 2007).

At this time, some plant preparations for the treatment of allergic rhinitis exist. These are mainly extracts from *Petasites* sp. or *Astragalus membranaceus* (Fisch.) Bunge declared as dietary supplements. For the so-called Ze 339 extract from *Petasites hybridus* (L.) G. Gaertn. et al. inhibition of allergen-induced cell response, airway inflammation, and airway hyperreactivity in mice could be observed (Brattström et al. 2010). In a randomized, double-blind, placebo-controlled crossover study with 18 subjects, it was shown that extract Ze 339 relieves nasal obstruction as a consequence of allergic rhinitis more effectively than desloratadine. The extract consists mainly of sesquiterpene metabolites (Dumitru et al. 2011).

The ISAAC Phase Three studies detected an increase in the prevalence of asthma, allergic rhinoconjunctivitis, and eczema (Asher et al. 2006). As pathogenic immune reactions are on the rise, so will be the cost for the treatment of symptoms. Novel efficient treatment options are highly needed. In this field, mushroom could play at least a supporting role, as some species seem to possess antiallergic activities.

The chapter presents an overview about mushrooms with in vitro and/or in vivo detected antiallergic activities. Immunosuppressive properties which result from cytostatic and other effects which are not directly related to allergies are not in the focus of this review.

4.2 Medicinal Mushrooms with Antiallergic Activities

4.2.1 *Agaricus subrufescens*

The edible mushroom *Agaricus subrufescens* Peck (Agaricaceae), also known as almond mushroom, is distributed in North and South America and well investigated for its health-promoting properties. Today, it is worldwide cultivated and used as a medicinal food to prevent and to treat many diseases, e.g. cancer and diabetes (Guthmann 2016). It is also named *A. brasiliensis* Wasser et al. or *A. blazei* Murrill. For an explanation of discrepancies regarding its nomenclature, see Wisitrassameewong et al. (2012). The bioactive compounds are mainly polysaccharides (ß-glucans) with immunomodulating activities. Antiallergic effects have been found in vitro and in animal assays.

A chloroform-soluble extract inhibited the degranulation of mouse bone marrow-derived mast cells as shown by the decreased release of ß-hexosaminidase. Besides it reduced the production of IL-6, prostaglandin D(2), and leukotriene C(4) in PMA plus A23187-induced cells (Song et al. 2012).

The influence of a water extract (0.01, 0.1 or 1 g/kg body weight, p.o.) was investigated on mast cell-mediated anaphylaxis-like reactions in mice in comparison to the influence of the reference compound dinatrium cromoglycate. The extract inhibited compound 48/80-induced systemic anaphylaxis-like reaction, ear-swelling response, and passive cutaneous anaphylaxis-like reaction. Moreover, the extract dose dependently reduced compound 48/80-induced or anti-dinitrophenyl IgE-mediated histamine release from rat peritoneal mast cells (Choi et al. 2006a). Asthma-induced mice treatment with a hot water *Agaricus* extract (350 mg/mouse/day, p.o.; day 0 till day 17 after primary immunization with ovalbumin [OVA]) caused significant downregulation of OVA-specific antibody responses of IgG1 and IgE but not of IgG2a and significantly decreased total cell numbers, levels of IL-5, and eosinophil numbers in bronchial alveolar lavage fluids. The results suggest that the extract ameliorates the Th1/Th2 balance from the skewed Th2 conditions. It was assumed that ß-glucans are not the responsible compounds in the extract (Takimoto et al. 2008).

AndoSan™ is a mushroom extract, mainly containing *A. blazei* (82%), but also *Hericium erinaceus* (Bull.:Fr.) Pers. (15%) and *Grifola frondosa* (Dicks.:Fr.) Gray (3%). It was given p.o. either a day before or 19 days after the immunization of mice with OVA (s.c.). The mice were sacrificed on day 26. It was found that the extract both, when given before or after immunization, reduced the levels of anti-OVA IgE (Ellertsen and Hetland 2009). An *Agaricus* extract alone, p.o., had similar effects on the serum IgE levels after OVA sensitization in mice. Besides, IL-4 and IL-5 production in OVA-restimulated splenocytes were significantly decreased (Bouike et al. 2011). The effects were mediated through the activation of macrophages by epithelial cells, the promotion of naïve T cells into Th1 cells (Bouike et al. 2011), and the amelioration of a skewed Th1/Th2 balance (Hetland et al. 2011).

4.2.2 *Armillaria ostoyae*

Armillaria ostoyae (Romagn.) Herink is a basidiomycete from the family Physalacriaceae (Fig. 4.1a, b). It was first described in 1900 as *A. solidipes* from Peck and later renamed *A. ostoyae* (Peck 1900; Romagnesi 1970). It is an edible mushroom when preprocessed by cooking. *A. ostoyae* is a saprotrophic-parasitic fungus; it infects various trees, in North America especially Douglas firs (*Pseudotsuga menziesii*). The biggest and heaviest organism on earth is an exemplary of *A. ostoyae* in Oregon, USA (Schmitt and Tatum 2008). *A. ostoyae* can produce bioluminescence (Rishbeth 1986). Different metabolites have been isolated from this mushroom, belonging to the class of meroterpenes, in which a sesquiterpene part is connected to a polyketide part. These metabolites are mainly called

Fig. 4.1 (**a**, **b**) Fruiting bodies of *Armillaria ostoyae*

melleolides and exhibit antibacterial and antifungal effects (Midland et al. 1982; Donnelly et al. 1985; Momose et al. 2000; Bohnert et al. 2011; Bohnert et al. 2014; Chen et al. 2015).

Crude extracts from *A. ostoyae* fruiting bodies and mycelia obtained by soxhlet extraction using dichloromethane inhibited the degranulation of RBL-2H3 cells. The mycelial extract showed higher potency (IC_{50} 21.5 μg/mL), whereas the fruiting body extract had an IC_{50} value of 115.1 μg/mL. Isolated substances melleolide H (IC_{50} value 99.9 μM) and J (IC_{50} value 39.5 μM) also showed this activity (Merdivan 2016; Merdivan et al. 2017a).

4.2.3 *Bulgaria inquinans*

Bulgaria inquinans (Pers.:Fr.) Fr. (Phacidiaceae), poor man's licorice, is an ascomycete growing on branches and bark of dead *Carpinus*, *Castanea*, *Fagus*, *Quercus*, and other trees. It is distributed worldwide. An ethanol extract, p.o., 300 and 600 mg/kg, dose dependently inhibited histamine release from mast cells induced by histamine and scratching behavior of mice induced by compound 48/80 and serotonin. It did not inhibit scratching behavior induced by histamine (Jiang et al. 2005).

4.2.4 *Cordyceps militaris*

Cordyceps militaris (L.:Fr.) Link (Cordycipitaceae) grows as a parasite on *Lepidoptera*. Similar to the famous *Ophiocordyceps sinensis*, it is used as a traditional medicine for treating several diseases including allergy in East Asia (Das et al. 2010). An ethyl acetate extract of the fungi, grown on germinated soybean, inhibited antigen-induced degranulation of mast cells (RBL-2H3) with an IC_{50} value of 28.5 μg/mL and the release of IL-4 and TNFα from these cells. In mice, antigen-induced passive cutaneous anaphylaxis response was inhibited with an ED_{50} value of 665 mg/kg. On a molecular level, the inhibition of the phosphorylation of Syk,

ERK, p38, and JNK expression was shown. Isoflavonoids like genistein and daidzein and their glycosides and adenosine should be responsible for the inhibition of degranulation. Cordycepin as a typical compound from *C. militaris* did not exhibit degranulation inhibitory activity (Oh et al. 2011). It can be assumed that the observed activities are at least partly caused by compounds which originate from the soybean substrate.

4.2.5 *Flammulina velutipes*

The edible mushroom *Flammulina velutipes* (Curtis) Singer (Physalacriaceae) grows on the stumps of different trees and may be found from September to March in temperate regions. It can be cultivated and is widely used in East Asian cuisine (Japanese name: *Enoki*). An ethanol extract of the mushroom (250 mg/kg body weight/day, p.o.) showed significant antiallergic effects in an oxazolone-induced type IV allergy model in male mice. The extract was given 3 days before challenge with oxazolone (5 days after sensitization). Application of the extract 3 days before the sensitization and hot water extract had no effect (Sano et al. 2002). In a mouse allergy model, antiallergic effects could be detected for the protein FIP-*fve* (114 amino acids, 13 kDa) which has been isolated from the fruit bodies of the mushrooms. BALB7c mice were immunized twice i.p. with OVA in an interval of 2 weeks. Before and during each period of immunization, mice were treated with FIP-*fve* (200 µg/mouse, p.o., total five doses). Mice receiving FIP-*fve* during sensitization had a decreased OVA-specific IgE response with a Th1-predominant cytokine profile. These mice were protected from systemic anaphylaxis-like symptoms induced by subsequent oral challenge with OVA. It could be shown that FIP-*fve* induced a Th1-predominant allergen-specific immune response. Surprisingly the protein retains its activity after p.o. administration (Hsieh et al. 2003).

4.2.6 *Ganoderma lucidum* and *Ganoderma tsugae*

Mushrooms of the genus *Ganoderma* (Ganodermataceae, Polyporales) belong to the most important medicinal mushroom species worldwide. The most famous species *G. lucidum* is probably a complex of different species (Zhou et al. 2015) and also known as *Reishi* or *Ling Zhi*. It has been used for medical purposes in China since ancient time. The annual world production of *Ganoderma*-derived products is about 2.5 billion USD (Bishop et al. 2015). *G. lucidum* grows in decaying logs or tree stumps and can effectively be cultivated. *G. tsugae*, the hemlock reishi mushroom, is closely related to *G. lucidum*. Both species are distributed worldwide.

The mushrooms exhibit a broad spectrum of biological activities including antitumor, antiviral, antidiabetic, anti-inflammatory, and antiallergic activities. The beneficial health properties are mainly attributed to polysaccharides and triterpenes, e.g. ganoderic acids (Paterson 2006; Bishop et al. 2015; Guthmann 2016). One investigation found that ganoderic acids C and D (concentration 0.4 and 2 mg/ml),

isolated from *G. lucidum*, inhibited histamine release from rat mast cells that was induced by compound 48/80 and concanavalin A (ConA) (Kohda et al. 1985). The chloroform extract from the culture medium had similar effects. Oleic acid (Tasaka et al. 1988a) and cyclooctasulfur (Tasaka et al. 1988b) have been identified as effective compounds in the medium extract.

A methanol extract of *G. lucidum* (100 and 300 mg/kg p.o., rich in triterpenes) inhibited scratching, an itch-related response, induced by intradermal injections of an extract of salivary gland of the mosquito as pruritogen in mice (Andoh et al. 2010). The extract (10–1000 mg/kg) inhibited dose dependently also scratching induced by 5-hydroxytryptamine, α-methyl-5-hydroxytryptamine, and proteinase-activated receptor-2-activating peptide SLIGRL-NH_2 but not those induced by histamine, substance P, and compound 48/80 (Zhang et al. 2010). The results suggest that the extract relieved allergic itch through peripheral action and that mast cells and H_1 histamine receptors are not the primary sites of the antipruritic action of the extract (Andoh et al. 2010).

G. tsugae supplementation alleviated bronchoalveolar inflammation in an airway sensitization and challenge model with female BALB/c mice. In this allergic model, mice were weekly sensitized by i.p. injection of OVA three times and challenged with aerosolized OVA twice. *G. tsugae*, given p.o. as a supplement to feed (2.0–6.6 g/kg feed) for 5 weeks, significantly decreased infiltration of inflammatory cells and the secretion of inflammatory mediators into the local tissues of lungs and airways (Lin et al. 2006). A triterpene-rich methanol extract (1, 2, or 5 mg/day for 2 weeks p.o.) led to comparable results so that the effects can be attributed to triterpenes (Chen and Lin 2006).

ASHMI® is a traditional Chinese medicine containing *Ganoderma lucidum* as one component (besides *Sophora japonica* and *Glycyrrhiza uralensis*). In a preliminary study with 91 subjects with moderate to severe persistent asthma, the preparation improved lung function and reduced symptom scores (Wen et al. 2005). A phase I study confirmed safety and tolerability of the preparation in patients with asthma (Kelly-Pieper et al. 2009). A review of anti-inflammatory and antiallergic activities of *G. lucidum* is given by Bhardwaj et al. (Bhardwaj et al. 2014).

4.2.7 *Hypsizigus marmoreus*

Hypsizygus marmoreus (Peck) H.E. Bigelow (Tricholomataceae), beech mushroom, lives as a saprophyte on *Fagus* and other trees. The edible mushrooms are cultivated for culinary purposes especially in Japan and Korea. Besides bioactive polysaccharides and proteins, they contain interesting isoprenoids, the hypsiziprenols (Guthmann 2016). The p.o. application of an ethanol extract of *H. marmoreus* for 3 days at a dose of 250 mg/kg b.w. exhibited antiallergic effects on an oxazolone-induced type IV allergy in male ICR mice, characterized by a severe ear edema, changes in different cytokine levels, and diminished serum antioxidative activity. The mushroom extract prevented the increase of serum IL-12 and the decrease in the serum level of IL-2, spleen natural killer cell activity, and serum

antioxidant activity. The effects result from inhibitory actions on antigen-presenting cells like macrophages, inhibition of production and/or release of IL-12, and suppression of oxidative stress (Sano et al. 2002; Yoshino et al. 2008).

4.2.8 *Inonotus obliquus*

Inonotus obliquus (Fr.) Pil. (Polyporaceae), the Chaga mushroom, is the sterile stage of a wood-destroying fungus parasitizing on trunks mostly of birch. It has been used in the traditional medicine of Eastern Europe for the treatment of cancer, digestive system diseases, and other illnesses. In Russia, medicinal preparations are commercially available. Triterpenes, polysaccharides, and polyphenolic pigments are the main bioactive compounds (Shashkina et al. 2006).

A hot water extract of Chaga mushrooms inhibited the systemic anaphylactic shock induced by compound 48/80 in mice. The extract was applicated i.p. 30 min before administration of compound 48/80. Whereas 100% of the animals in the control group (only compound 48/80) died, all mice treated with 2.5 mg extract/mouse survived. Besides, the extract given p.e. or p.o. significantly reduced the total IgE levels in the animals sensitized by OVA and slightly affected the production of IgG1. Spleen cells harvested from the OVA-sensitized mice that had received the extract p.o. showed a significant increase in Th1-derived responses, e.g. the production of IFN-γ (Yoon et al. 2013). In another investigation 50, 100, or 200 mg/kg of a hot water extract were given p.o. to OVA-sensitized BALB/c mice. When the extract was administered after the second immunization with OVA, it significantly suppressed the OVA-induced increase in serum IgE and IgG(2a). In ex vivo studies, spleen cells were isolated from mice sensitized with OVA and treated with 100 mg/kg of the extract. Compared to the controls, ConA stimulation resulted in lower IL-4 production and increased IFN-γ production. Moreover, IL-4, IFN-γ, and IL-2 were significantly reduced after ConA stimulation in isolated CD4(+) T cells (Ko et al. 2011). Injection of an ethanol extract (high and low dose) into asthmatic mice (asthma was caused by injection and inhalation of OVA) resulted in a significant alleviation of histopathological damages. It was concluded that the extract inhibited the expression of phosphor-p38 MAPK and corrected the imbalance of IFN-γ/IL-4 and the number of inflammatory cells (Yan et al. 2011).

4.2.9 *Phellinus linteus*

Phellinus linteus (Berk.:M.A.Curtis) Teng (Hymenochaetaceae) occurs in tropical and subtropical regions and lives as a saprophyte on *Cassia*, *Quercus*, and other trees. The mushrooms are known to have a broad spectrum of biological activities and have been used as traditional medicine in oriental countries for a long time (Silva 2010; Guthmann 2016). Oral application of a water extract from the fruiting bodies inhibited the compound 48/80-induced systemic anaphylaxis reaction and ear-swelling response in mice. Besides, the anti-dinitrophenyl (anti-DNP)

IgE-mediated passive systemic and cutaneous anaphylaxis reaction was inhibited. In vitro, the extract dose dependently reduced histamine release from rat peritoneal mast cells (RPMC) activated by compound 48/80 or anti-DNP IgE, decreased the compound 48/80-induced calcium uptake into RPMCs, increased the level of intracellular cyclic adenosine monophosphate (cAMP), and inhibited the compound 48/80-induced cAMP reduction in RPMC. It was suggested that the extract might serve as an effective therapeutic agent for allergic diseases (Choi et al. 2006b). Besides, extracts prepared from the mycelium of the mushrooms have been tested for inhibiting activities on the IgE-dependent mouse triphasic cutaneous reaction. The triphasic reaction was induced in the ear of BALB/c mice passively sensitized with anti-DNP IgE by painting with DNP 24 h later. Ear swelling appeared triphasically with peak responses at 1 h, 24 h, and 8 days after the challenge. Methanol- and water-soluble fractions given p.o. at a dose of 100 mg/kg inhibited the first and second phase of ear swelling. The most potent fraction was the boiling water-soluble fraction. It inhibited dose dependently (30–300 mg/kg) all phases, inhibited vascular permeability increase caused by passive cutaneous anaphylaxis and histamine, and ear swelling caused by TNFα (Inagaki et al. 2005).

4.2.10 *Pleurotus ostreatus*, *Pleurotus pulmonarius*, and *Pleurotus eryngii*

The oyster mushroom – *Pleurotus ostreatus* (Jacq.:Fr.) P. Kumm – is an edible basidiomycete from the Pleurotaceae family. It is a saprophytic and parasitic fungus, mainly thriving on deciduous trees and widely cultivated for culinary purposes. In nature, fruiting bodies occur late in the year, which makes *P. ostreatus* a winter mushroom.

The oyster mushroom was subjected to different clinical trials regarding its antiallergic and antiasthmatic properties. One randomized, placebo-controlled, double-blind clinical trial was investigating the effect of *P. ostreatus* on recurrent respiratory tract infections (RRTI). Atopic persons tend to have a higher risk of such infections in comparison to healthy subjects. The application of a commercially available syrup P4H® p.o. over a period of 6 months resulted in a stable serum IgE titer in the verum group, whereas in the placebo group, the amount of IgE in serum was rising. The blood eosinophil count decreased in the verum group where it remained unchanged under placebo. The effect was stronger in atopic than in nonatopic persons. P4H® comprised of pleuran and vitamin C (concentration 10 mg/mL each), and placebo consisted of 10 mg/mL vitamin C. Pleuran is a branched β-glucan insoluble in alkali (Karácsonyi and Kuniak 1994). One main drawback of this study was the determination of surrogate parameters only. Nevertheless, the results showed a possible response to the administration of *P. ostreatus* in RRTI (Jesenak et al. 2014).

Another study from the same author measured hard clinical endpoints in a multicentric, double-blind, placebo-controlled, and randomized design investigating the effect of pleuran administration on prevention of RRTIs and immunomodulatory activity in children. Verum, placebo, and treatment period were the same as

mentioned in the study above. Treatment with verum led to significantly lower respiratory morbidity, alteration of immunoglobulin composition, and a temporal decrease of $CD8^+$ cytotoxic T cells. This points to a better immune defense against pathogens (Jesenak et al. 2013). Thus, *P. ostreatus* can exhibit an influence on the immune system which increases defense against pathogens and lowers markers for allergy.

Pleurotus pulmonarius (Fr.:Fr.) Quél, the Indian Oyster or Lung Oyster (Japanese: *Usuhiratake*) exhibits different beneficial activities. Proteins from the water extract inhibit the angiotensin-converting enzyme (ACE) with an IC_{50} of 12 μg/mL (Ibadallah et al. 2015). A protein/polysaccharide complex of *P. pulmonarius* inhibited development and progression of liver cancer (Xu et al. 2012). Further, β-D-glucans from *P. pulmonarius* have an antinociceptive effect (Smiderle et al. 2008a, b; Baggio et al. 2010; Baggio et al. 2012). The antinociceptive effect could also be beneficial for patients, who struggle with inflammation as a result of an allergic reaction.

Polysaccharides of *P. pulmonarius* attenuated and prevented intestinal inflammation symptoms in a mouse model. TNF-α levels decreased in tissue and increased IL-1β attenuation (Lavi et al. 2010). A β-D-glucan from this mushroom exhibited a dose-dependent anti-inflammatory activity in a mouse model measuring leukocyte migration to inflammatory tissue (Smiderle et al. 2008a).

The powder of fruiting bodies of *P. pulmonarius* caused a significant decrease of sneezing and nasal rubbing in BALB/c mice. The effect was observed when the powder was administered in a dose of 500 mg/kg body weight for 2 weeks or at a dose of 200 mg/kg body weight for 4 weeks. The IgE levels did not decrease. The powder did not reduce histamine-induced nasal rubbing and sneezing via an antagonistic effect. In an in vitro model using RBL-2H3 rat basophils, a decrease of compound 48/80 triggered histamine release could be observed. It seems possible that *P. pulmonarius* reduced the symptoms of allergic rhinitis through inhibition of histamine release from immune cells (Yatsuzuka et al. 2007).

An ethanolic extract (250 mg/kg body weight/day) of *Pleurotus eryngii* (DC.) Quél., the king trumpet mushroom, exhibited antiallergic effects on oxazolone-induced type IV allergy in mice, similar to extracts from *Flammulina velutipes* and *Hypsizygus marmoreus* (see above). The extract was applied p.o. 3 days before the challenge with oxazolone (Sano et al. 2002).

4.2.11 *Tricholoma populinum*

Tricholoma populinum Lange is a basidiomycete from the family Tricholomataceae. It is a mushroom building mycorrhizas with different poplar species (Grubisha et al. 2012). Expansion of the mycelium is mainly by vegetative growth, not through sexual reproduction by spores (Gryta et al. 2006). As *T. populinum* is a mycorrhiza fungus, fruiting bodies (Fig. 4.2a, b) are only formed in connection to the symbiotic partner and cannot be cultivated but must be collected by wild harvesting. Nevertheless, it is possible to cultivate the mycelium.

Fig. 4.2 (**a**, **b**) Fruiting bodies of *Tricholoma populinum*

In 1977 mushroom collector Herbert Schäfer published a case report about effects of *T. populinum* against thromboangiitis obliterans, a chronic relapsing inflammatory illness, which affects mainly distal arteries of the extremities. Etiology is mainly unknown but seems to be caused by an allergic-hyperergic effect and based on an autoimmune process. Thromboangiitis obliterans can lead to loss of extremities (Pschyrembel 1998). Mr. Schäfer suffered from severe, tearing pain in the abdominal and pelvic region and felt muscular pain even under light-duty and wound pain, especially in the skin. He was not able to walk longer distances without pain; climbing stairs was nearly impossible. Ca. 1 h after the intake of fruiting bodies of *T. populinum*, he felt a weak, pleasant sensation, which reduced his wound pain and caused subtle tickling. He then investigated the effects of dechallenge and rechallenge. Consuming the fruiting bodies of *T. populinum* for a period of time, a positive effect was observed for a few months after the dechallenge. Thereafter, illness symptoms worsened again. Mr. Schäfer utilized the fruiting bodies of *T. populinum* for two 2-month periods every year. In his report, he has described the positive effect of *T. populinum* consumption on allergic rhinitis by testing on his wife and a complete absence of symptoms was observed (Schäfer 1977).

In the 1980s different studies on the immunosuppressive action of *T. populinum* were conducted, resulting in the isolation of ergosterol peroxide as an active ingredient. Ergosterol peroxide reduced the production of antibodies in the hemolysis-plaque assay and the proliferation of mitogen-stimulated lymphocytes in the lymphocyte transformation assay (Lindequist 1987; Lindequist et al. 1989a, b; Kreisel et al. 1990). The dichloromethane extract from fruiting bodies of *T. populinum* inhibited the degranulation of RBL-2H3 cells and the IL-2 release from Jurkat T cells. The degranulation inhibiting effect could only be observed when fruiting bodies were processed with heat. Extracts from lyophilized fruiting bodies showed no effect (IC_{50} >500 μg/mL), but when lyophilized fruiting bodies were mildly heated for a prolonged period, the extract showed this effect again (IC_{50} 224.2 μg/mL). Extracts from fruiting bodies dried using increased temperature displayed a slightly stronger influence (IC_{50} 161.8 μg/mL) (Merdivan 2016; Merdivan et al. 2017b).

An overview on activities of medicinal mushrooms regarding allergic reactions is presented in Table 4.1.

Table 4.1 Overview on activities of medicinal mushrooms regarding allergic reactions

Mushroom	Active principle	Biological effect in respect to allergy	Reference
Agaricus subrufescens	Chloroform extract, (hot) water extract, AndoSan™	Inhibition of IL-5,6, PGD(2), LTE-C(4) release; anaphylaxis-like reaction; IgG1, IgE production	Choi et al. (2006a), Takimoto et al. (2008), Ellertsen and Hetland (2009), Bouike et al. (2011), Hetland et al. (2011), and Song et al. (2012)
		IL-5↓, total cell number and eosinophil count in mice bronchial alveolar fluid↓	
Armillaria ostoyae	Sesquiterpene aryl esters	Degranulation of RBL-2H3 cells↓	Merdivan (2016) and Merdivan et al. (2017)
Bulgaria inquinans	Ethanol extract	Histamine release from mast cells↓	Jiang et al. (2005)
Cordyceps militaris	Ethyl acetate extract, isoflavonoids (?)	Inhibition of degranulation of RBL-2H3 cells, IL-4 and TNF-α release↓	Das et al. (2010) and Oh et al. (2011)
		Syk, ERK, p38, JNK expression↓	
Flammulina velutipes	Ethanol extract, protein FIP-*fve*	Type IV allergy in mice model↓, IgE response in cells↓	Sano et al. (2002) and Hsieh et al. (2003)
Ganoderma lucidum	Ganoderic acids (triterpenes), chloroform extract, oleic acid, cyclooctasulfur, medium extract, ASHMI®	Histamine release↓; scratching↓; itch-related response↓	Kohda et al. (1985), Tasaka et al. (1988a), Tasaka et al. (1988b), Kelly-Pieper et al. (2009), Andoh et al. (2010), and Zhang et al. (2010)
Ganoderma tsugae	Whole fruiting bodies, triterpene-rich extract	Infiltration of inflammatory cells, secretion of inflammatory mediators into lung and airway tissue in a mouse model↓	Chen and Lin (2006)
Hypsizigus marmoreus	Ethanol extract	Type IV allergy in a mouse model↓, blocking of increase in IL-12 and decrease in IL-2 serum levels, spleen natural killer cell activity, and serum antioxidant activity	Sano et al. (2002) and Yoshino et al. (2008)

(continued)

Table 4.1 (continued)

Mushroom	Active principle	Biological effect in respect to allergy	Reference
Inonotus obliquus	Hot water, ethanol extract	Inhibition of anaphylactic shock in mouse model	Yan et al. (2011), Ko et al. (2011) and Yoon et al. (2013)
		IgE↓, IFN-γ↑, IL-4↓, IL-2↓, histopathological damages↓ in mouse model	
		Increase in IgE and IgG(2a)↓, IL-4 production↓, IFN-γ production↑ in mouse spleen cells ex *vivo*	
		IL-4, IFN-γ, and IL-2↓ in CD4+ cells	
		Histopathological damages in asthmatic mice↓ (possibly phosphor-p38 MAPK expression↓, imbalance correction of IFN-γ/IL-4, number of inflammatory cells↓)	
Phellinus linteus	Water extract, fractions	Degranulation of RPMCs↓, intracellular cAMP↑	Inagaki et al. (2005) and Choi et al. (2006b)
		Systemic anaphylaxis and ear swelling in mice↓, passive systemic and cutaneous anaphylaxis reaction in mice↓	
		Triphasic cutaneous reaction in mice↓	
Pleurotus ostreatus	Pleuran (β-glucan)	IgE in human serum↓, BEC↓, CD8+ cells↓, alteration of immunoglobulin composition	Jesenak et al. (2013, 2014)
Pleurotus pulmonarius	β-Glucans	Antinociceptive effects, TNF-α↓, IL-1β↓, sneezing↓, nasal rubbing↓ in mice, leukocyte migration to inflammatory tissue in a mouse model↓	Yatsuzuka et al. (2007), Smiderle et al. (2008b), Lavi et al. (2010) and Baggio et al. (2010, 2012)
		Histamine release from RBL-2H3 cells↓	
Pleurotus eryngii	Ethanolic extract	Type IV allergy in mouse model↓	Sano et al. (2002)
Tricholoma populinum	Dichloromethane extract, fractions	Degranulation of RBL-2H3 cells↓	Lindequist (1987, 1989a, b), Kreisel et al. (1990), and Merdivan (2016)

4.3 Conclusions

The analysis of described antiallergic activities of mushrooms shows that only a relatively small number of mushroom species has been investigated for such effects. The available results lead to the conclusion that fungi could possess promising antiallergic properties. To explore this potential, it is necessary to verify the results in further test systems, to elucidate the mode of action, to conduct clinical trials, to identify the responsible bioactive compounds, and to ensure safety and quality of resulting products. In the case of success, mushrooms or mushroom-derived compounds can become a prophylactic and/or therapeutic opportunity in diseases like allergic rhinitis, allergic asthma, allergic itch, food allergy, and urticaria.

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