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Review

Antimicrobial properties of the mushroom *Agaricus blazei* – integrative review

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ABSTRACT

Infectious diseases associated with antimicrobial resistance are considered to represent an important public health problem. In this regard, the mushroom *Agaricus blazei* Murrill contains several bioactive substances that promote significant functional properties, among them, antimicrobial activity, which has attracted the interest of the scientific community. Thus, the aim of this study was to determine whether evidence of the antimicrobial action of *A. blazei* has been reported in the literature. In this integrative review, manuscripts held in research databases available online were examined with a view to answering the question "Does the mushroom *A. blazei* exert antimicrobial activity against Gram-negative and/or Gram-positive bacteria?" Only eight scientific articles that have addressed the antimicrobial properties of *A. blazei*, *in vitro* and *in vivo*, were found, all characterized as pre-clinical, *i.e.*, with level VII evidence. Most authors have found that the *A. blazei* extract promotes an antimicrobial effect against peritonitis, as well as deadly oral infections, especially those caused by Gram-positive bacteria. However, the scientific data currently available are not sufficient to verify the antimicrobial aspect of the mushroom *A. blazei* and thus further investigation is required.

Introduction

Infectious diseases have become a major public health problem worldwide. In recent years, antibiotics have been instrumental in therapy against infections caused by various pathogens (Huttner et al., 2013). However, there is an increasing resistance to traditional antibiotics resulting in increased morbidity and mortality, prolonged hospital stays and increased hospital costs (Davey and Marwick, 2008; Piddock, 2012; Thabit et al., 2015).

Data show that approximately 70% of the bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly used for the treatment (Lambert et al., 2010; Mertz et al., 2015). In most countries, this rise in antimicrobial resistance has been found not only in relation to hospital-acquired but also community-acquired infections (Odonkor and Addo, 2011; Abella et al., 2015; Fistarol et al., 2015).

The emergence of antimicrobial resistance is facilitated by several factors, which are related to bacteria or humans. Antibiotic resistance is related to particular aspects associated with the overall progress of bacteria and these cannot generally be interrupted by humans, for instance, the mutation of bacteria, which is one of the determining factors of resistance (Licking, 1999; Mah and O'Toole, 2001; Stokes and Gillings, 2011; Arenz and Wilson, 2016). However, the inadequate application of drug therapy with antibiotics in humans, with a lack of appropriate criteria or incorrect dose, treatment period, active agent etc., can directly influence the bacterial resistance to this type of drug (Morgan et al., 2011; Meyer et al., 2013).

Studies suggest that the mushroom *Agaricus blazei* Murrill, cultivated in Brazil, contains several bioactive substances responsible for its medicinal properties (Kasai et al., 2004; Kawamura et al., 2005; Ellertsen et al., 2006; Cordeiro and Bach, 2006; Smiderle et al., 2011; Firenzuoli et al., 2007; Machado et al., 2007; Hsu et al., 2008; Padilla et al., 2009; Jumes et al., 2010; Ishii et al., 2011; Carneiro et al., 2013; Uyanoglu et al., 2014; Bertéli et al., 2014), notably glucans which, in addition to promoting an immunomodulatory response, can induce an increase in the antimicrobial action of this fungus (Ohno et al., 2001; Sorimachi et al., 2001; Smyth et al., 2002; Shimizu et al., 2002; Kaneno et al., 2004; Takimoto et al., 2004; Kasai et al., 2004; Kawamura et al., 2005; Ellertsen et al., 2006; Yuminamochi et al., 2007; Smiderle et al., 2011). Some studies carried out in animals and *in vitro* have indicated that pro-inflammatory mediators can induce the phagocytosis of

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Staphylococcus aureus and *Mycobacterium tuberculosis*, respectively (Riollet et al., 2000; Kisich et al., 2002). It has been suggested that the interpretation of these results could be extrapolated to *A. blazei* because this mushroom promotes the growth of various cytokines, particularly pro-inflammatories. Thus, the serum levels resulting from the use of chemokines observed in studies on *A. blazei* (Sorimachi et al., 2001; Bernardshaw et al., 2005; Ellertsen et al., 2006; Chan et al., 2007; Johnson et al., 2009) could enhance the phagocyte power of immune cells and promote the effectiveness of the response to infection by pathogenic microorganisms.

The significant increase in the number of bacteria which are resistant to a broad spectrum antibiotics has become an urgent public health problem worldwide (WHO, 2011; Kelly et al., 2016; Khudaibergenova, 2015). Considering the rapid spread of multidrug resistance, the development of new antimicrobial agents which act on newly adapted microorganisms has become a priority (Laxminarayan et al., 2013; Torjesen, 2013). Some researchers have focused on the development of antibiotics from natural products that can control infection without encouraging the emergence of resistant bacterial strains (Gilbert et al., 2010; Soković et al., 2014). Mushrooms can be considered a source of natural antibiotics due to the presence of certain compounds of interest, such as terpenes, sesquiterpenes, steroids, anthraquinone and derivatives of benzoic acid, quinolines, oxalic acid, peptides and proteins (Alves et al., 2012).

Even before the advent of the resistance of micro-organisms to conventional antibiotics, there was considerable interest in the study of natural products for the therapeutic treatment of infections promoted by these organisms. In this context, the aim of this review paper is to determine whether there is scientific evidence available to support the antimicrobial action of the mushroom *A. blazei*.

Methods

This study is characterized as an integrative review of the scientific literature and the aim was to answer the following question: "Does the mushroom *Agaricus blazei* Murrill exert antimicrobial activity against Gram-negative and/or Gram-positive bacteria"?

The survey was conducted considering publications indexed in the following databases: Bireme Library, Cochrane, Homeoindex, Lilacs, Pubmed/Medline, SciElo and ScienceDirect, using 'antimicrobial agents' as controlled descriptors and 'medicinal mushrooms' and '*Agaricus blazei* Murrill' as uncontrolled descriptors. These descriptors were used in their Portuguese language versions in the Lilacs and SciElo databases. Subsequently, a reverse lookup was held by considering the references cited in the articles researched. Scientific research publications reporting the antimicrobial action of the mushroom *A. blazei* Murrill, in Portuguese, English or Spanish, regardless of the year of publication, adopting any kind of method, were defined as inclusion criteria.

Data were collected during the period of September–December 2014. The documents were found by way of a literature review and accessed in collections available online. The selected articles were read in full for the purpose of further critical analysis and categorization. Data relating to the journal, author and type of study were also evaluated. The studies were then categorized based on the level of evidence: Level 1: systematic review; Level 2: randomized clinical trial; Level 3: cohort study; Level 4: case–control study; Level 5: series of cases; Level 6: expert opinion; Level 7: pre-clinical trial (*in vivo*/*in vitro*) as described by Bork (2005). The impact factor of the journals in which the research included in this study was published was identified using data from the Journal Citation Reports (JCR).

Results

The total number of published manuscripts addressing the antimicrobial action of the mushroom *A. blazei* were eight, from the years 1994–2014. The impact factors of the journals in which these publications appeared, determined for the year 2014, ranged from 0.263 to 3.045 (Table 1). Regarding the category of the studies, according to the design adopted, it was found that all were pre-clinical trials; seven performed *in vitro* and two of the studies included in the sample group involved research on animals. Only the study by Bernardshaw et al. (2005) involved both methods cited above, that is, *in vivo* and *in vitro*. It should be noted that all *in vivo* studies were predominantly carried out on mice, with the inclusion of a control group besides the test group.

With regard to the types of *A. blazei* mushroom extracts evaluated, it was observed that in two studies a commercially available aqueous solution was evaluated, that is, AndoSan™ (Immunopharma AS, Høvik, Norway) composed of *A. blazei* mushrooms (82%), *Hericeum erinaceus* (15%) and *Grifola frondosa* (3%) (Bernardshaw et al., 2005, 2006). The other authors used extracts obtained from mushrooms *in natura*, specifically the fruiting bodies of the Basydiomicetes, using as solvents: hexane, chloroform and methanol (Osaki et al., 1994); water and ethanol (Zhuqiu and Zhang, 2001); ethanol (Lund et al., 2009); methanol (Stojkovic et al., 2014.); and water (Soković et al., 2014). Mazzutti et al. (2012) investigated the use of the supercritical fluid extraction process to obtain the *A. blazei* extract using ethanol as a cosolvent with carbon dioxide (CO_2) and subsequently compared this method with other conventional extraction procedures (extraction by maceration followed by liquid–liquid partition, hexane and hydrodistillation) using other solvents, such as hexane, dichloromethane, ethyl acetate, ethanol and water.

In studies which included animals in the sample group the use of an orogastric intubation catheter was found to be the administration route for the *A. blazei* extracts (Bernardshaw et al., 2005, 2006). There was a variety of microorganisms tested in the studies analyzed, with a predominance of Gram-positive bacteria: *Salmonella typhi* (Osaki et al., 1994); *Staphylococcus aureus*, *Bacillus sabtilis*, *Escherichia coli* (Zhuqiu and Zhang, 2001); *Streptococcus pneumoniae* serotype 6B pneumococus (Bernardshaw et al., 2005); coliforms (enterococci, a-hemolytic, hemolytic and non-hemolytic streptococci) (Bernardshaw et al., 2006); oral mutans streptococci (*Streptococcus mutans* UA159 and *Streptococcus sobrinus* 6715) (Lund et al., 2009); *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa* (Mazzutti et al., 2012); *Listeria monocytogenes* (Stojkovic et al., 2014); and *P. aeruginosa* (Soković et al., 2014).

Discussion

This research identified that there is currently a shortage of data obtained from scientific studies on the antimicrobial action of the mushroom *A. blazei* available. This finding may be due to the importance of other *A. blazei* properties, such as the immunomodulatory and antitumor properties, reflecting in the scientific literature and increasingly prompting researchers to verify these functions when adopting the various designs for their studies. It is noteworthy that there was a great diversity of places where the publications that deal with antimicrobial activity were performed; however, the English language was predominant. The values for the ISI impact factors of the journals in which the publications appeared reveal that there is quality in the methodology employed by the authors, promoting a reduction in the bias which could interfere in our results.

Table 1
Distribution of manuscripts according to the identification, type of study, level of evidence, publication year, journal features and antimicrobial action of *Agaricus blazei*.

Antimicrobial action *Agaricus blazei*	Type of study/level of evidence	Manuscript authors	Journal	Journal Citation Reports (2014)
Bactericidal action against *Salmonella typhi.*	Preclinical study (animals/*in vitro*)	Osaki et al., 1994	*Yakugaku Zasshi*	0.263
Extracts of *A. blazei* and aqueous ethanol, did not exercise antimicrobial activity against the strains tested (*S. aureus, B. sabtilis, E. coli*).	Preclinical study (animals/*in vitro*)	Zhuqiu and Zhang, 2001	*Journal Food Science*	2.203
Protective effect against *S. pneumoniae* 6B infection (24 h when administered before or together with the inoculation). No effect on antibiotic pneumococci in *vitro*.	Preclinical study (animals/*in vitro*)	Bernardshaw et al., 2005	*Scandinavian Journal of Immunology*	1.739
Reduction in bacteremia and increased survival (↓ lethal septicemia) in mice with fecal peritonitis.	Preclinical study (animals/*in vitro*)	Bernardshaw et al., 2006	*Shock*	3.045
The ethanol extract (100%) inhibited the growth of *Streptococcus mutans* UA159 and *Streptococcus sobrinus* 6715 using the diffusion method in agar. In tests of MIC and MBC, the three extracts (50%, 75% and 100%) had antimicrobial properties.	Preclinical study (animals/*in vitro*)	Lund et al., 2009	*Pharmaceutical Biology*	1.241
A. blazei extracts obtained from low pressure techniques (using various solvents) as well as by supercritical fluid extraction had a higher antibacterial activity toward Gram positive bacteria (*S. aureus* and *B. cereus*). However, the extracts tested against Gram-negative bacteria (*E. coli*, *P. aeruginosa*) can be classified as weak inhibitors.	Preclinical study (animals/*in vitro*)	Mazzutti et al., 2012	*The journal of supercritical fluids*	2.371
Ethanol extract of *A. blazei* showed greater antimicrobial activity against the growth of *Listeria monocytogenes* when compared to other mushrooms.	Preclinical study (animals/*in vitro*)	Stojkovic et al., 2014	*Food Funct*	2.791
Aqueous extract of *A. blazei* caused a significant reduction in virulence factors (pyocyanin production, motility) and biofilm formation of *Pseudomonas aeruginosa*.	Preclinical study (animals/*in vitro*)	Soković et al., 2014	*Molecules*	2.416

MIC, minimal inhibitory concentration; MBC, minimal bactericidal concentration; JCR, Journal Citation Reports.
The arrows indicate stimulation or inhibition promoted by *A. blazei*.

The categorization of all studies as preclinical trials, together with the small number of articles published in the scientific literature, suggests that there is a need for more research to address the antimicrobial function of *A. blazei*, including the adoption of other methods, especially *in vivo* testing.

The antimicrobial properties of *A. blazei* have been confirmed in most research studies using *in vitro* methods (Osaki et al., 1994; Lund et al., 2009; Mazzutti et al., 2012; Stojkovic et al., 2014; Soković et al., 2014) and *in vivo* testing mice, noting that in this sample group the mushroom extract exerted action against microorganisms that cause lethal infections caused by pneumococci (Bernardshaw et al., 2005) and fecal peritonitis (Bernardshaw et al., 2006). However, Zhuqiu and Zhang (2001) found no antibacterial effects of *A. blazei* against four different types of microorganisms analyzed employing the minimum inhibitory growth method. In addition, other researchers have found that there was no antimicrobial effect of *A. blazei* using an *in vitro* method, although they did observe this property in mice (Bernardshaw et al., 2005). The reason for the negative results obtained in these two studies is probably based on the fact that the antimicrobial mechanism of action of bioactive substances present in the mushroom requires engagement with the immune system, especially the innate immune system, which cannot be demonstrated *in vitro* (Lull et al., 2005).

The results for research which confirmed the antimicrobial activity of extracts of the mushroom *A. blazei* mostly identified greater inhibition for the Gram-positive bacteria (compared with Gram-negative bacteria), such as *Salmonella typhi*, *Streptococcus pneumoniae*, *Streptococcus mutans, Streptococcus sobrinus*, *Staphylococcus aureus, B. cereus*, *L. monocytogenes* and coliforms. Koneman et al. (1999) suggest that the hypothesis which explains these data is based on the structural differences presented by Gram-negative microorganisms, such as a greater number of flow pumps or the presence of an outer membrane on the thin peptidoglycan layer (Schweizer, 2003; Lister et al., 2009; Breidenstein et al., 2011).

The scientific evidence obtained from all studies analyzed in this review is closely related to the type of mushroom extract adopted. Due to the significant influence of certain environmental and methodological factors, the type and quantity of bioactive constituents of *A. blazei* may vary according to the cultivation method, climatic and soil conditions, use of raw or dehydrated mushrooms, use of dry extract, type of solvent extraction, methodology employed for the preparation of the solutions and storage procedure (Dai et al., 2010; Lim et al., 2012; Montoya et al., 2013). It is important to note that in the two studies where the *in vivo* antimicrobial effect of *A. blazei* was observed (Bernardshaw et al., 2005, 2006), a commercial aqueous extract was used as the reagent.

Although this product is widely used by the Japanese population, the description of the chemical composition of this extract is highly relevant in order to identify the possible compounds responsible for the antibacterial property and guide future research, and this was not carried out in the studies in which it was used as a reagent (Stojkovic et al., 2013; Su et al., 2016).

Alves et al. (2012) conducted a review in order to describe the antimicrobial properties of extracts obtained from various mushrooms and highlight some of the active compounds identified, including compounds of low and high molecular weight. The researchers found that mushrooms have several antimicrobial substances represented by low molecular weight compounds which are mostly secondary metabolites, such as terpenes, sesquiterpenes and other steroids, anthraquinones, benzoic acid derivatives and quinoline, as well as primary metabolites such as oxalic acid. However, peptides and proteins are considered to be the major antimicrobial compounds of high molecular weight present in mushrooms. Data in the literature indicate greater antimicrobial activity of mushroom extracts against Gram-positive bacteria.

However, in this research the mushroom *A. blazei* was not mentioned.

Currently, it is well established in the literature that the basiodimycete *A. blazei* contains various bioactive compounds that promote a variety of functional properties, acting individually and/or synergistically. Thus, it is important to understand which active substances play a role in the antimicrobial action. However, the scientific literature does not provide information on which bioactive compound in *A. blazei* exercises this function or on the mechanism of action. However, among the hypotheses suggested by researchers some compounds are notable, such as β-glucans (Gonzaga et al., 2009; Yamanaka et al., 2012), antioxidants (Silva et al., 2009; Mourão et al., 2011; Carvajal et al., 2012; Jia et al., 2013; Hakime-Silva et al., 2013; Wu et al., 2014), ergosterol (Zou, 2006; Gao et al., 2007; Hong and Gu, 2007; Hetland et al., 2008; Shu and Lin, 2011), tocopherol (Tsai et al., 2007), agaritine (Endo et al., 2010), phenolic compounds (Soares et al., 2009) and nucleotides and nucleosides (Oliveira et al., 2010).

Some researchers have suggested that the antimicrobial action promoted by *A. blazei* mushroom extracts can be explained based on the premise that β-glucans stimulate the synthesis and secretion of cytokines by macrophages (Sorimachi et al., 2001), especially the pro-inflammatory compounds, and activate the complement system (Shimizu et al., 2002). *A. blazei* contain a significant amount of β-glucans (Hetland et al., 2000; Hetland and Sandven, 2002; Godshall et al., 2003) which, in addition to stimulating the innate immune system, exert an antimicrobial effect (Shin et al., 2005; Chan et al., 2009).

Recently, Hetland et al. (2013) published a review which aimed to compare the antimicrobial effects of the following types of polysaccharides: β-glucans, pectin and commercial *A. blazei* mushroom extract (AndoSan™). These researchers demonstrated that β-glucans are present in the structure of yeasts and mushrooms and that pectin is present in *Plantago major* L., these having anti-infection properties in various models of mice against microorganisms, including bacteria.

The antimicrobial property of β-glucans has been verified *in vitro* in macrophages infected with *M. tuberculosis* (Hetland and Sandven, 2002) and *in vivo* in mice infected with *Mycobacterium bovis* (Hetland et al., 1998). The β-glucans promote the stimulation of the innate immune system through their connection with certain specific receptors on immune cells, such as Toll-like receptor 2 (TLR2), dectin-1 and CD11b/18. However, mushrooms may contain molecular substances other than β-glucans, which can similarly activate an innate immune response (Dalonso et al., 2015).

The AndoSan™ extract containing *A. blazei*, as well as two other types of mushroom, in its composition, has been analyzed in two studies (Bernardshaw et al., 2005, 2006), and its antimicrobial action has been confirmed. This is probably exerted by the mushroom *A. blazei*, since it is present in greater quantity in this extract when compared to the other fungi.

The probable mechanism of action associated with the antimicrobial effects of *A. blazei* mushroom extract (AndoSan™) is increased serum levels of pro-inflammatory cytokines MIP-2, which is equivalent to interleukin-8 (IL-8) in humans, and tumor necrosis factor (TNF-α) in mice that received *A. blazei* mushroom extract (Bernardshaw et al., 2005). Alternatively, this protective effect could be promoted by *A. blazei*-mediated innate immunity.

In a study by Bernardshaw et al. (2006) using a model of peritonitis in mice it was found that the AndoSan™ extract exerted an antimicrobial action and the researchers suggested that the mechanism is based on the inhibitory action of TLR-4 receptor-mediated cell stimulation of NF-kB activation *via* TLR-2. This mechanism may explain the protective effect of the extract in this model of sepsis induced by Gram-negative microorganisms (Tryggestad et al., 2013).

According to Hetland et al. (2013), this extract was notable among the other polysaccharides investigated in this study, that is, β-glucans and pectin, since it was more effective in terms of its antimicrobial action, based on previously reported results (Bernardshaw et al., 2005, 2006).

However, Soković et al. (2014) hypothesized that the mechanism of action associated with the antimicrobial property promoted by the mushroom *A. blazei* is not based on the stimulation of innate immunity, but could be explained by the induction of anti-quorum (anti-QS). Anti-QS detection compounds have been shown to disrupt the formation of biofilms and consequently make them more susceptible to antibiotic bacteria. These compounds are also able to reduce the virulence factor of the bacteria and promote the elimination of bacteria in animal models (Ta and Arnason, 2016).

One study investigated the effect of an aqueous extract of *A. blazei* on the virulence factors of the quorum system (QS) and biofilm formation against the bacterium *P. aeruginosa*. The results show that the aqueous extract of *A. blazei* exhibited antibacterial action and also anti-quorum activity. The extract had an effect on all mechanisms tested, promoting a reduction in biofilm formation and motility and decreasing the synthesis of pyocyanin pigment. The researchers suggested that this data obtained for the aqueous extract of *A. blazei* may be used for the prevention and/or control of the growth of *P. aeruginosa* (Soković et al., 2014).

One of the substances present in *A. blazei* is linoleic acid (Mazzutti et al., 2012), which is considered to be one of the bioactive components that promote the bactericidal activity of this mushroom (Fortes and Novaes, 2006). Linoleic acid is considered to be an essential unsaturated fatty acid, because the human body does not have the biological capacity to synthesize it (Sanhueza et al., 2002). This fatty acid has several functions, notably reducing the serum levels of triglycerides and cholesterol, decreasing the risk of allergies, cancer and atherosclerosis and antimicrobial activity. The probable mechanism of action of the antimicrobial activity promoted by the linoleic acid is the ability of this fatty acid to break the membranes of bacterial cells and cause cell lysis (Lee et al., 2002).

In a recent study the antimicrobial activity of phenolic compounds from different species of mushrooms has been identified and quantified. The researchers found that the phenolic compounds 2,4-dihydroxybenzoic acid and protocatechuic acid have relatively high antimicrobial activity against most Gram-negative and Gram-positive bacteria. Furthermore, inhibition provided by the phenolic compounds was greater than that of the antibiotics used for the treatment of infection promoted by methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA was inhibited by 2,4-dihydroxybenzoic, vanillic, syringic (MIC = 0×5 mg ml^{-1}) and *p*-coumaric (MIC = 1 mg ml^{-1}) acid. Based on these results the researchers concluded that the presence of carboxylic acid (COOH), two hydroxyls (OH), groups in the *ortho* positions of the benzene ring and also a methoxyl group (OCH_3) in the *meta* position appears to be important in relation to the anti-MRSA activity (Alves et al., 2013).

On the other hand, *A. blazei* contains a variety of other compounds, such as ergosterol (Takaku et al., 2001), other types of fatty acids (Huang et al., 2011), polysaccharides (Hu et al., 2015) and alkaline substances (Ohno et al., 2001) which can also play an important role in the synergistic antimicrobial action. However, only one of the studies analyzed in this review reported the isolation and identification of the bactericidal substance 13-hydroxy-*cis*-9,*trans*-11-octadecadienoic (13*ZE*-LOH) extracted from the fruiting body of *A. blazei* using chloroform-methanol as a solvent (Osaki et al., 1994).

Another issue to be clarified, based on scientific theory, is related to which route for the administration of the *A. blazei* extracts employed favors greater absorption of the bioactive substances and at the same time is the most natural in relation to humans. In

this regard, studies by Bernardshaw et al. (2005, 2006) have confirmed that the oral administration of the *A. blazei* extract in mice promoted antimicrobial action. However, some studies in humans (Johnson et al., 2009; Lima et al., 2012) in which other *A. blazei* mushroom properties were evaluated did not identify any effect when administering the extract of this fungus orally.

Based on the data presented it appears that there is still not sufficient scientific evidence to support the antimicrobial action of *A. blazei* mushroom. The favorable results obtained in the majority of *in vitro* and *in vivo* studies regarding this property have attracted the interest of the scientific community encouraging further research.

Authors' contributions

All authors contributed in collecting and analyzing data besides drafting parts of the paper. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

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