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MYCOPHARMACEUTICALS FROM WILD BASIDIOMYCETES: CURRENT RESEARCH AND FUTURE PROSPECTS

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Basidiomycetes found in forest ecosystems have been used traditionally as food and medicine for centuries, and various studies have validated many of their health benefits. In recent years, the focus in medicinal basidiomycetes has increased, and several notable trends in their application and research have been observed. In light of the emerging literatures, this review attempts to summarise and discuss evidences from the past decade on the importance of exploring basidiomycetes for their pharmacological properties. It also aims to serve as a critical reference for research works focused on the potentials of wild basidiomycetes in Malaysia, as well as from worldwide, to produce a diverse range of bioactive metabolites. Special attention is given to the low-molecular weight bioactive compounds produced in cultured mycelium and culture broth of these macrofungi. It further highlights the unique attributes of wild bioluminescent basidiomycetes species which hold great potential to be harnessed for mycopharmaceuticals with commercial applications in healthcare industries.

Keywords: Wild mushrooms, bioluminescent basidiomycetes, bioactivity, mycochemicals, methicillin-resistant *Staphylococcus aureus* (MRSA), *Neonothopanus nambi*

INTRODUCTION

The United Nations Environment Programme has identified Malaysia as one of the 17 megadiverse countries in the world based on the estimations of the country's species richness and endemism (Rintelen et al. 2017). Although an estimated 8300 and 12,000 plant species were reported in Peninsular Malaysia and East Malaysia, respectively (Saw et al. 2010), information on the diversity of Malaysian fungi is still lacking (Samsudin & Abdullah 2019). Recognising this gap in our biodiversity information, researchers from the Forest Research Institute Malaysia and Universiti Malaya embarked on a joint project to compile and document the list of fungal species reported in Peninsular Malaysia. Based on published literatures, a checklist of approximately 4000 species of distinct taxa of fungi from all divisions was published (Lee et al. 2012). This comprehensive checklist of fungi, however, has not fully documented all the fungal species found in Malaysia. It is likely that many more species of fungi can be discovered and documented if more systematic surveys and studies are conducted over long-term periods (Lee et al. 2012).

Basidiomycota, a major lineage of higher fungi comprising more than 40,000 species including most of the macrofungi group, represents approximately one third of all known fungal species (He & Zhao 2021). Macrofungi from the basidiomycetes group, collectively referred to as mushrooms, are characterised by the ability to produce spore-bearing fruiting bodies visible to the naked eye (Bakray et al. 2020). They have the ability to grow on different substrates based on their ecological classification as saprophytic (organic matter of dead organisms, including decaying wood and dead animals), parasitic (pathogens in living plants) or symbiotic (mycorrhizal) association with plant roots (Parveen et al. 2017). Therefore, basidiomycetes play an important role in the decomposition of lignocellulosic materials, carbon cycling and symbiotic relationships essential for forest ecosystems (Mustapha & Zawawi 2022). Previous studies have shown that the diversity of basidiomycetes is high in

Malaysian lowland and highland forests (Seelan et al. 2014, Bakray et al. 2020). Despite these records, it is estimated that about 70% of the total basidiomycetes species in the country have yet to be described (Mohammad et al. 2020). Results from a survey at Imbak Canyon in Sabah where about 47% of the collected wild basidiomycetes were characterised as unidentified groups lacking morphological references, supported the expected high macrofungal diversity in our tropical forest ecosystems (Viviannye et al. 2019).

Economic importance of edible and medicinal basidiomycetes

The global market for edible and medicinal basidiomycetes is projected to grow from USD48.8 billion in 2022 to USD83.5 billion in 2030, at a compound annual growth rate (CAGR) of 7% (Mushrooms: Global Strategic Business Report 2023). The recent increase in experimental-based evidence to validate pharmacological activities observed in basidiomycetes for centuries, could partly be the reason for a positive trend. Edible basidiomycetes (mushrooms) have attracted considerable interest for centuries as a quality food source with high nutritional and functional values (Varghese et al. 2019, Anusiya et al. 2021). Recently, Samsudin and Abdullah (2019) reviewed the available literatures on edible mushrooms from Malaysia, with an emphasis on their nutritional properties. Their review which was regarded as an extension to the previous checklist of Malaysian fungi by Lee et al. (2012), showed that Malaysia is indeed a natural repository for wild and cultivated edible basidiomycetes with numerous benefits. Apart from the nutritional benefits, basidiomycetes are also valued for their medicinal properties. About 270 species have been reported to be potentially useful for human health (Persad & Neergheen 2023). These include non-edible medicinal species such as *Ganoderma lucidum* (Curtis) Karst (reishi or ling zhi) and *Lignosus rhinocerotis* (Cooke) Rivarden (tiger milk mushroom) known for health promoting properties, and are available commercially in the form of powdered extracts (Samsudin & Abdullah 2019). Other well-known medicinal species include *Hericium erinaceus* (Bull.: Fr.) Pers. (lion's mane), *Lentinula edodes* (Berk.) Singer (shiitake), *Grifola frondosa* (Dicks.) Gray (maitake), *Schizophyllum commune Fr. (split gill), Inonotus obliquus* (Pers.: Fr.) Pilat (chaga) and *Trametes versicolor* (L.) Lloyd (Fokunang et al. 2022, Cateni et al. 2022, Rokos et al. 2023).

Biological activities of basidiomycetes metabolites: overview and current research

Basidiomycetes are known to produce a diverse array of bioactive metabolites in the fruiting body and mycelia in response to biotic and abiotic stresses, to help in its survival and coexistence with other species in the macrocosm (Panda & Tayung 2014, Chaturvedi et al. 2018). These metabolites also exhibit an overwhelming number of biological and pharmacological activities important in the treatment of numerous human diseases (Grundemann et al. 2020, Ogidi et al. 2020, Chopra et al. 2021). Thus, basidiomycetes make up a vast and yet largely untapped source of valuable natural products with the potentials to be developed as mycopharmaceuticals or basidiomycetes-derived drugs (Badalyan & Rapior 2020, Al-Obaidi et al. 2021). Basidiomycetes produce high-molecular weight metabolites such as polysaccharides (mainly β-glucans), proteins, lipids and lectins, as well as a diverse array of low-molecular weight compounds such as terpenoids, polyketides and alkaloids (Varghese et al. 2019, Niego et al. 2021). It is estimated that more than 130 biological activities have been reported for these metabolites (Gargano et al. 2017). In recent years, the interest in beneficial properties of basidiomycetes has increased considerably and there have been several notable trends in research focus. In this context, preventive and curative effects of mycopharmaceuticals on cancer, cardiovascular diseases, atherosclerosis and hypertension has taken precedence (Chang & Buswell 2022, Chugh et al. 2022, Elkhateeb & Daba 2022). Other pharmacological effects include hepatoprotective, immunomodulatory, neuroprotective and neuron regenerative, antidiabetic, antioxidant, anti-inflammatory, hypocholesterolemic, antiasthmatic, antiviral and antimicrobial (Ma et al. 2018, Cateni et al. 2022). The following section highlights some

of the current literature and reviews on this subject.

Research on the properties of basidiomycetes-derived polysaccharides has gained much interest over the years. Some current researches are on the hepatoprotective effects of β-glucans from *G. lucidum* against acute liver injury (Chen et al. 2022), and synergistic effects of β-glucans from *Agaricus bisporus* (J.E. Lange) Imbach with the anticancer drug doxorubicin to induce antitumor activity on breast tumor cells (Rutckeviski et al. 2022). Beta-glucans from *G. lucidum* also demonstrated the ability to restore disordered gut microbiota and metabolism in type 2 diabetic rats (Chen et al. 2020), and inhibit proliferation of colorectal cancer cells and induced cell death via apoptosis (Ruan et al. 2023).

Immunomodulating metabolites from *G. lucidum*, *Pleurotus* spp., *S. commune*, *L. edodes* and others have also gained much interest in human immunotherapy (Chopra et al. 2021). Immunomodulators from basidiomycetes have the ability to activate innate immune system components such as natural killer cells, neutrophils and macrophages, and stimulate cytokines secretion. These cytokines, in turn, activate the adaptive immune system by promoting antibody production to help the body fight against invading microorganisms or tumor cells, especially under immune-compromised conditions (Chaturvedi et al. 2018). Recent findings indicated potential immunomodulatory effects exerted by the terpenoids ganoderic acid A and C_1 from *G. lucidum* (Li et al. 2020), and polysaccharides from *Pleurotus citrinopileatus* Singer (Meng et al. 2023).

Metabolites from *H. erinaceus*, a well-studied species in Malaysia, have the ability to stimulate neurite outgrowth in brain and spinal cord cells indicating neuroregenerative functions in damaged nerves especially in early recovery stages (Samberkar et al. 2015, Phan et al. 2017). Recent progress in research has generated supporting results to show its potentials in mitigation and treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's (Badalyan & Rapior 2021). Thus, comprehensive evaluations of the neuroprotective terpenoids from *H. erinaceus* in clinical trials may serve to develop them into clinically approved drugs (Lee et al. 2020). *Lignosus rhinocerotis*, traditionally used in the treatment of asthma and other diseases, is another species studied extensively in Malaysia (Johnathan et al. 2021). Recently, a human trial study demonstrated that *L. rhinocerotis* supplement significantly suppressed the levels of cytokines involved in the initiation and persistence of inflammation in the airway and lung, showing improved respiratory health and immunity in patients (Tan et al. 2021).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a source of global pandemic in 2020, causing the pneumonia disease named as coronavirus disease 2019 (COVID-19) by WHO (Shereen et al. 2020). Bioactive metabolites from some basidiomycetes have been proven to exhibit antiviral effects which inhibit proliferation of a variety of viral strains (Shahzad et al. 2020). Moreover, metabolites such as triterpenoids and polysaccharides from basidiomycetes possess metabolic-modulating capabilities, which present advantageous prospects in immunomodulation for controlling hyperinflammatory responses in COVID-19 pathogenesis (Murphy et al. 2020, Hetland et al. 2021). Therefore, exploring the benefits of basidiomycetes metabolites as a new source of compounds against SARS-CoV-2 infection, could offer valuable alternatives in COVID-19 therapy (Arunachalam et al. 2022).

Utilisation of wild basidiomycetes in Malaysia

It is estimated that only 5% out of the total number of basidiomycetes species found worldwide have been explored for their beneficial values (Ogidi et al. 2020). Hence, ethnomycological studies to document the traditional uses of edible and medicinal basidiomycetes is important because such knowledge would lead to bioactivity discoveries and sustainable utilisation of the less-known wild species (Panda & Tayung 2014). Countries like China, Japan, India and Thailand have widely studied the traditional uses of wild basidiomycetes by their local communities (Anusiya et al. 2021). Whereas some early surveys by researchers at the Forest Research Institute Malaysia have documented species commonly used by the indigenous communities from Semai, Temuan, Bateq, Che Wong and

Jakun sub-tribes in Peninsular Malaysia (Chang & Lee 2004, Lee et al. 2009). These researchers observed that *L. rhinocerotis*, locally known as "cendawan susu rimau", was the most popular medicinal species used by most communities. Despite the continued efforts by others to document ethnomycological knowledge in Malaysia (Azliza et al. 2012, Lee & Mohammad 2020), the vast majority of basidiomycetes species found in various ecosystems have not been fully investigated for their beneficial properties (Fui et al. 2018).

Mycopharmaceuticals from wild basidiomycetes

Wild basidiomycetes from tropical forest ecosystems are deemed as a treasure trove of rich biodiversity and a source of new bioactive molecules (Chepkirui et al. 2019). In Malaysia, most investigations on the bioactivities of basidiomycetes were on well-known edible or medicinal species (Lau et al. 2014b, Omar et al. 2015, Samberkar et al. 2015, Abidin et al. 2016, Johnathan et al. 2021, Tan et al. 2021). To our knowledge, thus far, only handful studies explored the underutilised or wild basidiomycetes species for bioactive secondary metabolites with potential pharmacological properties (Getha et al. 2009, Chong et al. 2014, Chan & Chong 2020). A recent review on the biological properties of more than 70 basidiomycetes species native to North America, indicated the importance of exploring these wild species for valuable mycopharmaceuticals (Zeb & Lee 2021). Table 1 shows some of the metabolites isolated from wild basidiomycetes around the world exhibiting multiple therapeutic applications in humans.

In particular, many studies reported that the wild basidiomycetes represent a potentially rich source of antibacterial compounds against human pathogenic bacteria (Krupodorova et al. 2016, Chepkirui et al. 2019). Antimicrobial resistance (AMR) is currently one of the major threats to public health worldwide. Overuse and misuse of antibiotics can lead to the development of new survival strategies in bacteria which makes them resistant to most of the commonly used antibiotics in treatments (Clericuzio et al. 2021). One of the major AMR pathogens causing serious concern is methicillin-resistant *Staphylococcus aureus* (MRSA). The nosocomial or hospital-acquired MRSA strains exhibit resistance to multiple classes of approved antibiotics, and can cause serious and life-threatening infections (Himani et al. 2015). It is anticipated that the global incidence of AMR is likely to grow from 26% in 2018 to 40% by 2050, and such increases are expected to cost thousands of lives, increased hospital expenses and a negative social impact on people globally (Zeb & Lee 2021). Thus, there is an urgent need for continuous research towards developing new antibacterial drugs against these dangerous pathogens (Terreni et al. 2021).

Basidiomycetes metabolites have shown potential activities as inhibitors of *S. aureus* and MRSA in past literatures (Vallavan et al. 2020). The main class of secondary metabolites from basidiomycetes are terpenoids, and they are known for their potent antibacterial activities (Duru & Cayan 2015, Dasgupta & Acharya 2019). An example of antibacterial terpenoid from wild basidiomycetes is the diterpenoid pleuromutilin from *Clitopilus passeckerianus* (Pilat) Singer and related species (Eyal et al. 2016). The derivative of this compound, retapamulin, was approved as a topical antibacterial drug for treating *S. aureus* skin infections (Shang et al. 2014). Other examples include a novel lanostane-type triterpenoid from *Jahnoporus hirtus* (Cooke) Nuss effective for treating *Enterococcus* bacterial infections such as urinary tract infections and meningitis (Zeb & Lee 2021), and sesquiterpenoids from *G. pfeifferi* Bres. exhibiting potent inhibition against MRSA (Ogidi et al. 2020).

Bioprospecting wild basidiomycetes for metabolites to combat antimicrobial resistance

An early exploration for antibacterial metabolites produced by wild polypores from Malaysia was carried out by Getha et al. (2009). These polypore basidiomycetes were previously isolated from diseased timber trees and other plantation crops by mycologists at the Forest Research Institute Malaysia (Mohd-Farid & Lee 2006). Majority of the studied species belong to the genera *Phellinus*, *Rigidoporus* and *Ganoderma*, with four unknown species, and most were isolated from diseased *Acacia*

Table 1 Bioactivities in metabolites extracted from some wild basidiomycetes reported in literature over the past 10 years

Basidiomycetes species	Country of origin	Source (solvent for extraction)*	Biological activity and active dose	Reference
Amanita muscaria	Tanzania	Fruiting body extracts (PE, E)	Antibacterial: *Shigella flexneri* & *Klebsiella oxytoca*, MIC[a] 1.56 mg mL^{-1}; Antifungal: *Candida albicans*, MIC 0.78 mg mL^{-1}	Chelela et al. 2014
Hyphodontia paradoxa	Poland	Fruiting body extract (E)	Antibacterial: *Micrococcus luteus*, MIC 0.156 mg mL^{-1}; *Bacillus subtilis*, MIC 0.313 mg mL^{-1}; *Staphylococcus aureus*, MIC 0.625 mg mL^{-1}	Nowacka et al. 2015
Anthracophyllum lateritium	Sri Lanka	Fruiting body extract (M)	Antioxidant: DPPH[b] radical scavenging activity, EC_{50}[c] 8 µg mL^{-1}; Cytotoxicity: RD[d], EC_{50} 18.8 **µg mL^{-1}**	Fernando et al. 2015
Ganoderma sp. MS3	Western Ghats, India	Fruiting body extract (EA)	Antibacterial: *S. aureus*, DIZ[e] 31.2 mm; *Escherichia coli*, DIZ 27.1 mm	Ramesh & Siva 2016
Lenzites quercina	Nigeria	Fruiting body extracts (EA, E, PE)	Anticancer: HeLa[f] & RD, IC_{50}[g] 0.11 & 0.46 µg mL^{-1}	Ogidi et al. 2017
Inonotus clemensiae	Nepal	Fruiting body extract (E)	Antibacterial: *S. aureus*, MIC 100 µg mL^{-1}; *Propionibacterium acnes*, MIC 100 µg mL^{-1}	Tamrakar et al. 2017
Tapinella atrotomentosa	Hungary	Fruiting body extract and compound (C)	Antibacterial: multiresistant *Acinetobacter baumannii*, MIC 6 µg mL^{-1}	Beni et al. 2018
Skeletocutis nivea	Kenya	Mycelial culture extract (EA)	Antibacterial: *B. subtilis*, MIC 4.69 µg mL^{-1}	Sum et al. 2018
Favolaschia calocera	Kenya	Mycelial culture extract (EA)	Antifungal: *C. tenuis*, MIC < 2.34 µg mL^{-1}	Sum et al. 2018
Pholiota mixta	Japan	Fruiting body extracts (water, E, H)	Antiinflammatory: depressed NO[h] to less than 20% of that in control	Yamada et al. 2019
Cortinarius balteatocumatilis	Japan	Fruiting body extracts (water, E, H)	Antiinflammatory: depressed NO to less than 20% of that in control	Yamada et al. 2019
Guepina helvelloides	Canada	Fruiting body extract (water)	Immunostimulatory: host immune system activation at 1 mg mL^{-1}	Deo et al. 2019
Gyroporus castaneus	France	Fruiting body extract (Ch)	Antibacterial: methicillin-resistant *S. aureus* (MRSA), MIC 125 µg mL^{-1}	Morel et al. 2021

continued

Table 1 Continued

Basidiomycetes species	Country of origin	Source (solvent for extraction)*	Biological activity and active dose	Reference
Coprinellus sp.	USA	Fruiting body extract (water)	Anticancer: MDA-MB-231[i], MCF-7[i] & BT-20[i] with IC_{50} 40, 120 & 150 µg mL^{-1}	Zeb & Lee 2021
Rhizopogon subgelatinosus	USA	Fruiting body extract (E)	Antiinflammatory: COX-2[j] enzyme inhibitory activity, IC_{50} 50 µg mL^{-1}	Zeb & Lee 2021
Scleroderma laeve	USA	Fruiting body extract (E)	Antioxidant: DPPH radical scavenging activity, IC_{50} < 20 µg mL^{-1}; Antiinflammatory: COX-2 inhibitory activity, IC_{50} 50 µg mL^{-1}; Antituberculosis: IC_{50} < 20 µg mL^{-1}	Zeb & Lee 2021
Astraeus pteridis	USA	Fruiting body extract (E)	Antituberculosis: *Mycobacterium tuberculosis*, IC_{50} < 20 µg mL^{-1}	Zeb & Lee 2021
Hygrocybe conica	Malaysia	Fruiting body extract (water)	Antioxidant: DPPH radical scavenging activity, EC_{50} 2.1 mg mL^{-1}	Chong et al. 2014
Neonothopanus nambi (strain FRIM550 / DSM 24013)	Malaysia	Mycelial culture filtrate extract (BA)	Antibacterial: *B. subtilis*, MIC 44 µg mL^{-1}; MRSA, MIC 625 µg mL^{-1}	Getha et al. 2013
			Antioxidant: Superoxide radical scavenging activity, IC_{50} 9.24 µg mL^{-1}; Elastase inhibitory activity: 55.3%	Getha et al. 2018

* PE = petroleum ether, E = ethanol, M = methanol, EA = ethyl acetate, C = chloroform, H = hexane, Ch = cyclohexane, BA = butyl acetate; a = minimal inhibitory concentration, b = 2,2-diphenyl-1-picrylhydrazyl, c = half-maximal effective concentration, d= rhabdomyosarcoma cells, e = diameter of inhibition zone, f = cervical cancer cells, g = half-maximal inhibitory concentration, h = nitric oxide production in murine macrophages, I = breast cancer cells, j = cyclooxygenase-2

mangium trees (Table 2). Basidiomycetes from the morphogroup polypores consist of species commonly known as forest pathogens. For example, *Ganoderma* spp., *Phellinus noxius* (Corner) G.Cunn, *Rigidoporus microporus* (Sw.) Overeem, and *Tinctoporellus epimiltinus* (Berk. & Broome) Ryvarden are known to cause red, brown, black and white types of woody root diseases in *A. mangium* (Lee 2002, Glen et al. 2009). Wild polypores were chosen deliberately for screening knowing that pathogenic polypores have not been sufficiently explored, and these unexplored species hold high prospects of discovering new mycopharmaceuticals (Panda & Tayung 2014). Getha et al. (2009) used submerged fermentation in liquid media to produce fungal metabolites from mycelia instead of cultivating the fruiting bodies in solid media. Past studies have shown that submerged cultivation has advantages such as shorter period of mycelial biomass and metabolites production, better quality control and lesser chance of contamination (Lau et al. 2014a). While others showed that considerable variation in chemical profiles of *H. erinaceus* extracts presented the differences in antioxidant capacities between mycelial, culture broth and fruiting body extracts (Wong et al. 2009). Numerous bioactive compounds are produced in mycelia under different submerged fermentation conditions, and are considered as favorable source of novel mycopharmaceuticals for the pharmaceutical industry (Anusiya et al. 2021).

Results from the bioprospecting study showed that metabolites of almost 50% of the total species screened from *Ganoderma* and *Rigidoporus* genera displayed significant inhibition against both *S. aureus* and *Bacillus subtilis* bacteria (Getha et al. 2009). *Phellinus* spp. showed lower number of hits, while both single species of *Tinctoporellus* and *Lentinus* genera were inactive. Interestingly, all four unidentified species exhibited strong activity against both bacteria (Table 2). Findings from this study lend weight to other reports that showed wild basidiomycetes as potential candidates for discovering antibacterial agents. Similarly, Lallawmsanga et al. (2016) had reported of strong antibacterial activity in extracts of wild basidiomycetes from forest reserves in India where almost 50% of the total screened displayed significant activity. Subsequently, the potential antibacterial extracts identified by Getha et al. (2009) were further investigated for activity against a MRSA pathogenic strain (Getha et al. 2013). The latter study observed that extract of an unidentified basidiomycetes coded FRIM550, showed the highest activity with a minimum inhibitory concentration (MIC) of 0.625 mg mL^{-1} against MRSA. Mycelial culture of FRIM550 was isolated from root samples of a red root rot infected *A. mangium* collected from Gemas, Negeri Sembilan (Mohd-Farid & Lee 2006). Interestingly, the strain exhibited higher anti-MRSA activity compared to that observed by Chan and Chong (2020) who found that the

Table 2 Basidiomycetes genera, the associated woody substrate they were isolated from, and number of isolates screened and active for antibacterial effects (adapted from Getha et al. 2009)

Basidiomycetes genera	Isolation source (woody substrate)	No. of isolates screened	No. (%) of active isolates*
Phellinus spp.	*Acacia mangium, Tectona grandis, Azadirachta excelsa, Hevea brasiliensis, Fraxinus formosa*	32	3 (9.4%)
Rigidoporus spp.	*Acacia mangium, Azadirachta excelsa, Hevea brasiliensis*	11	6 (54.5%)
Ganoderma spp.	*Acacia mangium, Hevea brasiliensis, Dryobalanops aromatica*	7	4 (57.1%)
Tinctoporellus spp.	*Acacia mangium*	1	0
Lentinus spp.	Decaying wood	1	0
Basidiomycetes (unidentified)	*Acacia mangium*	4	4 (100%)

* = Isolates with mycelial culture extract that showed percent inhibitory concentration (%IC) ≥ 90% against *Staphylococcus aureus* NBRC 12732 and *Bacillus subtilis* NBRC 3134 using assay methods described by Getha et al. (2009)

fruiting body extract of *G. boninense*, a polypore pathogen of oil palm basal stem rot, exhibited MIC of 1.25 mg mL^{-1} against MRSA. Molecular analysis based on nuclear ribosomal internal transcribed spacer (ITS) gene region identified FRIM550 as the bioluminescent basidiomycetes *Neonothopanus nambi* (Speg.) R.H. Petersen & Krisai (Getha et al. 2018). These findings hold much interest since studies from Thailand have shown that *N. nambi* produces a diverse group of bioactive secondary metabolites (Wisetsai et al. 2021). However, apart from the discoveries of researchers at Forest Research Institute Malaysia, none of the past literatures reported of bioactive compounds associated with anti-MRSA activity from this bioluminescent species.

Bioluminescent basidiomycetes: promising source for drug discovery

The bioluminescent basidiomycetes group consists of many species widely spread throughout the globe. Commonly observed on decaying wood or leaves, these species exhibit light emission in the mycelia, fruiting bodies or both, resulting from a biochemical process of luciferin oxidation catalysed by the enzyme luciferase (Kaskova et al. 2017). To date, all bioluminescent species belong to four distinct monophyletic lineages, namely the *Armillaria*, Mycenoid and *Lucipentes* lineages, and a lineage consisting of *Omphalotus* and *Neonothopanus* genera (Dutta et al. 2023). In Peninsular Malaysia, various bioluminescent species have been documented from different forest ecosystems (Chew et al. 2013, Chew et al. 2014, Chew et al. 2015). Among them was *N. nambi* which has been reported previously in Malaysia, and also in other tropical regions such as Thailand, Singapore and Vietnam (Chew et al. 2015).

Various species of wild non-edible bioluminescent basidiomycetes produce bioactive compounds with potential pharmacological activities. Among them were the novel cytotoxic compound omphaloprenol A active against human leukemia cells (Aoki et al. 2021), and an antibacterial ketone derivative active against *Helicobacter pylori* (Lee et al. 2022) from the fruiting bodies of *Omphalotus japonicus* (Kawam.) Kirchm. & O. K. Mill. The anticancer compound illudin S was reported previously from *O. japonicus*, making this species a potential candidate in mycopharmaceuticals development (Aoki et al. 2021). Investigations on bioactive secondary metabolites from bioluminescent species that make up the genus *Neonothopanus*, are mainly focused on *N. gardneri* and *N. nambi*. Metabolites in *N. gardneri* extracts exhibited significant antileishmanial activity against the promastigotes of *Leishmania amazonensis*, and antitumor effects in breast carcinoma (Vieira et al. 2022).

Neonothopanus nambi has been relatively studied more in recent years, presenting itself as a rich source of secondary metabolites with a diverse range of pharmacological properties. The wild strain *N. nambi* FRIM550 showed promising prospects as a potential producer of antibacterial metabolites to combat against MRSA pathogen. The active compound responsible for this activity was isolated and identified recently as the dimeric sesquiterpenoid aurisin A (Krishnasamy et al. 2023). These researchers reported that aurisin A exhibited strong *in vitro* activity against various reference and clinical MRSA strains at a range of MIC values of 3.91–7.81 μg mL^{-1}, and the compound displayed rapid bactericidal effect against the pathogens (Krishnasamy et al. 2023). They were also the first to report on the *in vitro* interactions between aurisin A and antibiotics commonly used against *S. aureus*, and evaluated the compound's ability to increase sensitivity of MRSA strains to these antibiotics. Aurisin A have been isolated by other researchers from *N. nambi* strains PW1 and PW2 (Kanokmedhakul et al. 2012), and from *Anthracophyllum* sp. BCC18695 (Intaraudom et al. 2013). The compound was previously reported to exhibit nematicidal (Buaart et al. 2011) and antimalarial (Intaraudom et al. 2013) activities, and cytotoxicity against breast and cholangiocarcinoma cancer (Kanokmedhakul et al. 2012), oral epidermoid carcinoma (Intaraudom et al. 2013), lung cancer (Boueroy et al. 2020) and cervical cancer (Boueroy et al. 2021) cells. The bioluminescent species also produced other groups of bioactive compounds showing different pharmacological activities, as shown in Table 3. Our findings on anti-MRSA activity and past reports on other bioactivities from *N. nambi*, showed the importance of bioluminescent species as attractive candidates to be explored further for a multitude of interesting compounds. Thus, the wild bioluminescent basidiomycetes present a potential source of mycopharmaceuticals

Table 3 List of secondary metabolites and the reported bioactivities from *Neonothopanus nambi*

Group	Compound	Biological activity	Reference*
Aristolane sesquiterpenoids	Nambinone A	Cytotoxicity: NCI-H187[a], IC_{50}: 69 µM	1
	Nambinone B	None reported	1
	Nambinone C	Cytotoxicity: NCI-H187, IC_{50}: 16.43 µM	1
	1-epi-nambinone B	None reported	1
	Axinysone B	Cytotoxicity: NCI-H187, IC_{50} 49.31 µg mL^{-1}	2
	4,8,14-trihydroxyilludala-2,6,8-triene	None reported	2
Sesquiterpenoids	Nambinone D	Cytotoxicity: NCI-H187, IC_{50}: 42.3 µM	1
Dimeric (aristolane) sesquiterpenoids	Aurisin A	Nematicidal: *Meloidogyne incognita*, 10 mg L^{-1} caused 100% larval mortality (48 hr treatment); 100 mg L^{-1} caused 100% larval mortality (30 min treatment)	3
		Antimalarial: *Plasmodium falciparum*, IC_{50} 0.8 µM; Cytotoxicity: NCI-H187, IC_{50} 1.55 µM; BC1[b], IC_{50} 3.72 µM; cholangiocarcinoma cells, IC_{50} 1.57-2.77 µM	1
		Antibacterial: *Pseudomonas aeruginosa*, MIC 128 µg mL^{-1} (moderate); *Bacillus cereus*, MIC 128 µg mL^{-1} (moderate)	2
		Cytotoxicity: A549[c], IC_{50} 10.43 µM (24 hr treatment)	4
		Cytotoxicity: HeLa[d], IC_{50} 6.65 µM; CaSki[d], IC_{50} 6.27 µM (24 hr treatment)	5
		Antibacterial: MRSA ATCC 33591, MIC 7.81 µg mL^{-1}; MRSA ATCC 700699, MIC 3.91 µg mL^{-1}	6
	Aurisin G	Cytotoxicity: NCI-H187, IC_{50} 5.03 µg mL^{-1}; KB[e], IC_{50} 1.45 µg mL^{-1}; MCF-7[b], IC_{50} 18.64 µg mL^{-1} Antibacterial: *P. aeruginosa*, MIC 128 µg mL^{-1} (weak)	2
	Aurisin K	Antimalarial: *P. falciparum*, IC_{50} 0.61 µM Antimycobacterial: *Mycobacterium tuberculosis*, MIC 23.84 µM Cytotoxicity: NCI-H187, IC_{50} 1.45 µM; KB, IC_{50} 6.87 µM	1
	Aurisin Z	None reported	7
		Cytotoxicity: NCI-H187, IC_{50} 9.4 µg mL^{-1} Antibacterial: *B. cereus*, MIC 128 µg mL^{-1} (weak)	2
p-terphenyls	Neonambiterphenyl A	Cytotoxicity: NCI-H187, IC_{50} 16.82 µg mL^{-1}; KB, IC_{50} 9.12 µg mL^{-1}; MCF-7, IC_{50} 11.82 µg mL^{-1} Antibacterial: *Staphylococcus aureus*, MIC 4 µg mL^{-1}; *P. aeruginosa*, MIC 128 µg mL^{-1} (weak); *Shigella sonnei*, MIC 128 µg mL^{-1} (weak)	2
	Neonambiterphenyl B	Cytotoxicity: NCI-H187, IC_{50} 5.6 µg mL^{-1}; KB, IC_{50} 40.9 µg mL^{-1} Antibacterial: *S. aureus*, MIC 8 µg mL^{-1}	2
Benzoquinones	Neonambiquinone A	Cytotoxicity: NCI-H187, IC_{50} 44.69 µg mL^{-1} Antibacterial: *S. aureus*, MIC 64 µg mL^{-1}	2

continued

Table 3 Continued

Group	Compound	Biological activity	Reference*
Scalarane sesterterpenoids	Nambiscalarane	None reported	7
		Cytotoxicity: A549 (moderate); HT29[f] (moderate); HCT-116[f] (moderate); HeLa (moderate) Antibacterial: *S. aureus*, MIC 16 µg mL^{-1}; *B. cereus*, MIC 16 µg mL^{-1}; *B. subtilis*, MIC 8 µg mL^{-1}	8
	Nambiscalarane B	Cytotoxicity: A549 (moderate); HT29 (moderate); HCT-116 (moderate)	8
	Nambiscalarane C	Cytotoxicity: HT29 (moderate); HCT-116, IC_{50} 14.33 µM	8
	Nambiscalarane D	Cytotoxicity: A549 (moderate); HT29 (moderate); HCT-116 (moderate); HeLa (moderate) Antibacterial: *B. subtilis*, MIC 16 µg mL^{-1}	8
	Nambiscalarane E	Cytotoxicity: A549 (moderate); HT29 (moderate); HCT-116, IC_{50} 13.41 µM; HeLa (moderate)	8
	Nambiscalarane F	Cytotoxicity: HCT-116 (moderate) Antibacterial: *S. aureus*, MIC 16 µg mL^{-1}	8
	Nambiscalarane G	Cytotoxicity: HCT-116, IC_{50} 16.53 µM	8
	Nambiscalarane H	None reported	8
Steroid	Ergosta-6,22-diene-3β,5,8α-Triol	None reported	7
Butyrolactone	Trans-α-hydroxy-γ-phenyl-Butyrolactone	None reported	7
Others	Methyl 4-butyramidobenzoate	None reported	7

a = small-cell lung cancer cells, b = breast cancer cells, c = lung adenocarcinoma cells, d = cervical cancer cells, e = epidermoid carcinoma, f = colon cancer cells;
Reference*: 1 = Kanokmedhakul et al. 2012, 2 = Sangsopha et al. 2020, 3 = Bua-art et al. 2011, 4 = Boueroy et al. 2020, 5 = Boueroy et al. 2021, 6 = Krishnasamy et al. 2023, 7 = Tsarkova et al. 2016, 8 = Wisetsai et al. 2021

with different pharmacological activities for therapeutic applications.

FUTURE PROSPECTS AND CONCLUSIONS

This review reported on the importance of basidiomycetes as a potentially rich, untapped source of new bioactive secondary metabolites. It further reaffirms the need to explore wild basidiomycetes in Malaysia which have not been adequately studied and harnessed for potential mycopharmaceuticals with various therapeutic applications. Thus, this review is pertinent to bring to limelight the pharmaceutical benefits of some of the underutilised wild basidiomycetes found in Malaysia, as well as globally. In past and recent studies by the Forest Research Institute Malaysia, wild basidiomycetes commonly known as forest pathogens were explored for antibacterial metabolites to combat multidrug-resistant strains of *S. aureus*. Encouraging findings indicated that an active compound from the bioluminescent basidiomycete *N. nambi*, represents promising chemical scaffolds for further *in vivo* studies on toxicity, efficacy and mechanisms of action to understand its practical application. In conclusion, Malaysia is a natural repository for basidiomycetes species with numerous pharmacological benefits yet to be discovered. Thus, the information and knowledge presented here thereof will certainly serve as an impetus for future studies in this field.

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