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Research review paper

Unexpected applications of secondary metabolites

Preeti Vaishnav [a], Arnold L. Demain [b,*]

[a] 206 Akshardeepp Apts., Near New Jain Temple, GIDC, Ankleshwar 393002, Gujarat, India
[b] Charles A, Dana Research Institute for Scientists Emeriti (R.I.S.E.), Drew University, Madison, NJ 07940, USA

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ABSTRACT

Secondary metabolites have been found to have interesting applications over and above their well-known medical uses, e.g., as antimicrobials, etc. These alternative applications include antitumor, cholesterol-lowering, immunosuppressant, antiprotozoal, antihelminth, antiviral and anti-ageing activities. Polyene antibiotics, such as amphotericin B, are of use as antiprion agents, antitumor drugs and against leishmaniasis. Other microbial natural products that show antibiotic activity are used against cancer e.g., doxorubicin, neomycin, β-lactams, bleomycin and rapamycin. Macrolide antibiotics, such as erythromycin, clarithromycin and azithromycin, improve pulmonary function in patients suffering from panbion cholitis. Pigments like prodigiosin and shikonin have antitumor activity, while violacein has anti-ulcer and antitumor activity and also acts as an antiprotozoal agent. Statins, in addition to lowering cholesterol and LDL levels, also decrease elevated C-reactive protein (CRP) levels independent of their cholesterol effects. Immunosppressants have many alternative effects: (i) Cyclosporin is proving useful in treatment of inflammatory disease such as asthma and muscular dystrophy. (ii) Rapamycin is extremely useful in preventing restenosis of stents grafted in balloon angioplasty. (iii) Tacrolimus and ascomycin help in treating inflammatory skin disease such as allergic contact dermatitis and psoriasis. Artemisinin, an antimalarial agent, is also showing antitumor activity. Other natural products, including those from plants (betulinic acid and shikonin), animals (bryostatins) and microbes (squalestatin and sophorolipids) have a multiplicity of potentially useful actions. Unexpected functions of known secondary metabolites are continuously being unraveled, and are fulfilling some of the needs of present day medicine and show great promise for the future.

Contents

1. Introduction . . . 224
2. Antibiotics . . . 224
   2.1. β-lactams . . . 224
   2.2. Tetracyclines . . . 224
   2.3. Aminoglycosides and Macrolides . . . 225
   2.4. Polyenes . . . 225
   2.5. Coumermycins . . . 225
   2.6. Glycopeptides . . . 225
   2.7. Ansamycins . . . 225
   2.8. Lincosamides . . . 225
   2.9. Isoxazolidinones . . . 225
   2.10. Pigmented antibiotics . . . 226
   2.11. Chloropeptins . . . 226
   2.12. Fosfidomycin . . . 226
3. Antitumor agents . . . 226
   3.1. Anthracyclines . . . 226
   3.2. Taxol . . . 226
   3.3. Epothilones . . . 226
   3.4. Bryostatins . . . 226

* Corresponding author. Tel.: +1 973 408 3937; fax: +1 973 408 3504.
E-mail address: ademain@drew.edu (A.L. Demain).

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4. Immunosuppressants . . . 227
5. Cholesterol-lowering agents . . . 227
6. Other agents . . . 228
6.1. Artemisinin . . . 228
6.2. Shikonin. . . . 228
6.3. Betulinic acid . . . 228
6.4. Sophorolipids . . . 228
7. Final comments . . . 228
References . . . 228

1. Introduction

Secondary metabolites, also referred to as natural products, are the products of metabolism not essential for normal growth, development or reproduction of an organism. These compounds serve to meet the secondary requirements of the producing organisms. They empower them to survive interspecies competition, provide defensive mechanisms and facilitate reproductive processes. Well known sources of secondary metabolites are plants, bacteria, fungi and marine organisms such as sponges, tunicates, corals and snails. Many secondary metabolites have proved invaluable as antibacterial or antifungal agents, anticancer drugs, cholesterol-lowering agents, immunosuppressants, antiparasitic agents, herbicides, diagnostics, and tools for research. Some of these have found to play a pivotal role in treatment or prevention of a multitude of biological disorders, many of which did not have any cure until these products were discovered.

In addition to their known activities and employment in combating disease, secondary metabolites reveal surprising additional activities which may be possible solutions to other diseases, some of which lack effective solutions. Many antibiotics, bacterial pigments, plant terpenoids, are also found to have anti-HIV, antitumor, anti-ageing, immunosuppressant, antiprotozoal and antihelminth activities, thus exhibiting multifarious applications in the sphere of medicine. Unraveling the novel applications of known secondary metabolites and exploiting a myriad of sources as microbes, plants and higher animals for screening new secondary metabolites are paving the way to treat "untreatable diseases", and help reduce mortality rates. In this review, we point out these other activities of useful secondary metabolites in the battle against life-threatening diseases in the hope that this will catalyze further efforts to apply these useful compounds against other forms of human disease. Of course, these further efforts will have to consider the possible toxicity of the compounds, resistance development and the possibility that humans may be resistant to them.

2. Antibiotics

Many antibiotics have a broad spectrum of activities (Table 1). For example, the majority of antitumor products used today in the fight against cancer were first discovered as antibiotics produced by microbes (Newman and Shapiro, 2008). These include actinomycin D (dactinomycin), anthracyclines (including daunorubicin, doxorubicin [adriamycin], epirubicin, pirirubicin, idarubicin, valrubicin, and amrubicin), glycopeptolides (bleomycin and phleomycin), the mitosane mitomycin C, anthracenones (mithramycin, streptozotocin, and pentostatin) and the endiyne calcheamycin attached to a monoclonal antibody (Mylotarg®).

2.1. β-lactams

The most well-known antibiotics are the β-lactams, i.e., penicillins and cephalosporins. Some β-lactam-based compounds also have activity as antitumor prodrugs (Xing et al., 2008). Also being considered are β-lactams as prodrugs that can specifically target tumor cells and as N-methylthiolated β-lactams which induce apoptosis (Kuhn et al., 2004). Apoptosis, also known as regulated cell death or programmed cell death, is different from necrosis in which cell death results from acute injury (Lederman, 2004). Apoptosis is required for normal development in which unneeded cells are eliminated. It occurs in three stages: (i) initiation occurs through activation of death receptors by a death signal such as damaged DNA; (ii) the enzyme caspase 3 is activated; (iii) caspase 3 cleaves effector molecules resulting in cell shrinkage, nuclear fragmentation and membrane blebbing. Induction of apoptosis is considered to be useful in fighting cancer.

2.2. Tetracyclines

Tetracyclines render prion aggregates susceptible to proteolytic attack (Borman 2002) and thus may be useful against prion diseases. Prion diseases include scrapie of sheep, spongiform encelopathy of cattle, Creutzfeldt–Jakob disease, fatal insomnia and Gerstmann–Struussler–Scheinker disease in humans (Forloni et al., 2002). These diseases, also known as transmissible spongiform encephalopathies (TSEs), are transmissible and cause neurodegenerative disorders of humans and animals for which no effective treatment is available. They are usually rapidly progressive and always fatal. They are associated with the conversion and accumulation of the alpha-helix rich prion protein (PrPC) into a beta-structure-rich, protease-resistant insoluble isoform (PrPSc) that is thought to be infectious. The normal isoform of this protein (PrP^c) is a copper-binding glycoprotein expressed at the surface of a number of cell types but principally neurons. The mechanism for the conversion of PrPC to PrPSc is poorly understood. PrPSc is a primary target for therapeutic strategies (Forloni et al., 2002). Both tetracycline and doxycycline reduce infectivity of prions. Although a number of other antiprion agents are known (e.g., quinacrine, polyanions, polyene antibiotics, anthracyclines [iododoxorubicin], chlorpromazine, Congo Red, tetrapyrroles, polyamines, antibodies and certain peptides), these are unable to pass the blood-brain barrier and/

Table 1
Alternative activities of antibiotics.

Antibiotic group	Unexpected activities
β-lactams	Antitumor (inducing apoptosis)
Tetracyclines	Antiprion, antimalaria
Aminoglycosides and macrolides	Pulmonary disease, immunomodulation, antitumor, antiparastic (leishmaniasis), antimalaria
Chloropeptins	Anti-HIV
Lincosamides	Antimalaria
Isoxazolidinones	Neurotransmission
Prodigines	Antiprotozoa, antimalaria, anticancer, immunosuppression
Polyenes	Imunomodulation, antiprion, antiviral, antitumor, anti-HIV, antiparasitic (leishmaniasis)
Coumermycins	Antitumor
Glycopeptides	Anti-HIV
Ansamycins	Anticancer, antiviral
Violacein	Antiprotozoal, antitumor, antiviral, anti-ulcer
Fosfidomycin	Antimalaria