Proceedings of the 7th World Congress on Recent Advances in Nanotechnology (RAN'22)
~~Lisbon Portugal~~ Virtual Conference – April 04 – 06, 2022
DOI: 10.11159/nddte22.001

Nanoscale Antimycotics and Antifungal Active Nanocomposites

Josef Jampilek[1,2]
[1]Department of Analytical Chemistry, Faculty of Natural Sciences, Comenius University, Ilkovicova 6, 842 15 Bratislava, Slovakia; josef.jampilek@gmail.com
[2]Department of Chemical Biology, Faculty of Science, Palacky University, Slechtitelu 27, 783 71 Olomouc, Czech Republic

Extended Abstract

Fungi are simple eukaryotic organisms that are able to colonize various environments. It is estimated that there are approx. 2 million different species. Fungi have been used by people in the kitchen, brewing, viticulture, folk medicine as well as in biotechnology for the production or biotransformation of various substances and in recent years are also popular for the green synthesis of nanoparticles. Biologically active secondary metabolites of fungi have become the inspiration for the design of drug structures [1,2]. Fungi are ubiquitous in nature and are vital for the recycling of nutrients contained in organic matter (most species of fungi are saprophytes). They coexist with other organisms on the basis of mutualism, commensalism, and unfortunately parasitism [3,4]. Some fungi attack humans, animals and plants; it is estimated that 270,000 species of fungi are associated with plants and 325 are known to infect humans. Fungi cause diseases ranging from superficial and cutaneous forms through complicated subcutaneous forms to systemic (invasive fungal infections) diseases. Mycoses are caused by colonization/proliferation/sporulation of fungi in tissues and body fluids. Another type of body damage with various clinical symptoms is caused by mycotoxins, which can be ingested in the diet or secreted by fungi in the body [3-5].

It is estimated that about a billion people worldwide suffer from fungal diseases. The severity ranges from asymptomatic to mild mucocutaneous infections to life-threatening systemic infections. Approximately 10 million people have mucosal candidiasis and more than 150 million people have serious fungal diseases with a major impact on their lives [6-8]. Superficial mycoses are most often caused by filamentous fungi (genera such as *Trichophyton*, *Epidermophyton* and *Microsporum*) and yeasts of genera *Candida* (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) and *Malassezia furfur*. In the last decade, they have shown high resistance to fluconazole, voriconazole and echinocandins. Invasive fungal infections are caused by *Candida*, *Aspergillus*, *Fusarium*, *Cryptococcus* and *Pneumocystis*. Increasing resistance, cross-resistance, and the occurrence of multidrug-resistant or completely resistant strains are evident in all of these genera. New pathogenic strains such as *Candida auris* or *Emergomyces* sp. have also been reported [5,8-14]. Mycotoxins (secondary toxic metabolites of fungi) are mainly excreted by *Aspergillus* sp. (*A. flavus*, *A. parasiticus*, *A. ochraceus*, *A. carbonarius*, *A. oryzae*), *Penicillium* sp. (*P. citrinum*, *P. camemberti*, *P. expansum*), *Fusarium* sp., *Alternaria* sp., *C. albicans*, *Stachybotrys chartarum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis* and contaminate fruits, vegetables, cereals, legumes, nuts, etc., and causing a serious threat to human and animal health around the world [15,16]. Diseases caused by ingestion, dermal exposure or inhalation of mycotoxins contaminating agricultural commodities before or after harvest are known as mycotoxicosis. Mycotoxins alone are estimated to cause 3.2 million cases and 50,000 hospitalizations per year in the EU. The most important and common mycotoxins are aflatoxins (B1, B2, G1 and G2), ochratoxin (A, B, C), citrinin, ergot alkaloids, patulin, zearalenone, trichothecenes, fumonisins, beauvercin, enniatins, butenolide, equisetine, candysarins. They are carcinogenic, hepatotoxic, nephrotoxic, damaging the epithelial, immune and nervous systems [15,16].

As above-mentioned, the development of resistance to several systemically administered drugs and the development of cross-resistant or multi-drug resistant strains are serious. In addition, most drugs are approved for the treatment of nail, skin and mucosal mycoses due to a narrow therapeutic window and limited bioavailability [17-19]. Antifungal agents can be divided either according to the mechanism of action for non-specific and specific acting or according to the purpose of use, i.e. approved for human/veterinary administration (antimycotics) or agricultural fungicides. Non-specific antifungals (disinfectants and antiseptics) are applied for topical/local treatment of the skin or mucous. Various essential oils (terpenoid-based compounds of natural origin) can be classified as non-specific fungicides. All fungicides with a specific

mechanism of action are summarized in FRAC Code List© [20]. Antimycotics are summarized, for example, in [21,22]. In general, specific antimycotics can be divided according to the mode of action to six classes. Although there are relatively many antimycotic drugs on the market, most drugs have been approved for topical application. From the group of so-called small molecules (not therapeutic proteins/antibodies) 1 polyene macrolide (amphotericin B), 3 echinocandins (anidulafungin, caspofungin, micafungin), 5 triazoles (fluconazole, isavuconazole, itraconazole, posaconazole, voriconazole), 1 naphthylmethylamine (terbinafine), 1 pyrimidine (flucytosine) and 1 benzofuran (griseofulvin) were approved for the treatment of systemic fungal infections [21,22]. Due to the fast development of resistance, a combination of at least two antimycotic drugs with different mechanisms of actions is recommended not only for the treatment of systemic mycoses but also for the treatment of superficial mycoses [23].

As can be seen, there has been no significant breakthrough in new systemically administered drugs in the last few years [22] and me-too drugs do not solve the problem of growing resistance [24], because if a fungal cell acquires resistance to one drug in the group, it will be resistant to the whole class. One of the reasons why the process of research and development of new antifungals is so complex is the fact that the eukaryotic nature of the fungal cell is very similar to the human cell. Therefore, it is very important to look for antifungals whose mechanism of action focuses on the specific structure of the fungal cell. The process of identifying substances with a new mode of action is relatively long and risky [25,26] and therefore the preparation of nanoparticles/nanoformulations of existing antifungals has become the first choice approach [27-36].

The aim of this contribution is to summarize the most recent results of nanoformulations of antifungal drugs/agricultural fungicides and other various antifungal active nanocomposites divided according to the materials used and discuss individual nanostructures suitable for their effective encapsulation. Nanosystems with magnetic, photothermal or photodynamic effects are also briefly described.

This study was supported by the Slovak Research and Development Agency (Grant No. APVV-17-0373).

References

[1] J. Singh, P. Gehlot, *New and Future Developments in Microbial Biotechnology and Bioengineering*. Amsterdam: Elsevier, 2021.

[2] S. Ghosh, R. Ahmad, M. Zeyaullah, S.K. Khare, "Microbial nano-factories: synthesis and biomedical applications," *Front. Chem.* vol. 9, 626834, 2021.

[3] M. Buckley. (2022, March 22). *The Fungal Kingdom: Diverse and Essential Roles in Earth's Ecosystem*. Washington (DC): American Society for Microbiology, 2008. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK559443.

[4] S. Fowler, R. Roush, J. Wise. (2022, March 22). "Diversity of microbes, fungi, and protists," in *Concepts of Biology*, OpenStax CNX, 2019, chapter 13. [Online]. Available: https://opentextbc.ca/conceptsofbiologyopenstax/chapter/fungi/.

[5] Fungal Infections. (2022, March 22). MSD and the MSD Manuals. Merck and Co., Inc., Kenilworth, NJ, USA. [Online]. Available: https://www.msdmanuals.com/home/infections/fungal-infections.

[6] F. Bongomin, S. Gago, R.O. Oladele, D.W. Denning, "Global and multi-national prevalence of fungal diseases-estimate precision," *J. Fungi* vol. 3, 57, 2017.

[7] M.G. Frias-De-Leon, R Pinto-Almazan, R. Hernandez-Castro, E. Garcia-Salazar, P. Meza-Meneses; C. Rodriguez-Cerdeira; R. Arenas; E. Conde-Cuevas; G. Acosta-Altamirano; E. Martinez-Herrera, "Epidemiology of systemic mycoses in the COVID-19 pandemic," *J. Fungi* vol. 7, 556, 2021.

[8] K.E. Pristov, M.A. Ghannoum, "Resistance of Candida to azoles and echinocandins worldwide," *Clin. Microbiol. Infect.* vol. 25, pp. 792-798, 2019.

[9] Y. Li, Y. Gao, X. Niu, Y. Wu, Y. Du, Y. Yang, R. Qi, H. Chen, X. Gao, B. Song, X. Guan, "A 5-year review of invasive fungal infection at an academic medical center," *Front. Cell. Infect. Microbiol.* vol. 10, 553648, 2020.

[10] C. Firacative, "Invasive fungal disease in humans: are we aware of the real impact?," *Mem. Inst. Oswaldo Cruz* vol. 115, e200430, 2020.

[11] A. Samaddar, A. Sharma, "Emergomycosis, an emerging systemic mycosis in immunocompromised patients: Current trends and future prospects," *Front. Med.* vol. 8, 670731, 2021.

[12] J. Kmeid, J.F. Jabbour, SS. Kanj, "Epidemiology and burden of invasive fungal infections in the countries of the Arab League," *J. Inf. Publ. Health* vol. 13, 2080-2086, 2020.
[13] J.P. Donnelly, S.C. Chen, CA. Kauffman, W.J. Steinbach, J.W. Baddley, P.E. Verweij, C.J. Clancy, J.R. Wingard, S.R. Lockhart, A.H. Groll, T.C. Sorrell, M. Bassetti, H. Akan, B.D. Alexander, D. Andes, E. Azoulay, R. Bialek, R.W. Bradsher, S. Bretagne, T. Calandra, A.M. Caliendo, E. Castagnola, M. Cruciani, M. Cuenca-Estrella, C.F. Decker, S.R. Desai, B. Fisher, T. Harrison, C.P. Heussel, H.E. Jensen, C.C. Kibbler, D.P. Kontoyiannis, B.J. Kullberg, K. Lagrou, F. Lamoth, T. Lehrnbecher, J. Loeffler, O. Lortholary, J. Maertens, O. Marchetti, K.A. Marr, H. Masur, J.F. Meis, C.O. Morrisey, M. Nucci, L. Ostrosky-Zeichner, L. Pagano, T.F. Patterson, J.R. Perfect, Z. Racil, E. Roilides, M. Ruhnke, C.S. Prokop, S. Shoham, M.A. Slavin, D.A. Stevens, G.R. Thompson, J.A. Vazquez, C. Viscoli, T.J. Walsh, A. Warris, L.J. Wheat, P.L. White, T.E. Zaoutis, P.G. Pappas, "Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the mycoses study group education and research consortium," *Clin. Inf. Dis.* vol. 71, pp. 1367-1376, 2020.
[14] H. Zhang, A. Zhu, "Emerging invasive fungal infections: clinical features and controversies in diagnosis and treatment processes," *Infect. Drug Resist.* vol. 13, 607-615, 2020.
[15] WHO. (2022, March 22). Mycotoxins. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/mycotoxins.
[16] T. Ekwomadu, "Toxic fungi: what's in your food?," *Sci. Today*, 2016. [Online]. Available: https://sciencetoday.co.za/2016/11/14/toxic-fungi-whats-in-your-food.
[17] WHO. (2022, March 22). Global Antimicrobial Resistance Surveillance System (GLASS) Early Implementation Protocol for the Inclusion of Candida spp., 2019. [Online]. Available: https://www.who.int/publications/i/item/WHO-WSI-AMR-2019.4.
[18] WHO. (2022, March 22). Antifungal Expert Group on Identifying Priority Fungal Pathogens: Meeting Report 2020. [Online]. Available: https://www.who.int/publications/i/item/9789240006355.
[19] WHO. (2022, March 22). Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2021. [Online]. Available: https://www.who.int/publications/i/item/9789240027336.
[20] FRAC Code List© 2021. (2022, March 22). [Online]. Available: https://www.frac.info/docs/default-source/publications/frac-code-list/frac-code-list-2021--final.pdf?sfvrsn=f7ec499a_2.
[21] R.K. Griffith, "Drugs used to treat fungal infections," in *Foye's Principles of Medicinal Chemistry*, 8th Edition, V.F. Roche, S.W. Zito, T. Lemke, D.A. Williams, Eds. Philadelphia: Wolters Kluwer, 2019, pp. 1260-1275.
[22] S.G. Revankar. (2022, March 22). "*Antifungal drugs*," in Merck Manual Professional Version. [Online]. Available: https://www.merckmanuals.com/professional/infectious-diseases/fungi/antifungal-drugs.
[23] M. Campitelli, N. Zeineddine, G. Samaha, S. Maslak, "Combination antifungal therapy: A review of current data," *J. Clin. Med. Res.* vol. 9, pp. 451-456, 2017.
[24] J. Jampilek, "How can we bolster the antifungal drug discovery pipeline?," *Future Med. Chem.* vol. 8, pp. 1393-1397, 2016.
[25] J. Jampilek, "Potential of agricultural fungicides for antifungal drug discovery," *Expert Opin. Drug Dis.* vol. 11, pp. 1-9, 2016.
[26] Y.L. Chang, S.J. Yu, J. Heitman, M. Wellington, Y.L. Chen, "New facets of antifungal therapy," *Virulence* vol. 8, pp. 222-236, 2017.
[27] J. Jampilek, K. Kralova, "Nano-antimicrobials: Activity, benefits and weaknesses," in Nanostructures for Antimicrobial Therapy, A. Ficai, A.M. Grumezescu, Eds. Amsterdam: Elsevier, 2017, pp. 23-54.
[28] J. Jampilek, K. Kralova, "Nano-biopesticides in agriculture: State of art and future opportunities," in *Nano-Biopesticides Today and Future Perspectives*, O. Koul, Ed. Amsterdam: Academic Press & Elsevier, 2019, pp. 397-447.
[29] J. Jampilek, K. Kralova, "Beneficial effects of metal- and metalloid-based nanoparticles on crop production," in *Nanotechnology for Agriculture – Advances for Sustainable Agriculture*. D.G. Panpatte, Y.K. Jhala, Eds. Singapore: Springer Nature, 2019, pp. 161-219.
[30] J. Jampilek, K. Kralova. "Impact of nanoparticles on toxigenic fungi," in *Nanomycotoxicology – Treating Mycotoxins in Nano Way*, M. Rai, K.A. Abd-Elsalam, Eds. London: Academic Press & Elsevier, 2020, pp. 309-348.

[31] J. Jampilek. K. Kralova, "Nanocomposites: Synergistic nanotools for management mycotoxigenic fungi," in *Nanomycotoxicology – Treating Mycotoxins in Nano Way*, M. Rai, K.A. Abd-Elsalam, Eds. London: Academic Press & Elsevier, 2020, pp. 349-383.
[32] D. Placha, J. Jampilek, "Graphenic materials for biomedical applications," *Nanomaterials* vol. 9, 1758, 2019.
[33] J. Jampilek, K. Kralova "Advances in drug delivery nanosystems using graphene-based materials and carbon nanotubes," *Materials* vol. 14, 1059, 2021.
[34] J. Jampilek, K. Kralova, "Benefits of chitosan-based and cellulose-based nanocomposites in food protection and food packaging," in *Biobased Nanotechnology for Green Applications*, H. Sarma, S.J. Joshi, R. Prasad, J. Jampílek, Eds. Cham: Springer Nature, 2021, pp. 121-160.
[35] D. Ziental, D.T. Mlynarczyk, B. Czarczynska-Goslinska, K. Lewandowski, L. Sobotta, "Photosensitizers mediated photodynamic inactivation against fungi," *Nanomaterials* vol. 11, 2883, 2021.
[36] J. Jampilek, K. Kralova "Advances in nanostructures for antimicrobial therapy," *Materials* vol. 15, 2388, 2022.