The Journal of Antibiotics
https://doi.org/10.1038/s41429-024-00723-5

Japan Antibiotics Research Association
The Society for Actinomycetes Japan

PERSPECTIVE

Crowdsourcing for mining new fungal sources for addressing the need for novel antibiotics against multidrug resistant pathogens

T. S. Suryanarayanan[1]

Received: 3 February 2024 / Revised: 18 March 2024 / Accepted: 22 March 2024
© The Author(s), under exclusive licence to the Japan Antibiotics Research Association 2024

Abstract

There are a limited number of new antibiotics to manage the health crisis caused by the evolution and spread of antimicrobial resistant (AMR) bacteria including multidrug resistant (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) ones. Bioprospecting fungi of less studied and extreme environments using new and less used older approaches could reveal novel antibiotics to manage MDR pathogens. Furthermore, I posit a crowdsourcing model which could substantially increase the chances of discovering novel antibiotics as well as new chemotypes for other therapeutic areas and considerably reduce the cost and time of this exercise.

Introduction

Human pathogenic microbes have rapidly developed resistance to existing antibiotics mainly due to the overuse and abuse of antibiotics and the spread of their antibiotic resistance genes among microbes through horizontal gene transfer. With the WHO classifying antibiotic resistance as one of the major public health threats of the 21st century [1], there is an urgent need for discovering antibiotic molecules with novel mechanisms of action, different scaffolds, and low potential for resistance. With the existing regulations, it is logical that such totally novel antibiotics would be effective for longer periods. I posit bioprospecting fungi of less studied habitats and a crowdsourcing method to obtain novel antibiotics and to reduce the cost and time of the exercise respectively.

The need to focus on fungi

The major drawback of searching for novel antibiotics among natural products is the repeated discovery of the same molecules. Fungi, as a reflection of their ecological success, possess diverse genomes which undergo major and rapid changes leading to adaptations enabling survival in harsh environments [2]. This could produce many phenotypic variants over short evolutionary time scale. Furthermore, secondary metabolite genes in fungi occur in clusters which exhibit variations due to gene loss and horizontal gene transfer; such variations and convergent evolution confer fungi with the ability to produce novel secondary metabolites [2]. Considering the fact that MDR pathogens would take relatively longer time to evolve resistance against an entirely new antibiotic when compared to mere chemical modifications of existing antibiotics, it would be judicious to bioprospect fungi, especially of less studied habitats for novel antibiotics.

Towards enhancing the chances of discovery of novel antibiotics

Fungi of extreme and less studied habitats

It would be prudent to screen fungi of less studied and extreme habitats [EH] to reduce the chances of rediscovering known bioactive compounds since such specialised habitats are abodes of many new species which are source of novel secondary metabolites [3]. It can be argued that with limited interaction webs owing to depauperate species richness in EH, antibiosis as a competitive mechanism may not be as diverse as in the species rich mesophilic environment. However, the unique species

✉ T. S. Suryanarayanan
t_sury2002@yahoo.com

[1] Vivekananda Institute of Tropical Mycology, Ramakrishna Mission Vidyapith, Chennai, India

Published online: 17 April 2024

present in EH could house exceptional biosynthetic gene clusters for secondary metabolites. Since in fungi, expression of genes governing responses to external stress differ widely between species and adaptations to extreme environments involves horizontal gene transfers leading to major changes in adaptations, the chances of finding novel metabolites in EH fungi are relatively high [4].

Fungal endophytes are an example of stressing the need to explore fungi of less studied ecological groups. They survive as non-pathogenic endosymbionts in plants, seaweeds, and lichens. Certain endophytes including *Colletotrichum*, *Xylaria*, *Trichoderma*, *Pestalotiopsis* and *Phomopsis* have a wide plant host range irrespective of the geographic or taxonomic connectivity of the plants [5]. Such endophytes may have a high diversity of secondary metabolites due to their interactions with diverse chemical milieu and different environmental conditions provided by different plant hosts and environments respectively. Indeed, endophytic *Trichoderma* species have greater metabolic potential attributable to their endophytic lifestyle when compared with the non-endophytic forms [6]. Genomes of endophytic *Xylariaceae* exhibit a large number of secondary metabolite gene clusters, gene duplications, and horizontal gene transfers and thus could be a good source of novel antibiotics. Fungi of other less studied habitats which need to be focused including lichenicolous, resinicolous, and endolithic fungi and those associated with marine sponges and corals, tropical peat, rumen, insect gut and exoskeleton, deep sea, and hypersaline environments.

Some methods to improve secondary metabolite production

Induction of silent genes

In fungi, unlike in many other eukaryotes, the genes governing secondary metabolism are clustered and remain silent when a fungus is grown in culture. Since stress induces genomic plasticity in fungi, culturing them under different stress conditions could activate the silent genes. Silent secondary metabolite genes could be activated by inhibition of chromatin signalling mechanisms, use of epigenetic modifiers, infecting the fungus with mycovirus, and co-culturing two or more different microbes from the same ecosystem. Although the nuances of the interactions between MDR pathogens and other microbes are not known clearly, it is likely that coculturing fungus and MDR pathogen could induce the fungus to produce specific novel chemicals active against the MDR. Here, chances of success in discovering a new antibiotic could be increased by using a fungus isolated from an environment where the MDR microbe interacts with it (e.g., hospital waste). The choice of species for coculture is not obvious. Interaction of unrelated species could increase the chemical diversity of resultant metabolites owing to lesser overlap in their genetic makeup. Alternatively, interaction between related species could augment each other's genetic lapses inducing the production of novel chemicals. Hence, an optimal combination of microbes to be cocultured should be arrived at using their genetic and metabolome analyses, and theoretical metabolic models of different fungi as has been tried for bacteria [7].

Crowdsourcing model to augment antibiotic discovery

Having stressed the need to explore fungi for novel antibiotics, the arduous task of collecting them from different habitats and screening them for antibiosis remains. These are daunting tasks and, considering the time taken and poor returns, pharma companies refrain from these exploratory exercises [8]. A crowdsourcing model involving undergraduate students, faculty, industries, national laboratories and culture-collection repositories to enhance the microbial genetic resource of a country [9] could be one solution to this problem. Applying this model for studying fungi for novel antibiotics involves training of faculties of colleges located close to less studied habitats (hot springs, salterns, deserts, etc) for isolation and characterisation of fungi. Such trained faculty design research-based curricula for undergraduate students and supervise their preliminary work on isolating fungi from less studied habitats and screening them for general antibiosis. This process leads to a student-mediated culture collection of fungi exhibiting antibiosis. As the next step, select strains from such collections are investigated by industry and national labs for production of unique antibiotics. The advantages of this model is that the industry would be saving time and money by avoiding the basic hunt for novel metabolites, students would get trained in research approach, and when the contribution of all the institutions involved is considered, it would lead to the enhancement of the genetic resource a country.

Conclusion

Antibiotic resistance is a global health problem that needs to be addressed by a multifaceted approach. Sensitising the public about judicious antibiotic use, improving sanitation and hospital waste management, and participation of non-profit and voluntary organisations in antibiotic discovery are some of the steps towards this direction. Concurrently, a sustained hunt for new antibiotic molecules to manage MDR pathogens is of paramount importance. The current

knowledge gained about the development and spread of antibiotic resistance would aid in reducing considerably the time taken for the evolution of resistance among pathogens to such novel molecules. In this context, fungi stand out as a source of novel natural products due to their enormous species diversity, variations in life style, and ability to compete as exemplified by their gamut of habitat occupation. Giving up the routine market model for developing antibiotics [10], a global collaboration involving students, faculty, industries, national laboratories and culture-collection repositories to screen fungi of stressed habitats for novel antibiotics would be productive to manage MDR pathogens as well as finding new chemotypes that can fuel drug discovery in other therapeutic areas. This crowdsourcing model would concurrently help in rapidly creating a large collection of rare fungal strains and enhance the biodiversity resource of a country.

Acknowledgements I thank Swami Dhyanagamyananda, Secretary, Ramakrishna Mission Vidyapith, Chennai for the facilities provided. I thank Dr. Prabhavathi Fernandes, Chair, WHO Antibiotic Prioritization Working Group, and Dr Kou-San Ju, Department of Microbiology and Member of the Infectious Diseases Institute, The Ohio State University for reading a draft of the manuscript and for providing valuable suggestions that have enhanced its focus.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. World Health Organization, Antibiotic resistance. WHO. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed 28 November 2023.
2. Naranjo-Ortiz MA, Gabaldón T. Fungal evolution: cellular, genomic and metabolic complexity. Biol Rev Camb Philos Soc. 2020;95:1198–232.
3. Baranova AA, Alferova VA, Korshun VA, Tyurin AP. Antibiotics from extremophilic micromycetes. Russ J Bioorg Chem. 2020;46:903–71.
4. Azami H, Watanabe Y, Sakai K, Nakahara H, Kojima H, Tokiwa T, Nonaka K, Noguchi Y, Nagano Y, Hirose T, Sunazuka T, Matsui H, Arima N, Abe K, Hanaki H, Iwatsuki M. Antifungal profile against *Candida auris* clinical isolates of tyroscherin and its new analog produced by the deep-sea-derived fungal strain *Scedosporium apiospermum* FKJ-0499. J Antibiot (Tokyo). 2024;77:156–62.
5. Suryanarayanan TS, Devarajan PT, Girivasan KP, Govindarajulu MB, Kumaresan V, Murali TS, Rajamani T, Thirunavukkarasu N, Venkatesan G. The host range of multi-host endophytic fungi. Curr Sci. 2018;115:1963–9.
6. Scott K, Konkel Z, Gluck-Thaler E, Valero David GE, Simmt CF, Grootmyers D, Chaverri P, Slot J. Endophyte genomes support greater metabolic gene cluster diversity compared with non-endophytes in *Trichoderma*. PLoS ONE. 2023;18:e0289280.
7. O'Brien EJ, Monk JM, Palsson BO. Using genome-scale models to predict biological capabilities. Cell. 2015;161:971–87.
8. Fernandes P, Martens E. Antibiotics in late clinical development. Biochem Pharm. 2017;133:152–63.
9. Suryanarayanan TS, Gopalan V. Crowdsourcing to create national repositories of microbial genetic resources: fungi as a model. Curr Sci. 2014;10:1196–1200.
10. Klug DM, Idiris FI, Blaskovich MA, von Delft F, Dowson CG, Kirchhelle C, Roberts AP, Singer AC, Todd MH. There is no market for new antibiotics: this allows an open approach to research and development. Wellcome Open Res. 2021;6:146.