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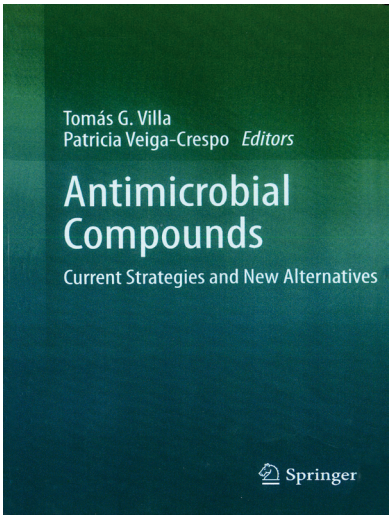

Antimicrobial compounds.
Current strategies and new alternatives

T.G Villa, P. Veiga-Crespo (eds.)

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Diseases have notably shaped the course of human history, especially when an unknown infection has "attacked" a population for the first time. Of the 1922 species of infectious agents recorded in databases, 632 are bacteria, 329 are fungi, 499 are helminths, 145 are protists, and 317 are viruses and prions. Until the 1930s, the treatment of infectious illnesses was mostly palliative; in most cases, physicians could only hope that their patients were strong enough to overcome the infection on their own. During the past 70 years, however, the morbidity and mortality associated with many communicable infectious diseases have significantly decreased in Western countries, largely because of the use of antibiotics and the implementation of well-planned vaccination strategies. Nonetheless, infectious diseases remain the second leading cause of death globally, responsible for more than 9 million deaths (16.2 %) per year. Infections of the lower respiratory tract, diarrheal diseases, HIV/AIDS, and tuberculosis are among the top ten causes of death worldwide.

The book *Antimicrobial compounds. Current strategies and new alternatives* describes the state of the art of antimicrobial research, including non-antibiotic therapeutic strategies in the fight against infectious diseases. The book contains eleven chapters written by several experts in the field, including its editors T.G. Villa and P. Veiga-Crespo.

The emergence of resistance in microbial strains to the current armamentarium of antibiotics is a major threat to public health worldwide. This problem has been made even worse given the slow development of novel antibiotics: since the early 1960s, only four new classes of antibiotics have been introduced. Indeed, the global antibiotics market is still dominated by antibiotic classes discovered half a century ago. Since then, most "new" antibiotics have been chemically tailored derivatives of these well-worn scaffolds.

In the genomic era, the availability of various genomics-based platforms including whole-genome sequencing, genotyping, gene expression profiling, and cloning, has resulted in new approaches to the increased production of known antibiotics and, perhaps more importantly, to the discovery of novel antimicrobial agents and targets (Ch. 1, 2, 5, 7, 9, 11). Most antibiotics come from soil actinomycetes, reflecting the historical bias of pharmaceutical screening programs toward these "easily" collected and culturable bacteria. Research into underexplored ecological habitats, such as marine ecosystems or insect symbiosis, have revealed new bacterial taxa that synthesize compounds with biocidal properties. Genome sequencing of known actinomycetes has revealed that these bacteria generally harbor >25 gene clusters encoding secondary metabolites. Because only one to four natural products are known from a typical bacterium under various culture conditions, researchers may thus far have discovered only 10 % of the natural products of screened strains and just 1 % of the molecules of global microbial producers. Genomics also facilitates the optimization of antibiotic biosynthetic processes in large-scale, cost-effective drug production, either by enhancing the flux of the desired bacterial pathways or by removing competitive biochemical pathways in the host.

The search for healing agents in plants can be traced to the ancient world. Ever since the very beginning of civilization, people have made use of plants to obtain relief from pain, heal injuries, and even to cure diseases. Plants are constantly under

attack by microbial pathogens. As part of their defensive arsenal, they synthetize antimicrobial peptides, such as "defensins" and "thionins," as well as other antimicrobial metabolites, including alkaloids, flavonoids, and essential oils (Ch. 3, 4). Essential oils are aromatic and volatile liquids whose main components are alcohols, aldehydes, lactones, and phenols. They are formed in specialized cells within the plant's stem or leaves and concentrated in its bark, leaves, or fruits. Essential oils have numerous properties, such as spasmolytic, immunomodulatory, psychotropic, expectorative, antibacterial, and antioxidative activities. Due to the broad range of antimicrobial and other effects, plants that produce essential oils have been used for medicinal purposes for over thousands of years. Today, essential oils are being investigated for the treatment of fungal-, bacterial-, and viral-based infectious diseases.

Extensive research efforts have recently been aimed at the development of novel antimicrobial compounds. Among them, antimicrobial peptides, commonly isolated from several organisms, have been considered for use as antimicrobial drugs (Ch. 4, 10). Antimicrobial peptides vary in their amino acid compositions and sizes (ranging from less than 5 to over 100 amino acid residues) and commonly have cationic and amphipathic properties. About 2300 antimicrobial peptides have been reported in the Antimicrobial Peptide Database and more than 100 peptide-based drugs are currently available, while another 500–600 candidates are in pre-clinical testing. Along with their antimicrobial activity, some antimicrobial peptides have immunomodulatory and antitumoral activities. Besides their isolation from natural organisms, antimicrobial peptides might be improved or created using computational tools. With these methodologies thousands of novel molecules can be generated, but they require high-through in vitro and in vivo validation, and therefore the parallel development of rapid assays.

The term "enzybiotics" was coined in 2001. It refers specifically to the antibacterial potential of bacteriophage enzymes actively produced during the phage lytic cycle and capable of degrading the bacterial cell wall. Recently, it was suggested that the term enzybiotics should refer to all enzymes displaying antibacterial and/or antifungal activity. In the literature, enzybiotics are also called "lytic enzymes" or "peptidoglycan hydrolases", as bacterial cell-wall peptidoglycans are their major targets.

Phage-based therapies consist of the administration of phage lytic enzymes or/and whole phages (Ch. 8). The recent dramatic increase in antibiotic resistance has stimulated renewed and intense interest in the therapeutic use of phages. Félix D'Herelle (one of the co-discoverers of bacteriophages) used phage therapy to treat bacterial dysentery in Paris as early as 1918, although for decades thereafter many scientists remained skeptical regarding his apparent success. Today, phages are already used as food preservatives; for example, the FDA-approved utilization of phages in cheese to control *Listeria monocytogenes*. Phages release their progeny from bacterial cells via two different pathways. Filamentous phages are continuously extruded from bacterial cells, without killing them, whereas non-filamentous phages induce host-cell lysis via highly evolved peptidoglycan hydrolases that quickly destroy the cell wall of the host bacterium.

Antimicrobial compounds is an exceptional review and update of information on alternative therapeutic solutions to the increasing problem of bacterial antibiotic resistance. This book is of great value to investigators working in the field of antimicrobial research and to students of several biomedical disciplines interested in deepening their knowledge of microbiology.

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