



Effect of Mushroom against Extended Spectrum Beta Lactamase (ESBL) Producing Microorganisms

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Authors' contributions

This work was carried out in collaboration among all authors. Authors HPV, FY and AE designed the study and wrote the first draft of the manuscript. Authors AE and FY revised the manuscript. Author AE checked English grammatical errors and formatting. All authors read and approved the final manuscript.

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ABSTRACT

According to the WHO global report, ESBL (Extended-Spectrum Beta-Lactamase)-producing microorganisms is the most common cause of urinary tract infection; hospital-acquired infection as well as a foodborne infection. These include *Escherichia coli*, *Salmonella*, *Shigella* and *Vibrio cholera*. The carbapenems which include doripenem, ertapenem, imipenem and meropenem are the known choice of medication for life-threatening infections which is caused by ESBL-producing microorganisms. Recently there is the emergence of carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas* which makes treatment an obstacle for the medical personnel for various infections. Natural products have been reported to be emerged as a potential possibility to be explored as antimicrobial drugs. The plant extracts could serve as an alternate source of resistance modifying agents owing to the wide variety of secondary metabolites (eg. flavonoids, phenols, tannins, alkaloids, etc). Mushroom are have been considered as a source that attracts the researchers to explore its properties as it has been established with various bioactive components that possess many health beneficial effects such as antimicrobial and antifungal compounds. In this paper, we summarize the information available in the literature on the ESBL, mushroom and current treatment, with a special focus on the three different types of mushrooms (*Fistulina hepatica*,

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Leucopaxillus giganteus and *Pleurotus Ostreatus*) against spectrum beta-lactamase (ESBL) producing microorganisms. Electronic databases including SciFinder, Web of Science, Science Direct, PubMed, and Google Scholar were screened using the following keywords: “antibacterial, antimicrobial, mushroom, ESBL, Enterobacter, *Fistulina hepatica*, *Leucopaxillus giganteus* and *Pleurotus Ostreatus*”. We intend to enhance understanding in the field and promote further work on the development of phytocomponent based antimicrobial compounds.

Keywords: *Extended-Spectrum Beta-Lactamase (ESBL); Fistulina hepatica; Leucopaxillus giganteus; Pleurotus ostreatus.*

1. INTRODUCTION

Extended-spectrum beta-lactamase (ESBL) delivering strains were first detected in the mid-1980s in Western Europe. They can hydrolyze third and fourth-generation cephalosporins and monobactams, but β -lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam inhibit these strains [1]. An initial outbreak by these living beings was trailed by endemicity in certain clinics [2,3].

ESBL refers to a group of enzymes encoded by plasmids found in Enterobacteriaceae. The majority of ESBL enzymes are mutations of temoneira (TEM) and sulfhydryl vector chemicals (SHV), as well as the cefotaximase (CTX-M) form lactamase. ESBLs are enzymes that were drawn through a narrow spectrum ancestor. Because of the hydrolytic activity, the ESBL enzyme can inactivate penicillins, aztreonam, and broad-spectrum cephalosporins, but not cephamycins (cefotaxim) or carbapenems, and is blocked through β -lactamase inhibitors, such as clavulanic acid [4].

A previous study discovered that the majority of ESBL-encoding genes, especially blaTEM, are borne on transmissible plasmids, suggesting that plasmids are one of the primary vectors for the spread of antibiotic resistance. This may explain why *E. coli* isolates in Malaysia have such a high prevalence of ESBL-producing bacteria and multidrug resistance [5,6].

Mushrooms can potentiate the antibacterial effect which further prompts the interruption of the microscopic organisms. Alves et al. [7] described that *Russula delica* extract was more synergistic effects than *Leucopaxillus giganteus* extract against *E. coli* 1 (resistant to Ampicillin, Ciprofloxacin, and Trimethoprim/Sulfasoxazole) and *E. coli* 2 (resistant to Amoxicillin/Clavulanic acid and Ampicillin); however, this extract exhibited stronger synergistic effect against ESBL *E. coli*. This study supported that the synergistic effects of mushroom extracts and

antibiotics, which may lead to protection against increasing microorganism's resistance.

Tapinella atromentosa has been shown to contain several compounds in previous research. Diphenyl-substituted tetronic acid pigments from *T. atrotomentosa* cultures have been identified as xerocomic acid and atromentic acid, according to researchers. The species produces pigments with terphenylquinone structures, such as orange-yellow flavomentin and violet spiromentin. The reddish-brown colour of *T. atrotomentosa*'s exterior sections is atromentin, a 4,4-dihydroxy analogue of polyporic acid. The genus also produces leucomentins, the colorless precursors of atromentin. Besides, the species is known to biosynthesize osmundalactone and bis-osmundalactone, which are lactone-type compounds [8]. Velvet rollrim is one of the few mushroom species that contains ecdysteroids of the ergostane type [9].

In this review, we summarize the information available in the literature on the ESBL, mushroom and current treatment, with a special focus on the three different types of mushrooms (*Fistulina hepatica*, *Leucopaxillus giganteus* and *Pleurotus ostreatus*) against spectrum beta-lactamase (ESBL) producing microorganisms. Electronic databases including SciFinder, Web of Science, Science Direct, PubMed, and Google Scholar were screened using the following keywords: “antibacterial, antimicrobial, mushroom, ESBL, Enterobacter, *Fistulina hepatica*, *Leucopaxillus giganteus* and *Pleurotus ostreatus*”. Careful attention was paid to select publications referring only to the effect of *Fistulina hepatica*, *Leucopaxillus giganteus* and *Pleurotus ostreatus* against ESBL-PE.

2. CURRENT TREATMENT

ESBL-producing *Enterobacteriaceae* (ESBL-PE) are closely related to the increased numbers of morbidity and mortality rate, prolonged hospital stay and increased cost. The increased cases of ESBL-PE have two contributing factors for its

occurrence, which is the potential for rapid spread and dissemination of the resistance mechanism and the uncontrolled use of antimicrobial agents and the inadequate infection control measures, precisely in the health care sector [8,10]. Treatments of these organisms are very crucial [11,12]. According to the WHO global report 2013, ESBL-PE is the most common cause of urinary tract infection, hospital-acquired infection as well as foodborne infection [13]. A meta-analysis which was conducted by Flokas et al. [14], revealed that in the pediatric population the prevalence of ESBL producers was estimated to be 9% with an annual increase of 3.2 % throughout the countries which includes Africa (15%), South Africa (12%), India (11%), Asia (7%) and in Europe (4%). A cross-sectional study which was conducted in Malaysia to detect the risk factors and spatial distribution of ESBL producing *Escherichia coli* at the meat market revealed that the overall occurrence of the organism was 48.8% and can lead to serious food contamination [15]. A study was conducted by researchers in Malaysia states that a clinical sample of *Klebsiella pneumoniae* which was isolated from patients showed various antibiotic-resistant genes and plasmid replicons [16].

The carbapenems which include doripenem, ertapenem, imipenem and meropenem are the known choice of medication for life-threatening infections which is caused by ESBL-PE [17]. Recently there is the emergence of carbapenem-resistant Enterobacteriaceae, which makes treatment an obstacle for the medical personnel for various infections. The usage of fosfomycin and nitrofurantoin were reported to exert a positive effect on the ESBL producers as reported by Ho et al. [18]. Colistin was once reported to have an adverse effect and toxic is still being used as the last choice of antibiotics at the present moment as there is no new emergence of antibiotics against this multidrug-resistant organism. The usage of tigecycline and Colistin as treatment of these organisms was also being reported. Colistin was considered as a treatment for multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [2]. The World Health Organization (2019) has released a red alert where all the medical personnel is at a critical standpoint between balancing the treatment of ESBL producing bacteria and at the same time to avoid further resistance mechanism being induced [19].

Natural matrices have been reported to be emerged as a potential possibility to be explored

as antimicrobial drugs. Mushroom are have been considered as a source that attracts the researchers to explore its properties as it has been established with various bioactive components that possess many health beneficial effects such as antimicrobial and antifungal properties [20]. Various wild medicinal mushrooms (*Lentinus edodes*, *Pseudoplectania nigrella*, *Leucopaxillus albissimus*) have been explored properties and showed a broad-spectrum antimicrobial activity [21,22]. Mushrooms have been studied for its diversity, broad functional group chemistry, chemical diversity and chirality of mushroom metabolites proves that it is rich in valuable bioactive [23]. Evidence was approved by the US FDA in 2007, known as retapamulin, the first molecule that originated from mushroom which was allowed to be used as antibacterial therapy for the treatment of impetigo, a skin infection caused by bacteria. Apart from that, pleuromutilin was also discovered with slight modification at the side chain and this molecule possesses antibacterial activity. The molecules are now under clinical surveillance to be used as systemic antibacterial treatment [24].

Besides direct antibacterial activity which is possessed by mushrooms derived extracts, it also has a synergistic interaction between the treatments and this indirectly allows the chance to lessen the therapeutic doses of antibacterial treatments and to protect against increasing bacterial resistance. Bioactive compounds such as flavonoids, benzoic acid and ribonuclease are responsible for anti-microbial activities which were revealed that mushroom has a large amount of these bioactive [9]. In research conducted by Hemaiswarya et al. [25], it has been reported that the synergism between natural products and antibiotics gives a promising effect in combating this multidrug-resistant organism. This evidence was also been strengthened by a study conducted by Chatterjee et al. [26] which shows edible mushroom has a positive effect against ESBL producing organisms.

3. MUSHROOM

3.1 *Pleurotus ostreatus*

3.1.1 Taxonomy

The common name of *Pleurotus ostreatus* is oyster. *P.ostrestus* is sometimes referred to as the tree oyster mushroom or the grey oyster

mushroom to differentiate it from other species in the genus [27].

3.1.2 Botanical description

The oyster mushrooms have three distinct parts- a fleshy shell or spatula-shaped cap (pileus) spanning 5-25 cm, a short or long lateral or central stalk called stipe and long ridges and furrows underneath the pileus called gills or lamellae. The gills stretch from the edge of the cap down to the stalk and bear the spores. The spores are smooth, cylindrical and germinate very easily on any kind of mycological media within 48-96 hrs. The mycelium of *Pleurotus* is pure white [28].

3.1.3 Origin and distribution

A species of oyster mushroom (*Pleurotus ostreatus*) was started to cultivate based on experimental in Germany by Flack during the year 1917 on tree stumps and wood logs. Block, Tsao and Hau perfected growing technology in the USA. In the early sixties, the cultivation of different varieties of oyster mushroom was started in India. Commercial cultivation was initiated in the mid-seventies [29].

The oyster mushroom is widespread in many temperate and subtropical forests throughout the world, although it is absent from the Pacific Northwest of North America, being replaced by *P. pulmonarius* and *P. populinus*. It is a saprotroph that acts as a primary decomposer of wood, especially deciduous trees, and beech trees in particular. It is a white-rot wood-decay fungus [30].

3.1.4 Chemical constituents

Oyster mushrooms are also known to be rich sources of different classes of compounds including; polysaccharides, terpenoids, peptides, polyphenol, proteins, flavonoids, fatty acid esters, sterols, glucans, steroids, ergosterol and propanoid [31].

3.1.5 Medicinal uses of *Pleurotus ostreatus*

It has been described as possessing antidiabetic, antibacterial, antineoplastic, antilipidemic, antimutagenic, antihypertensive, antilipidemic, hepatoprotective, immunomodulatory, antiarthritic, antioxidant, anticancer, eye health and antiviral activities (eg. Human Immunodeficiency Virus (HIV)) [31,32].

3.2 *Fistulina hepatica*

3.2.1 Taxonomy

The common name of is *Fistulina hepatica* is beefsteak polypore. *F. hepatica* is sometimes referred to as ox tongue or tongue mushroom [33].

3.2.2 Botanical description

It looks like a large tongue in a reddish-brown colour. The surface of the mushroom is rough. There are small pores on the creamy-white below of the fruit body. The spores are released from the pores. A young mushroom is in a pinkish-red colour. The age determines the dark colour of the mushroom. A red juice will splash out when cut it. The cut flesh looks like meat flesh [34].

3.2.3 Origin and distribution

It can often be seen on oaks and sweet chestnuts which grow from August to the end of the autumn. It also can found in either living or dead wood. It also grows from wounds on Eucalyptus trees in Australia. The infection of mushrooms causes brown rot on the trees [35].

3.2.4 Chemical constituents

Fistulina hepatica consists of different types of plant compounds such as terpenoids, aromatic glycosides, flavonoids, phenylpropanoids, alkaloids, fatty hydrocarbon, caffeic acid, p-coumaric acid, ellagic acid, protocatechuic acid, p-hydroxybenzoic acid and cinnamic acid [36].

3.2.5 Medicinal uses of *Fistulina hepatica*

It has been demonstrated promising results on chronic diseases such as diabetes, hypertension, cancer, cardiovascular diseases, etc. It has been shown to possess pharmacological therapeutic effects, like anti-inflammatory, anti-oxidant, antiviral, anti-bacterial, anti-parasitic, anti-fungal, nephroprotective, neuroprotective and hepatoprotective effects [36,37].

3.3 *Leucopaxillus giganteus*

3.3.1 Taxonomy

The common name of *Leucopaxillus giganteus* is giant leucopax. *L. giganteus* is sometimes

referred to as a giant funnel. It was formerly known as the “giant clitocybe” [38].

3.3.2 Botanical description

The cap of the mushroom is elongated up to 30-50 cm, rarely even 70 cm in diameter with a thickness of 1 to 1.4 cm at the half radius. The young mushrooms have caps structured in convex, with a margin that is rolled downwards. However, the mature mushrooms have caps that flatten out and eventually become shallowly funnel-shaped. The cap is smooth and creamy white. As the age increases, it may develop brown stains and circular cracks [39].

3.3.3 Origin and distribution

It can form fairy rings in grassy areas like pastures. It is can be seen along roadsides. In summer and autumn, it generates fruiting bodies. As it is a saprobic species, it takes nutrients by decomposing organic matter. It has a cosmopolitan distribution and happens throughout the temperature zone of the northern hemisphere. It is found in North America (eg. Pacific Northwest and the Rocky Mountains), Britain and Europe [40].

3.3.4 Chemical constituents

Leucopaxillus giganteus consists of a variety of bioactive compounds such as clitocine, phenols, flavonoids, mannitol, β -tocopherol, oxalic, fumaric acids, p-hydroxybenzoic and cinnamic acids [41].

3.3.5 Medicinal uses of *Leucopaxillus giganteus*

It has been described as possessing antidiabetic, antibacterial, antilipidemic, antihypertensive, hepatoprotective, neuroprotective, immunomodulatory, antioxidant, anticancer and antiviral. It has antibiotic activity against a variety of pathogenic bacteria such as *Bacillus cereus*, *Bacillus subtilis*, *Mycobacterium tuberculosis*, *Salmonella typhi*, and *Brucea abortus*. It also has been reported to enhance apoptosis (cell death) in human cervical cancer cells (HeLa) [41,42].

4. EFFECT OF MUSHROOMS ON ESBL PRODUCING BACTERIA

Mushrooms have been demonstrated to have broad-spectrum antibacterial activity against clinical pathogenic isolates. Mushroom

particularly has been proved to produce antibacterial metabolites naturally to protect them from the environment. Broad functional group chemistry, chirality and intense chemical diversity of metabolites produced by mushrooms prove a valuable source of bioactive components. (Eristanna et al., 2012) Multiple genetic elements are present in bacteria such as genes, integrons, plasmid and transposons which contribute to the antibiotic resistance phenotypes and this confers the genetic ability to acquire resistance to therapeutic drugs [43]. Mushrooms have been used as a functional food and prove a good candidate for the development of medicine and nutraceuticals. Mushrooms contain various nutrients and active metabolites which is not only contained in the fruiting bodies but also its mycelium [44] bacteria serve as host for multiple genetic elements like genes, integrons, transposons and plasmids that confer antibiotic resistance phenotypes. So they have the genetic ability to transmit and acquire resistance to drugs that are used as therapeutic agents [43].

A study conducted by Chatterjee et al. [3], has demonstrated that the hydroethanolic (60% v/v) extract of *Pleurotus ostreatus* has shown potent antibacterial activity against ESBL positive superbugs. A large number of active compounds were found in the mushroom such as protocatechuic acid, quercetin, gallic acid, coumaric acid, sinapic acid, apigenin, rutin. Qualitative phytochemical analysis of *Pleurotus* grown on yeast dextrose broth and banana agro-waste confirmed the presence of steroids, cardiac glycosides, terpenoids, and alkaloids [45]. Studies have shown that terpenoids particularly can inhibit the growth of bacteria by disrupting the cell wall and cytoplasmic membrane which further leads to cell lysis by the imbalance of macromolecules and ions in the cell [46-48].

Fistulina hepatica and *Leucopaxillus giganteus* have shown good bacteriostatic and bactericidal effects against some gram-negative and Gram-positive bacteria. The susceptible bacteria include MRSA (Methicillin-resistant *Staphylococcus aureus*), *M. morgani*, *S. epidermidis* and *E. faecalis* which were also major contributors to nosocomial infection. Besides that, the extracts combined with commercial antibiotics were also applied to a different pathogenic organism (MRSA and Extended-spectrum beta-lactamase-producing (ESBL) producing *E. coli*). A study that investigated the Hungarian mushroom species

by E. Liktor Busa et al. [8], has concluded that *F.hepatica* has not only showed potential broad antibacterial spectrum but also has demonstrated synergistic activity with cefuroxime against MRSA. *Leucopaxillus giganteus* has been used in the pharmaceutical industry for the extraction of clitocybin antibiotics and has proven to be effective against Gram-positive bacteria. Several authors have concluded the positive effects of fungus and antibiotics synergism therapy where the extracts have increased the efficacy of β lactam antibiotics [7,49,50].

Plant extracts could be an alternate source of resistance modifying agents because of the diverse variety of secondary metabolites such as flavonoids, alkaloids, phenols, tannins, terpenes, saponins, etc. These secondary metabolites could be potential as antimicrobial and resistance modifiers. Plant extracts that act ligand; have the ability to bind to target protein leading to modification or inhibition of target protein. Plant extracts bind to allosteric sites of the target protein and inhibit the pathogenic activity. This permits the herbals to act as effective modulators of host-related cellular processes through transcription and translation activity; immune response; mitosis; cell death programme and signal transduction. Therefore, the plant compounds are not only killing the microorganisms but also inhibiting the key mechanism of the pathogenic process, thereby, the microorganism may have a decreased ability to develop resistance to natural components.

The key events responsible for resistance to antibiotics in bacteria is chromosomal mutations or genetic transfer by plasmids; inactivation of antibiotic by bacterial enzymes; target site modification; inactivation of efflux pumps; and biofilm formation by a complex aggregation of microbes [51].

The alkaloids play important role in interfering with bacterial DNA and affect cell division and apoptosis. Flavanoids enhance the membrane permeability and disruption in the bacterial cell wall. They damage the membrane proteins present in the cell wall. Moreover, quinones disrupt the surface-exposed adhesin proteins, cell wall polypeptides and membrane-bound enzymes which are the main targets in the microbial cell. The combined or synergistic actions displayed by the bioactive compounds present in a single plant extract could be attributed to the wide range of target proteins' components such as receptors, membrane

proteins, enzymes, ion channels, antibodies, transport proteins, etc [52]. Thus, bacteria are not able to easily develop resistance to the multiple or chemically complex bioactive compounds present in plant extracts than those for a single chemical compound [53].

5. CONCLUSION

The information summarized in this review highlights the potentiality of some mushrooms (*Fistulina hepatica*, *Leucopaxillus giganteus* and *Pleurotus ostreatus*) as alternative agents against ESBL-producing microorganisms. Currently, the problem of ESBL-producing microorganisms is posing a global therapeutic challenge and is continuously threatening our community. Despite global awareness of the antibiotic crisis and intense research from the scientific community, new effective antibiotics are struggling to emerge. Therefore, researchers found that plant-based antimicrobials could be potential in the development of novel, effective and promising therapeutics.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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