A Review on Antimicrobial Activity of Mushroom (Basidiomycetes) Extracts and Isolated Compounds

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Abstract

Despite the huge diversity of antibacterial compounds, bacterial resistance to first-choice antibiotics has been drastically increasing. Moreover, the association between multiresistant microorganisms and nosocomial infections highlight the problem, and the urgent need for solutions. Natural resources have been exploited in the last years and among them, mushrooms could be an alternative source of new antimicrobials. In this review, we present an overview of the antimicrobial properties of mushroom extracts and highlight some of the active compounds identified, including low- and high-molecular weight (LMW and HMW, respectively) compounds. LMW compounds are mainly secondary metabolites, such as sesquiterpenes and other terpenes, steroids, anthraquinones, benzoic acid derivatives, and quinolines, but also primary metabolites such as oxalic acid. HMW compounds are mainly peptides and proteins. Data available from the literature indicate a higher antimicrobial activity of mushroom extracts against gram-positive bacteria. Among all the mushrooms, *Lentinus edodes* is the most studied species and seems to have a broad antimicrobial action against both gram-postive and gram-negative bacteria. Plectasin peptide, obtained from *Pseudoplectania nigrella*, is the isolated compound with the highest antimicrobial activity against gram-positive bacteria, while 2-aminoquinoline, isolated from *Leucopaxillus albissimus*, presents the highest antimicrobial activity against gram-negative bacteria.

Abbreviations

CSAP:	*Cordyceps sinensis* antibacterial protein
CFU:	colony forming unities
ERSP:	erythromycin-resistant *Streptococcus pyogenes*
HMW:	high-molecular weight compounds
IC_{50}:	concentration inhibiting 50% of the growth
IZD:	internal zone diameter
LMW:	low-molecular weight compounds
M:	mycelium
MIC:	minimal inhibitory concentration
MRSA:	methicillin-resistant *Staphylococcus aureus*
MRSE:	methicillin-resistant *Staphylococcus epidermidis*
PABA:	*para*-aminobenzoic acid
PRSP:	penicillin-resistant *Streptococcus pneumonia*
VREF:	vancomycin-resistant *Enterococcus faecium*

Introduction

Mushroom bioactivity

For a long time, mushrooms have been playing an important role in several aspects of human activity. Edible mushrooms, for example, are used extensively in cooking and make up part of low-calorie diets. Mythology is extensively garnished by mushrooms and is typically associated with gnomes, fairies, and other fairytale personages. The psychedelic and consciousness expansion properties of some species have pushed mushrooms to become part of some religions. Even toxic mushrooms have found a place of relevance, because of the uniqueness of their compounds that evolved naturally as a protection against consumption [1].

Wild and cultivated mushrooms contain a huge diversity of biomolecules with nutritional [2] and/or medicinal properties [3–5]. Due to these

properties, they have been recognized as functional foods, and as a source for the development of medicines and nutraceuticals. Fruiting bodies, mycelia, and spores accumulate a variety of bioactive metabolites with immunomodulatory, cardiovascular, liver protective, antifibrotic, anti-inflammatory, antidiabetic, antiviral, antioxidant, antitumor, and antimicrobial properties [3–14].

The frequent use of mushrooms is based on three main assumptions: first, they are used as part of a regular diet for their nutritional value (since they are rich in water, minerals, proteins, fibers, and carbohydrates, and are low-caloric foods due to a low content in fat [2]); secondly, fruiting bodies are also appreciated for their delicacy (they are palatability enhancers of flavor and aroma when associated to other foods); and thirdly, mushrooms are widely used for medicinal purposes. Their pharmacological action and therapeutic interest in promoting human health have been known for thousands of years [5, 15, 16].

In particular, mushrooms could be a source of natural antibiotics, which can be LMW and HMW, respectively, compounds. LMW compounds are mainly secondary metabolites such as sesquiterpenes and other terpenes, steroids, anthraquinone and benzoic acid derivatives, and quinolines, but also primary metabolites such as oxalic acid (**Fig. 1**). HMW compounds mainly include peptides and proteins.

It is estimated that there are about 140 000 species of mushrooms on earth, and of these only 22 000 are known and only a small percentage (5%) has been investigated. Therefore, there is

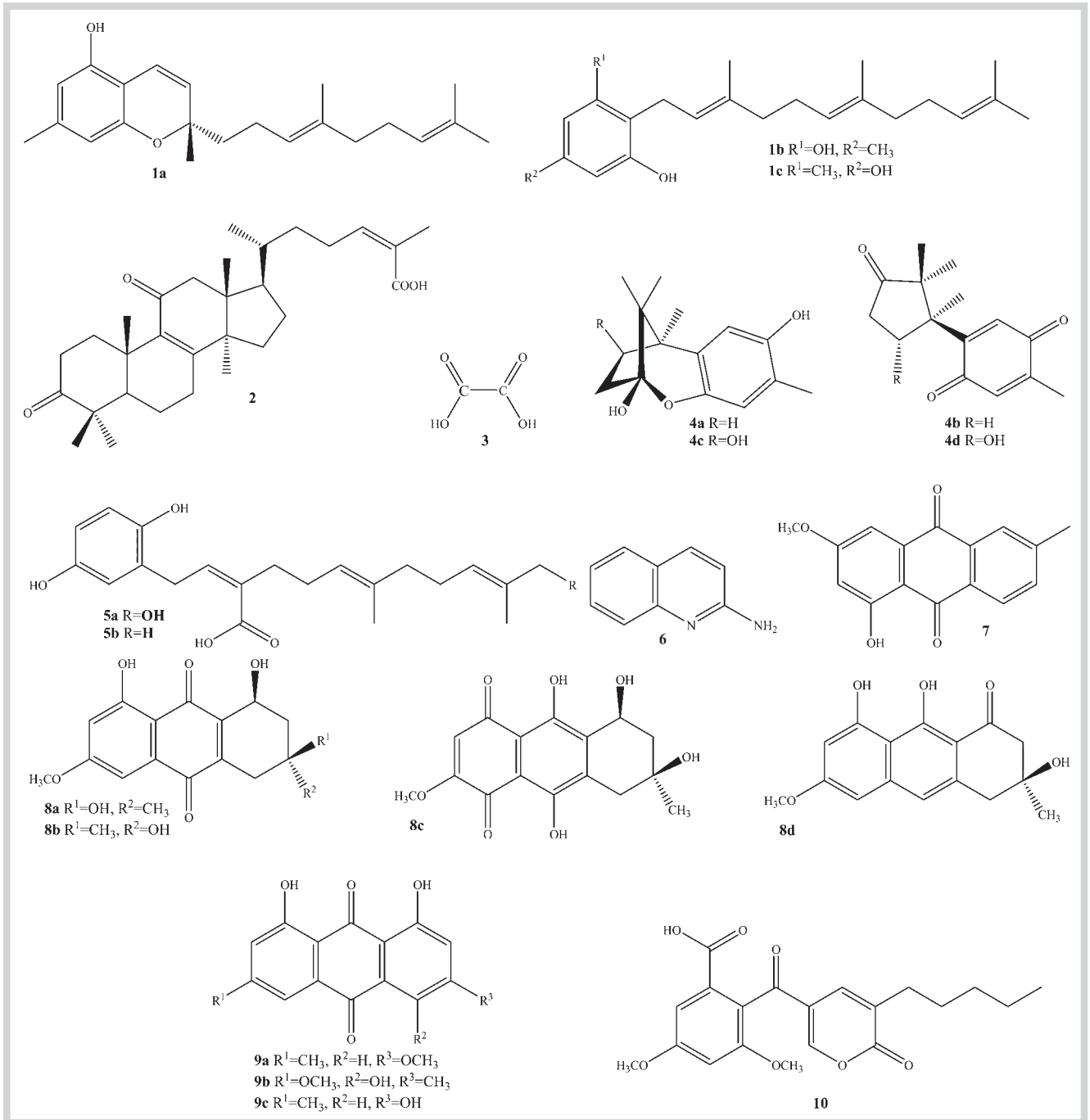

Fig. 1 Chemical structure of the low-molecular weight (LMW) compounds with antimicrobial potential found in mushrooms.

much to explore about mushroom properties and potential applications [4].

Bacteria and drug discovery

The development of antibiotics has been one of the most important scientific achievements of the last seventy years. These compounds act in several ways, by interfering in metabolic processes or in the organism structures [17]. The mechanism of action is mostly related with interferences in the synthesis of the cell wall, modification of plasmatic membrane permeability, interferences in chromosome replication, or in protein synthesis [18]. The cell wall is responsible for the shape and rigidity of bacterial cells, acting as an osmotic barrier [19]. The peptidoglycan content in the cell wall varies between 10% and 60% for gram-negative and gram-positive bacteria, respectively [20,21].

Antiparietal antibiotics act in one of the phases of peptidoglycan synthesis, being classified according to that phase. Phosphomycin, D-cycloserine, glycopeptides (bacitracin, vancomycin, teicoplanin), and beta-lactams (penicillins, cephalosporins, carbapenemics, monobactamics) are some examples of this group [22].

Otherwise, other antibiotics such as ascolistin and daptomycin act at the cell membrane level. Aminoglycosides and tetracyclines, macrolides, oxazolidines, quinupristin and dalfopristin, clindamycin, and chloramphenicol inhibit protein synthesis by interfering with 30 s or 50 s ribosomal subunits. Quinolones, rifampicin, and metronidazol inhibit nucleic acid synthesis. Sulfonamides and trimetoprim are antimetabolic antibiotics that inhibit the metabolic chain of PABA, essential to cell growth [23].

Despite the huge diversity of antibacterial compounds, bacterial resistance to first-choice antibiotics has been drastically increasing. Some examples are microorganisms such as *Klebsiella* spp. and *Escherichia coli*, which produce broad-spectrum beta-lactamase or present resistance to third-generation cephalosporins. Other examples include MRSA, *Enterococcus* spp., which is resistant to vancomycin [24,25], *Acinetobacter* spp. with an increasing resistance to carbapenems and colistin [26], and *Pseudomonas* spp., which is resistant to aminoglycosides, carbapenemics. and/or cephalosporins [24].

Diseases that were easily healed are nowadays becoming a serious problem due to emergent antibiotic resistance [27,28]. The association between multiresistant microorganisms and hospital infections certainly highlights this problem and the urgent need for solutions [29]. In 2010, the World Health Organization advised all countries to implement control procedures for the propagation of drug multiresistant bacteria, highlighting the risks associated to the absence of alternative therapies against those microorganisms [30].

Therefore, the research of new antimicrobial substances effective against pathogenic microorganisms resistant to current drugs is crucial. New groups of organisms, such as marine, have been increasingly explored in the last years, and among them, mushrooms could be an alternative source for new antimicrobials. In this review, we provide an overview about the antimicrobial properties of mushroom extracts and highlight selected compounds. The databases searched were Medline (1980 to March 2012) and Web of Science (2001 to March 2012) including scientific articles and conference proceedings. Search terms were: "mushrooms", "antimicrobial activity", and "antimicrobials". An exhaustive literature search was performed, but only mushroom extracts and isolated compounds with positive results were included.

Antimicrobial Activity Against Gram-Positive Bacteria

Methodologies

Different methodologies have been used to assess antimicrobial activity of mushroom extracts and compounds, including the microdilution method, the disk diffusion method, the agar streak dilution method based on radial diffusion, and a method with the incorporation of the extract in the culture medium and further determination of colonies. Therefore, the results for antimicrobial activity are expressed in different unities (**Tables 1** and **2**).

The microdilution method comprises microdilutions of the extract in liquid medium using microplates to determine MIC or IC_{50} values. In the disk difusion method, the extract is incorporated in disks at different concentrations, and the halo of growth inhibition is determined and represented by IZD (internal zone diameter) values. The agar streak dilution method based on radial diffusion is most widely used in extracts and implies the extract application in circular holes made in solid medium. The result might be expressed in IZD or MIC values. Regarding the fourth method, the extract is incorporated in the culture medium and then CFU are determined.

Mushroom extracts with antimicrobial activity

Numerous mushroom extracts have been reported as having antimicrobial activity against gram-positive bacteria (**Table 1**).

Agaricus bisporus, the most cultivated mushroom in the world, should be highlighted. Its methanolic extract revealed MIC = 5 µg/mL against *Bacillus subtilis*, even lower than the standard ampicillin (MIC = 12.5 µg/mL) [31], and also showed activity against *Bacillus cereus, Micrococcus luteus, Micrococcus flavus, Staphylococcus aureus*, and *Staphylococcus epidermidis* [15,32,33]. Other *Agaricus* species have also demonstrated antimicrobial activity. *Agaricus bitorquis* and *Agaricus essettei* methanolic extracts showed an inhibitory effect upon all the tested gram-positive bacteria [15]. *Agaricus silvicola* methanolic extract also revealed antimicrobial properties against *Bacillus cereus* (MIC = 5 µg/mL), *Bacillus subtilis* (MIC = 50 µg/mL), and against *Staphylococcus aureus* (MIC = 5 µg/mL), lower than the standard ampicillin (MIC = 6.25 µg/mL) [31]. The mycelium of *Agaricus* cf. *nigrecentulus* and *Tyromyces duracinus* (ethyl acetate extracts) showed activity only against *Staphylococcus saprophyticus* [34].

The ethanolic extracts of *Armillaria mellea* mycelium showed an antibacterial effect against *Sarcina lutea*; however, no activity was observed upon other gram-positive bacteria [35]. However, the ethanolic extract of their fruiting bodies showed broad-spectrum antimicrobial activity [36].

The most studied mushroom of the genus Boletus is *Boletus edulis*. Its methanolic mushroom showed lower antimicrobial activity than other species studied by Ozen et al. [32]. Nevertheless, Barros et al. [31] reported an MIC = 5 µg/mL against *Staphylococcus aureus*, lower than ampicillin (MIC = 6.25 µg/mL).

Cantharellus cibarius methanolic extract demonstrated good activity against *Bacillus subtilis* and *Staphylococcus aureus* [31,32,37]. This mushroom also showed activity against *Bacillus cereus* in some studies [32,37], but it was not so effective in another report [31], which could be related to the different methodologies used to evaluate antimicrobial activity.

Clitocybe alexandri methanolic extract presented significant activity against *Bacillus subtilis* and *Micrococcus luteus* [38]. Kalyoncu et al. [36] tested antimicrobial activity of chloroform and ethanolic extracts from *Clitocybe geotropa*, the latter showing asignificant capacity against *Bacillus cereus*.

Table 1 Mushroom extracts with antimicrobial activity against gram-positive bacteria.

Microorganism	Mushroom[a]	Results	References
Actinomyces naeslundii	*Lentinus edodes*	CFU = 0–3.30 (± 5.48) × 10^6 MIC = 0.05–20 mg/mL	[53,54,67]
Actinomyces viscosus	*Lentinus edodes*	MIC = 0.05–20 mg/mL	[54]
Bacillus cereus	*Agaricus bisporus, Agaricus bitorquis, Agaricus essettei, Agaricus silvicola, Armillaria mellea, Boletus edulis, Cantharellus cibarius, Clitocybe alexandri, Clitocybe geotropa, Cortinarius sp., Gloeoporus thelephoroides, Hexagonia hydnoides, Hydnum repandum, Hypholoma fasciculare, Irpex lacteus* (M), *Lactarius camphorates, Lactarius delicious, Lactarius piperatus, Lactarius volemus, Laetiporus sulphureus, Lentinus edodes, Lepista nuda, Leucopaxillus giganteus* (M), *Macrolepiota procera, Meripilus giganteus* (M), *Meripilus giganteus, Phellinus sp., Pleurotus ostreatus* (M), *Pleurotus ostreatus, Ramaria botrytis, Ramaria flava, Rhizopogon roseolus, Sarcodon imbricatus, Sparassis crispa, Tricholoma portentosum*	IZD = 5–21 mm MIC = 5 µg/mL – 100 mg/mL	[11,15,31,32,34–38,45–48,50,55]
Bacillus megaterium	*Lentinus edodes*	CFU = 0 (total inhibition)	[52]
Bacillus pumilis	*Lentinus edodes*	IZD = 14 mm	[50]
Bacillus subtilis	*Agaricus bisporus, Agaricus bitorquis, Agaricus essettei, Agaricus silvicola, Armillaria mellea, Cantharellus cibarius, Clitocybe alexandri, Clitocybe geotropa, Cortinarius sp., Ganoderma lucidum, Hygrophorus agathosmus, Hypholoma fasciculare, Lactarius delicious, Lactarius piperatus, Laetiporus sulphureus, Lentinus edodes, Lepista nuda,* *Leucopaxillus giganteus* (M), *Meripilus giganteus* (M), *Navesporus floccosa, Paxillus involutus* (M), *Phellinus rimosus, Pleurotus ostreatus* (M), *Pleurotus ostreatus, Ramaria botrytis, Ramaria flava, Rhizopogon roseolus, Sparassis crispa, Suillus collitinus, Tricholoma acerbum, Tricholoma portentosum*	IZD = 5–28 mm MIC = 5 µg/mL – 300 mg/mL	[11,15,31,35–40,44–50,54,55,71]
Enterococcus faecalis	*Lentinus edodes*	IZD = 8 mm	[50]
Enterococcus faecium	*Lentinus edodes*	MIC > 1.5 – > 5 0 mg/mL	[54]
Lactobacillus casei	*Lentinus edodes*	CFU = 5.00 (± 7.07) × 10^{-1} – 9.28 (± 2 .76) × 10^2 MIC = 0.05–15 mg/mL	[53,54,67]
Listeria innocua	*Lentinus edodes*	IZD = 8 mm	[11]
Listeria monocytogenes	*Lentinus edodes, Pycnoporus sanguineus* (M),	IZD = 11–13 mm	[11,34,50]
Staphylococcus sp.	*Lentinus edodes*	IZD = 12 mm	[50]
Staphylococcus aureus	*Agaricus bisporus, Agaricus bitorquis, Agaricus essettei, Agaricus silvícola, Armillaria mellea, Boletus edulis, Cantharellus cibarius, Clitocybe geotropa, Cortinarius sp., Cortinarius abnormis, Cortinarius ardesiacus, Cortinarius archeri, Cortinarius austroalbidus, Cortinarius austrovenetus, Cortinarius austroviolaceus, Cortinarius coelopus, Cortinarius clelandii, Cortinarius [Dermocybe sp, Dermocybe canaria, Dermocybe kula], Cortinarius fulvoiubatus, Cortinarius ianthinus, Cortinarius memoria-annae, Cortinarius persplendidus, Cortinarius sinapicolor, Cortinarius submagellanicus, Cortinarius tricholomoides, Cortinarius vinosipes, Ganoderma lucidum, Hydnum repandum, Hygrophorus agathosmus, Hypholoma fasciculare, Irpex lacteus* (M), *Lactarius camphoratus, Lactarius delicious, Lactarius piperatus, Lactarius volemus, Laetiporus sulphureus, Lentinus edodes, Lepista nuda, Leucopaxillus giganteus* (M), *Macrolepiota procera, Meripilus giganteus* (M), *Meripilus giganteus, Morchella elata* (M), *Morchella esculenta* var. *vulgaris* (M), *Navesporus floccosa, Nothopanus hygrophanus* (M), *Paxillus involutus* (M), *Phellinus rimosus, Pleurotus eryngii* (M), *Pleurotus ostreatus* (M), *Pleurotus sajor-caju, Pycnoporus sanguineus* (M), *Ramaria botrytis, Ramaria flava, Sparassis crispa, Suillus collitinus*	CFU = 2.1 × 10^4 IZD = 8–24 mm MIC = 5 µg/mL – 50 mg/mL IC_{50} < 0.01 – ≥ 2.00 mg/mL	[10,11,15,31–37,39,40,44,46–50,52,54,55]
MRSA	*Lentinus edodes, Phellinus linteus*	IZD = 12 mm MIC = 500 µg/mL	[50,51]
Staphylococcus epidermidis	*Agaricus bisporus, Hygrophorus agathosmus, Lentinus edodes, Pleurotus sajor-caju, Suillus collitinus*	IZD = 11–27 mm MIC = 7.81–62.5 µg/mL	[11,33,44,50]
Streptococcus gordonii	*Lentinus edodes*	MIC = 0.075–50 mg/mL	[54]
Streptococcus mitis	*Lentinus edodes*	MIC = 0.075–15 mg/mL	[54]
Streptococcus mutans	*Lentinus edodes*	CFU = 2.15 (± 5.58) × 10^5 MIC = 0.1–10 mg/mL	[53,54,67]
Streptococcus oralis	*Lentinus edodes*	MIC = 0.1 – > 50 mg/mL	[54]
Staphylococcus saprophyticus	*Agaricus cf. nigrecentulus* (M), *Tyromyces duracinus* (M)	IZD > 12 mm	[34]
Streptococcus pyogenes	*Lentinus edodes*	CFU = 6.0 × 10^4	[52]
Streptococcus salivarius	*Lentinus edodes*	MIC = 0.1–10 mg/mL	[54]

Table 1 *(continued)*

Microorganism	Mushroom[a]	Results	References
Streptococcus sanguinis	*Lentinus edodes*	CFU = 2.53 (± 0.62) × 10^6 – 5.06 (± 1,58) × 10^6 MIC = 0.075–50 mg/mL	[53, 54, 67]
Streptococcus sobrinus	*Lentinus edodes*	MIC = 0.075–20 mg/mL	[54]
Micrococcus flavus	*Agaricus bisporus, Agaricus bitorquis, Agaricus essettei, Laetiporus sulphurous, Ramaria flava*	IZD = 20–23 ± 1 mm	[15, 47, 48]
Micrococcus luteus	*Agaricus bisporus, Agaricus bitorquis, Agaricus essettei, Clitocybe alexandri, Laetiporus sulphurous, Lentinus edodes, Ramaria flava*	IZD = 10–21 ± 1 mm	[15, 38, 47, 48, 52]
Sarcina lutea	*Armillaria mellea* (M), *Armillaria mellea, Clitocybe geotropa, Meripilus giganteus* (M), *Meripilus giganteus, Morchella costata* (M), *Morchella esculenta* var. *vulgaris* (M), *Paxillus involutus* (M), *Pleurotus ostreatus* (M), *Sparassis crispa*	IZD = 8–27 mm	[35, 36]

[a] Acetone, chloroform, ethanol, ethyl acetate, methanol, dichloromethane, ether, xylene, or water extracts. M – mycelium, the other samples refer to the fruiting body; MRSA – methicillin-resistant *Staphylococcus aureus*. The antimicrobial activity is expressed in CFU (colony forming unities), MIC (minimal inhibitory concentrations), IZD (internal zone diameter), or IC_{50} (concentrations inhibiting 50% of the growth) values

The genus Cortinarius is one of the most diverse genera of mushrooms. Ethyl acetate extracts of *C. ardesiacus, C. archeri, C. atrosanguineus, C. austrovenetus, C. austroviolaceus, C. coelopus, C. [Dermocybe canaria], C. clelandii, C. [D. kula], C. memoria-annae, C. persplendidus, C. sinapicolor, C. vinosipes*, and 47 other collection samples not identified to the species level, exhibited IC_{50} values of ≤ 0.09 mg/mL against *Staphylococcus aureus* [10]. However, in a study reported by Ozen et al. [32], *Cortinarius sp.* methanolic extracts showed lower activity against *Staphylococcus aureus*. This demonstrates the effect of solvent extraction in the type and concentration of compounds present in the final extract and, consequently, the spectrum of antimicrobial activity.

Ganoderma lucidum is one of the most famous traditional medicinal mushrooms. Various extracts have been found to be equally effective when compared to gentamycin sulphate, the acetone extract being the most effective. This mushroom had moderate inhibition against *Bacillus subtilis* and *Staphylococcus aureus* for any extract [39], but in the study reported by Sheena et al. [40], its methanolic extract showed poor antimicrobial activity. Other authors described the capacity of the aqueous extract to inhibit 15 types of gram-positive and gram-negative bacteria, with the highest inhibition exhibited against *Micrococcus luteus* [41].

Ethyl acetate extracts of *Phellinus* sp., *Gloeoporus thelephoroides*, and *Hexagonia hydnoides* inhibited *Bacillus cereus* growth, while the same extract of *Nothopanus hygrophanus* mycelium presented inhibitory activity against *Listeria monocytogenes* and *Staphylococcus aureus. Irpex lacteus* mycelium extract was the most effective, presenting a broad spectrum of activity [34].

The antimicrobial activity of *Pycnoporus sanguineus* has been known since 1946, when Bose isolated poliporin, a compound active against gram-positive and gram-negative bacteria and without toxicity in experimental animals. Rosa et al. reported inhibition against *Listeria monocytogenes* and *Staphylococcus aureus* [34]. Smânia et al. [42, 43] showed that this mushroom produces cinnabarine, an orange pigment active against *Bacillus cereus, Staphylococcus aureus, Leuconostoc mesenteroides, Lactobacillus plantarum*, and several *Streptococcus* spp. Cinnabarine was more active against gram-positive than gram-negative bacteria [34].

The chloroform extract of *Hygrophorus agathosmus* and dichloromethane of *Suillus collitinus* were active against all the tested gram-positive bacteria. The highest antibacterial activity was seen in the extract of *H. agathosmus* against *Staphylococcus epidermidis* and *Bacillus subtilis*, with MIC values 7.81 µg/mL lower than the reference antibiotic streptomycin (MIC = 15.62 µg/mL). MIC values (15.62 µg/mL) against *Staphylococcus aureus* were equal to the ones of streptomycin. *Suillus collitinus* showed MIC values much higher than the standard [44].

One nonedible mushroom, *Hypholoma fasciculare* (methanolic extract), presented high antimicrobial activity against gram-positive bacteria, namely *Bacillus cereus, Bacillus subtilis*, and *Staphylococcus aureus* [37].

All the tested gram-positive bacteria were susceptible to methanolic extracts of *Lactarius* species and *Tricholoma portentosum* [32, 45, 46]. Among *Lactarius* species (*L. piperatus, L. camphorates, L. volemus, L. delicious*), *L. camphoratus* methanolic extract was the one with greater antimicrobial activity [32]. Methanolic extracts of *Ramaria botrytis* and the ethanolic extract of *Ramaria flava* inhibited the growth of gram-positive bacteria better than gram-negative bacteria [47]. The antimicrobial effect of the ethanolic extract of *Laetiporus sulphureus* was tested by Turkoglu et al. [48] and strongly inhibited the growth of the gram-positive

Table 2 Mushroom compounds with antimicrobial activity against gram-positive bacteria.

Microorganism	Compound (mushroom)	Results	References
Bacillus cereus	Confluentin (**1a**), Grifolin (**1b**) and Neogrifolin (**1c**) (*Albatrellus flettii*); 3,11-Dioxolanosta-8,24(*Z*)-diene-26-oic acid (**2**) (*Jahnoporus hirtus*); Oxalic acid (**3**) (*Lentinus edodes* M); Proteins and peptides: Plectasin (*Pseudoplectania nigrella*)	IZD = 17 mm MIC = 10 µg/mL – ≥ 128 mg/L	[56, 59, 63]
Bacillus subtilis	Peptides: Peptaibol Boletusin, Peptaibol Chrysospermin 3 and Peptaibol Chrysospermin 5 (*Boletus* spp.); Protein (*Cordyceps sinensis*); Enokipodins A, B, C and D (**4a–d**) (*Flammulina velutipes* M); Ganomycin A and B (**5a, b**) (*Ganoderma pfeifferi*)	MIC > 100 000 g/L IZD = 11–28 mm	[57, 58, 61, 64]
Bacillus thuringiensis	Plectasin (*Pseudoplectania nigrella*)	MIC = 0.5 mg/L	[63]
Corynebacterium diphtheriae	Plectasin (*Pseudoplectania nigrella*)	MIC = 8 mg/L	[63]
Corynebacterium jeikeium	Plectasin (*Pseudoplectania nigrella*)	MIC = 2 mg/L	[63]
Corynebacterium lilium	Peptaibol Boletusin, Peptaibol Chrysospermin 3 and Peptaibol Chrysospermin 5 (*Boletus* spp.)	IZD = 23–25 mm	[64]
Enterococcus faecalis	**1a, 1b** and **1c** (*Albatrellus flettii*); **2** (*Jahnoporus hirtus*); Plectasin (*Pseudoplectania nigrella*)	MIC = 0.5 µg/mL – ≥ 128 mg/L	[56, 63]
Enterococcus faecium; VREF	Plectasin (*Pseudoplectania nigrella*)	MIC = 32–64 mg/L	[63]
Micrococcus flavus	**5a, b** (*Ganoderma pfeifferi*)	IZD = 25–26 mm	[57]
Staphylococcus aureus	Peptaibol Boletusin, Peptaibol Chrysospermin 3 and Peptaibol Chrysospermin 5 (*Boletus* spp.); Proteins (*Cordyceps sinensis*); 6-Methylxanthopurpurin-3-*O*-methyl ether (**7**), (1S,3S)-Austrocortilutein (**8a**), (1S,3R)- Austrocortilutein (**8b**), (1S,3S)-Austrocortirubin (**8c**) and Torosachrysone (**8 d**) (*Cortinarius basirubencens*); Physcion (**9a**), Erythroglaucin (**9b**) and Emodin (**9c**) (*Cortinarius* sp.); **4a–d** (*Flammulina velutipes* M); **5a, b** (*Ganoderma pfeifferi*); **3** (*Lentinus edodes* M); Ribonuclease (*Pleurotus sajor-caju*); Plectasin (*Pseudoplectania nigrella*);Fraction B (*Pycnoporus sanguineus*); Coloratin A (**10**) (*Xylaria intracolarata*)	IZD = 12–24 mm MIC = 0.156 mg/L–50 000 g/L IC_{50} = 0.7–> 50 µg/mL IC_{50} = 34 ± 4 µM	[10, 42, 57–64]
MRSA	Plectasin (*Pseudoplectania nigrella*);	MIC = 32 mg/L	[63]
Staphylococcus epidermidis; MRSE	Plectasin (*Pseudoplectania nigrella*)	MIC = 8 mg/L	[63]
Streptococcus sp.	Peptaibol Chrysospermin 3 (*Boletus* spp.)	IZD = 9 mm	[60]
Streptococcus faecalis	**3** (*Lentinus edodes* M.)	IZD = 13 mm	[59]
Streptococcus group A, B, C, G	Fraction B (*Pycnoporus sanguineus*)	MIC = 0.019–0.039 mg/mL	[42]
Streptococcus pneumonia; PRSP	Plectasin (*Pseudoplectania nigrella*)	MIC = 0.5 mg/L	[63]
Streptococcus pyogenes; ERSP	Plectasin (*Pseudoplectania nigrella*)	MIC = 0.125 mg/L	[63]

M – mycelium, the other samples refer to the fruiting body. The antimicrobial activity is expressed in MIC (minimal inhibitory concentrations), IZD (internal zone diameter), or IC_{50} (concentrations inhibiting 50% of the growth) values. VREF – vancomycin-resistant *Enterococcus faecium;* MRSA – methicillin-resistant *Staphylococcus aureus*; MRSE – methicillin-resistant *Staphylococcus epidermidis*; PRSP – penicillin-resistant *Streptococcus pneumonia;* ERSP – erythromycin- resistant *Streptococcus pyogenes*

bacteria tested, including *Bacillus subtilis, Bacillus cereus, Micrococcus luteus*, and *Micrococcus flavus*.

The *Lepista nuda* methanolic extract had a good action on gram-positive bacteria, more specifically on *Bacillus cereus, Bacillus subtilis*, and *Staphylococcus aureus* [37, 49].

Ishikawa et al. reported the inhibitory activity of *Lentinus edodes* ethyl acetate extract against *Bacillus cereus, Bacillus subtilis, Staphylococcus aureus*, and *Staphylococcus* epidermidis [11]. This mushroom (aqueous extract) as well as the *n*-BuOH fraction of the *Phellinus linteus* methanol extract demonstrated good activity against MRSA [50, 51]. Furthermore, *Streptococcus pyogenes* was very sensitive to the *Lentinus edodes* chloroform extract [52]. The ability of *L. edodes* extracts to improve oral health has also been extensively researched, since it showed a strong bactericidal effect upon *Streptococcus mutans*, which is strongly implicated in dental caries and tooth decay [53, 54].

The mycelium of *Leucopaxillus giganteus* (methanolic extract) presented antimicrobial capacity, inhibiting only gram-positive bacteria and, in decreasing order, *Staphylococcus* aureus > *Bacillus cereus* > *Bacillus subtilis* [55]. The authors stated that the most promising nitrogen source to produce mushrooms with an increased content in bioactive compounds that inhibit gram-positive bacteria growth was $(NH_4)_2HPO_4$.

The methanolic extracts of *Phellinus rimosus* and *Navesporus floccosa* showed moderate inhibition of *Bacillus subtilis* and *Staphylococcus aureus* [40].

Pleurotus ostreatus and *Meripilus giganteus* showed broad-spectrum antimicrobial activity. The maximum effect was shown by the ethanolic extracts of *Pleurotus ostreatus* against *Sarcina lutea* [35].

The ether extract of *Pleurotus sajor-caju* showed high antibacterial activity against *Staphylococcus aureus*, whereas *Staphylococcus epidermidis* showed high sensitivity for the ethanol extract [33].

Overall, it should be pointed out that the most susceptible gram-positive bacteria to mushroom inhibitory action are *Staphylococos aureus, Bacillus cereus*, and *Bacillus subtilis. Agaricus bisporus* [15, 32, 33], *Agaricus bitorquis* [15], *Boletus edulis* [31, 32], *Cantharellus cibarius* [31, 32, 37], *Lentinus edodes* [11, 50, 54], and different *Cortinarius* sp. [10] seem to be a good option to inhibit *Staphylococos aureus*, and in some cases, *Bacillus cereus* and *Bacillus subtilis*. Studies with microorganisms related to nosocomial infections and multiresistance cases such as *Enterococcus faecalis, Enterococcus faecium*, and MRSA are scarce. Nevertheless, in the few studies available, *Lentinus edodes* [50] was reported to inhibit *Enterococcus faecalis, Enterococcus faecium*, and MRSA. The latter

microorganism was also inhibited by *Phellinus linteus* [51] and *Pleurotus ostreatus* [50]. It is important to develop new studies with different mushroom species and, moreover, with these microorganisms that are so problematic to human health.

Antimicrobial compounds from mushrooms

Most studies on mushrooms with antibacterial activity describe the action of its extracts without identifying the compounds responsible for this activity. However, some compounds have been described as active against gram-positive bacteria (**Table 2**). Five of these compounds are terpenes. Confluentin (**1a**), grifolin (**1b**), and neogrifolin (**1c**) from *Albatrellus fletti* showed activity against *Bacillus cereus* and *Enterococcus faecalis.* The best result was for *Enterococcus faecalis* (MIC 0.5 to 1.0 mg/mL) [56]. Ganomycin A and B (**5 a, b**), isolated from *Ganoderma pfeifferi*, showed activity against *Bacillus subtilis, Micrococcus flavus*, and *Staphylococcus aureus* (15–25 mm zones of inhibition at a concentration of 250 µg/mL [57].

A steroid, 3,11-dioxolanosta-8,24(Z)-diene-26-oic acid (**2**), was isolated from the *Jahnoporus hirtus* mushroom and revealed activity against *Bacillus cereus* and *Enterococcus faecalis* [56].

Four sesquiterpenes with antimicrobial activity were described. The enokipodins A, B, C, and D (**4a–d**), isolated from the mycelium of *Flammulina velutipes,* with activity against *Bacillus subtilis,* but only enokipodins A and C showed activity against *Staphylococcus aureus* [58].

Oxalic acid (**3**), an organic acid, isolated from the mycelium of *Lentinus edodes,* showed activity against *Bacillus cereus, Staphylococcus aureus*, and *Streptococcus faecalis* [59].

Coloratin A (**10**), a benzoic acid derivative isolated from *Xylaria intracolarata,* inhibited *Staphylococcus aureus* [60].

Eight compounds anthraquinone derivatives were also reported due to their antibacterial activities. 6-Methylxanthopurpurin-3-*O*-methyl ether (**7**), (1*S*,3*S*)-austrocortilutein (**8a**), (1*S*,3*R*)-austrocortilutein (**8b**), (1*S*,3*S*)-austrocortirubin (**8c**), and torosachrysone (**8 d**), isolated from the mushroom *Cortinarius basirubencens*, and physcion (**9a**), erythroglaucin (**9b**), and emodin (**9c**), isolated from other species of *Cortinarius*, were all effective against *Staphylococcus aureus* [10].

In addition to the LMW compounds already mentioned, several antimicrobial compounds with HMW have also been described, in particular, proteins and peptides.

CSAP (*Cordyceps sinensis* antibacterial protein-N-terminal sequence ALATQHGAP), isolated from *Cordyceps sinensis,* showed strong activity against *Staphylococcus aureus* and poor activity against *Bacillus subtilis.* However, the antibacterial action of this protein was bacteriostatic [61].

The ribonuclease isolated from *Pleurotus sajor-caju* showed activity against *Staphylococcus aureus,* acting on RNA [62].

The peptide plectasin, isolated from *Pseudoplectania nigrella*, is a macromolecule belonging to the class of defensins, present in animals and plants, which acts at the cell wall, more specifically in the synthesis of peptidoglycan. This peptide showed activity against *Bacillus cereus, Bacillus thuringiensis, Corynebacterium diphtheriae, Corynebacterium jeikeium, Enterococcus faecalis, Enterococcus faecium,* VREF, *Staphylococcus aureus,* MRSA, *Staphylococcus epidermidis,* MRSE, *Streptococcus pneumonia,* PRSP, and *Streptococcus pyogenes*. The *in vitro* action of plectasin against *Streptococcus pneumoniae* is comparable to the action of penicillin and vancomycin [63].

The peptides peptaibol boletusin, pepteibol chrysospermin 3, and peptaibol chrysospermin 5 (isolated from *Boletus spp.*) allow for the opening of pores for ion transport, and showed activity against *Bacillus subtilis, Corynebacterium lilium*, and *Staphylococcus aureus*. The peptaibol chrysospermin 3 also showed activity against *Streptococcus* sp. [64].

Fraction B from *Pycnoporus sanguineus*, obtained by Smânia et al. [42], whose main constituent is a phenoxazin-3-one-type pigment, showed activity against *Staphylococcus aureus* and *Streptococcus* A, B, C, and G. Lower values of MIC were obtained against *Streptococcus* strains.

The mechanisms of action of most of the compounds described above are not available in the literature.

Antimicrobial Activity Against Gram-Negative Bacteria

Methodologies

The same methodologies already described for gram-positive bacteria are also used in the evaluation of mushroom extracts or compounds antimicrobial activity against gram-negative bacteria. The results are presented in **Tables 3** and **4**.

Mushroom extracts with antimicrobial activity

The antimicrobial activity against gram-negative bacteria shown by different mushroom extracts is not so extensive and is shown in **Table 3**.

The results for *Agaricus bisporus* are contradictory. Barros et al. [31] and Öztürk et al. [15] found no activity against gram-negative bacteria, while Ozen et al. [32] and Tambeker et al. [33] reported positive activity mainly against *Escherichia coli*, but also against *Pseudomonas aeruginosa, Enterobacter aerogenes, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi*, and *Salmonella typhimurium.* However, these divergences may be due to different methods and concentrations used. *Agaricus bitorquis* methanolic extract had some effects against three of the gram-negative bacteria, namely *Yersinia enterocolitica, Klebsiella pneumoniae*, and *Proteus vulgaris* [15]. *Agaricus essettei, Agaricus silvicola, Agaricus silvaticus*, and *Agaricus* cf. *nigrecentulus* did not show any antibacterial activity against gram-negative bacteria [15, 31, 34].

Ethanolic extracts of *Armillaria mellea* fruiting bodies revealed better antimicrobial activity than chloroform extracts and mycelium extract upon gram-negative bacteria [35, 36].

According to Barros et al. [31, 37], *Cantharellus cibarius* showed no activity against gram-negative bacteria, as opposed to Ozen et al. [32], who reported there was activity against *Escherichia coli* and *Pseudomonas aeruginosa*.

Enterobacter aerogenes and *Escherichia coli* were inhibited by the methanolic extract of *Clitocybe alexandri* [38]. *Clitocybe geotropa* chloroform and ethanolic extracts inhibited the growth of all gram-negative bacteria tested, with *Proteus vulgaris* being the most sensitive [36].

Beatttie et al. [10] reported anti-*Pseudomonas aeruginosa* activity of the genus *Cortinarius* and its subgenus, *Dermocybe* (methanolic extracts). Four species were tested, namely *C. abnormis, C. austroalbidus, C.* [*D. kula*], *C. persplendidus*, and eleven *Cortinarius* collection samples not identified to the species level, obtaining IC_{50} values ≤ 0.09 mg/mL against *P. aeruginosa*.

The acetone extract from *Ganoderma lucidum* showed strong antibacterial activity, mainly against *Klebsiella pneumonia* [39]. Further studies indicate that the antimicrobial combination of *G. lucidum* extracts with chemotherapeutic agents (ampicillin, cefazolin, oxytetracycline, and chloramphenicol) resulted in syner-

Table 3 Mushroom extracts with antimicrobial activity against gram-negative bacteria.

Microorganism	Mushroom[a]	Results	References
Cupriavidis	*Lentinus edodes*	IZD = 15 mm	[50]
Enterobacter aerogenes	*Agaricus bisporus, Clitocybe alexandri, Hygrophorus agathosmus, Meripilus giganteus* (M), *Paxillus involutus* (M), *Pleurotus ostreatus* (M), *Pleurotus sajor-caju, Rhizopogon roseolus, Suillus collitinus*	IZD = 8–22 mm MIC = 15.62–125 µg/mL	[33, 35, 38, 44]
Enterobacter cloacae	*Armillaria mellea, Clitocybe geotropa, Meripilus giganteus* (M), *Meripilus giganteus, Paxillus involutus* (M), *Pleurotus ostreatus* (M), *Sparassis crispa*	IZD = 10–20 mm	[35, 36]
Enterobacter faecalis	*Armillaria mellea, Clitocybe geotropa, Meripilus giganteus* (M), *Meripilus giganteus, Sparassis crispa*	IZD = 8–14 mm	[35, 36]
Escherichia coli	*Agaricus bisporus, Armillaria mellea* (M), *Armillaria mellea, Boletus edulis, Cantharellus cibarius, Clitocybe alexandri, Clitocybe geotropa, Cortinarius sp., Ganoderma lucidum, Hydnum repandum, Irpex lacteus* (M), *Lactarius camphoratus, Lactarius delicious, Lactarius piperatus, Lactarius volemus, Laetiporus sulphureus, Lentinus edodes, Lepista nuda, Leucoagaricus cf. cinereus* (M), *Macrolepiota procera, Marasmius sp.* (M), *Marasmius cf. bellus* (M), *Meripilus giganteus* (M), *Meripilus giganteus, Morchella costata* (M), *Morchella hortensis* (M), *Navesporus floccosa, Paxillus involutus* (M), *Phellinus rimosus, Pleurotus eryngii* (M), *Pleurotus ostreatus* (M), *Pleurotus sajor-caju, Rhizopogon roseolus, Sparassis crispa, Suillus collitinus*	IZD = 8–27.40 ± 0.19 mm MIC = 250 µg/mL – > 50 mg/mL	[32–36, 38–40, 44, 46, 48–50, 54, 71]
Fusobacterium nucleatum	*Lentinus edodes*	CFU = 2.40 (± 3.11) × 10^2 – 7.56 (± 4.28) × 10^6 MIC = 0.9–20 mg/mL	[53, 54, 67]
Klebsiella aerogenes	*Lentinus edodes*	IZD = 9 mm	[50]
Klebsiella pneumoniae	*Agaricus bisporus, Agaricus bitorquis, Ganoderma lucidum, Lactarius piperatus, Lentinus edodes, Lepista nuda, Pleurotus sajor-caju, Ramaria flava*	IZD = 4–31.60 ± 0.10 mm MIC = 0.5 mg/mL	[11, 15, 33, 39, 46, 47, 49, 50, 55]
Morganella morganii	*Agaricus bisporus, Agaricus bitorquis, Agaricus essettei, Laetiporus sulphurous*	IZD = 4.5 ± 0.5 mm	[15, 48]
Neisseria subflava	*Lentinus edodes*	CFU = 9.49 (± 2.60) × 10^6 – 1.50 (± 0,50)×10^8	[53, 67]
Porphyromonas gingivalis	*Lentinus edodes*	MIC = 0.05–10 mg/mL	[45]
Prevotella intermedia	*Lentinus edodes*	CFU = 2.00 (± 2.83) × 10^1 – 2.60 (± 6.66) × 10^5 MIC = 0.05–15 mg/mL	[53, 54, 67, 68]
Prevotella nigrescens	*Lentinus edodes*	MIC = 0.1–15 mg/mL	[54]
Proteus mirabilis	*Lentinus edodes*	IZD = 4 mm	[11]
Proteus vulgaris	*Agaricus bisporus, Agaricus bitorquis, Armillaria mellea, Clitocybe geotropa, Laetiporus sulphureus, Meripilus giganteus* (M), *Meripilus giganteus, Pleurotus ostreatus* (M), *Pleurotus sajor-caju, Sparassis crispa*	IZD = 5.5 ± 0.5–19 mm	[15, 33, 35, 36, 48]
Pseudomonas aeruginosa	*Agaricus bisporus, Boletus edulis, Cantharellus cibariusCortinarius sp., Cortinarius abnormis, Cortinarius ardesiacus, Cortinarius archeri, Cortinarius austroalbidus, Cortinarius austrovenetus, Cortinarius austroviolaceus, Cortinarius coelopus, Cortinarius clelandii, Cortinarius [Dermocybe sp., Dermocybe canaria, Dermocybe kula], Cortinarius fulvoiubatus, Cortinarius ianthinus, Cortinarius memoria-annae, Cortinarius persplendidus, Cortinarius sinapicolor, Cortinarius submagellanicus, Cortinarius tricholomoides, Cortinarius vinosipes, Ganoderma lucidum, Hydnum repandum, Lactarius camphoratus, Lactarius delicious, Lactarius piperatus, Lactarius volemus, Laetiporus sulphureus, Lentinus edodes, Lepista nuda, Macrolepiota procera, Navesporus floccosa, Phellinus rimosus, Pleurotus sajor-caju, Ramaria flava*	IZD = 6–20 mm MIC = 0.5–100 mg/mL IC_{50} = 0.04 – > 2.00 mg/mL	[10, 32, 33, 39, 40, 45, 46, 48–50]
Pseudomonas maltophila	*Lentinus edodes*	IZD = 6 mm	[11]
Salmonella enteritidis	*Laetiporus sulphureus, Ramaria flava*	IZD = 4–5 ± 1 mm	[37, 40]
Salmonella poona	*Lentinus edodes*	IZD = 9 mm	[50]
Salmonella typhi	*Agaricus bisporus, Ganoderma lucidum, Pleurotus sajor-caju*	IZD = 7.00 ± 0.18–20.60 ± 0.14 mm	[33, 39]
Salmonella typhimurium	*Agaricus bisporus, Armillaria mellea* (M), *Armillaria mellea, Clitocybe geotropa, Ganoderma lucidum, Hygrophorus agathosmus, Irpex lacteus* (M), *Lepista nuda, Meripilus giganteus* (M), *Meripilus giganteus, Morchella costata* (M), *Morchella elata* (M), *Morchella esculenta* var. *vulgaris* (M), *Morchella hortensis* (M), *Navesporus floccosa, Paxillus involutus* (M), *Phellinus rimosus, Pleurotus ostreatus* (M), *Pleurotus sajor-caju, Sparassis crispa, Suillus collitinus,*	IZD = 6–16 mm MIC = 15.62–125 µg/mL	[33–36, 40, 44, 49]
Serratia marcescens	*Lentinus edodes*	IZD = 10 mm	[50]
Veillonella dispar	*Lentinus edodes*	CFU = 1.37 (± 0.31)×10^7 – 2.35 (± 1.09)×10^7	[53, 67]
Veillonella parvula	*Lentinus edodes*	MIC = 0.3–20 mg/mL	[54]
Yersinia enterecolitica	*Agaricus bitorquis, Laetiporus sulphureus, Lentinus edodes, Ramaria flava*	IZD = 5–16 mm	[11, 15, 47]

[a]Acetone, chloroform, ethanol, ethyl acetate, methanol, dichloromethane, ether, xylene, or water extracts. M – mycelium, the other samples refer to the fruiting body. The antimicrobial activity is expressed in CFU (colony forming unities), MIC (minimal inhibitory concentrations), IZD (internal zone diameter), or IC_{50} (concentrations inhibiting 50 % of the growth) values

Table 4 Mushroom compounds with antimicrobial activity against gram-negative bacteria.

Microorganism	Compound (mushroom)	Results	References
Achromobacter xyloxidans	**6** (*Leucopaxillus albissimus*)	MIC = 32 µg/mL	[69]
Acinetobacter baumannii	**6** (*Leucopaxillus albissimus*)	MIC = 128 µg/mL	[69]
Agrobacterium rhizogenes	Protein (*Clitocybe sinopica*)	MIC = 0.14 µM	[70]
Agrobacterium tumefaciens	Protein (*Clitocybe sinopica*)	MIC = 0.14 µM	[70]
Agrobacterium vitis	Protein (*Clitocybe sinopica*)	MIC = 0.28 µM	[70]
Burkholderia cenocepacia	**6** (*Leucopaxillus albissimus*)	MIC = 16 µg/mL	[69]
Burkholderia cepacia	**6** (*Leucopaxillus albissimus*)	MIC = 32 µg/mL	[69]
Burkholderia multivorans	**6** (*Leucopaxillus albissimus*)	MIC = 16 µg/mL	[69]
Cytophaga johnsonae	**6** (*Leucopaxillus albissimus*)	IZD = 16 mm	[69]
Escherichia coli	Proteins (*Cordyceps sinensis*); **5a, b** (*Ganoderma pfeifferi*); Fraction B (*Pycnoporus sanguineus*); **10** (*Xylaria intracolarata*)	IZD = 4–16 mm MIC = 0.625 mg/mL–100 000 g/L	[42, 57, 60, 61]
Klebsiella pneumoniae	**3** (*Lentinus edodes* M); Fraction B (*Pycnoporus sanguineus*); **10** (*Xylaria intracolarata*)	IZD = 12–22 mm MIC = 0.625 mg/mL	[42, 59, 60]
Proteus mirabilis	**5a, b** (*Ganoderma pfeifferi*)	IZD = 15 mm	[57]
Proteus vulgaris	Protein (*Cordyceps sinensis*); **3** (*Lentinus edodes* M)	IZD = 12 mm MIC = 75 000 g/L	[59, 61]
Pseudomonas aeruginosa	**7, 8a-8 d** (*Cortinarius basirubencens*); **9a–c** (*Cortinarius sp.*); **3** (*Lentinus edodes* M); **6** (*Leucopaxillus albissimus*); Ribonuclease (*Pleurotus sajor-caju*); Fraction B (*Pycnoporus sanguineus*); **10** (*Xylaria intracolarata*)	IZD = 15–16 mm MIC = 128 µg/mL–1.250 mg/mL IC_{50} = 1.5–> 50 µg/mL IC_{50} = 51 ± 6 µM	[10, 42, 59, 62, 64, 68]
Pseudomonas fluorescens	**3** (*Lentinus edodes* M); Ribonuclease (*Pleurotus sajor-caju*)	IZD = 13 mm IC_{50} = 186 ± 12 µM	[59, 62]
Serratia marcescens	**5a, b** (*Ganoderma pfeifferi*)	IZD = 15–16 mm	[57]
Salmonella enteritidis	**10** (*Xylaria intracolarata*)	IZD = 16 mm	[60]
Salmonella typhi	Protein (*Cordyceps sinensis*); Fraction B (*Pycnoporus sanguineus*)	MIC = 0.312 mg/mL – 50 000 g/L	[42, 61]
Stenotrophomonas maltophilia	**6** (*Leucopaxillus albissimus*)	MIC = 32 µg/mL	[69]
Xanthomonas malvacearum	Protein (*Clitocybe sinopica*)	MIC = 0.56 µM	[70]
Xanthomonas oryzae	Protein (*Clitocybe sinopica*)	MIC = 0.56 µM	[70]

M – mycelium, the other samples refer to the fruiting body. The antimicrobial activity is expressed in MIC (minimal inhibitory concentrations), IZD (internal zone diameter), or IC_{50} (concentrations inhibiting 50 % of the growth) values

gism or antagonism, with synergism observed when combined with cefazolin against *Bacillus subtilis* and *Klebsiella oxytoca* [40, 65].

The mycelium extract from *Leucoagaricus* cf. *cinereus, Marasmius* cf. *bellus*, and *Marasmius* sp. were capable of inhibiting the growth of *Escherichia coli*. Within the family *Tricholomataceae*, species from the genus *Marasmius* have long been known to produce interesting secondary metabolites [66].

The *Hydnum repandum* methanolic extract was mainly active against *Pseudomonas aeruginosa. Escherichia coli* was found to be the most sensitive bacteria to methanolic extracts of *Lactarius* species [32]. However, no activity of *Lactarius delicious* against *E. coli* was observed [45, 46].

The *Laetiporus sulphureus* ethanolic extract had a lower antibacterial spectrum against gram-negative bacteria, having no activity against *Klebsiella pneumonia* [48].

On three occasions, namely with the *Pseudomonas* sp., *Lentinus edodes* aqueous extract was significantly more active than ciprofloxacin (positive control), whereby it gave markedly greater zones of inhibition. This result is of important clinical significance, as *P. aeruginosa* is emerging as a major etiological of the nosocomial infection [50]. *L. edodes* mycelium had no effect on *Escherichia coli, Pseudomonas fluorescens, Klebsiella pneumoniae*, and *Camphylobacter jejuni* [52].

Extracts from *Lentinus edodes* showed a strong bactericidal effect against *Prevotella intermedia*, which is associated with gingivitis. This mushroom was capable of significantly reducing dental plaque deposition [53, 54, 67, 68].

The *Lepista nuda* methanolic extract was effective against *Escherichia coli* and *Pseudomonas aeruginosa* [49].

Tambeker et al. [33] reported the antimicrobial ability of several extracts of *Pleurotus sajor-caju. Escherichia coli, Enterococcus aerogenes, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* were most sensitive to ethanolic, methanolic, and xylene extracts.

Overall, among the tested gram-negative bacteria, *Escherichia coli* and *Klebsiella pneumoniae* are the most susceptible to mushrooms' inhibitory effect. *Agaricus bisporus* [32, 33], *Lentinus edodes* [50, 54], *Ganoderma lucidum* [39, 40], and *Lepista nuda* [49] seem to have higher antimicrobial activity against those microorganisms. *Pseudomonas aeruginosa* was inhibited by *Clitocybe alexandri* [38], *Boletus edulis, Cantharellus cibarius* [32], *Ganoderma lucidum* [39], and *Cortinarius* sp. [10] extracts. Studies with *Enterobacter aerogenes* and *Serratia marcescens* are scarce, and due to the importance in the area of multiresistance, they should be carrried out to assess sensibility to extracts from mushroom species.

Antimicrobial compounds from mushrooms

Some of the compounds previously discussed have also been described for their action against gram-negative bacteria (**Table 4**).

Terpenes **5a** and **5b**, isolated from *Ganoderma pfeifferi*, showed moderate activity against *Escherichia coli, Proteus mirabilis*, and *Serratia marcescens* [57].

The organic acid **3**, isolated from the mycelium of *Lentinus edodes,* showed activity against *Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa*, and *Pseudomonas fluorescens* [59].
The benzoic acid derivative **10**, isolated from *Xylaria intracolarata*, showed activity against *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa*, and *Salmonella enteritidis.* For this compound, the highest inhibition (22 mm) was found in *Klebsiella pneumonia,* which is higher than the control (gentamicin, 14 mm) [60].
Compounds **7, 8a–d** (*Cortinarius basirubescens*), and **9a–c** (*Cortinarius* spp.) were effective against *Pseudomonas aeruginosa* [10].
The quinoline **6**, isolated from *Leucopaxillus albissimus*, showed activity against *Achromobacter xyloxidans, Acinetobacter baumannii, Burkholderia cenocepacia, Burkholderia cepacia, Burkholderia multivorans, Cytophaga johnsonae,* and *Pseudomonas aeruginosa.* Among the thirteen microorganisms tested, *Cytophaga johnsonae* was the most strongly inhibited (16 mm) [69].
Some proteins have also been reported against gram-negative bacteria. The protein CSAP, isolated from *Cordyceps sinensis* and already mentioned above, showed activity against *Escherichia coli, Proteus vulgaris*, and *Salmonella typhi* [61], while the protein (N-terminal sequence SVQATVNGDKML) isolated from *Clitocybe sinopica* was active against *Agrobacterium rhizogenes, Agrobacterium tumefaciens, Agrobacterium vitis, Xanthomonas malvacearum*, and *Xanthomonas oryzae* [70].
Ribonuclease (*Pleurotus sajor-caju*) showed activity against *Pseudomonas aeruginosa* and *Pseudomonas fluorescens,* acting at the RNA level [62].
Fraction B (*Pycnoporus sanguineus*) showed activity against *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Salmonella typhi* [42].
Unfortunatly, the mechanism of action of each one of the isolated compounds is not completly clear and described in the available reports.

Concluding Remarks

The present review focuses on the antimicrobial effects of mushrooms from all over the world, and their isolated compounds. It will certainly be useful for future scientific studies. Both edible and nonedible mushrooms showed antimicrobial activity against pathogenic microorganisms, including bacteria associated with nosocomial infections (*Pseudomonas aeruginosa, Pseudomonas maltophila, Listeria monocytogenes, Staphylococcus aureus, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Serratia marcescens*) and multiresistance (MRSA, MRSE, VREF, PRSP, ERSP).
Data available from the literature indicates that mushroom extracts and isolated compounds exhibit higher antimicrobial activity against gram-positive than gram-negative bacteria. Among all the mushrooms, *Lentinus edodes* is the best-studied species and seems to possess broad antimicrobial action against both gram-positive and gram-negative bacteria. Species from the genera *Boletus, Ganoderma*, and *Lepista* appear promising for future studies, if one considers the positive activity and limited number of publications. Considering the low number of studies with individual compounds, Plectasin peptide, isolated from *Pseudoplectania nigrella*, revealed the highest antimicrobial activity against gram-positive bacteria.
The comparison of the results reported by different authors is difficult, due to the diverse methodologies used to evaluate antimicrobial activity of mushroom extracts or isolated compounds. Therefore, the standardization of methods and establishment of cut-off values is urgent. The knowledge about the mechanisms of action of different compounds might lead to the discovery of new active principles for antimicrobial activity. Furthermore, the application of cytotoxicity assays is also important to evaluate the effects on humans in the range of the *in vitro* tested concentrations.
The research on mushrooms is extensive and hundreds of species have demonstrated a broad spectrum of pharmacological activities, including antimicrobial activity. Although there are a number of studies available in the literature, they are almost entirely focused on the screening of antibacterial properties of mushroom extracts. In fact, there is a gap in the identification of the individual compounds responsible for those properties, and only a few low-molecular weight compounds and some peptides and proteins have been described. After elucidation of their mechanism of action, these mushroom metabolites or other related compounds could be used to develop nutraceuticals or drugs effective against pathogenic microorganisms resistant to conventional treatments.

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Conflict of Interest

The authors have no conflicts of interest.

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