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Article review: Alternative and complement medicinal fungi toward antibiotics resistance

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Abstract

Antimicrobial resistance (AMR) is a rapidly growing emerging health problem worldwide due to its ability to reduce the effectiveness of conventional antibiotics and complicate their use. The medicinal fungi (used traditionally in the treatment of some diseases) are known to produce a broad spectrum of biologically active compounds with anti-inflammatory, immunomodulatory, and antimicrobial effects. Recent research has shown that the fungi can be used as substitutes or addition to traditional antibiotics to increase efficacy or counteract the resistant strains. This review was used to analyze the antimicrobial action of medicinal fungi, its clinical use, combinations with antibiotics, and difficulties in standardization and clinical translation. Medicinal fungi are a potentially promising strategy to overcome antibiotic resistance through the incorporation of their therapeutic uses.

Keywords: *Ganoderma lucidum*, *cordyceps sinensis*, *centinula edodes*, gram-negative bacteria, Iraq

1. Introduction

1.1 Global antimicrobials

Antimicrobial resistance (AMR) is considered to be one of the most severe dangers to humanity in the 20th and 21st centuries. Drug-resistant infections according to the latest bio-data of the world kill over 1.2 million people each year and it would increase to 10 million or more by 2050 unless there is an immediate intervention ^[1]. The indiscriminate and inappropriate use of antibiotics in medicine and agricultural animal husbandry accelerates the emergence of more effective strains and reduces the effectiveness of human interactions ^[2]. The economic consequences are also costly, as antimicrobials are expected to cause significant economic losses due to rising healthcare costs and scarcity ^[3].

1.2 Antibiotics

For several months, they were considered a revolutionary achievement in medicine, but now their effectiveness against drug-resistant pathogens has weakened. As *Staphylococcus aureus*, *P. aeruginosa*, *Klebsiella strongylii*, and *E. coli* modernus, such as Francisco pumps, have determined their target, specifically the choice of the enzymatic comedic agent ^[4]. Furthermore, the path to antibiotic development has slowed significantly, with a common plan being very long over the past three decades ^[5]. This growing need has intensified the need to replace or complement modern treatments that target specific viral sites ^[6].

1.3 Original use of medicinal fungi

Viral fungi have been partly derived from animals for centuries. In traditional medicine, *Ganoderma lucidum* (Reishi), *Cordyceps sinensis* and *Centinula edodes* (Shiitake) have been prescribed for compensation, fatigue, systemic disorders, and other endocrine disorders ^[7]. In Japan, Shiitake mushrooms are considered both medicinal and medicinal, reflecting their role as functional nutrients ^[8]. Similarly, in Africa and South America, fungal extracts have been used to heal wounds, reduce fever, and prevent infection ^[9]. These considerations take into account ethnopharmacology and are part of recent scientific studies investigating their antimicrobial and immunomodulatory properties ^[10].

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2. Objectives of the update

This study aims to provide a comprehensive overview of medicinal fungi as potential alternatives or complements to antibiotics. It discusses their classification and diversity, their bioactive compounds, antimicrobial mechanisms, interactions with beneficial bacteria, various evidence and precedents, safety considerations, and the future. The ultimate goal is to assess how medicinal fungi can be integrated into antimicrobial strategies to mitigate the global virus and antimicrobial crisis^[11].

2.1 Basis of antimicrobial action medicinal fungi exhibit multiple pathways to inhibit or kill bacterial pathogens

Disruption of Bacterial Cell Walls Some fungal polysaccharides and proteins interact with components of bacterial cell walls, weakening their integrity and causing dissolution. For example, beta glucan from *Ganoderma lucidum* exhibits potent activity against both Gram-positive and Gram-negative bacteria by disrupting the stability of the peptidoglycan layer^[12].

2.2 Inhibition of protein synthesis

Terpenoids and lectins from fungi interfere with the bacterial ribosome, leading to impaired translation and protein synthesis. In numerous studies, extracts from *Cordyceps militaris* have been shown to inhibit ribosome function in *Escherichia coli* and *Staphylococcus aureus*, resulting in reduced bacterial growth^[13].

2.3 Biofilm inhibition and quorum sensing biofilms and their formation

Fungal extracts may be used to prevent the development of biofilms and quorum sensing systems, reduce bacterial virulence and antibiotic resistance^[14, 15].

2.4 Immunomodulatory effects

Polysaccharides and other compounds improve immune responses of hosts to activate phagocytosis and cytokine production, which help to eliminate bacteria. The specific antimicrobial effect on opportunistic pathogens is achieved mainly by this indirect mechanism in immunocompromised patients^[16].

2.5 Synergism in conventional antibiotics

It has been demonstrated in numerous studies that fungal extracts have the ability to increase the antibiotic effect, decrease minimum inhibitory concentrations (MICs), and overcome partial resistance. Indicatively, addition of *Cordyceps* extracts to beta-lactams or aminoglycosides led to a dramatic enhancement in the inhibitory effect on multidrug-resistant bacterial strains^[17, 18].

3. Diversity of medicinal fungi

3.1 Classification and taxonomy

There are two phyla of medicinal fungi, *Basidiomycota* and *Ascomycota*, containing edible and inedible species of medicinal value. Some of the most significant genera that have been identified in the recent studies include *Ganoderma*, *Cordyceps*, *Tinula*, *Pleurotus*, and *Hericium*^[12]. *Ganoderma* species, and especially *Ganoderma lucidum* or Reishi / Lingzhi, are the most investigated ones. The terpenoids, organic polysaccharides and proteins are widely varied in their vegetative structures and spores^[13].

Cordyceps species are high-value cordycepin and nucleoside analogues that are antimicrobial and immunomodulatory^[14]. The second most common mushroom species in the world is called shiitake mushroom (*Lentinula edodes*). It is a nutritional food with a high content of β -glucans and lentinan as well as antimicrobial peptides^[15]. *Pleurotus ostreatus* (oyster mushroom) is described as a mushroom that produces lovastatin, antibacterial, and antifungal-active polysaccharides independently^[16].

Hericium erinaceus (lion's mane) is mainly investigated in relation to its neuroprotective properties, although it can also generate bioactive metabolites with antibacterial and systemic action^[17].

3.2 Biological organisms in medicinal mushrooms

There is a great diversity of secondary autotrophic and radioactive polysaccharide rhodopsins produced by a wide variety of fungi. The principal antimicrobial classes are:

1. **Polysaccharides** (β -glucans, heteroglucans) that important constituents of fungal cells^[18]. These compounds increase immune responsiveness, stimulate macrophages, dendritic cells, as well as natural killer cells and have direct antimicrobial activity against Gram-positive and Gram-negative bacteria^[19].
2. **Triterpenoids:** The *Ganoderma lucidum* special compounds block bacterial enzymes, interfere with cellular glycation and block quorum sensing^[20].
3. **Lectins:** Photoreceptors on bacterial cell walls are attached to fungal lectins rendering them unable to colonize^[21].
4. **Peptides and proteins:** Fungal antimicrobial peptides (AMPs) include those produced by *Pleurotus* and *Lentinula* and are bactericidal and antifungal^[22].
5. **Phenolic compounds:** Fungal phenolics can serve as antioxidants, but they upset the microbial structure, which is one of the causes of their antibacterial effect^[23].

3.3 Examples of antimicrobial medicinal fungi

A number of fungi have been demonstrated to be active in laboratory and clinical trials against pathogens^[24]:

1. ***Ganoderma lucidum*:** Shows inhibitory effects against *Staphylococcus aureus*, *Escherichia coli*, and *Capsulatum*. The bacteria also induce phagocytic cell-mediated bacterial killing^[25].
2. ***Cordyceps militaris*:** Produces cordycepin, which has been experimentally proven to inhibit the activity of test bacteria and *Pseudomonas aeruginosa*^[26].
3. ***Lentinula edodes*:** Lentinan, a beta-glucan from shiitake mushrooms, enhances immune function and demonstrates activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA)^[27].
4. ***Pluturus ostreatus*:** Its aromas inhibit intestinal bacteria such as *Salmonella typhi* and *Shigella astrocytoma*^[28].

5. ***Hericium erinaceus***: In addition to its neuroprotective effects.

4. Clinical applications

4.1 Respiratory tract infections

Research has shown promising and systematic efficacy in eliminating respiratory tract infections, especially infections caused by antibiotic-resistant bacteria. For example, *Ganoderma lucidum* has antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, two of the most common causes of respiratory tract infections. Clinical studies have shown significant improvement in the treatment of chronic obstructive pulmonary disease (COPD) patients who took *Ganoderma* extract supplements, demonstrating their role in stimulating the immune response and reducing inflammation [29, 30].

4.2 Gastrointestinal infections

Certain compounds of fungal origin have been investigated as having the ability to combat gastrointestinal pathogens. *Cordyceps militaris* has been shown to be inhibitory to *Helicobacter pylori* that cause gastric ulcers and gastric cancer. *Ganoderma lucidum* extracts have also been shown to be antifungal agents against *Candida albicans* which causes fungal gastroenteritis [31, 32].

4.3 Skin infections

Medicinal mushrooms when used topically are considered as treatment of skin infections. Extracts of *Cordyceps militaris* have been shown to have antifungal effect against *Staphylococcus aureus* and *Malassezia* that cause most diseases, including acne and seborrheic dermatitis. Recipes that include fungal extracts are produced to support the skin barrier and lower microbial load, which could be of benefit to traditional skin treatment [33-35].

5. Safety and toxicity

Although medical mushrooms are safe in general, there is no risk that is highly associated with the use of the mushroom that may be mild i.e. periodical gastrointestinal disturbance, or allergy. However, monitoring of the quality of mushroom supplements is also needed as one health risk can be the contamination with heavy metal, or mycotoxins. Therefore, the cultivation procedures must be standardized and quality-guaranteed, to ensure that the use of fungal-based treatments is safe [36-38].

6. Challenges and future prospects

6.1 Quality control

Bioactive compounds were found in different concentrations in various strains of fungi and cultivation did not provide much assurance in standardizing medicinal fungal products. Consequently, uniform cultivation, collecting and processing procedures should be established to obtain a stable quality and therapeutic effectiveness [39].

6.2 Clinical validation

There are limited clinical trials to test the effectiveness of medicinal fungi along with preclinical data. To unravel the therapeutic capabilities of fungal-derived compounds in

different clinical aspects, diverse and large-scale, controlled clinical trials are required [40].

6.3 Regulatory considerations

In most countries around the world, medicinal fungi regulation remains inconsistent, with certain areas having no detailed protocols concerning their utilization in medical practice. The regulatory environment should be harmonized to support the inclusion of medicinal fungi into the national health systems.

7. Conclusion

Medical fungi are an attractive future option in alternative or adjuvant therapy against antibiotic-resistant infections. Due to their wide variety of action and their ancient roots in traditional medicine, they hold promise in contemporary drug therapy. However, concerted actions are required in the domains of standardization, clinical validation and regulatory coordination to realize their full clinical potential. As research and development continues, medicinal fungi may play a central role in solving the worldwide issue of antimicrobial resistance.

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