

# Book Reviews

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**Drug Discovery from Nature.** Edited by Susanne Grabley and Ralf Thiericke (Hans-Knoll-Institut für Naturstoff-Forschung e.V., Jena, Germany). Springer-Verlag, Berlin. 1999. xix + 347 pp. 15 × 23.5 cm. DM 193,00 (ca. US \$123.00). ISBN 3-540-64844-5.

This edited book highlights the importance of new methods and summarizes recent achievements in the search for novel biologically active natural products. The book is divided into five sections: Introduction (Chapters 1 and 2); Technical Aspects (Chapters 3–6); Natural Products from Microbial Sources (Chapters 7–10); Biochemistry and Molecular Biology Based Methods (Chapters 11–13), and Applications (Chapters 14–18). The editors, in collaboration with other researchers, are the authors of six of the chapters.

Chapter 1, “The Impact of Natural Products on Drug Discovery”, covers selected aspects of the major historical achievements in the chemistry of bioactive natural products and focuses primarily on natural products from microorganisms and terrestrial plants.

The second chapter, “Recent Developments in Drug Discovery Technologies”, deals with the recent development of new strategies in developing bioassays for high-throughput screening (HTS) using novel biochemical and genetic approaches. The authors stress the importance of developing new and reliable mechanism-based high-throughput bioassays suitable for the discovery and development of new drugs. This chapter could more logically have been included in the second part of the book.

In the second section, Chapter 3, entitled “A Central Natural Products Pool—New Approach in Drug Discovery Strategies”, describes a research program involving European pharmaceutical companies and academic researchers with the aim of constructing a library of natural products for biological screening. The concepts of the program are briefly but effectively explained; particularly interesting are graphs that provide information about the sources of leads (plants, microorganisms, synthesis, derivatives, animals, marine and aquatic), as well as about the main chemotypes in the “Natural Product Pool” library.

Chapter 4 deals with “Automation Strategies in Drug Discovery”, in which a detailed overview of the development of HTS is presented. The text is very instructive, covering several aspects of HTS, including a historical perspective, economic aspects, sample sourcing, sample handling, screening systems, and data handling. It is worth mentioning that combinatorial synthesis is considered as the main source of samples for HTS.

In Chapter 5, the authors present several typical cases of lead discovery in a chapter entitled “Synergistic Use of Combinatorial and Natural Product Chemistry”. After an introduction on the subject of combinatorial synthesis, examples of natural product based combinatorial synthesis are given. The use of natural products as templates in combinatorial synthesis is also described, as in the case of steroids, taxol derivatives, and other examples. This chapter is a good example of how useful a well-devised combinatorial synthesis approach can be for the synthesis of analogues and derivatives of biologically active natural products.

Chapter 6 is a brief discussion on “Supercritical Fluid

Extraction—Novel Strategies in the Processing of Biomaterials”. This chapter is too short for such a wide subject; it presents the principles of SFE and a few applications for the extraction of natural products.

The third section, “Natural Products from Microbial Sources”, is devoted to a description of the microbial sources of natural products. Considering the statement in Chapter 7 that “almost 20,000 microbial metabolites and approximately 100,000 plant products have been described so far”, I found it rather disappointing that plants and animals (both marine and terrestrial) have been completely overlooked as sources of natural products. This chapter is a short overview of the historical aspects involving the discovery of natural products from terrestrial microbes.

Chapter 8, entitled “The Chemical Screening Approach”, presents a particular method used for monitoring the isolation of natural products based on thin-layer chromatography analysis. However, the procedure clearly has limitations, particularly as compared with HPLC with analysis by a photodiode array detector, which can provide much more information; this is especially important when the chromatographic profile is used for chemical dereplication. Nevertheless, the structural variety of the new compounds isolated using such a TLC chemical screening approach is impressive and clearly shows its potential as an alternative method for new lead discovery.

Chapter 9, “Myxobacteria as Producers of Secondary Metabolites”, is an excellent account on bioactive natural products from a rather unexplored source of secondary metabolites. Chemical investigations on myxobacteria began only recently, but this source has rapidly attained a central position because of the discovery of the epothilones, cytotoxic macrocycles that have the same mechanism of action as Taxol. The chapter includes a brief historical introduction, followed by a thorough review of myxobacteria biology and biochemistry, then moving to natural products production and isolation. The authors present details of myxobacteria culture conditions, improved methods for the extraction of natural products, and a selected group of relevant natural products with potent biological activities. From the point of view of a natural products chemist, this was one of the most enjoyable chapters in the book.

Chapter 10, “Trends in Marine Biotechnology”, is a very brief review of natural products from marine microorganisms, a rapidly expanding area of research. Because of achievements published during the last two years, this chapter is almost out-of-date. However, the authors highlight some crucial questions, such as the challenge of growing marine microorganisms in artificial media, the isolation of “true” marine microorganisms, and the potential of marine microbials as a new source for biologically active natural products.

The fourth section, “Biochemistry and Molecular Biology Based Methods”, includes three chapters. Chapter 11, “Structure Modification via Biological Derivatization Methods”, focuses on different approaches for natural products structure diversification through biochemical manipulation of microorganisms. It includes coverage of enzyme-catalyzed reactions to modify a natural product template, precursor-directed biosynthesis, nonenzymatic biotransformations, metabolic manipulation, enzyme inhibition,

mutasynthesis, and genetic engineering. The use of isolated enzymes for the transformation of natural products is discussed in some detail, demonstrating the potential of a growing area for the synthesis of natural product derivatives and analogues.

Chapter 12, "Molecular Biological Aspects of Antibiotic Biosynthesis", deals with the investigation of the genomes of microorganisms for the production of new antibiotics. This is an important emerging area of research toward a better understanding of secondary metabolism regulation. The introduction to this chapter includes coverage of the complementation of blocked mutants, the use of heterologous probes for hybridization to genomic libraries, cloning of biosynthetic genes via resistance genes, reverse genetics, and cloning based on consensus sequences. The well-explained introduction of this chapter is followed by several applications of the above techniques. This chapter is clearly written for those who are not familiar with the terms of genetic biochemistry and is an excellent account of the importance of genetics in establishing particularities of biosynthetic pathways.

In Chapter 13, "Combinatorial Biosynthesis of Antibiotics", the author stresses the importance of genetic approaches to modify biosynthetic steps for the production of new antibiotics. The biosynthesis of new actinorhodin, erythromycin, and tetracycline derivatives are nicely illustrated and discussed in detail. Both Chapters 12 and 13 are complementary and show the importance of genetic sciences for better exploring biosynthesis routes for the generation of new natural products.

The fifth section, entitled "Aspects in Application", covers diverse subjects. Chapter 14, "Impact of Natural Products on Cell Biology: Low-Molecular Mass Effectors of Folding Helper Proteins", discusses relevant aspects of protein structure and function in the introduction, followed by studies of the mechanism of action at the molecular level of selected macrocyclic natural products. The relevance of this subject is that natural products are useful not only as biologically active agents but also as biochemical tools for better understanding enzyme activity.

Chapter 15, "Novel Antibacterial Drugs from Microorganisms", could have been included in the third section. It presents a short review of new compounds, with an emphasis on compounds active against resistant strains of microorganisms. The mechanisms of action of some substances are also summarized. Although the antimicrobial activity of only a limited number of compounds is discussed, the structural diversity is impressive.

Chapter 16, "New Antibiotics with Novel Modes of Action", could have been combined with Chapter 15. There is some overlap in the subjects of both chapters, and the information contained in both is complementary.

Chapter 17, "Synthetic Combinatorial Libraries: a New Tool for Antimicrobial Agent Discovery", discusses only the generation of a particular peptide library, based on antibiotic peptide models. Many more examples could have been included in this chapter.

Chapter 18, "Strobilurins and Oudemansins", presents a historical perspective on the development of new synthetic fungicides based on natural leads isolated from terrestrial fungi. The authors discuss the isolation and occurrence of these antifungal natural products, as well as their mechanisms of action, total synthesis, and structure-activity relationships.

In summary, this book provides a good overview of modern methods of bioactive natural products discovery, screening, and development, but is far from being the

comprehensive work that its title suggests. As has been pointed out, some chapters are excellent, but many others are below expectations, if one considers the importance of the topics discussed. The overall subject is strongly focused on natural products from terrestrial microbes, and consequently the many important achievements in plant and marine natural products discovery and development are absent. The chapters are well written, and only a very few mistakes in the text and in the structures were found. This monograph is recommended for students and researchers who are interested in new approaches to natural products discovery and development.

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**Heilpflanzen 1999—Herbal Remedies (CD-ROM).** By T. Brendler, J. Gruenwald, C. Jaenicke (Institut für Phytopharmaka, Berlin). Medpharm Scientific Publishers, Stuttgart, Germany, 1999. 20MB hard drive space required, 32 MB RAM, compatible with MS Windows 95, 98, NT. DM/sFr 224,000. ISBN 3-88763-071-8.

The dietary supplement industry has been experiencing an enormous herbal growth over the past few years. For anyone involved with the industry, this would be an excellent, easy to use CD-ROM. It is especially useful for anyone dealing with herbal formulation, substantiation, and natural pharmacy within the dietary supplement industry. Alternative medicine physicians, pharmacists, herbalists, supplement scientists, and pharmacognosists will benefit from this aid. Over 700 plants and 800 drugs are featured, all of which can be searched in selected languages and by using wildcards. Each plant has subfolder categories including synonyms, common names, etymology, botany, habitat (a world map showing the location and the appropriate times of flowering and harvesting), color photos, and drugs isolated. All the text and illustrations can be printed. Text files can also be created. Unfortunately, the color photos cannot be exported to other files or applications (e.g., Power Point).

The "drugs" subfolder is further broken down into other folders such as toxicology, substances, indications, safety, literature, usage, synonyms, pharmacology, and specifications. While the drug literature references seem to be up to date, the chemical substances sometimes do not match with the cited references or are outdated. For example, *Asimina triloba* L. (Dun) has literature references on acetogenins contributing to the activity, but acetogenins are not listed in the substances folder. Another improvement I (being a chemist) would recommend for the drugs section is to place the chemical structures in the substances folder. This could be added to future editions.

There are three ways to search the database. One can search for plants, drugs, or literature. Plants can be listed alphabetically by scientific names or other names (common names). Wildcards can be used to optimize complicated searches. Specific plants can be found by listing the family name alone or in combination with a wildcard search (e.g., "Papaveraceae" plus \*papaver\* yields three hits: two different scientific names and one synonym. A double click

on any one links you into the plant information screen. Drugs can be searched by indication (e.g., dysentery, fever, ulcers), substances (chemical), and pharmacopoeias. Literature references include the full titles for journal citations, which is always nice to see. The user can also create bookmarks, to which personal notes and comments can be added. The user has the opportunity to create their own personal library from this CD-ROM. In summary, I find this CD-ROM to be a great value and is an asset to my book/CD-ROM collection on plants.

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**Jiaogulan: China's "Immortality Herb".** By M. Blumert and J. Liu (Guiyang Medical College). Torchlight Publishing, Inc., Badger, CA 93603. 1999. 79 pp. 14 × 21.5 cm. \$7.95. ISBN 1-887089-16-0.

This book gives an informative overview of the adaptogen and antioxidant herb jiaogulan, known as China's Immortality Herb. This herb has similar characteristics to the well-known ginseng and is especially interesting medically as an adaptogen, or stress protectant, in cancer therapy, cardiovascular, hypertension, and other indications. Such literature is necessary and welcome given the increasing interest in herbal products both as "natural food products" and as alternative medical treatments by both the general and scientific/medical communities. The efficacy of traditional herbals has been proven by use in China both in centuries past and at the current time. However, the recent focus of research has been aimed at applying modern technology to prove the validity and value found in herbal formulations, to substantiate their medical value, and to develop safe and effective herbal drugs.

The book contains seven chapters and an appendix. Chapter One explains the terms adaptogen and antioxidant and how jiaogulan falls into these categories. Chapter Two describes the traditional use of jiaogulan and its modern medical discovery by Dr. T. Takemoto. Chapter Three enumerates the therapeutic qualities of jiaogulan, giving a general summary and describing the animal and clinical studies for each action. General botanical and cultivation information are found in Chapter Four. Chapter Five provides a brief description of the chemical constituents, concentrating on the most important of the active principles, the saponins. Chapter Six lists the different manufactured forms of jiaogulan and suggested therapeutic dosages. Chapter Seven is arranged in a question/answer format for frequently asked questions, and the appendix lists sample sources of the herb.

This book is more comprehensive than most monographs/pamphlets on specific herbal formulations. The presentation of clinical studies is especially welcome and needed to validate the medical effectiveness and safety of natural products; such detailed mechanistic studies are not often presented in herbal information booklets. Each chapter also contains extensive reference material for further detailed information. The chapter on chemical constituents describes the general composition of the saponin class and compares it with certain steroids. However, specific com-

pounds or structures are not given, and the chemical structure of an entire saponin is not presented graphically.

This book remains an excellent reference for providing an overview of the scientific studies on this important Chinese herb and allows the reader to judge the potential of its medical benefits in a scientific manner.

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**Medicinal and Aromatic Plants—Industrial Profiles:**

**Cannabis: The Genus *Cannabis*.** Edited by David T. Brown (University of Portsmouth, UK). Harwood Academic Publishers, Amsterdam, The Netherlands. 1998. xi + 286 pp. 17 × 24.5 cm. \$100.00. ISBN 90-5702-291-5.

This book is well written and organized and provides good information about the genus *Cannabis* plant and its products. The book contains 10 chapters, plus a preface, to the series, a preface, and an index. A very brief summary of each chapter will give the gestalt of the book.

Chapter 1 provides an excellent historical account of the use and abuse of cannabis across many cultures and centuries. Chapter 2 discusses the taxonomy and nomenclature, the botanical features, and the growth cycle of the genus *Cannabis*. It provides a fairly detailed historical account of the cultivation and subsequent processing of the plant and also briefly discusses different cannabis products from different parts of the world. Chapter 3 gives a very short summary of the chemistry of cannabis. The writer enumerates the different structural types of cannabinoids with some examples and a brief discussion on their biogenesis and also gives a short discussion on the chemical variation in cannabis. Chapter 4 covers the analytical and legislative aspects of cannabis in four sections. The first section is concerned with forensic definitions of cannabis and its products as a controlled drug of abuse. The second section addresses related offenses and attitudes. The third section describes the different analytical techniques used in forensic analysis of cannabis and its products, while the fourth section deals with the pharmaceutical quality of cannabis products. Chapter 5 discusses the nonmedicinal uses of the cannabis plant. This chapter provides an overview of the plant as a contemporary source of a wide range of useful materials such as textiles, paper, rope, oil as a foodstuff, and cosmetics. Chapter 6 describes the advances in the receptor pharmacology of cannabinoids. This chapter gives a good overview of what is known about the cannabinoid receptors and their ligands; it describes the pattern of distribution of these receptors and their effector systems, and it also discusses the effects mediated by cannabinoid receptors as well as the distribution, formation, release, and fate of anandamide. Chapter 7 deals with the therapeutic potential for cannabis and its derivatives. In several countries of the world, cannabis remains a schedule 1 substance under controlled substance acts. The writer records the available clinical evidence on the efficacy of the crude drug as well as of THC and other cannabinoid derivatives. Chapter 8 describes the available clinical evidence that supports the use of cannabis and cannabinoids in pain relief. Chapter 9 deals very briefly with cannabis addiction. Chapter 10 describes the side

effects of cannabis use including acute intoxicating effects, cardiovascular effects, endocrine effects, pulmonary effects, psychiatric effects, and neurological and behavioral effects.

This book is recommended to all libraries and especially to those individuals with a specific interest in cannabis.

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**Alkaloids: Chemical and Biological Perspectives, Vol. 13.** Edited by S. William Pelletier (University of Georgia). Elsevier Science, Amsterdam, The Netherlands. 1999. xvii + 429 pp. 15 × 23 cm. \$264.00. ISBN 0-08-043403-7.

The most recent edition to this series of volumes edited by S. William Pelletier presents five chapters authored by researchers who are experts on the group of alkaloids or methodology that they recount.

The first chapter, by John W. Daly, H. Martin Garraffo, and Thomas F. Spande, is a monumental review of amphibian alkaloids (over 480 references) that builds on previous reviews of the subject, including an earlier chapter by Daly and Spande in Volume 4 of this series. The presentation, by structural class, includes subsections on elucidation, synthesis, occurrence, and activity for each group of alkaloids. The information is clearly presented, and highlights include a complete discussion of the elucidation of the novel analgesic epibatidine, as well as a solid presentation of current evidence for the dietary hypothesis for the lipophilic amphibian alkaloids. An extensive appendix tabulates the distribution of 20 classes of these alkaloids along with their pertinent spectral data.

The second chapter, by U. Anthoni, C. Christophersen, and P. H. Nielsen, covers the cyclotryptophans and cyclotryptamines. The compounds are presented according to their occurrence in bacteria, fungi, plants, or animals. In many cases the characteristic chemistry and biological activity are clearly discussed, and those alkaloids warrant-

ing further study are noted. Concluding sections call attention to the biosynthesis and possible biological roles of the cyclotryptamines and, despite the uncertainty of the latter, make a strong case for the physiological significance of the tryptophan–cyclotryptophan cyclization.

Chapter 3, by P. W. Le Quesne, Y. Dong, and T. A. Blythe, covers the nonbasic pyrrole alkaloids identified over the last 15 years. This review is a balanced report of the structure elucidation, synthesis, and biological activity of a small collection of fascinating compounds, and it will be a useful foundation for future considerations of naturally occurring pyrroles.

The fourth chapter, by B. S. Joshi and S. W. Pelletier, describes the structure elucidation of the polycyclic diterpenoid and norditerpenoid alkaloids over the last 15 years. This review is a remarkable testimony to the power of modern NMR techniques. In many cases, the spectral data and chemical interconversions between particular alkaloids are described in detail. Finally, the relative toxicities and physiological activities of a number of these compounds are discussed.

The final chapter, by I. Ojima and D. M. Iula, is a short presentation of the syntheses of piperidine, “izidine”, and quinazoline alkaloids based on transition metal catalyzed carbonylation reactions. Some of the routes to these compounds seem to be short and stereoselective, and the carbonylation reactions occur early in the syntheses. Hopefully this methodology will be developed with an eye to convenience, as the apparatus for high-pressure reactions is not always available. Disconcertingly, there are a number of mistakes in the figures and captions of the schemes.

This volume provides essential information for those needing a current, full view of its topics, and while the price seems prohibitive for a personal library, it should be available in every good chemistry library.

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