

Insight into secondary metabolites of *Stachybotrys*, *Memmoniella*, *Doratomyces* and *Graphium* between benefits and harmful

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Abstract

Stachybotrys, *Memmoniella*, *Doratomyces* and *Graphium* all these genera belonging to Class: Sordariomycetes. This review is to demonstrate description, ecology, and secondary metabolites from *Stachybotrys*, *Memmoniella*, *Doratomyces* and *Graphium* and some of their reported biological activities. Besides, describing the importance and potentials of those fungi in order to encourage for further studies to each genus metabolites and purify already known metabolites.

Keyword: *stachybotrys*; *memmoniella*; *doratomyces*; *graphium*; secondary metabolites; biological activities

Introduction

Drug discovery has focused on microbial sources where nearly 80% of the world's antibiotics have their origins. These sources have almost entirely been from soils collected from around the world, but new microbial habitats need to be examined for microbiota that produces useful bioactive compounds. Fungi and other microorganisms represent an invaluable source of natural product bioactive compounds, which are exploited in various contexts, ranging from crop protection to human medicine [1]. Fungi in general and endophytic fungi especially are excellent sources of novel, bioactive natural products. Although the antimicrobial bioactivities are the most easily assayed and other activities include anticancer, insecticidal, antiviral, anthelmintic, anti-plasmodial and immunomodulatory [2].

Schueffler and Anke, [3], reported that "between 2009 to 2013" approximately 100, 000 fungal species are known and more than one million are expected. The variety of species allow that fungi continue to be a rich source of new metabolites. Besides the traditional fungal isolates, an increasing interest in endophytic and in marine-derived fungi has been notice. Terrestrial fungi have produced many therapeutically significant molecules. However, the potential of marine fungi has only been investigated to a limited extent. In addition new screening strategies based on innovative chemical, biological, and genetic approaches have led to novel fungal metabolites in recent years. [3]. Several fungi engage in pharmaceutical industry, enzymes, food, and some take part in

biotechnology, while some are sources of natural products with diverse chemical entities and wide applications. Fungi are well known biotechnological tools that have various applications in the fields of industry. Thanks to their ability to produce set of prestigious enzymes that is eco-friendly and can replace harmful chemicals used in those industries. [4-15].

This review highlights on Class: Sordariomycetes genera (*Stachybotrys*, *Memmoniella*, *Doratomyces* and *Graphium*) secondary metabolites. Also, screen for, and discover novel metabolites produced by those potent fungi in order to be involved in additional applications. Moreover, describing the unique chemical diversity of these fungal genera involved in medical, pharmaceutical, agricultural applications. Also highlight the harmful side of these filamentous fungus if present.

***Stachybotrys*, *Memmoniella*, *Doratomyces*, *Graphium*, description and ecology**

The genus *Stachybotrys* belong to Ascomycota division; Class: Sordariomycetes; Order: Hypocreales; Family: Stachybotryaceae. Colonies usually blackish, hyaline or brightly coloured in one species only; conidiophores erect or suberect, unbranched or branched, hyaline or dark-pigmented, smooth or roughened, sometimes covered in part with dark granules, with apical clusters of phialides; phialides elliptical, subclavate or broadly fusiform usually with a small opening; phialoconidia sliming down to form slimy glistening heads, one-called, dark pigmented or hyaline, smooth or rough, sometimes covered with

dark granules, sometimes with longitudinal striations, elliptical, reniform, oval, subspherical or lemon-shaped (Figure, 1). The most common *Stachybotrys* species is *Stachybotrys chartarum* and *Stachybotrys elegans*. *Stachybotrys chartarum*; colonies slow-growing attaining 2.2 cm in diameter after 10 days on malt extract agar at 25C. *Stachybotrys chartarum* is worldwide and has been isolated from soil. *Stachybotrys elegans*; colonies attaining 4.5 cm in diameter after 7 days on malt extract agar at 25C, Conidia hyaline and broadly fusiform elliptical, ovate or subglobose [14, 16].

The genus *Memmoniella* belong to Ascomycota division; Class: Sordariomycetes; Order: Hypocreales. Colonies dark coloured velutinous or powdery; conidiophores erect, unbranched or sometimes forked, dark coloured, smooth or minutely verruculose; conidiogenous cells phialidic, in groups of up to 10 at the tip of conidiophore, clavate, cylindrical or elliptical; conidia in long persistent chains, one-celled, dark colour, smooth or echinate. The most common species is *Memmoniella echinate*; colonies moderately growing, attaining 5 cm in diameter after 10 days on malt extract agar at 25C, margin white changing to greyish towards the center (Figure, 2). *Memmoniella echinate* is very widely distributed common in soil and on cellulosic substrates and is known to be a good cellulose decomposer. *Memmoniella* is a related genus to *Stachybotrys*, but in the former, the phialoconidia do not slime down but are held together in long chains [14, 16].

The genus *Doratomyces* belong to Ascomycota division; Class: Sordariomycetes; Order: Microascales; Family: Microascaceae. *Doratomyces* is a genus of the fungi imperfecti, closely related to *Scopulariopsis* (Figure, 3). Colonies greyish to black, velvety, floccose

or powdery; conidiophores aggregated to form erect synnemata, each with a sterile stalk and fertile head; head composed of a central axis of anastomosing hyphae branching towards outside and bearing conidiogenous cells at the ultimate branchlets; annellophores ampulliform or lageniform; conidia born in long chains, dark, i-celled, elliptical, ovate or subglobose, rounded or apiculate at the apex, truncate at the base, smooth or roughened. *Doratomyces* differs from *Trichurus* by the absence of sterile hairs interspersed with the fertile hyphae of synnematal head. *Doratomyces* widespread in agriculture soil and the most common species is *Doratomyces stemonitis*. *Doratomyces stemonitis* colonies slow-growing attaining 1.8 cm in diameter on malte extract agar after 7 days at 25C, margin whitish conidial areas dark grey, becoming black in age, surface synnematosus; synnemata up to 1200 um high with globose to elongate or cylindrical fertile heads [14, 16].

The genus *Graphium* belong to Ascomycota division; Class: Sordariomycetes; Order: Microascales; Family: Microascaceae (Figure, 4). *Graphium* is a genus of the fungi imperfecti. Colonies dark coloured with erect synnemata, synnemata stout, darkly pigmented, each capped by a slimy head, individual element of each synnema diverging at the apex, branching penicillately; conidiogenous cells annelliform, born in verticils at the tips of branches, subulate or cylindrical; conidia (annelliconidia) cylindrical or widge-shaped, rounded at the apex, truncate at the base, hyaline or subhyaline, smooth, one-celled, produced in basipetal succession, but gathered in slimy heads. *Graphium* colonies attaining 4.5 cm in diameter after 7 days on oat meal agar at 25C. *Graphium* was isolated from soil containing cellulosic materials [14, 16].

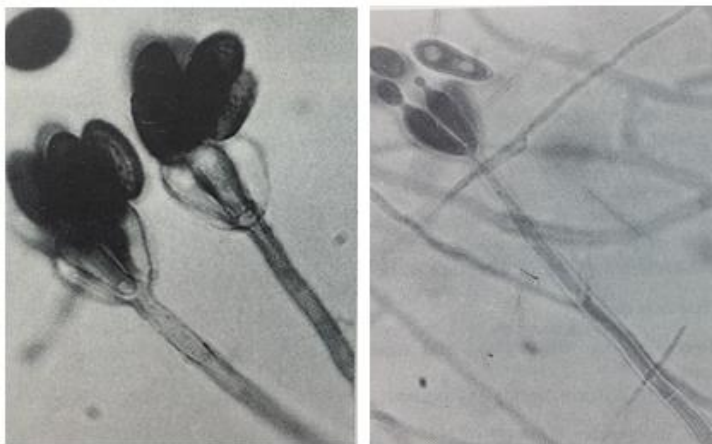


Figure (1). *Stachybotrys* spp., different species, Photo was taken by Dr. Moubasher AH. [16].

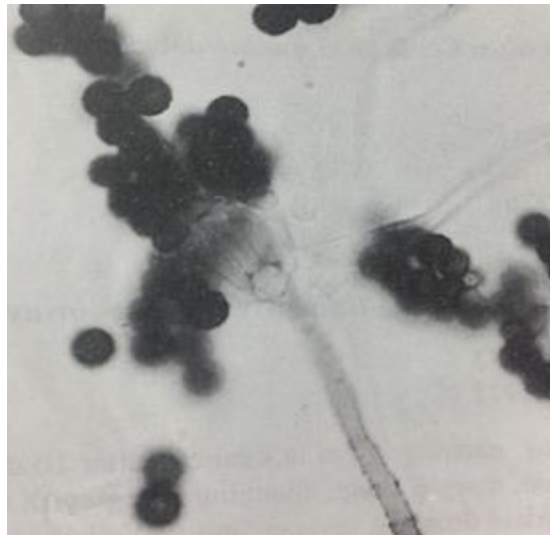


Figure (2). *Memnoniella* spp., different species, Photo was taken by Dr. Moubasher AH. [16].



Figure (3). *Doratomyces* spp., different species, Photo was taken by Dr. Moubasher AH. [16].

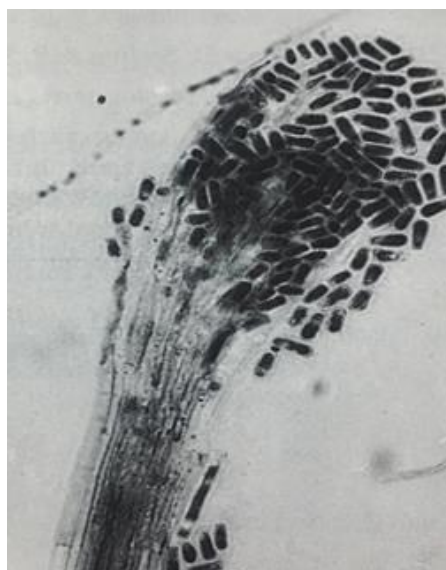


Figure (4). *Graphium* spp., different species, Photo was taken by Dr. Moubasher AH. [16].

Stachybotrys secondary metabolites

The genus *Stachybotrys* produces a broad diversity of secondary metabolites, including macrocyclic trichothecenes, atranones, and phenylspirodrimanes. Although the class of the phenylspirodrimanes is the major one and consists of a multitude of metabolites bearing various structural modifications, few investigations have been carried out. This review highlighted the secondary metabolites produced by different *Stachybotrys* species [17]. Micro-scale extracts from 5 different *Stachybotrys* strains, which were cultured on different media, spontaneous dialdehyde/lactone isomerization was observed for some of the isolated secondary metabolites, and novel stachybotrychromenes were quantitatively investigated. The metabolite profiles of *Stachybotrys* species are considerably influenced by different factors (Time of growth and substrates) and different species [17].

The genus *Stachybotrys* can be found in nature as well as in the indoor environment, and cellulose-rich substrates containing high moisture levels are generally required for *Stachybotrys* growth [18]. Fungal growth in water-damaged buildings poses serious human health risks and can lead to allergic and respiratory issues [19]. *Stachybotrys chartarum* has been the subject of considerable attention due to transitory associations with idiopathic pulmonary loss in infants [20] and disease symptoms called sick building syndrome [21]. There are still controversial discussions concerning the role of *Stachybotrys* within these reported cases, concluding that there is inadequate evidence that exposure to mycotoxins is causally related to the adverse human health effects [22]. Nevertheless, *Stachybotrys* produces a broad variety of toxic secondary metabolites, which are of relevance in the indoor environment concerning human health [23, 24]. The most common species among this genus are *Stachybotrys elegans* and *Stachybotrys chartarum*, which were also found in the indoor environment [14]. *Stachybotrys chartarum*, is a toxic fungi, and common found in indoor air and causing mycotoxicosis, chronic fatigue, allergic diseases and other health problems

Searching for novel and bioactive molecules of microbial origin for drug development, *Stachybotrys* and *Memmoniella* fungi generally have been found to be a rich source of novel and bioactive secondary metabolites of great importance. Results of phylogenetic analyses were in agreement that the *Memmoniella* is paraphyletic to *Stachybotrys*. Interestingly, most *Memmoniella* spp. were found to produce the similar chemical substances. Up until now, almost 200 secondary metabolites belonging to diverse structural types of trichothecene, triprenyl phenol, diterpenoid,

isochroman, polyketide, cochlioquinone and cyclic peptide have been discovered. Most of these fungal metabolites were reported to possess several interesting biological activities, such as disruption of the complement system, inhibition of TNF- α release, endothelin receptor antagonism, anti-influenza A virus, antimalarial, inhibition of avian myeloblastosis virus protease, cholesterol esterase, tyrosine kinase, farnesyl-protein transferase, squalene synthase and human heart chymase as well as stimulation of plasminogen, fibrinolysis, thrombolysis [25].

Memmoniella secondary metabolites

Memmoniella, according to phylogenetic analyses, is paraphyletic to *Stachybotrys*, and both produce similar secondary metabolites. Many secondary metabolites belonging to various chemical classes including trichothecene, triprenyl phenol, diterpenoid, isochroman, polyketide, cochlioquinone and cyclic peptide have been reported to be produced by this fungus [25]. *Memmoniella* produces many trichothecenes which are sesquiterpenoid mycotoxins such as trichodermin, trichodermol and phenylspirodrimanes [26]. On the other hand, Phenylspirodrimanes are signature secondary metabolites of both *Memmoniella* and *Stachybotrys* [27]. This generous production of secondary metabolites is accompanied with promising different biological activities including antiviral, antimalarial, TNF- α release inhibition, endothelin receptor antagonism. Also as potent inhibitor of tyrosine kinase, cholesterol esterase, farnesyl-protein transferase, human heart chymase squalene synthase, and stimulator of plasminogen, fibrinolysis, thrombolysis [25].

Doratomyces secondary metabolites

Doratomyces microsporus is a famous producer of keratinase [28]. This species is a non-toxins producer, and it has a promising capability to biodegrade human stratum corneum [29]. *Doratomyces* has a considerable role in biodegradation of biphenyls compounds, especially species *Doratomyces nanus*, *Doratomyces purpureofuscus*, *Doratomyces verrucisporus* [30, 31]. On the other hand, *Doratomyces* was reported as statins producer [32, 33]. Adding valproic acid to *Doratomyces microsporus* culture induced production of seven antimicrobial compounds that showed activity against *Staphylococcus aureus* and several methicillin-resistance *S. aureus* (MRSA) [34].

Graphium secondary metabolites

Marine-derived fungi are well known as rich sources of bioactive natural products. Indole alkaloids, isolated from a variety of marine-derived fungi

especially *Graphium* genus, have attracted considerable attention for their diverse, challenging structural complexity and promising bioactivities, and consequently, indole alkaloids have potential to be pharmaceutical lead compounds [35]. Graphiumins A–J, bearing structurally rare DKPs with a phenylalanine-derived indolin substructure, were isolated from the culture broth of the marine-derived fungus *Graphium* sp. OPMF00224. Graphiumins A–J Compounds inhibited yellow pigment production by methicillin-resistant *Staphylococcus aureus* [36].

Fungi show remarkable potency to bioremediate hydrocarbons with complex structure and long-chain length such as *Neosartorya*, *Graphium*, *Aspergillus*, *Talaromyces*, *Cephalosporium*, *Penicillium* and others these genera were isolated from soil polluted with petroleum and also found to be the effective organisms for bioremediation of hydrocarbons in crude oil [37]. Kaur et al., [38], reported that *Graphium* spp. has the ability to biodegrade methyl-*tert*-butyl ether

Conclusion

Fungi are a noble and consistent source of unique natural products with a high level of biodiversity and also yield several compounds having different pharmaceutical activities, which is currently attracting scientific researches. Every study conducted on *Stachybotrys*, *Memmoniella*, *Doratomyces* and *Graphium* resulted in discovery of new metabolites or pointing to a possible application, which made these genera potential source of pharmaceuticals and attracted attention for further investigations of their important bioactivities properties. *Stachybotrys*, *Memmoniella*, *Doratomyces* and *Graphium* are known for their capability of producing various biologically active compounds with medical applications as antimicrobial, anticancer, anti-influenza A virus, antimalarial and others.

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