European Journal of Medicinal Chemistry 126 (2017) 631–651

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Antifungal potential of marine natural products

Ebaa M. El-Hossary [a], Cheng Cheng [b], Mostafa M. Hamed [c], Ashraf Nageeb El-Sayed Hamed [d], Knut Ohlsen [e], Ute Hentschel [f], Usama Ramadan Abdelmohsen [b, d, *]

[a] National Centre for Radiation Research & Technology, Egyptian Atomic Energy Authority, Ahmed El-Zomor St. 3, El-Zohoor Dist., Nasr City, Cairo, Egypt
[b] Department of Botany II, Julius-von-Sachs Institute for Biological Sciences, University of Würzburg, Julius-von-Sachs-Platz 3, 97082 Würzburg, Germany
[c] Drug Design and Optimization Department, Helmholtz Institute for Pharmaceutical Research Saarland, Saarland University, Campus E8.1, 66123 Saarbrücken, Germany
[d] Department of Pharmacognosy, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt
[e] Institute for Molecular Infection Biology, University of Würzburg, Josef-Schneider-Straße 2/D15, 97080 Würzburg, Germany
[f] GEOMAR Helmholtz Centre for Ocean Research, RD3 Marine Microbiology, and Christian-Albrechts University of Kiel, Düsternbrooker Weg 20, 24105 Kiel, Germany

ARTICLE INFO

Article history:
Received 26 August 2016
Received in revised form
7 November 2016
Accepted 10 November 2016
Available online 14 November 2016

Keywords:
Marine microorganisms
Marine invertebrates
Marine natural products
Secondary metabolites
Fungal infections
Antifungal activity

ABSTRACT

Fungal diseases represent an increasing threat to human health worldwide which in some cases might be associated with substantial morbidity and mortality. However, only few antifungal drugs are currently available for the treatment of life-threatening fungal infections. Furthermore, plant diseases caused by fungal pathogens represent a worldwide economic problem for the agriculture industry. The marine environment continues to provide structurally diverse and biologically active secondary metabolites, several of which have inspired the development of new classes of therapeutic agents. Among these secondary metabolites, several compounds with noteworthy antifungal activities have been isolated from marine microorganisms, invertebrates, and algae. During the last fifteen years, around 65% of marine natural products possessing antifungal activities have been isolated from sponges and bacteria. This review gives an overview of natural products from diverse marine organisms that have shown *in vitro* and/or *in vivo* potential as antifungal agents, with their mechanism of action whenever applicable. The natural products literature is covered from January 2000 until June 2015, and we are reporting the chemical structures together with their biological activities, as well as the isolation source.

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* Corresponding author. Department of Botany II, Julius-von-Sachs Institute for Biological Sciences, University of Würzburg, Julius-von-Sachs-Platz 3, 97082 Würzburg, Germany.
E-mail address: usama.ramadan@uni-wuerzburg.de (U.R. Abdelmohsen).

http://dx.doi.org/10.1016/j.ejmech.2016.11.022
0223-5234/

1. Introduction

Fungi are important components of most ecosystems on earth. Every heathy human is confronted with thousands of fungal spores every day and is colonized by fungi without developing diseases [1,2]. However, in immunocompromised persons, infections caused by fungal pathogens such as *Candida spec.* or *Aspergillus spec.* can result in disease and even death [3]. For example, *Candida albicans*, a common colonizer of mucosal surfaces of the gut, is ranked among the top five infectious agents causing sepsis [4]. Of particular concern is the trend to more therapy-resistant strains of *C. albicans* and other non-albicans species such as *Candida glabrata* that have intrinsically reduced susceptibility to antifungal compounds [5,6]. Nowadays, invasive candidiasis is the most common fungal disease among hospitalized patients, and it is associated with mortality rates of up to 40% even when patients receive antifungal therapy [7,8]. Similarly, the mold *Aspergillus fumigates* has become a major pathogen in cancer patients. Although humans are constantly inhaling conidia of *Aspergillus spec.,* the innate immunity of healthy individuals is sufficient to clear the organism without the development of antibody- or cell-mediated, acquired immunity [9]. However, immunocompromised persons are at high risk to develop severe invasive diseases due to *Aspergillus,* with mortality rates ranging from 40 to 90% in high-risk populations [10]. As for *Candida* infections, treatment success is increasingly jeopardized by the resistance to antimycotic drugs [11]. Further important fungal pathogens, including *Cryptococcus neoformans* and *Pneumocystis jirovecii*, also mostly affect patients with weakened immune systems, particularly persons with HIV/AIDS [12]. In general, invasive diseases caused by fungal pathogens are difficult to treat, and they are associated with high mortality rates. The increasing number of immunocompromised patients due to the medical progress (e.g., transplantation medicine) represents a great challenge for the treatment of pathogenic fungi [13]. Invasive fungal diseases are clearly an area of significant unmet medical need that should stimulate the search for new antifungal molecules [14].

On the other hand, plant diseases caused by fungal pathogens have been recognized as a worldwide threat to the agricultural industry [1,15]. Control of plant fungal infections is very important to the production of food, and it has a significant impact on the agricultural use of land, water, fuel, and other inputs [16,17]. The filamentous ascomycete fungus *Magnaporthe oryzae* is one of the most common fungal plant pathogens and the causal agent of rice blast disease, which is considered the most destructive disease of rice in the world [18]. Another example of fungal plant pathogens is the fungus *Botrytis cinerea.* It is known as gray mold and can infect more than 200 plant species [19]. Stem or black rust (caused by *Puccinia graminis* f. sp. *tritici*), stripe or yellow rust (caused by *Puccinia striiformis* f. sp. *tritici*), and leaf or brown rust (caused by *Puccinia triticina*) are three rust diseases which occur on wheat. Black rust is one of the most devastating diseases affecting wheat crops [20,21]. *Fusarium graminearum*, an ascomycete fungus, is a highly destructive pathogen for all cereal species. High economic losses occur when the floral tissues become co-infected with *F. graminearum* and other *Fusarium* species. *Fusarium* infections reduce grain quality, rather than lowering grain yield, and result in mycotoxin-contaminated grain [22,23]. The fungus *Blumeria graminis,* an ascomycete belonging to the Erysiphales, causes powdery mildews on grasses, including the top worldwide agricultural crops of wheat and barley [24].

The marine environment provides a valuable platform for the discovery of new biologically active compounds [25–30]. More than 4000 bioactive marine natural products have been reported since 1985 [31,32]. They have been discovered in a wide range of marine organisms, such as marine invertebrates [33–36], marine plants [37–39], their associated microorganisms [40–44] and sediment-derived microorganisms [45–47]. They possess a wide spectrum of bioactivities, including antimicrobial [45,48–50], antiviral [51–53], antituberculosis [54–56], antiprotozoal [57–60], immunomodulatory [61,62], anti-oxidant [63,64], anti-inflammatory [65,66], antidiabetes [67–69], anticancer [70–72], and anti-Alzheimer's [73–75] activities. In this review, a selection of marine natural products exhibiting potent antifungal activity is discussed. In the supplementary data, a list of other marine natural products with moderate antifungal activities is presented in Table S1. In this table, the name, chemical nature, isolation source (marine organism), and the antifungal activity of each marine natural product are presented. Publications that describe extracts, structurally uncharacterized marine natural products, or molecules with weak antifungal activity have been excluded from this review. Fig. 1 gives an overview of marine-derived natural products with antifungal activity that were reported in the literature up to mid-2015. Based on these considerations, it can be estimated that roughly two-thirds of all reported marine antifungal compounds are derived from sponges and bacteria. Within the individual groups, sponges are the predominant sources for antifungal compounds, closely followed by bacteria, which could be also associated with marine sponges in some cases (Fig. 1). Interesting and underexplored sources include marine microorganisms such as bacteria and fungi, with only a handful of reports describing their antifungal secondary metabolites. Although there are several excellent reviews of marine bioactive compounds [43,76–88], to our knowledge, this is the first comprehensive review to our knowledge that focuses on marine antifungal compounds and summarizes their currently known chemical and biological properties.

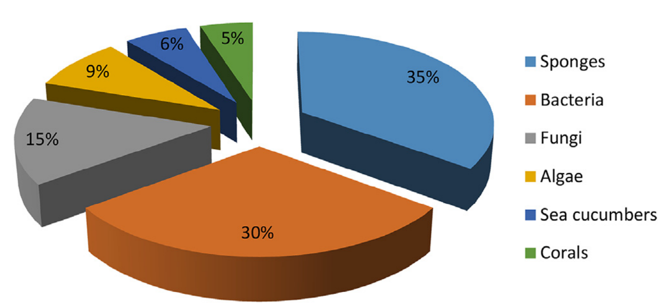

Fig. 1. Percentage distribution of antifungal marine natural products (MIC less than 5 μg/mL), according to their source of isolation (data collected from MarinLit 2015 and literature until mid-2015).