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Review

Natural Products as a Source for Novel Antibiotics

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Natural products have historically been of crucial importance in the identification and development of antibacterial agents. Interest in these systems has waned in recent years, but the rapid emergence of resistant bacterial strains has forced their re-evaluation as a route to identify novel chemical skeletons with antibacterial activity for elaboration in drug development. This overview examines the current situation, highlights new natural product systems which have been found, together with re-examination of some old ones, and new technologies for their identification. While natural products certainly have the potential to re-emerge as a key start-point in antibacterial drug discovery, reports of new or reinvestigated structures need to be supported with sufficient quality chemical (solubility, stability), biochemical (including toxicity in particular, along with target information) and microbiological [minimum inhibitory concentration (MIC) and resistance frequency] validation data to assist in the identification of promising hit structures and to avoid wasted effort from trawling over already cultivated territory. This is particularly important in a resource-limited research environment.

The Need for New Antibiotics

The emergence of antimicrobial resistance (AMR), which began very soon after the introduction of antibiotics but has accelerated markedly over the last decade, has focused attention on the sustainability of current modern medical practice in the global arena [1–3]. From the perspective of an individual patient or an institutional health provider, assumptions – which have taken root over the past 70 years or so – about the nature, availability, and outcomes of hitherto successful treatment protocols are being challenged as community and hospital-acquired infections become more problematic [4]. The very success of antimicrobial drug discovery and therapies developed in the modern era has fostered a level of complacency that is likely to require substantial revision of medical practice in the coming decades if we wish to maintain the standards of healthcare to which we have become accustomed, or to improve healthcare in underdeveloped countries [5]. Warnings of doomsday scenarios, perhaps dismissed all too readily in recent years, are beginning to look ever more plausible, especially with the recent emergence of colistin-resistant bacteria in China and even in the UK [6,7]. Fortunately, the urgency of the task is now becoming more widely known and accepted, and has attracted the attention of governments and policymakers [8–18], and led to the establishment of action groups (Antibiotic Action; http://antibiotic-action.com) and charities (Antibacterial Research UK, ANTRUK; www.antibioticresearch.org.uk). That a concerted global approach is required, and that this will need to be an ongoing effort because all cells are capable of developing resistance to xenobiotics, has been recognised [19,20]. A particular focus of current attention are the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Enterobacter* species) which are not only responsible for a wide range of infections but are also increasingly resistant to common antibacterial drugs [21]. Application of antibiotics in agriculture and farming exacerbates environmental dispersal, and the implication for human use has been considered [22].

Trends

Although the emergence of AMR has strained drug discovery efforts, natural products chemistry has been de-emphasised relative to other approaches.

Natural products continue to provide new chemical structures with high levels of antibacterial activity.

New methodologies for the cultivation of bacteria and the identification of novel natural products offer opportunities not previously possible.

An excellent example of the value of the use of natural products as start-points for antibacterial discovery comes from the detailed examination of the viridicatumtoxins, which provide inspiration for new tetracycline antibiotics, and of colistin, which provides new-generation polymixin systems.

The structural modularity of many natural product-derived antibacterials allows a building-block approach which can be exploited for the rapid construction of new chemical systems.

Reinvigoration of this approach is fully justified as a fast route to address the AMR problem.

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The emergence of AMR has coincided with, or perhaps in part been caused by, an unfortunate series of circumstances. First, the antibacterial drug pipeline is currently very poorly populated [23–25]. Second, commercially-driven models for drug development within the pharmaceutical industry, so successful during the past century, are looking very fragile for new antibacterial drug development in the 21st century [12]. Third, restructuring within the industry has seen a loss of financial and human resources which translates to a serious diminution of drug-discovery capability [26–29]. Fourth, it now appears that there are challenges relating to bacterial cell wall ingress and egress which are unique to antibacterial drug discovery, and which significantly negatively impact on the probability of success [30–35]. Although changes in the financial structure which supports antibacterial drug development and use are surely needed [36], it nonetheless remains a productive activity, and antibacterials still comprise the biggest share of the global drug portfolio [37]. However, there is no doubt that high levels of collaboration will be necessary to address this problem, and an interesting case-study of an effective academic–industrial partnership leading to antibacterial drug discovery highlights that a combination of chance, determination, and adequate funding can generate material outcomes [38]. However, a recent note of caution, highlighting the need for adequate multidisciplinary training in the way this should be done, has been emphasised if academic laboratories are to make a valuable contribution in this endeavour, and not generate misleading outcomes [39,40].

An underpinning ethos crucial to the success of modern antibacterial therapy has been the concept of the 'magic bullet' – that is, a small-molecule drug which is both selectively lethal for bacteria and capable of mammalian administration. Alternative non-compound approaches (such as antibody, probiotic, phage, and vaccine therapies) have recently been considered in detail and their potential assessed [41]. Assuming that we adhere to the small-molecule approach, a key question arises: how do we go forward to identify new drugs? Over the past century natural products have provided a crucial start-point in antibacterial therapies and drug discovery [42], and, because antibacterially active natural products appear to occupy an unusual chemical property space [30,43–45], this strategy still offers excellent opportunities for exploitation in drug development [46]. This realisation has led to a renaissance of interest in natural products for the identification of new members of the 'antibiotic-ome' (defined as natural products with antibiotic activity), and their application in antibacterial drug discovery in the genomics era [38,42,43,47–62]. That this need not necessarily result from random screening has been demonstrated very recently by the establishment of a relationship between protein-targeted or riboprotein-targeted antibacterial agents and their physicochemical properties [43]. This review attempts to show that recent developments in the natural products arena continue apace, and that reasons to expand work in this area are even greater under current circumstances. In modern parlance, such an approach is referred to as 'forward genetics', 'forward pharmacology', 'classical pharmacology', or 'phenotypic drug discovery' [63], and there is an increasing realisation that it need not rely completely on serendipity, but that design rules may be identified [64,65], and some time ago an overview of the various databases listing natural products has appeared [66]. Although natural product isolation is often criticised for the fact that it only re-isolates known substances, and indeed this a serious disadvantage of this approach for the discovery of novel antibiotics, novel chemotypes continue to be discovered [42,67,68]. Natural sources of new antimicrobials and resistance-modifying agents include land plants [69–71], fungi [72], lichens [73], endophytes [74], as well as marine plants [75–78], seaweeds [79], corals [80], and other marine microorganisms [81,82]. A high-throughput screening approach for the discovery of natural product antibiotics has recently been reported [83], while chem-informatic approaches [84] and enhanced methodology for the identification of antibiotics [85] and producing strains [86] have also been developed. Of great significance is the development of novel genomic-type approaches to find small molecules with antibacterial activity, and it is likely that this will become an important avenue for the identification of novel opportunities in the future [87–90]. The particular value of natural products for the disruption of bacterial biofilms has been