Commentary

Penicillium and *Talaromyces* Species as Rich Sources of Medicinal Natural Products: Past, Present and Future

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Abstract: Filamentous fungi have long served as prolific producers of pharmacologically active natural compounds. Among them, species of *Penicillium* and *Talaromyces* occupy a central role in the history of natural product derived medicine. Penicillin, originally discovered from *P. notatum* in 1928, has transformed medicine and infectious disease through introducing the first widely effective antibacterial agent, inaugurating the antibiotic era. In the 1930s, it was discovered that *P. griseofulvum* and *P. aethiopicum* were able to synthesize griseofulvin, a landmark antifungal product. The first statin-like compound, compactin (mevastatin), was discovered in *P. citrinum* in the 1970s. Mycophenolic acid, first identified in *P. brevicompactum*, was discovered as a result of a hunt for antibacterial agents for *Bacillus anthracis*. Subsequently, its derivative, mycophenolate mofetil, was shown to inhibit inosine monophosphate dehydrogenase in lymphocytes; and since then, mycophenolic acid has become a key immunosuppressant for organ transplantation and autoimmune diseases. Historically, *Penicillium* and *Talaromyces* were separated primarily based on morphological criteria. In the beginning of this millennium, sequencing of multiple genetic markers revealed that some "*Penicillium*" species" actually formed a monophyletic group nested within *Talaromyces*, rather than clustered with the main *Penicillium* lineage. Both *Penicillium* and *Talaromyces* possess genomes rich in biosynthetic gene clusters responsible for producing polyketides, non-ribosomal peptides, terpenoids, and mixed-class metabolites. Most, if not all, of the known medicinal natural compounds produced by the *Penicillium* and *Talaromyces* species are synthesized by these biosynthetic gene clusters. Recent rigorous *in silico* analysis and genomic mining have revealed far more biosynthetic gene clusters than known metabolites.

Keywords: *Penicillium*; *Talaromyces*; antibiotic; antifungal; genome; polyketide

We read with interest the editorial published by Lutfun Nahar on the launching of a new journal that aims to address various aspects of innovative research on medicinal natural products [1]. Filamentous fungi have long served as prolific producers of pharmacologically active natural compounds. Among them, species of the genera *Penicillium* and *Talaromyces* occupy a central role in the history and modern development of natural product derived medicine. The most iconic fungal natural product, penicillin, originally discovered from *P. notatum* and subsequently reclassified as *P. chrysogenum* (although with dispute as a result of recent molecular evidence), by Alexander Fleming in 1928 transformed medicine and infectious disease through introducing the first widely effective antibacterial agent, inaugurating the antibiotic era [2]. Penicillin's β-lactam structure inhibits bacterial cell wall synthesis by targeting penicillin-binding proteins, leading to selective bactericidal activity. Subsequent industrial fermentation by *P. chrysogenum* strains, improved through classical mutagenesis and later genetic engineering, dramatically increased yields and enabled production at an industrial scale. Besides producing antibiotics, it was discovered in the 1930s that other *Penicillium* species, including *P. griseofulvum* and *P. aethiopicum*, were able to synthesize griseofulvin, a landmark natural antifungal product [3]. After overcoming challenges of limited solubility and poor bioavailability, advances in formulation in the 1950s/1960s have enabled effective oral delivery. Griseofulvin ultimately became the first systemic drug for dermatophyte infections, used for tinea capitis, tinea corporis, and onychomycosis before later antifungals such as terbinafine and the azoles emerged.

In addition to antimicrobial compounds, penicillia also gave rise to other medicinal natural products that have brought prevention and treatment of various diseases to the next level. The first statin-like compound, compactin (mevastatin), was discovered in *P. citrinum* in the 1970s [4]. It inhibits 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the key enzyme catalyzing the rate-limiting step in cholesterol biosynthesis. Although compactin itself was not commercialized, its discovery has opened the conceptual door for the discovery of subsequent statins, especially lovastatin from *Aspergillus terreus* (*Aspergillus* is a genus closely related to *Penicillium* and *Talaromyces* [5]) and ultimately to synthetic statins, such as atorvastatin and simvastatin. All these developments were crucial for reshaping global cardiovascular therapeutics, such as the treatment of hyperlipidemia, ischemic heart disease, stroke, etc. Apart from the statins, several *Penicillium* metabolites showed potent immunomodulatory activities. Mycophenolic acid, first identified in *P. brevicompactum*, was in fact discovered as a result of a hunt for antibacterial agents capable of inhibiting *Bacillus anthracis*, the causative agent of anthrax [6]. Although mycophenolic acid showed strong antibacterial, antiviral, antifungal and antitumor activities, its clinical use was initially limited by toxicity concerns. The major therapeutic breakthrough emerged in the 1990s, when its derivative, mycophenolate mofetil, was produced. Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase, blocking guanosine nucleotide synthesis in lymphocytes; and since then, mycophenolic acid has become a key immunosuppressant widely used in patients undergoing organ transplantation and for treatment of autoimmune diseases [7].

Historically, the genera *Penicillium* and *Talaromyces* were separated primarily based on morphological criteria: *Penicillium* was defined by its characteristic brush-like conidiophores (penicilli), whereas *Talaromyces* was known for its sexual reproductive structures, including cleistothecia containing asci and ornamented ascospores. However, in the beginning of this millennium, sequencing of multiple genetic markers [e.g., internal transcribed spacer regions, β-tubulin, calmodulin, RNA polymerase II subunits (RPB1 and RPB2)] revealed that some "*Penicillium*" species, mainly those of the former "*Penicillium* subgenus *Biverticillium*" actually formed a monophyletic group nested within *Talaromyces*, rather than clustered with the main *Penicillium* lineage [8]. As a result, approximately 60 species formerly placed in *Penicillium*, particularly those with subgenus *Biverticillium*, were transferred to *Talaromyces*. Subsequent results on mitochondrial genome sequencing and phylogenetic analysis have also confirmed the basis of reclassification [5]. Such reclassification and subsequent studies have revolutionized our understanding on the biology of these two fungal genera, including their medicinal natural products.

Both *Penicillium* and *Talaromyces* possess genomes rich in biosynthetic gene clusters responsible for producing polyketides, non-ribosomal peptides, terpenoids, and mixed-class metabolites. Most, if not all, of the known medicinal natural compounds produced by the *Penicillium* and *Talaromyces* species are synthesized by the biosynthetic gene clusters of the corresponding fungi. Recent rigorous in silico analysis and genomic mining have revealed far more biosynthetic gene clusters than known metabolites [9]. For example, our previous sequencing and subsequent downstream studies revealed that the genome of *T. marneffei* (previously called *P. marneffei*), a thermal dimorphic pathogenic fungus endemic in Southeast Asia [10,11], encoded a high diversity of at least 23 polyketide synthase genes and two putative polyketide synthase-non-ribosomal peptide synthase hybrid genes [12,13]. Such a high number of biosynthetic gene clusters was much more than other thermal dimorphic pathogenic fungi, such as *Coccidioides immitis* and *Histoplasma capsulatum*. A number of secondary metabolites and pigments of *T. marneffei* have been characterized, although just representing the tip of the iceberg [14,15]. All these indicate that a vast number of natural products remain undiscovered. Moreover, many of these biosynthetic gene clusters are "silent", in the sense that they are not expressed under standard laboratory conditions. However, implementation of activation strategies, such as modification of culture methods, co-cultivation with other microorganisms, or CRISPR-based promoter replacement, could lead to new discoveries in both as well as other closely related genera, further expanding their medicinal potential [16,17]. For example, a recent study showed that by adding dimethyl sulfoxide and sea salt to the culture medium, a marine-derived *Penicillium* species was able to produce novel disulfide-linked resorcylic acid lactone dimers [16]. In parallel to all these developments are advances in bioinformatics tools, artificial intelligence algorithms, computational speed and networking technologies, which in the future will markedly improve genome analysis and mining, resulting in fishing out more biosynthetic gene clusters as well as their corresponding potential medicinal natural products from the *Penicillium* and *Talaromyces* species [9,18].

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