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Mini review

# Antibiotics from neglected bacterial sources

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ABSTRACT

The current crop of antibiotics in clinical use are either natural products or their derivatives. However, the rise of a multitude of different antibiotic resistant human pathogens has meant that new antibiotics are urgently needed. Unfortunately, the search for new antibiotics from traditional bacterial sources often results in a high rediscovery rate of known compounds and a low chance of identifying truly novel chemical entities. To overcome this, previously unexplored (or under investigated) bacterial sources are being tapped for their potential to produce novel compounds with new activities. Here, we review a number of antibiotic compounds identified from bacteria of the genera *Burkholderia*, *Clostridium*, *Lysobacter*, *Pantoea* and *Xenorhabdus* and describe the potential of organisms and their associated metabolites in future drug discovery efforts.

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## Introduction

Although microbes are the purveyors of a multitude of human maladies, human medicine and disease treatment also owe a great deal to microorganisms. This is because microorganism-derived natural products or their synthetic analogues represent a large proportion of the drugs that are currently in clinical use (Newman and Cragg, 2012). This is especially true when it comes to infectious diseases therapy and the use of antibiotics (Newman and Cragg, 2012). Because they have been structurally optimised over time by nature for their inherent biological purpose, natural product antibiotics are often highly active and highly specific for their cellular targets (Koehn and Carter, 2005).

However, after these compounds were introduced into clinical practice, antibiotic-resistant bacteria began to emerge. As antibiotic usage has increased, there has been a concomitant rise in the number and type of drug-resistant microorganisms, with many of these strains disseminating across the globe (Woodford et al., 2011). Many bacteria, particularly in hospital settings, exhibit resistance to multiple drug classes (multidrug resistant or MDR) making treatment a challenge. This is particularly applicable to nosocomial pathogens, such as *Pseudomonas aeruginosa*, enterobacteria, *Acinetobacter baumannii*, *Staphylococcus aureus* and *Enterococcus* spp. (Boucher et al., 2009). Furthermore, extensively drug-resistant strains of *Mycobacterium tuberculosis* have recently emerged and drug resistance in pathogenic fungi (e.g. *Candida albicans*, *Aspergillus* spp.) and parasites (*Plasmodium* spp.) is also on the rise (Almeida Da Silva and Palomino, 2011; Gillespie and Singh, 2011; Pfaller, 2012; Sa et al., 2011). To make a grim situation worse, only a few new antibiotics have been commercialised in recent years and there are a limited number present in the pipeline of big pharma, who, for the most part, have decreased their funding for antibiotic drug discovery (Payne et al., 2007; So et al., 2011). Most of the recent new drugs (ceftobiprole, daptomycin, tigecycline) derive from pre-existing chemical scaffolds and exhibit activity mainly against Gram-positive pathogens, constituting alternative treatments for infections by methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) (Appelbaum, 2012). While it is important to tackle these resistant pathogens, the major threat of multidrug resistance comes from Gram-negative pathogens, on which new drugs remain poorly active (Freire-Moran et al., 2011; Walsh and Fischbach, 2010). This perfect storm of increasing drug resistance in pathogens, combined with the decreased development of new chemical entities able to curb this incursion, threatens to plunge the world back into the pre-antibiotic era unless changes are made rapidly (Appelbaum, 2012; Bush et al., 2011; Fischbach and Walsh, 2009).

The good news is that there is hope that this situation can be improved. This hope comes not only in the form of new antibacterial compounds, but also new sources of these compounds. Well known bacterial sources of antibiotics include Actinomycetes, predominantly from the genus *Streptomyces* (Watve et al., 2001), myxobacteria (Wenzel and Muller, 2009), cyanobacteria (Welker et al., 2012), *Bacillus* (Fickers, 2012; Hamdache et al., 2011) and *Pseudomonas* species (Gross and Loper, 2009). In the past, many antibiotics were discovered through antibacterial screening programs, usually by cultivating bacteria from soil samples and isolating their secondary metabolites (Zotchev et al., 2012). However, this culture-based approach has been almost completely

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abandoned due to the high rate of rediscovery of known compounds (Baltz, 2006). New technologies dependent upon genome sequencing have started to complement, and in some cases take over from, historical culture-based approaches. With the completion of many bacterial genome sequences, it has become evident that many more bacteria than previously thought have the ability to produce secondary metabolites (Donadio et al., 2007; Letzel et al., 2013; Udwary et al., 2011). Furthermore, even well-studied producer organisms have been shown to have more genes for secondary metabolite production than there are currently described natural products. For example, some *Streptomyces* species, whose biosynthetic repertoire was thought to be only three to five secondary metabolites, actually possess more than 20 genomic regions encoding known or predicted biosynthetic pathways (Nett et al., 2009; Omura et al., 2001). Such results have led to the development of the genome mining approach to natural product discovery, where the genome sequence of an organism is first scanned for its secondary metabolic potential before culturing is attempted (Winter et al., 2011). However, many of the natural product biosynthesis gene clusters unearthed through genome mining appear to be silent under standard culture conditions, making their associated products difficult to isolate and characterise (Scherlach and Hertweck, 2009).

Intriguingly, bacterial genomics has also shown that many bacteria previously regarded as incapable of producing natural products, actually contain the genetic material for the biosynthesis of secondary metabolites (Donadio et al., 2007; Letzel et al., 2013). These "neglected producers" include bacteria from unusual habitats and distant branches of the eubacterial phylogenetic tree. Genomic studies have also shown that sequencing of bacterial genomes of diverse origins can lead to the identification of novel enzyme functionalities (Wu et al., 2009). It is estimated that only 10% of the natural products from screened strains and less than 1% of the total available natural products have been identified, meaning that there is a multitude of metabolites awaiting discovery (Fischbach and Walsh, 2009; Watve et al., 2001). This percentage could be further underestimated when one considers all bacteria that are unculturable. Again, DNA sequencing approaches, such as metagenomics, have been used to study environmental DNA or niches where non-culturable bacteria may be present, such as sponge-associated microbiomes and soil samples (Banik and Brady, 2010; Piel, 2011). Several compounds with antibiotic activity have been identified by such studies, such as the anti-*Candida* theopalauamide, from the sponge symbiont *Entotheonella palauensis* (Schmidt et al., 1998; Schmidt et al., 2000) or the anti-MRSA tetarimycin, from an environmental DNA-expressed gene cluster (Kallifidas et al., 2012). Taken together, these concepts suggest that a good place to start looking for novel antibacterial structures is amongst bacteria that have the ability to produce secondary metabolites, but have not been intensively studied.

In this review, we aim to illustrate the diversity of sources for the discovery of biologically active natural products, by providing selected examples of compounds from bacteria that can be considered "neglected producers". Although there may be other natural products produced by the genera mentioned in this report, we have focused on those with antibiotic activity that show promise for future development, or have been well studied. In doing so, we outline several secondary metabolites from the genera *Burkholderia* and *Lysobacter*, plant- and insect-associated bacteria and anaerobic bacteria. The information presented below shows that "neglected bacteria" are not only able to generate secondary metabolites, but that many of these compounds have novel chemical structures and, in some cases, unique modes of action and activities.

## Burkholderiales as sources of natural products

The genus *Burkholderia* is a phenotypically and genotypically diverse group of organisms that inhabit a variety of niches ranging from soil and water to infected humans (Coenye and Vandamme, 2003). The genus contains a number of primary and opportunistic human pathogens, including *Burkholderia pseudomallei*, the causative agent of the melioidosis, as well as the *Burkholderia cepacia* complex (Bcc), which are emerging as a small, but important source of infections in cystic fibrosis patients (de Vrankrijker et al., 2010; Vial et al., 2007). Like many clinically relevant Gram-negative organisms, *Burkholderia* spp. are resistant to several commonly used antibiotics (Rose et al., 2009). However, many species are also capable of producing a variety of biologically active metabolites, ranging from toxins, such as bongkrekic acid (Moebius et al., 2012), to antifungal compounds, such as rhizoxin (Partida-Martinez and Hertweck, 2005).

One group of antibacterial compounds from *Burkholderia* species are the enacyloxins (Knappe et al., 2008; Mahenthiralingam et al., 2011). The enacyloxins were originally identified in *Frateuria* sp. W-315 in the course of a Japanese antifungal screening program and represent a group of eight closely related antibacterial compounds (Watanabe et al., 1982). Recently, *Burkholderia ambifaria* was shown to also produce enacyloxins, and it was in this organism that the biosynthetic pathway was recently elucidated (Mahenthiralingam et al., 2011). Screening over 250 isolates from the Bcc for activity against multidrug resistant (MDR) Gram-negative organisms, the authors were able to show that 13% of the *B. ambifaria* strains analysed produced enacyloxins. Furthermore, they showed that these polyene antibiotics are the products of a hybrid non-ribosomal peptide synthase-polyketide synthase (NRPS-PKS) encoded by an 84 kb genomic island within the *B. ambifaria* genome (Mahenthiralingam et al., 2011). It is unknown as yet, whether the same pathway also produces this compound in *Frateuria* sp. W-315.

Of the enacyloxcins, enacyloxin IIa (Fig. 1) was shown to have the most potent antibacterial activity against both Gram-positive and Gram-negative organisms (Watanabe et al., 1982; Watanabe et al., 1994). Subsequent studies have shown enacyloxin IIa to be highly active against MDR Gram-negative organisms such as *Burkholderia multivorans* and *A. baumannii*, however, inactive against *P. aeruginosa* (Mahenthiralingam et al., 2011). Enacyloxin IIa acts by inhibiting protein synthesis, through binding to elongation factor EF-Tu and blocking its release from the ribosome (Cetin et al., 1996). The identification of the enacyloxin biosynthetic gene cluster opens the door to the possibility of engineering novel enacyloxin derivatives with improved activity profiles.

## The genus *Janthinobacterium*

Other bacteria from the order Burkholderiales have also been shown to produce biologically active secondary metabolites. Antibacterial compounds, such as the janthinocins (O'Sullivan et al., 1990) and the antifungal compounds violacein (Pantanella et al., 2007) and jagaricin (Graupner et al., 2012) have been identified from *Janthinobacterium* species. *Janthinobacterium* spp. are Gram-negative, motile bacteria that have been isolated from a wide range of habitats including the Antarctic (Mojib et al., 2011), as symbionts of insects (Zhang et al., 2011a) and amphibians (Brucker et al., 2008; Harris et al., 2009), and from plants and the environment (Kang et al., 2007; Kim et al., 2012).

Janthinocin A, B and C were isolated in 1990 from a water isolate of *Janthinobacterium lividum* (O'Sullivan et al., 1990). These macrocyclic decapeptide lactones were shown to have activity equal to or better than vancomycin against a range of Gram-positive aerobes

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