Antibacterial Secondary Metabolites from Basidiomycetes

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Fungi are a rich source of secondary metabolites with several pharmacological activities such as antifungal, antioxidant, antibacterial and anticancer to name a few. Due to the large number of diverse structured chemical compounds they produce, fungi from the phyla Ascomycota, Basidiomycota and Muccoromycota have been intensively studied for isolation of bioactive compounds. Basidiomycetes-derived secondary metabolites are known as a promising source of antibacterial compounds with activity against Gram-positive bacteria. The continued emergence of antimicrobial resistance (AMR) poses a major challenge to patient health as it leads to higher morbidity and mortality, higher hospital-stay duration and substantial economic burden in global healthcare sector. One of the key culprits for AMR crisis is Staphylococcus aureus causing community-acquired infections as the pathogen develops resistance towards multiple antibiotics. The recent emergence of community strains of S. aureus harbouring methicillin-resistant (MRSA), vancomycin-intermediate (VISA) and vancomycin-resistant (VRSA) genes associated with increased virulence is challenging. Despite the few significant developments in antibiotic research, successful MRSA therapeutic options are still needed to reduce the use of scanty and expensive second-line treatments. This paper provides an overview of findings from various studies on antibacterial secondary metabolites from basidiomycetes, with a special focus on antistaphylococcal activity.

Basidiomycota bioactive natural products antibacterial antimicrobial resistance

1. Introduction

Antimicrobial resistance (AMR) crisis is associated with more than 2 million hard-to-treat infectious diseases. The Center for Disease Control and Prevention (CDC) reported that increasing mortality rate at an average of 23,000 deaths per year was recorded in developing countries [1]. Major pathogen that contributes to the AMR incidence is *Staphylococcus aureus* with the emergence of multidrug-resistant strains such as methicilin-resistant (MRSA), vancomycin-intermediate (VISA) and vancomycin-resistant (VRSA) *S. aureus* [2][3][4]. The rising incidence of these resistant pathogens leads to inadequate antimicrobial therapeutic effects that are related to poor healthcare outcome in patients. Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains also account for an increasing proportion of hospital-acquired MRSA (HA-MRSA) infections [3][5]. These pathogenic strains of *Staphylococci* with their intrinsic virulence factor can cause a diverse array of life-threatening infections [4]. The high antibiotic selective pressure in crowded populations, like in Asia, creates an environment that allows rapid development and successful spread of multidrug-resistant pathogens such as HA-MRSA and CA-MRSA [3][6]. The

last resort treatment for MRSA infections is vancomycin [2]. However, current loss in sensitivity toward vancomycin limits the conventional therapeutic choice for *Staphylococcal* infections [2][7].

Fungal secondary metabolites have been reported as a potential source of bioactive compounds with antibacterial activity. The accidental discovery of penicillin from fungi in 1929 by Fleming drew attention of scientific community to the possible role of fungi as antibiotics and this has contributed to the isolation and development of other antibiotics [8]. Fungi are rich sources of secondary metabolites with diverse bioactivities, many that have been developed into important pharmaceutical products. With more than 15,000 secondary metabolites discovered to date, fungi stand out as an important group of microbes in bioactive natural products research [9]. Advances in analytical chemistry, computational tools, and drug discovery research have enabled the development of some fungal-derived antimicrobial compounds with potential therapeutic effects to be used individually or in adjunctive therapies to control difficult-to-treat pathogens [10]. Secondary metabolites from saprotrophic and easily cultivable fungi of the phyla Ascomycota, Muccoromycota and Basidiomycota have been studied intensively [11].

Previous studies have shown that secondary metabolites from basidiomycetes have a wide range of pharmacological activities including antimicrobials [12]. Basidiomycetes, from the phylum Basidiomycota, are a group of higher fungi with distinctive fruiting bodies and reproductive structures with edible and non-edible properties. Mushroom-forming fungi, mostly from the basidiomycete group, have been used as remedies for various diseases owing to their ability to produce compounds with high structural diversity, including terpenes, anthraquinone, derivatives of benzoic acid, quinolines, cyclic peptides, steroids, sesquiterpenes, oxalic acid, epipolythiopiperazine-2,5 diones and polysaccharides [13][14]. Traditionally, bioactive components have been extracted from fruiting bodies or mycelial extracts of mushrooms [15]. They are known to produce secondary metabolites with a range of pharmacological activities including antimicrobial, antioxidant, anti-angiogenesis, anticancer, immunomodulatory and anti-inflammatory [16].

In many studies, however, antimicrobial activities of different extracts of mushroom were reported without identifying the active compound/s responsible for the observed high activity against Gram-positive bacteria [13][17][18]. Despite the challenges faced in explorative studies to access the bioactive metabolites originating from fruiting bodies of mushrooms as they occur temporarily in the environment, their importance has been significant in recent decades [13]. With regards to this, more studies have been focusing on metabolites produced from submerged fermentation of mycelial culture of mushrooms where frequently these metabolites differ from those of fruiting bodies [19]. This work is a brief review on antistaphylococcal activities of Basidiomycetes that have been reported.

2. Antimicrobial Resistance (AMR)

Antimicrobial resistance is described as lowered efficiency or loss of antibiotics' effectiveness against pathogens and this is a major problem in the medical sector globally. Antimicrobial resistance is correlated with high medical costs because of a longer period of disease, additional testing and needless usage of second-line treatments [1][5]. As mentioned by the Organization for Economic Co-operation and Development (OECD), the key risk factor for development of resistance is excessive usage or intake of antibiotics [6][20][21]. The high emergence of AMR has led

to a shift change in therapeutic practices towards use of newer wide-spectrum drugs and increased usage (42%) of last resort classes of antibiotics such as vancomycin [6]. Many reports have indicated that the resistance epidemiology is global and spreads through nations and across borders [20].

In vitro antibacterial activity of antibiotics is typically determined by biological assays. The most popular methods include agar well diffusion, disc diffusion, minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and time kill assays [22]. Clinical breakpoints used as interpretive criteria to consider susceptibility of a bacterial isolate to an antimicrobial agent are provided by the Clinical and Laboratory Standards Institute (CLSI) [23][24], the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and/or the US Food and Drug Administration (FDA).

In agar well diffusion assay, a hole was punched into agar inoculated with the test organism and filled with the antibiotic solution. Alternatively, a filter paper disc containing antibiotic was placed on inoculated agar. In both methods, zone of inhibition produced by the diffusion of antibiotic compound into the agar was measured. Due to the agar being an aqueous preparation, non-polar compounds do not diffuse as well as polar compounds, thus producing smaller diameter of inhibition zones despite their higher activity. This could be a limitation in the agar diffusion method [25][26]. The MIC is defined as the lowest concentration of a drug that inhibits the growth of bacteria after incubation. The MBC of a drug is determined upon reading of MIC by streaking the broth dilutions onto general or selective agar with 24–48 h of incubation. Absence of growth of the viable organisms on agar indicated the lowest broth dilution of drug, which caused a 99.9% suppression of the bacterial growth. The most appropriate in vitro approach to study bactericidal activity of a vast variety of antimicrobial agents is the time-kill assay [22]. The outcome of this assay indicates if an antimicrobial effect is dependent on exposure time or concentration of the drug. The assay is often used as initial descriptive analysis in pharmacodynamic analysis of a drug [22][27].

Preventing the development of resistant bacterial strains is important to ensure the effectiveness of current drugs in managing dangerous and life-threatening infections as an attempt to reduce the severity of AMR crisis [28][29]. Thus, there is an urgent need to carry out continuous research and development of new antibacterial drugs to counter the loss in efficacy of current antibiotics [28][30][31].

3. Multidrug Resistant *Staphylococcus aureus* and Antibacterial Drug Discovery from Basidiomycetes

Staphylococcus aureus infections produce wide spectrum of pyogenic lesions involving several organs, and it can cause hospital outbreaks and community acquired infections. Selective pressure on the bacteria due to high consumption of wide-spectrum antibiotics could stimulate the emergence of antibacterial resistant strains. Burden of infections in low-income countries is high since the solution to overcome this crisis is by replacing ineffective first line antibiotics to more costly second line or third line antibiotics [6]. Thus, the development of new antibiotics, combination drugs, bioprospecting for potential antibacterial natural compounds and improved drug delivery systems are some of the current strategies to control the antimicrobial resistance threat [6][32].

Emergence of HA-MRSA strains are associated with profligate use of antibiotics in healthcare settings [33]. The MRSA strains have demonstrated resistance to a range of antibiotics belonging to isoxazoyl penicillin group (methicillin, oxacillin, flucloxacillin), cephalosporins and carbapenems [34][35][36]. The first MRSA variant strain was isolated in United Kingdom in 1961 after methicillin was introduced in 1959 [37][38][39][40]. Thereafter, the changing epidemiology of variants of the strains found in many other countries like Europe, Australia, Japan and United States eventually makes MRSA as a major threat in nosocomial infections worldwide [20]. MRSA has more propensity to develop resistance to macrolides, quinolones and aminogylycosides, and this led to reduced therapeutic options [34][35][36][41][42]. In hospitals worldwide, a high prevalence of MRSA with rates above 50% has been documented [43][44]. A new variant strain of CA-MRSA was reported to be prevalent in Asian healthcare settings. This was documented by several studies which showed an occurrence rate of 2.5% in Thailand and 38.8% in Sri Lanka [45].

Emergence of antimicrobial resistance in *S. aureus* to glycopeptide group of antibiotics which is the last resort of staphylococcal treatment, became a global concern in managing staphylococcal infections [29]. Three classes of limited vancomycin susceptibility strains of *S. aureus* that have emerged in different locations around the world are VISA, heterogeneous VISA (hVISA) and VRSA [37][46]. Owing to the dynamic re-organisation of cell wall metabolism, VISA and hVISA strains have thickened cell walls with decreased glycopeptide cross-linking [44]. The first report of VISA and hVISA was detected in Japan in 1996 and 1997, respectively, while VRSA from a hospital in the United States was reported in 2002 [47]. The resistance phenotypic of VISA (Minimum Inhibitory Concentration: 8 µg/mL) has the ability of reverting back to the susceptibility phenotype towards vancomycin when the selective pressure is removed (MIC at 2 µg/mL) [48].

Prevalence of VRSA strains have been documented in South Nigeria (0–6%), Zaria, North Nigeria (57.7%), South India (1.4%), Australia, South Africa, Scotland, Hong Kong, Thailand and Korea (0–74%) [39][48][49][50]. No reports of vancomycin-resistant *S. aureus* (VRSA) have been documented in Malaysia [51]. The emergence of antibiotic resistance globally could lead to serious problems of limited therapeutic options available [52]. The emergence of VISA and VRSA strains causes more life-threatening infections in the healthcare sector [53][54]. Scanty and expensive drugs like teicoplanin, daptomycin and linezolid are also being used as next therapeutic options for MRSA infection due to the limited sensitivity of vancomycin [15][35][54][55][56].

Basidiomycetes derived secondary metabolites are known as a promising source of antibacterial compounds with activity against Gram-positive bacteria in natural product discovery. Crude extracts of natural products were reported to target on cell wall biosynthesis and cell membrane permeability as their mechanism of action to exhibit antibacterial activity [57]. Many species have been studied for their potential to produce bioactive secondary metabolites with antibacterial activity against MRSA and other drug resistant bacteria [58][59][60][61][62][61][63][64][65][66][67][68].

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