SCIENTIA **FUNG RUM**

Using mushroom-forming fungi in preventing and reducing mycotoxins in cereal products

Uso de macromicetos para prevenir y reducir las micotoxinas en productos de cereales

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RESUMEN

Antecedentes: El control biológico de las enfermedades de los cereales causadas por hongos micotoxigénicos forma parte de los métodos alternativos a desarrollar para asegurar la producción de alimentos y forrajes, debido a los efectos negativos que estos hongos tienen sobre el rendimiento de los cultivos y su producción potencial de micotoxinas.

Objetivo: Actualizar el conocimiento sobre el potencial de los hongos formadores de hongos como agentes de control biológico de especies de hongos micotoxigénicos, actuando como: antagonistas en residuos de cultivos, fuente de extractos activos con propiedades antifúngicas y/o antimicotoxinas y como agentes detoxificantes en procesos de fermentación en estado sólido en cereales contaminados.

Métodos: Se realizó una revisión bibliográfica de los trabajos publicados, analizando los temas principales, así como las especies con mayor potencial como agentes de control biológico de los hongos micotoxingénicos.

Resultados y conclusiones: Los macromicetos se podrían usar como antagonistas en residuos de cultivos o granos, como fuentes de extractos activos con propiedades antifúngicas y/o antimicotoxigénicas y como agentes desintoxicantes. Una integración de estos tres potenciales da lugar a un proceso amigable con el medio ambiente para la producción de granos seguros y hongos comestibles.

Palabras clave: aflatoxinas, *Aspergillus*, cereales, *Fusarium*, hongos, tricotecenos

ABSTRACT

Background: Biological control for cereal diseases caused by mycotoxigenic fungi is part of the alternative methods to be developed to secure food and feed production, recognizing the negative effects these fungi have on crop yield and their potential production of mycotoxins.

Objective: Update recent knowledge about the potential of mushroom-forming fungi as biological control agents of mycotoxigenic fungi species, acting as antagonists on crop debris, as source of active extracts with antifungal and/or antimycotoxin properties and as detoxifying agents in solid-state fermentation processes of contaminated cereals.

Methods: A literature review of the published works was carried out, the main topics were analyzed, as well as the species with the greatest potential of biological control agents of mycotoxingenic fungi.

Results and conclusions: Mushroom forming fungi could be used as antagonists on crop debris or grains, as sources of active extracts with antifungal and/or antimycotoxin properties, and as detoxifying agents. An integration of these three potentials gives rise to an environment friendly process for production of both safe grains and edible mushrooms.

Keywords: aflatoxins, *Aspergillus*, cereals, *Fusarium*, mushrooms, trichothecenes

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INTRODUCTION

World cereal production increases continuously since several years, but there are subsequent losses due to contamination of produced grains by heavy metals, pesticides and mycotoxins rendering crops not suitable as food. Mycotoxins are naturally occurring secondary metabolites, produced by filamentous fungi that are toxic to humans and animals. Consumption of food containing high levels of these contaminants may cause illness. Most of these molecules are difficult to degrade; they resist high temperatures and chemicals. They are gaining worldwide attention because of the significant economic losses associated with their effects on animal and plant productivity, human health, and national and international trade.

Fusarium Head Blight (FHB) of small-grain cereals such as wheat and barley and *Gibberella* Ear Rot (GER) and *Fusarium* Ear Rot (FER) of maize are three devastating fungal diseases affecting crops worldwide. They produce the so-called field mycotoxins, zearalenone (ZEA), trichothecenes (TCTB, among which deoxynivalenol (DON) is the best known, and TCTA), and fumonisins (FB). The mycotoxins accumulate in the grains themselves, even in healthy looking ones with apparent good quality. Depending on the climatic conditions, the occurrence and level of contamination at harvest can be high.

Cereals and maize are also particularly sensitive to mycotoxin accumulation during storage. Storage mycotoxins are produced after harvest, by fungi of the genus *Aspergillus* and *Penicillium* in poor storage and ventilation conditions in silos. The main storage mycotoxins are aflatoxins and ochratoxins. Under certain climatic conditions, *Aspergillus* spp. and aflatoxin contamination begins in the field on maize. With the expected evolution of the climate in Europe, it is likely that field contaminations will develop significantly (Battilani *et al.*, 2016). The aflatoxins are considered to be the most toxic of the mycotoxins, aflatoxins B1, B2, G1 and G2 being the principal aflatoxins of concern. They are produced by *Aspergillus fumigatus* and *A. parasiticus*. Ochratoxins are produced by *A. ochraceus* and related species, *A. niger*, as well as *Penicillium verrucosum* and certain other *Penicillium* species (Rodrigues, 2016).

Minimisation strategies for mycotoxins have included the use of relatively resistant varieties and good pre-harvest agricultural practices. Fungicides are frequently applied to manage the contamination of grains by *Fusarium* spp. or *Aspergillus* spp., but their efficacies are generally lower than 50 % (Haidukowski *et al.*, 2005; Loos *et al.*, 2004). In addition, the effect of fungicides is rarely statistically significant when addressing grain contamination by mycotoxins. Mycotoxin production is suspected to be part of the adaptive response of the fungus to stressful conditions such as exposure to antifungal compounds (Ponts, 2015; Martins *et al.*, 2016), and the accumulation is modulated by complex interactions between different fungal species (Scarpino *et al.*, 2015). This explains observations such as increasing mycotoxin levels in rice grain treated with tebuconazole in field conditions (Dors *et al.*, 2013), or the induction of the production of DON by strobilurins during *in vitro* studies (D'Mello *et al.*, 2001).

Another drawback with current fungicides is the development of resistances, including resistance to synthetic fungicides that mimic natural fungicides. Strobilurins are a recent example of synthetic fungicides which application has led to the emergence of resistant fungal strains (Walker *et al.*, 2009). Using successively different molecules with different physiological targets in pathogenic fungi is an accepted strategy for limiting the development of resistances. Unfortunately, the catalogue of available efficient molecules is limited. Compounds that inhibit mycotoxin production without inhibiting fungal growth may be useful for mycotoxin control without incurring a rapid spread of resistant strains. Consequently, new molecules with various activities are needed in the near future. In addition, nowadays, consumers and industry ask for environment friendly solutions to tackle the problems of plant pathology and food safety due to mycotoxins. In this context, searching for natural compounds to control fungal pathogens of plants and their production of mycotoxins is a challenge shared by research institutes and actors of agriculture.

Avoiding the primary contamination of plant by minimising the inoculum is another strategy. The most important sources of inoculum are ascospores, from the sexual stage, and macroconidia, from the anamorph stage. Chlamydospores and hyphal fragments can also act as sources of inoculum (Leplat *et al.*, 2013). They mainly originate from crop debris remaining on soil after harvest of previous diseased crop. Toxigenic *Fusarium* or *Aspergillus* species can survive and multiply on maize stubble or small grain cereal straw and soil for

several years. Crop rotation, crop residue management and biological control by treating the debris with antagonists are levers to minimize this inoculum (Sarrocco and Vannacci, 2018). Biocontrol agents acting as an antagonist, a mycoparasite and a competitor for natural substrates have been proposed (Xue *et al.*, 2014; Palazzini *et al.*, 2017). Microbial decomposition of crop residues is a natural process, which can be supported by adding stimulating nutrients or selected microorganisms for starving the niche of the inoculum.

Biological postharvest treatments for mycotoxin removal might represent a promising strategy to decrease mycotoxin content in contaminated grains (McCormick, 2013). Most of the microorganisms able to modify or metabolise field and storage mycotoxins are bacteria or yeasts (Martínez Tuppia *et al.*, 2017; Wilson *et al.*, 2017; Zhu *et al.*, 2017; Peng *et al.*, 2018), but filamentous fungi can also detoxify ochratoxins (Chen *et al.*, 2018) or aflatoxins (Scarpari *et al.*, 2014).

A mushroom forming fungus is defined as a macrofungus with a distinctive fruiting body that is large enough to be seen with the naked eye and to be picked up by hand, and can be either a Basidiomycete or an Ascomycete, aerial or underground (Chang and Miles, 1992). They generally colonize complex substrates for long times or form mycorrhizas. Among the abundant biodiversity of mushroom forming fungi, over 2,300 wild useful species have been identified, and more than 40 species are currently cultivated for producing food (Savoie *et al.*, 2013). Most of the cultivated species are white rot fungi degrading lignocellulose organic matter. As white rot fungus, many mushroom forming fungi might have ability to compete effectively for the available nutrients in the ecological niche of crop debris on soil, and in this way colonise it and exclude the pathogen. It seems very likely that mushroom forming fungi do contain compounds with important biological properties due to the deep history of interactions between fruit bodies and potentially fungivorous animals or fungal pathogens (Largeteau and Savoie, 2010; Money, 2016). The vegetative mycelia need also antibacterial and antifungal compounds to survive in their natural environments.

We propose here a survey of potential of mushroom forming fungi as biological control agents of mycotoxigenic fungi, acting: (i) as antagonists on crop debris for reducing primary inoculum of mycotoxigenic fungi in fields, (ii) as source of active extracts with antifungal and/or antimycotoxin properties that could be used for controlling the accumulation of mycotoxin during the cultivation period and at storage of grains, (iii) as detoxifying agents in solid-state fermentation processes of contaminated cereals. The objectives are to highlight the opportunities to use mushroom forming fungi to prevent and reduce mycotoxins in cereal products, and to point the remaining challenges to be faced for the development of an integrated mycotoxin management in cereals using mushroom properties.

COMPETITION ON CROP DEBRIS

Infected crop debris staying on or in soils between two crops are the main inoculum source of *Fusarium* spp. Chlamydospores containing macroconidies allow *Fusarium* species to survive unfavourable conditions and thus to overwinter in soil or on crop residues until suitable temperature and humidity facilitate a new cycle of infections. In the sexual cycle of *F. graminearum*, perithecia on the crop residues are abundant in spring, as warm moist weather conditions are favourable for their maturation, and they release ascospores (Shah *et al.*, 2018). Treatment of crop debris to reduce *Fusarium* primary inoculum in fields is one of the biocontrol strategy that is subject of work. Microorganisms accelerating residue degradation and/or being antagonistic against *F. graminearum* can be used (Legrand *et al.*, 2017). As an example, the endophytic fungus *Clonostachys rosea* (formerly known as *Gliocladium roseum*) is a soil-borne ascomycete that exhibits suppressing ability of *F. graminearum* perithecial production when applied on crop residues (Xue *et al.*, 2014). Several saprophytic fungi with good ability to colonise wheat straws or maize stalks and to suppress sporulation of pathogenic *Fusarium* spp. had been selected for their potential as biocontrol agents. Their efficiency for reducing colonisation of stalk pieces by pathogenic *Fusarium* spp. were sometimes significant, but not consistent (Luongo *et al.*, 2005). For being efficient, an antagonist has to be present in sufficient quantity at the right time and place and to use nutrients more efficiently than the pathogen in case of exploitation competition (Legrand *et al.*, 2017).

White-rot fungi are basidiomycetes that are capable of degrading the lignin component of lignocellulose substrates in addition to cellulose and hemicelluloses and are suitable for the colonization and degradation

of wood and forest litters. They play an important role in the cycling of carbon and other elements. Most of the edible mushrooms that are cultivated on agricultural by-products (straw, stalk, wood ships, etc.) are white rot fungi. We postulate here that white rot fungi inoculated on crop debris would exploit them efficiently and deprive *Fusarium* species of nutrients in this niche. The first challenge to be addressed is the inoculation of crop debris on soils (Legrand *et al.*, 2017). The use of cultivated mushroom species has benefits. Due to the life cycle of mushroom forming fungi, spores have to be collected from fruiting bodies, which could be fastidious to obtain. In edible mushroom cultivation, primary mycelium can be obtained from germination of spores, from a piece of a specific fruiting body, or from several germplasm providers. For producing inoculum that is usually called the spawn, the primary mycelium is developed on sterilized cereal grain (wheat, rye, millet or sorghum) (Sanchez, 2004). The mycelium-coated grains are then mixed with various lignocellulosic wastes at rates varying from 0.8 to 8 % depending on the species and conditions, and the mycelium can rapidly colonize the substrate from a grain that is a protecting and nutritive habitat. Adding several lignocellulosic materials in the spawn improved the competitiveness of the mycelium by increasing the number of inoculation points and inducing enzymatic complexes for breaking down lignocelluloses (Mata *et al.*, 1998). Mixing this spawn with crop debris on the soils could be a way to introduce the antagonist of *Fusarium* spp. Spawn making companies already exist in various countries and would rapidly be able to produce inoculum for the treatment of crop debris in fields if this treatment is adopted.

The outcome of the competition between white rot mushroom and *Fusarium* species will depend on the composition of the plant debris, the climatic conditions (temperature, water availability, relative concentrations of O_2 and CO_2) and the interaction with other microorganisms present on the debris. Changes in these factors can reverse interaction outcomes because different species display contrasting sensitivities and/or patterns of response to these variables (Hiscox *et al*. 2018). Generally, a_w has a greater influence on fungal growth than temperature but a_w and temperature interact. Regarding water availability (a_w) and temperature, there is some information available for both mycotoxinogenic fungi and white rot mushrooms

For *Fusarium graminearum*, maximum growth rates were obtained at the highest a_w and 25 °C and no or very slight growth was observed at 5 °C, regardless of a_w levels assayed (Ramirez *et al.*, 2006). The minimum a_w for growth was estimated to be 0.869 and 0.854 for *F. verticillioides* and *F. proliferatum*, respectively (Samapundo *et al.*, 2005), but at 15 °C no growth of *F. verticillioides* occurred at a_w lower than 0.95 (or matric water potential -7.0 MPa) (Jurado *et al.*, 2008). Matric potential refers directly to forces required to remove water bound to the matrix (soil or plant debris). From the work of Marin *et al.* (1995) we extrapolate that at high a_w (>0.98), growth at 15 °C represented 45 % and 55 % of growth at 25 °C for *F. moniliforme* and *F. proliferatum* respectively, since growth at 4 °C represented 16 % and 28 % of growth at 15 °C for *F. moniliforme* and *F. proliferatum* respectively. For three *Aspergillus flavus* strains, the minimum a_w needed for mycelial growth was 0.91 at 25 and 37 °C. At 15 °C, only one isolate grew, and it was at 0.99 a_w (Lahouar *et al.*, 2016). For white rot mushrooms, linear growth rate of three species of *Pleurotus* (oyster mushroom) at 15 °C was measured to be 36 to 64 % that at 25°C. It was 62 % for *Lentinula edodes*, shiitake (Zervakis *et al.*, 2001). This highlights that mushroom forming fungi withstand better low temperatures than the mycotoxigenic fungi. Mushroom species have large geographic ranges, and adaptation of geographical populations and/or varieties of the species to different climates and habitats could be expected. As an example, *Agaricus bisporus* (button mushroom) is known to extend from the boreal region of Alaska to the equatorial climate of Congo and from coastal dunes to mountains of above 3000 m elevation (Largeteau *et al.*, 2011). We postulate that it will be easy to select mushroom species and strains that are competitive for the colonisation of crop debris at temperatures below 15 °C, when mycotoxigenic fungi are inactive.

Basidiomycetes are known to be more sensitive to changes in water potential than ascomycetes. The optimum growth of various wood decay basidiomycetes, including *Pleurotus ostreatus* was measured between 0.999 and 0.990 a_w (water potential -0.1 to -1.4 MPa) and growth ceased between -0.97 and 0.95 a_w (Magan *et al.*, 1995). For *Agaricus bisporus* and *A. bitorquis*, -3 MPa (0.985 a_w) was found to stop growth, and growth decreased below -1.0 MPa (0.990 a_w). In mushroom cultivation substrates based mainly of cereal straw, this

favourable water potential is obtained with moisture contents in the range 60-80 % (Philippoussis and Diamantopoulou, 2011). Compared to mycotoxigenic fungi, mushroom forming fungi are less tolerant to water stress due to low water potential and would be less competitive on plant debris under dry conditions.

Finally, the strength of white rot mushrooms for colonizing the crop debris in intercrops and exclude mycotoxigenic fungi is the strong capacity to breakdown the lignocellulosic material and their better adaptation to low temperature, but their weakness is their need of higher values of water availability for expressing their potential of colonisation. The feasibility of the proposed treatment of crop debris to reduce primary inoculum of mycotoxigenic fungi in fields, have to be experimented in microcosms and in fields. The efficiency of a large diversity of mushroom species either inoculated after harvest or introduced at the following spring could be tested.

ANTIFUNGAL COMPOUNDS FROM MUSHROOM FORMING FUNGI ACTIVE AGAINST MYCOTOXIGENIC FUNGI IN CEREALS

In addition to exploitation competition through resource depletion and physical exclusion, mushroom-forming fungi may act by interference competition through antibiosis, which might reinforce their ability to reduce the inoculum reservoir. In a review of the literature from 1999 to 2012 on antifungal activity of mushroom extracts and isolated compounds, the authors found that 52 species had been reported for their antifungal properties (Alves *et al.*, 2013). More than 80 % are edible mushrooms, since their extracts might be generally be recognized as safe for use. As an example, ethanolic extracts of *Hydnum repandum*, a mycorrhizal species commonly known as the sweet tooth or hedgehog mushroom and broadly distributed in Europe and Asia, had strong antifungal effects on various *Fusarium* species (Spremo *et al.*, 2017).

Most studies on mushrooms with antifungal activity were on crude or partially simplified extracts without identification of the compounds responsible for this property (Alves *et al.*, 2013). Bioactive substances isolated from higher fungi belong to different chemical groups: (i) secondary metabolites (acids, terpenoids, polyphenols, sesquiterpenes, alkaloids, lactones, sterols, metal chelating agents, nucleotide analogues and

vitamins) ii) proteins and glycoproteins; and (iii) high molecular mass polysaccharides (Erjavec *et al.*, 2012). Some specific mushroom β-glucans are already used in clinical treatment for their antitumor and immunomodulatory properties, and are known as elicitors of plant defence response (Ryan, 1987), but they have no direct antifungal activity. Recently volatile compounds from edible mushrooms have been proposed as safe agents for controlling fungal diseases (Oka *et al.*, 2015). Most investigations with mushroom metabolites have been on antagonistic effect to human pathogens for the therapeutics of human disorders, and less on the plant disease control (Chen and Huang, 2009).

Bioactive proteins from mushroom forming fungi with activity against mycotoxigenic species

A dozen of bioactive proteins and protein extracts from mushrooms have been selected for their antifungal activity on several species (Erjavec *et al.*, 2012). In a recent overview of the biocontrol properties of Basidiomycetes, Sivanandhan *et al.* (2017) inventoried 15 known antifungal active compounds, half were antifungal proteins. As an example of fungal proteins that have been tested in the field of agricultural crop protection, Tamavidins are biotin-binding proteins from the oyster mushroom *Pleurotus cornucopiae* that can be expressed in transgenic rice and, as such, they provide resistance to the important rice-pathogenic fungus *Magnaporthe oryzae* (Takakura *et al.*, 2012). Homologous to genes coding for Tamavidins were found also in *Galerina marginata* (poisonous), *Hypholoma sublateritium* (edible, cultivable) (Bleuler-Martinez *et al.*, 2012). However, humans and animals require biotin to be supplied in the diet and biotin deficiency that may result to an exposure to biotin-binding proteins can lead to developmental delays in children, or hair and skin abnormalities in affected individuals (Dakshinamurti *et al.*, 2017).

To our knowledge, antifungal proteins from cultivable edible mushrooms have not been tested for their activity against mycotoxigenic *Fusarium* species. However, since several years, a group at the China Agricultural University works on mushroom proteinaceous compounds with biological activities, including antifungal activity against *F. oxysporum*, a soil born pathogens with a broad host range (Ng *et al.*, 2016) (Table 1). Ganodermin from the medicinal mushroom *Ganoderma lucidum* (Wang and Ng, 2006), Eryngin from

Pleurotus eryngii (Wang and Ng, 2004), Pleurostrin from *Pleurotus ostreatus* (Chu *et al.*, 2005) and Hypsin, from *Hypsizigus marmoreus* (Lam and Ng, 2001a), were shown to inhibit mycelial growth of *F. oxysporum* and other fungal plant pathogens. Hypsin and several other mushroom peptides or proteins having different molecular masses and N-terminal sequences are ribosom inactivators (Lam and Ng, 2001a): Pleuturegin from sclerotia of *Pleurotus tuberingium* (Wang and Ng, 2001), Lyophilin from *Lyophillum shimeji* (Lam and Ng, 2001b), Flammulin and Velutin, from *Flammulina velutipes* (Wang and Ng, 2000; Wong *et al.*, 2010), Agrocybin from *Agrocybe cylindracea* (Ngai *et al.*, 2005), Lentin from *Lentinula edodes* (Ngai and Ng, 2003), and Cordymin from *Cordyceps militaris* (Wong *et al.*, 2011) are other mushroom proteins with antifungal properties that showed no effect on *Fusarium oxysporum* or *Aspergillus fumigatus* when tested, but they could be tested against mycotoxigenic *Fusarium* species and their production of mycotoxins.

Defensins are cysteine-rich antimicrobial peptides that may also have antifungal activity. Defensins are common in vertebrates, but fungi, plants, and many invertebrates produce defensin-like peptides structurally similar to the β-defensins from vertebrates (Silva *et al.*, 2014). Defensins are frequently reported to induce membrane permeabilization of fungal cells (Thevissen *et al.*, 1996), or to induce deposition of chitin on the tips of growing hyphae and consequently retard hyphal growth (Lin *et al.*, 2010). Copsin from the mushroom *Coprinopsis cinerea* is a famous antibacterial defensin (Essig *et al.*, 2014). There is a potential for identifying new defensins with antifungal and anti mycotoxin properties in mushroom forming fungi.

Lectins form one major group of glycan binding proteins and can be relatively specific depending on their composition, site specific modifications and tertiary structure of the glycan. Chitin in cell wall of fungi might be the target of antifungal lectins. Several plant lectins have antifungal activities against *Fusarium* species (Mohsen *et al.*, 2018). Nikitina *et al.* (2017) recently reviewed lectins from mycelia and fruiting bodies of basidiomycetes. The ability to synthesize lectins is widespread among higher basidiomycetes and their hemagglutinating activity is species and strain dependent (Mikiashvili *et al.*, 2006). Carbohydrate specificity also depends on lignocellulosic growth substrate used for producing mushrooms. It is possible to regulate lectin production and obtain preparations with different carbohydrate specificities by substitution of lignocellulosic material and strains (Davitashvili, *et al.*, 2008; 2011). The development stage of mushroom forming fungi is also to be taken into account. In *P. ostreatus*, the mycelial lectins were mostly specific for mannose, whereas the highest inhibition toward the fruit body lectins was obtained with N-acetyl-d-glucosamine and N-acetyl-d-galactosamine for one lectin fraction and with galactose for other ones (Davitashvili, *et al.*, 2010). In mushrooms, lectins are factors of the interactions with other fungi. The recognition and binding of the *A. bisporus* fruiting body lectin to *Lecanicillium fungicola* cell wall glucogalactomannan contributes to the development of the dry bubble disease on the button mushroom (Bernardo *et al.*, 2004). Lectins of *L. edodes* either stabilize or activate laccases produced by the fungus (Vetchinkina *et al.*, 2008). There is no clear report on mushroom lectins with antifungal activities against mycotoxigenic fungi, but due to their diversity,

TABLE 1: Mushroom proteins active against *Fusarium oxysporum* that have been extracted from fruiting bodies of mushroom forming fungi

NAME	ORIGIN	ACTIVITY	MOLECULAR MASS kDA	IC50 OR ACTIVE CONCENTRATION TESTED	REFERENCES
Hypsin	*Hypsizigus marmoreus*	Ribosone-inactivation	20	14.2 µM	Lam and Ng, 2001a
Alveolarin	*Polyporus alveolaris*	Ribonuclease or lectin	28	120 µg/ 15 µL/disc	Wang *et al.*, 2004
Eryngin	*Pleurotus eyngii*	Thaumatin-like	10	72 g/12 µL/disc	Wang and Ng, 2004
Trichogin	*Tricholoma giganteum*	Ribonuclease or lectin	27	16 and 80 µg/ 15 µL/disc	Guo *et al.*, 2005
Ganodermin	*Ganoderma lucidum*	Unknown+	15	12.4 µM	Wang and Ng, 2006
CMP	*Cordyceps militaris*	protease	12	>1.6 µM / disc	Park *et al.*, 2009
Unnamed	*Pleurotus sajor-caju*	ribonuclease	12	30 µmol on disc	Ngai and Ng, 2004

the possibility of modulation by cultivation conditions and the known activities, they are good candidates as molecules for controlling these fungi and their production of mycotoxins.

Various enzymes are produced by mushroom forming fungi to explore and use their environment, and they may contribute to an antifungal activity. Several studies reported that enzymes playing critical roles in cell wall degradation of fungi could be used for controlling fungal pathogens *in vitro* (Deng *et al.*, 2018). A protease from *Trichoderma harzianum* inhibits spore germination of *Aspergillus flavus* and *A. fumigatus*, and is proposed as a potential means of controlling fungal diseases (Deng *et al.*, 2018). An isolated serine protease from a *Streptomyces* species proved to be active against *Fusarium udum* (Sing and Chhatpar, 2011). A large variety of proteases has been revealed in mushroom forming fungi and some show unique characteristics that could be exclusive to Basidiomycetes (Sabotič *et al.*, 2007). Subtilases are a class of serine proteases ubiquitous in fungi where they play a role in nutrition acquisition or in host invasion by contributing to the digestion of the cuticles, but gene duplication and sequence diversification have likely resulted in functional diversifications of fungal subtilases beyond simple nutrient utilization (Li *et al.*, 2017). A subgroup of subtilisin-like proteases from ascomycete and basidiomycete fungi, belonging to the pyrolysin family has been defined (Faraco *et al.*, 2005). For instance, most proteases of the genus *Pleurotus* feature the characteristics of alkaline subtilases (Eisele *et al.*, 2011). This makes mushroom forming fungi a large, untapped pool of novel proteases with potential for controlling mycotoxigenic fungi.

Beta-1,3-glucanases are considered to be one component of a broad generalised defence mechanism of plants against pathogen attack. Beta-1,3-glucanase from seeds of *Jatropha curcas* exerted *in vitro* antifungal activity against *Rhizoctonia solani* Kuha and *Gibberella zeae* (anamorph *Fusarium graminearum*) (Wei *et al.*, 2005). Fungi also produce beta-1,3-glucanases that have a physiological role in cell division, differentiation and nutritional role related to mycoparasitic activity. *Trichoderma harzianum* is an antagonist of a large variety of plant pathogens. Among different mechanisms for antagonism, it is able to produce lytic enzymes for the degradation of the fungal cell wall to assimilate further the intracellular contents of its hosts. Both β-1,3-glucanase and α-1,3-glucanase contribute to the antifungal

activity (Ait-Lahsen *et al.*, 2001; Benítez *et al.*, 1998). These enzymes are produced in large quantities by vegetative mycelium of mushroom forming fungi that could be used as source of enzyme production or as direct antagonists of mycotoxigenic fungi.

Phenolic compounds from fruiting bodies of edible mushrooms, with potential of activity against mycotoxigenic fungi

Both flavonoids and phenolic acids are lipophilic and can diffuse through the fungal membrane to penetrate into the cell and interfere in metabolic pathways involved in cell wall and membrane structures or transmembrane transport (Ansari *et al.*, 2013). The resistance to mycotoxin accumulation of some cultivars of cereals or maize has been correlated with their content of phenolic compounds having a role in inhibiting growth and/or toxin production by fungi (Atanasova-Penichon *et al.*, 2016).

Plant flavonoids have promising ability to inhibit spore development and limit mycelium hyphae elongation of plant pathogens (Mierziak *et al.*, 2014). Flavones and flavanones were active against *F. graminearum*, *F. culmorum*, *F. avenaceum* with low half maximal inhibitory concentrations (IC50 <4.8 mM) (Atanasova-Penichon *et al.*, 2016). Many reports ensure that mushroom contains flavonoids, but edible mushrooms such as *A. bisporus* and *P. ostreatus* have been shown unable to synthesize them because they do not have, in their genome, genes coding the main enzymes involved in their metabolic pathway. In addition, no significant absorption was noticed from fruiting bodies cultivated in flavonoid-enriched substrates (Gil-Ramírez *et al.*, 2016). Phenolic acids can be divided into two major groups, derivatives of benzoic acid having C1–C6 backbone such as p-hydroxybenzoic or syringic acids, and derivatives of cinnamic acid having C3–C6 backbones, such as p-coumaric, caffeic, ferulic, chlorogenic acids (Ferreira *et al.*, 2009). Ferulic acid and cinnamic acid were found to be more abundant in heads of FHB-resistant barley varieties than in those of susceptible ones, following *F. graminearum* inoculation (Bollina and Kushalappa, 2011). Atanasova-Penichon *et al.* (2016) reviewed the antioxidant secondary metabolites in cereals with potential involvement in resistance to *Fusarium* and mycotoxin accumulation. Their fungicidal efficiency has been characterized against different *Fusarium* species and the authors proposed a ranking of phenolic acids for their toxicity toward *F. graminea-*

rum as follows: chlorogenic acid < p-hydroxybenzoic acid < caffeic acid < syringic acid < p-coumaric acid < ferulic acid. In fact, more lipophilic compounds display a more efficient antifungal activity on *Fusarium graminearum* (Ponts *et al.*, 2011). However, it is noteworthy that a same phenolic acid can have contrasted effects, depending on the dose used, cultivation conditions and the species. For example, *Fusarium verticillioides* growth was significantly reduced at 20 mM of ferulic acid, but it was stimulated at 1.0 mM (Ferrochio *et al.*, 2013), and *F. langsethiae* growth was reduced at 1.0 mM but stimulated at 0.5 mM (Ferruz *et al.*, 2016).

Phenolic acids are the main phenolic compounds in mushroom forming fungi that are proposed to be used as an easily accessible source of natural antioxidants (Nowacka *et al.*, 2014). Recently, ethanolic extracts, known to be rich in phenolic compounds, from fruiting bodies of *Hydnum repandum*, and methanolic extracts of *Stereum subtomentosum* and *Bjerkandera adusta*, showed antifungal effects on *F. verticillioides*, *F. proliferatum* and *F. graminearum* (Spremo *et al.*, 2017). Phenolic acids have been measured in various species, but depending on the analytical methods used, not all the phenolic acids had been searched in all the studied mushrooms. Table 2 shows data on mushroom contents for the six phenolic acids having fungicidal activity against *F. graminearum* according to Atanasova-Penichon *et al.* (2016).

Among the three compounds with the highest antifungal effect on *F. graminearum*, syringic acid had not been frequently searched in mushroom forming fungi, whereas p-coumaric acid was assayed in 69 and ferulic acid in 41 mushroom samples out 76 mushrooms analysed in the works reported in Table2. Both p-coumaric acid and ferulic acid were detected in 41 % of the samples where they were searched. In table 2, the highest content of p-coumaric acid is for *Psathyrella candolleana* (66.4 mg kg^{-1}) collected in Turkey (Dündar *et al.*, 2015). *Agaricus arvensis*, *Lactarius indigo*, *Pholiota mutabilis*, contain more than 25 mg p-coumaric acid kg^{-1}. The highest contents of ferulic acid are in *Boletus frostii* (100 mg kg^{-1}), an American species widely distributed, and in the cultivated oyster mushroom, *Pleurotus ostreatus* (20 mg kg^{-1}).

However, it is noteworthy that for a same species, significant differences in concentrations are reported in different articles. In Table 2, samples of *A. bisporus* were analysed in six different studies, and p-coumaric acid was found in only three samples (2 to 10 mg kg^{-1}). In a study comparing different white hybrids and a brown strain of *A. bisporus* grown simultaneously in an experimental facility (Gasecka *et al.*, 2018), the concentration of p-coumaric acid was higher in the brown strain than in the white ones. Ferulic acid concentration in *A. bisporus* was 13 and 16 mg kg^{-1} in the studies reported by Geseacka *et al.* (2018) and Palacios *et al.* (2011), whereas it was not detected in two other studies (Kim *et al.*, 2008; Muszyńska *et al.*, 2015).

Cinnamic acid has been detected at concentrations higher than 10 mg kg^{-1} in *Agaricus subrufescens* (Kim *et al.*, 2008), *A. arvensis*, *A. sylvicola*, *A. romagnesii* (Barros *et al.*, 2009), *Boletus edulis* (Yahia *et al.*, 2017), *Ganoderma lucidum* (Heleno *et al.*, 2013); fruiting bodies of *Cantharellus cibarius* and *Picipes badius* (formely *Boletus badius*) (Muszyńska *et al.*, 2015), *Hygrophorus agathosmus* and *Tricholoma sulphureum* (Vaz *et al.*, 2011).

Phenolic acids from mushrooms have also antifungal potentials against producers of Aflatoxins or Ochratoxins. Methanolic extracts from fruiting bodies of *Cordiceps militaris* containing p-hydroxybenzoic acid and cinnamic acids revealed antifungal potential against *A. fumigatus* and *A. ochraceus* (Reis *et al.*, 2013). *P*-hydroxybenzoic and cinnamic acids identified in *Ganoderma lucidum* revealed antifungal activity against *Aspergillus fumigatus*, *A. ochraceus*, *A. niger*, with higher activity than the fungicides used as standards (Heleno *et al.*, 2013). Methanolic extracts containing these compounds proved to have higher antioxidant potential than corresponding water extracts rich in polysaccharides (Heleno *et al.*, 2012).

The present survey of the literature shows that significant levels of phenolic compounds can be found in mushroom forming fungi, but the available data varies between authors for a same species and it is difficult to select *a priori* mushroom species with an interesting composition in phenolic acids that could be a source of extracts as anti-*Fusarium* product. Apart from differences in analytical methods between laboratories expertise, the quality of the samples analysed might be affected by the development stage of the mushroom, the storing delay and conditions before analyses, the ecosystems they come from or the substrates and conditions used for their cultivation, intraspecific variations due to genetic diversity. Further screenings for obtaining extracts with interesting

phenolic composition and antifungal activity should be on mushroom species with high levels of available biodiversity that can be cultivated under controlled conditions, and for which strain selection are possible. This is the case of the cultivated edible mushrooms such as several species of *Agaricus* or *Pleurotus*. Selection of very efficient strains could be completed with improvement of their capacities by breeding programs that are currently performed on these species for other traits (Savoie *et al.* 2013).

TABLE 2: Phenolic acids concentrations in mushroom forming fungi

References	Mushroom species	Edibility	Phenolic acids (mg Kg⁻¹)					
			Ferulic acid	P-couma-ric acid	Syringic acid	Caffeic acid	P-hydroxybenzoic acid	Chloroge-nic acid
Barros *et al.*, 2009	*Agaricus arvensis*	edible	_	48.7	_	_	70.1	_
Gasecka *et al.*, 2018	*A. arvensis*	_	11	16	nd	13	nd	57
Muszyńska *et al.*, 2015	*A. biporus*	edible	nd	nd	-	-	7.0	-
Kim *et al.*, 2008	*A. bisporus*	edible	nd	nd	nd	nd	nd	nd
Reis *et al.*, 2013	*A. bisporus*	edible	-	2.3	-	-	nd	-
Barros *et al.*, 2009	*A. bisporus*	edible	-	nd	-	-	25.6	-
Palacios *et al.*, 2011	*A. bisporus*	edible	16	10.4		15.5	15.4	63.7
Gasecka *et al.*, 2018	*A. bisporus (mean 7 strains)*	edible	13	8.7	nd	15.5	15.4	63.7
Gasecka *et al.*, 2018	*A. bitorquis*	edible	11	nd	nd	14	nd	56
Gasecka *et al.*, 2018	*A. campestris*	edible	18	11	nd	1	28	nd
Barros *et al.*, 2009	*A. romagnesii*	toxic	-	nd	-	-	32.4	-
Gasecka *et al.*, 2018	*A. silvaticus*	edible	10	15	34	3	18	nd
Barros *et al.*, 2009	*A. silvicola*	edible	-	45.7	-	-	238.7	-
Gasecka *et al.*, 2018	*A. subrufescens*	edible	14	5	56	22	15	62
Kim *et al.*, 2008	*A. subrufescens (blazei)*	edible	nd	nd	22	nd	nd	nd
López-Vázquez *et al.*, 2017	*Amanita caesarea*	edible	-	-	-	-	-	564.4
Yahia *et al.*, 2017	*A. flavocconia*	non-edible	2.1	nd	-	nd	145.4	nd
Yahia *et al.*, 2017	*A. pantherina*	toxic	nd	nd	-	257.6	90.0	36.9
Dundar *et al.*, 2015	*Armillaria tabescens*	edible	--	0.6	62.6	nd	-	-
Muszyńska *et al.*, 2015	*Boletus badius*	edible	1.5	13.9	-	-	1.3	-
Dundar *et al.*, 2015	*B. edulis*	edible	-	5.5	38.9	6.1	-	-
Yahia *et al.*, 2017	*B. edulis*	edible	nd	nd	-	-	34.0	nd
López-Vázquez *et al.*, 2017	*B. edulis*	edible	-	-	-	-	-	1001.7
Palacios *et al.*, 2011	*B. edulis*	edible	nd	0.9	-	15.1	24.1	62.8
Yahia *et al.*, 2017	*B. frostii*	edible	100.0	nd	-	nd	nd	nd
Yahia *et al.*, 2017	*B. Luridus*	edible	nd	nd	-	53.0	nd	185.3
Palacios *et al.*, 2011	*Calocybe gambosa*	edible	14.5	nd	-	14.9	11.3	63.0
Nowacka *et al.*, 2014	*Calvatia excipuliformis*	toxic	trace	0.2	-	nd	2.19	-
López-Vázquez *et al.*, 2017	*Cantharellus cibarius*	edible	-	-	-	-	-	108.2
Palacios *et al.*, 2011	*C. cibarius*	edible	10.4	nd	-	16.3	15.7	nd
Muszyńska *et al.*, 2015	*C. cibarius*	edible	nd	nd	-	-	nd	-
Nowacka *et al.*, 2014	*Clitocybe cinerea*	non-edible	trace	nd	-	nd	4.5	-
Nowacka *et al.*, 2014	*Coprinus micaceus*	edible	nd	6.0	-	nd	25.1	-
Reis *et al.*, 2012a	*Cortinarius caperatus*	edible	-	nd	-	-	25.9	-
Nowacka *et al.*, 2014	*Cratarellus cornucopiodes*	edible	trace	0.3	-	nd	12.7	-

concluye Tabla 2.

REFERENCES	MUSHROOM SPECIES	EDIBILITY	PHENOLIC ACIDS (MG KG^{-1})					
			FERULIC ACID	P-COUMA-RIC ACID	SYRINGIC ACID	CAFFEIC ACID	P-HYDROXYBENZOIC ACID	CHLOROGE-NIC ACID
Palacios *et al.*, 2011	C. cornucopioides	edible	14.0	nd	-	nd	6.3	nd
Vaz *et al.*, 2011	Fistulina hepatica	edible	-	nd	-	-	41.9	-
Kim *et al.*, 2008	Flammulina velutipes	edible	9	nd	nd	17	nd	26
Kim *et al.*, 2008	Ganoderma lucidum	edible	nd	nd	nd	nd	nd	nd
Dundar *et al.*, 2015	Helvella leucopus	non-edible	-	57.0	nd	nd	-	-
Dundar *et al.*, 2015	H. queletii	non-edible	-	nd	4.6	nd	-	-
Vaz *et al.*, 2011	Hygrophorus agathosmus	edible	-	8.6	-		nd	-
Vaz *et al.*, 2011	H. olivaceo-albus	edible	-	nd	-	-	7.4	-
Palacios *et al.*, 2011	H. marzuolus	edible	nd	4.7	-	14.6	5.5	nd
Kim *et al.*, 2008	Inonotus obliquus	edible	22	nd	nd	nd	263	nd
Nowacka *et al.*, 2014	Laccaria amnethystea	edible	nd	1.9	-	nd	17.7	-
Palacios *et al.*, 2011	Lactarius deliciosus	edible	11.4	nd	-	15.5	21.4	62.7
Barros *et al.*, 2009	L. delicious	edible	-	nd	-	-	22.7	-
Yahia *et al.*, 2017	L. indigo	edible	nd	30.5	-	nd	11.6	3.2
López-Vázquez *et al.*, 2017	L. indigo	edible	-	-	-	-	-	222.4
Vaz *et al.*, 2011	L. salmonicolor	edible	-	nd	-	-	3.4	-
Reis *et al.*, 2012a	Lentinula edodes	edible	-	nd	-	-	1.6	-
Kim *et al.*, 2008	L. edodes	edible	nd	nd	nd	nd	nd	nd
Barros *et al.*, 2009	Lepista nuda	edible	-	3.7	-	-	29.3	-
Barros *et al.*, 2009	Lycoperdon molle	edible	-	4.0	-	-	41.7	-
Nowacka *et al.*, 2014	L. perlatum	edible	nd	1.9	-	nd	3.7	-
Kim *et al.*, 2008	Phellinus linteus	edible	nd	nd	nd	13	6	23
Nowacka *et al.*, 2014	Pholiota mutabilis	edible	trace	29.1	-	1.4	24.8	-
Reis *et al.*, 2012a	Pleurotus eryngii	edible	-	1.0	-	-	0.1	-
Kim *et al.*, 2008	P. eryngii	edible	nd	nd	nd	nd	nd	nd
Dundar *et al.*, 2015	P. ostreatus	edible	-	nd	25.4	2.5	-	-
Reis *et al.*, 2012a	P. ostreatus	edible	-	0.8	-	-	1.6	-
Palacios *et al.*, 2011	P. ostreatus	edible	20.2	11.1		nd	4.7	nd
Kim *et al.*, 2008	P. ostreatus	edible	nd	nd	nd	nd	nd	19
Dundar *et al.*, 2015	Psathyrella candolleana	edible	-	66.4	12.5	3.2	-	-
Barros *et al.*, 2009	Ramaria botrytis	edible	-	nd	-	-	14.0	-
Yahia *et al.*, 2017	Russula emetica	non-edible	5.2	nd	-	nd	nd	nd
Yahia *et al.*, 2017	Sarcodon imbricatus	non-edible	nd	nd	-	nd	nd	20.7
Barros *et al.*, 2009	S. imbricatus	edible	-	nd	-	-	33.2	-
Kim *et al.*, 2008	Sparassis crispa	edible	nd	37	5	18	34	nd
Yahia *et al.*, 2017	Strobilomyces floccopus	non-edible	nd	nd	-	79.9	80.0	nd
Vaz *et al.*, 2011	Suillus collinitus	edible		nd	-	-	14.1	-
Vaz *et al.*, 2011	S. mediterraneensis	non-edible		nd	-	-	2.0	-
Barros *et al.*, 2009	Tricholoma acerbum	edible		nd	-	-	29.7	-
Dundar *et al.*, 2015	T. populinum	edible		4.2	nd	3.6	-	-
Vaz *et al.*, 2011	T. sulphureum	non-edible		nd	-	-	2.6	-

Nd= non detected, - = not searched in the analysis of extracts.

Other specific compounds from mushroom forming fungi with antifungal activity

Several molecules with potential as fungicides has been identified and isolated from mushroom forming fungi. There are few examples with concern on mycotoxigenic fungi. Three are given bellow.

The first fungicides in the family of Strobilurins were isolated from wood-rotting mushroom fungi, including one called *Strobilurus tenacellus* and chemists synthetized and improved on these natural fungicides (Vincelli, 2012). Strobilurins act to inhibit the mitochondrial respiratory chain at the level of Complex III, which results in cellular oxidative stress triggered by electrons escaping from the respiratory chain, which can be detoxified by mitochondrial superoxide dismutase (Kim *et al.*, 2007). Strobilurin fungicides were reported to be hardly effective on several occasions against different *Fusarium* species few years after their introduction, but natural resistance to trifloxystrobin has been shown in populations of *F. graminearum* (Dubos *et al.*, 2011). Consequently, Strobilurins are not efficient for controlling these fungi.

Antimicrobial terpenoids are potentially present in many mushrooms forming fungi and cultivating mushrooms as biosources for these compounds is worth being studied (Shen *et al.*, 2017). Rufuslactone from *Lactarius rufus* was found to inhibit the mycelial growth of *F. graminearum* (Luo *et al.*, 2005), and chrysotrione A and B from *Hygrophorus chrysodon* showed moderate antifungal activity on *F. verticillioides* whereas they were more active for controlling another phytopathogenic fungus, *Alternaria brassica* (Gilardoni *et al.*, 2007).

1-octen-3ol and 10-oxo-trans-8-decenoic acid are volatile secondary metabolites found in many mushrooms. They contribute to the "mushroom-like" aroma and possess antifungal activities against the mycotoxigenic fungus *Penicillium expansum* (Okull *et al.*, 2003). This survey of potent antifungal compounds from mushroom forming fungi shows they are various, and some might be active against mycotoxigenic fungi. However, it is also worth finding natural compounds having an effect on the mycotoxin production for completing fungicide or fungistatic properties.

ANTI-MYCOTOXIN COMPOUNDS FROM MUSHROOM FORMING FUNGI

In this section, mushroom compounds with potential activity on the production of mycotoxins by *Aspergillus*

spp. and other mycotoxigenic fungi have been discussed, with emphasis on phenolic compounds and antioxidants because they have been shown to inhibit the production of some mycotoxins.

Mushroom extracts inhibiting the production of aflatoxins

Published works on the control of mycotoxin production by mushroom-forming fungi are mainly for aflatoxins produced by *Aspergillus parasiticus* or *A. flavus* and lignocolous white rot fungi, *Lentinula edodes*, *Trametes versicolor*, *Pleurotus* spp. The polyketide aflatoxin is looked as a secondary defence system protecting the fungus from excess reactive oxygen species (ROS) (Hong *et al.*, 2013). Production of aflatoxin was observed to be related to the peroxidation of the fungal cellular membranes and fatty acid β-oxidation in both the peroxisome and mitochondria (Maggio-Hall *et al.*, 2005). That explains why antioxidants have been taken into consideration, and reported for their efficacy for controlling aflatoxin production (Zhao *et al.*, 2018).

Culture filtrates of *L. edodes* were shown to be able to inhibit aflatoxin production by *A. parasiticus* with a direct relation between aflatoxin inhibition and β-glucan content of the lyophilised filtrates (Reverberi *et al.*, 2005). Such extracts were shown to stimulate the antioxidant system of the mycelium by the induction of a transient and modulated oxidative burst perceived by ApyapA transcription factor of *A. parasiticus* (Reverberi *et al.*, 2006). Bioactive compounds secreted in the culture filtrates of *T. versicolor,* as well as lyophilised solid of mycelium grown on agricultural residues, inhibited the production of aflatoxin in maize kernels inoculated with *A. flavus* (Scarpari *et al.*, 2014). The Afyap1 transcription factor of *A. flavus* was involved (Scarpari *et al.*, 2016).

For both *L. edodes* and *T. versicolor*, significant differences in aflatoxin inhibition rate among different tested isolates were evidenced, although the same cultural conditions were used. They were attributed to differences in quality rather than the quantity of the inhibiting compounds (Zjalic *et al.*, 2006), but improvement of the yield of β-glucan production by *L. edodes* strains using oxidative stress inductors leaded to higher aflatoxin inhibiting capacity (Reverberi *et al.*, 2004). In addition to mycelium, fruiting bodies can also be a source of active compounds. A water-soluble complex of polysaccharides possessing β-(1, 4)-glucan backbones and peptides extracted at high tempera-

ture from fruiting bodies of *L. edodes* inhibited AFB1 production by *A. flavus*, with an IC50 of < 10 μg mL⁻¹ (Li *et al.*, 2015).·

Finally, the efficacy of mushroom extracts as inhibiters of the production of aflatoxin is due, on the one hand, to the presence of compounds with intrinsic antioxidant activity and, on the other hand, to the stimulation of the antioxidant system of the toxigenic fungi.

Mushroom extracts inhibiting the production of other mycotoxins

Lentinula edodes extracts were also proposed to boost the antioxidant enzyme activity of a biocontrol agent and contribute to control patulin biosynthesis, promoting the antioxidant activity of *Penicillium expansum* on apples (Tolaini *et al.*, 2010; Wang *et al.*, 2013). They also can elicit and regulate the biosynthesis of ochratoxin A by *Aspergillus ochraceus* (Reverberi *et al.*, 2008). Methanolic extracts from fruiting bodies of *Agaricus boshui* are also active against *Penicillium verrucosum* producing OTA (Reis *et al.*, 2012b).

We did not find data on the regulation of the biosynthesis of *Fusarium* toxins by this kind of mushroom extracts. However, in addition to aflatoxin, ROS, antioxidants and Yap-like bZIP factors are also known to be involved in regulation of the biosynthesis of *Fusarium* mycotoxins such as trichothecenes, fumonisins and ZEN. Response to oxidative stress and fungal secondary metabolism are indeed intertwined. It seems likely that for instance, the production of DON and its acetylated derivatives is probably a part of an adaptive response to oxidative stress from the ROS produced by the host plant as an early defence mechanism in response to infection by *F. graminearum* (Ponts, 2015). Oxidative stress with H_2O_2 could be a pre-requisite for the biosynthesis of DON. Both stress responses and the regulation of DON synthesis are mediated by the transcription factor FgAP1 that activates the transcription of antioxidant enzymes (Montibus *et al.*, 2013). A link was established between antioxidant and antiradical properties of flavonoids and their effects on trichothecenes production by *F. culmorum* and *F. graminearum* (Bilska *et al.*, 2018). Microalgae phenolic extracts rich in chlorogenic acid showed antifungal and antimycotoxigenic activities (Scaglioni *et al.*, 2018), as well as maize extracts do (Atanassova-Penichon *et al.*, 2014). Synergic effect between different compounds present in the extracts also influences their antimycotoxigenic

activity (Scaglioni *et al.*, 2018). Natural antioxidants such as ferulic acid may contribute to limit the production of fumonisins in maize kernels (Picot *et al.*, 2013).·

Phenolic compounds and antioxidant activity from mushrooms inhibiting the production of mycotoxins

Antioxidant activities appeared above as regulators of the production of various mycotoxins and searching for mushroom forming fungi with high contents in antioxidants is of interest. Mushroom extracts with antioxidant properties might contribute both to fight the up regulation of synthesis of mycotoxins by oxidative stress (Zhao *et al.*, 2018) and to protect against their toxicity (Da Sylva *et al.*, 2018). Actually, mushrooms are currently proposed to be used as an easily accessible source of natural antioxidants mostly due to their richness in phenolic compounds, and have attracted much interest as functional foods. The total phenol concentration is currently measured in mushroom samples for an estimation of their potential as antioxidant in functional food. It is determined most of the time in extracts by the Folin-Ciocalteu's phenol reagent method (Savoie, 2008). Gil-Ramírez *et al.* (2016) who used a direct measurement of total phenolic compounds without extraction on 24 samples from 24 species belonging to 18 genera, reported values ranging from 1 to more than 14 mg gallic acid equivalent (GAE) g⁻¹ mushroom powder, depending on the species. For the button mushroom *A. bisporus*, total phenolic contents ranged from 1 to 16 mg GAE g⁻¹ when both white and brown strains, and both cultivars and wild strains were taken into account (Alvarez-Parrilla *et al.*, 2007; Barros *et al.*, 2009; Dubost *et al.*, 2007; Gan *et al.*, 2013; Gasecka *et al.*, 2018; Gil-Ramirez *et al.*, 2016; Palacios *et al.*, 2011; Reis *et al.*, 2012a; Savoie *et al.*, 2008). Comparing these intraspecific and interspecific range shows the variability of the data and the necessity to characterize the factors responsible of variations in total phenolic contents.

The efficiency of selected phenolic acids to modulate *in vitro* the biosynthesis of mycotoxins has been demonstrated for various toxins. Ferulic, chlorogenic, and caffeic acids have been shown as efficient inhibitors of TCTB production by *Fusarium graminearum* and *F. culmorum* (Boutigny *et al.*, 2009; Gauthier *et al.*, 2016), TCTA by *F. langsethiae* and *F. sporotrichioides* (Ferruz *et al.*, 2016), and fumonisins by *F. verticillioides* (Atanasova-Penichon *et al.*, 2014; Beekrum *et al.*, 2003).

However, there is a strain and concentration dependent effect of phenolic acids on *Fusarium* toxin synthesis. Ferulic acid used at concentrations that did not affected the mycelial growth rate can either limit or enhance the accumulation of TCTB by *F. graminearum* (Boutigny *et al.*, 2009; Ponts *et al.*, 2011). In regards to synthesis of fumonisins, Ferrochio *et al.* (2013) showed that ferulic acid activated their production at low concentrations while inhibited it at higher ones.

Richness of mushroom extracts in phenolic compounds (Table 2) is discussed above. It is noteworthy that co-occurrence of several compounds are found in various works. Mixture of phenolic acids and other active compounds, as found in natural mushroom extracts, might have different potentials than single molecules. Whereas mixtures of phenolic compounds with antioxidant activities might limit the production of mycotoxins, some studies show that there was no clear correlation between the antioxidant properties of natural and natural-like phenolic compounds tested singly and their ability to inhibit fungal growth and mycotoxinogenic capacity of *Fusarium culmorum* (Pani *et al.*, 2014). Other properties of the individual compounds due to their chemical structures and mode of action might have higher effects. The potential of a mushroom extract can only partly be predicted by its known composition, and it will have to be evaluated experimentally.

DETOXIFICATION

Biotransformation of mycotoxins performed with purified enzymes isolated from bacteria, fungi and plants has recently been reviewed (Loi *et al*, 2017). Laccases (E.C. 1.10.3.2 benzenediol: oxygen oxidoreductase) are an interesting group of N glycosylated multicopper blue oxidases that oxidize a large number of both phenolic and non-phenolic compounds that may be involved in degradation of aflatoxins. Most of the mushroom-forming fungi are producers of laccases. Motomura *et al.* (2003) reported a high aflatoxin B1 degradation activity from *Pleurotus ostreatus* in cultures at 25 °C and pH 4.0-5.0, possibly linked to the enzymatic oxidation handled by laccases or peroxidases (Yehia, 2014). Treatments of maize seeds or milled seeds, with culture filtrates of *Trametes versicolor* rich in laccases activities, showed a significant degradation of aflatoxin B1 content after 7 days of the treatment (Scarpari *et al.*, 2014). Aflatoxin B_1 treated with pure laccase enzyme

from *T. versicolor* (and recombinant laccase produced by *A. niger*) was significantly metabolized to degradation products with chemical properties that vastly differ from the parent molecule. Concomitant significant loss of mutagenicity, as evaluated in the *Salmonella typhimurium* mutagenicity assay, was observed (Alberts *et al.*, 2009). The degrading activity of Lac2 pure enzyme from *P. pulmonarius* towards aflatoxin was enhanced by the addition of natural phenolic compounds as redox mediators (Loi *et al.*, 2016).

Concerning the degradation of other mycotoxins besides the above-mentioned activity towards aflatoxins, laccases are also able to degrade ZEN. This was shown with a *T. versicolor* preparation (Banu *et al.*, 2013). The laccase-mediator system was used with a laccase from *P. eryngii*, for combined mycotoxin degradation in vitro. DON was not affected whereas AFB1, FB1, OTA, ZEN and T-2 toxin were at least partly degraded, as well as combinations of AFB1 and ZEN, but without relevant synergistic nor additive effects (Loi *et al.*, 2018). In combination of FB1 and T-2 toxin, a strong additive effect was reported for T-2 toxin degradation whereas FB1 degradation was drastically reduced. Most of the cultivated edible mushrooms are white rot fungi, they are laccase producers and they degrade lignocellulosic substrate, which leaves a white rot residue during the degradation of lignin. Laccases extracted from mushrooms or cultivation substrates of white rot fungi mycelium have been used in the removal of many emerging contaminants that are difficult to decompose (Chang *et al.*, 2018). Numerous laccase isoenzymes have been achieved in various species of fungi, with dissimilar physicochemical and kinetic properties. There are various laccase isoforms in a same fungal strain. These isoforms could be expressed at different phases of the fungal life cycle or under diverse cultivation conditions (Baldrian, 2006; Othman *et al.*, 2018). It would be possible to select several ones with interesting activity for *Fusarium* mycotoxin degradation.

Solid-state fermentation process with edible white rot mushroom forming fungi for biological detoxification of aflatoxin B_1 and other mycotoxins is worth being developed. Methods of myceliation of agricultural substrates proposed for producing functional foods with health benefits (Kelly and Langan, 2013) could also contribute to mitigate the mycotoxin risk. This was recently tested at the laboratory scale by cultivating *P. eryngii* on a mixture containing corn con-

taminated with aflatoxin B$_1$. The mycotoxin was degraded and edible fruiting bodies free of aflatoxin B$_1$, or its metabolite aflatoxicol, were produced (Branà *et al.*, 2017). The resulting detoxified cultivation substrate could also be used in feed rations. Agro-based spent mushroom substrate from *Pleurotus* spp. and *Agaricus bisporus* have been known to be suitable for applications of ruminant feedstock (Mohd Hanafi *et al.*, 2018). Otherwise, many mushroom forming fungi can be cultivated on starch rich materials such as cereal grains in solid-state fermentation, and both nutrients and antioxidant activities of the cereals are enhanced after being fermented by edible mushrooms (Han, 2003; Han *et al.*, 2005; Zhai *et al.*, 2015). The process could also have consequences on the final content in mycotoxins. Grains with low concentrations of mycotoxins would be cleaned up and enriched in nutrients after solid-state fermentation, and could be used as food.

CONCLUSION

Within this review, we were interested of the potential of mushroom-forming fungi for mitigation of mycotoxin contamination in cereal products. Many mushroom species are a food source and exhibit a rich source of bioactive compounds in preventing or treating various types of human and animal diseases. Some have been proposed as source of antifungal compounds against phytopathogenic fungi. A couple of species are subjects of works in progress for their potential as biocontrol agents of mycotoxinogenic fungi contaminating food and feed at storage. There are untapped potentials to interact with the accumulation of mycotoxins in cereals products, from the field to the final product. Extracts or purified metabolites from cultivable edible mushrooms having antifungal and/or antimycotoxin activities could be used as alternatives to fungicides in integrated crop protection strategies. Mycelium could be used as biocontrol agents being antagonists of mycotoxigenic fungi on crop debris. Mycelium could be used as degrader of mycotoxins in grains or straws and stalks and for enriching them in nutrients and antioxidant properties before their use as feed or food. Ultimately, edible mushrooms would be produced from contaminated materials that could not be detoxified.

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