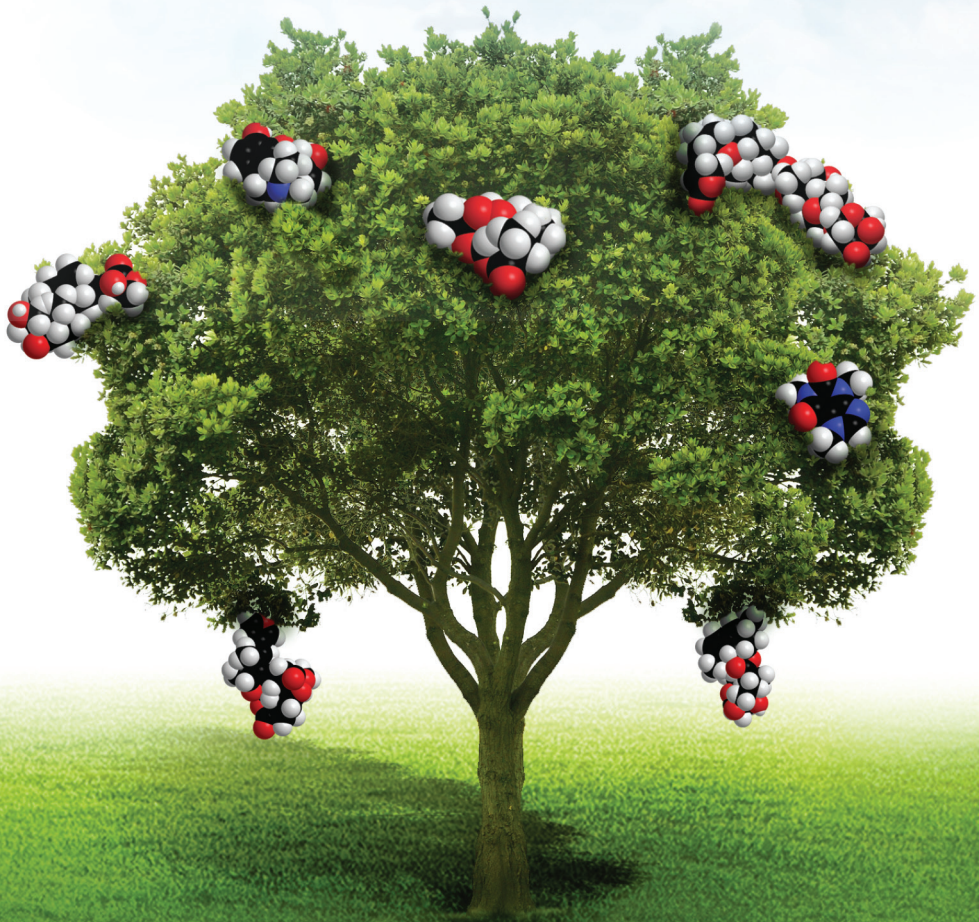
Tapping Molecular Wilderness

Drugs from Chemistry–Biology–Biodiversity Interface



Yongyuth Yuthavong

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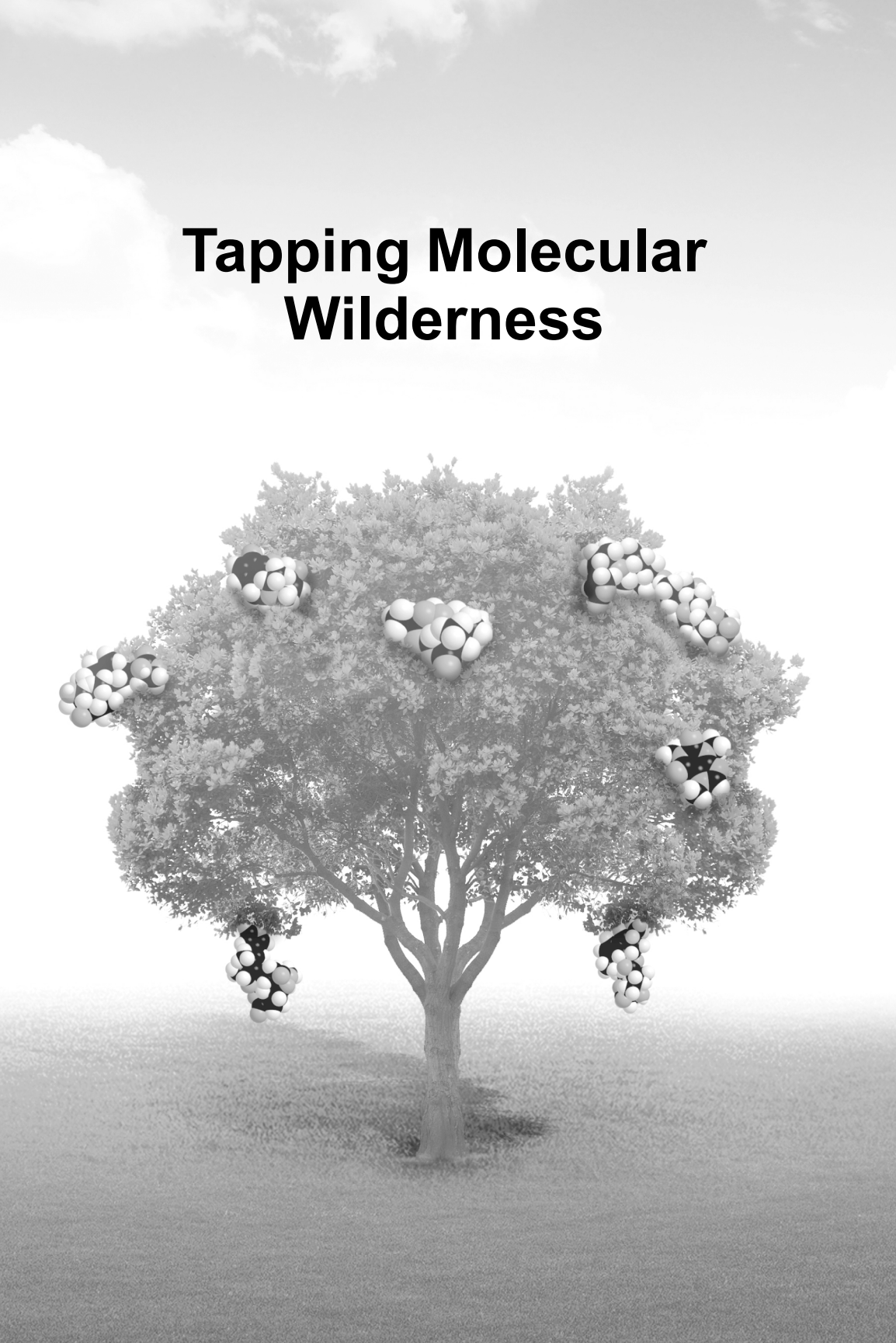

Tapping Molecular Wilderness

Drugs from Chemistry–Biology–Biodiversity Interface

Yongyuth Yuthavong

Pan Stanford Publishing

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20150810

International Standard Book Number-13: 978-981-4613-60-6 (eBook - PDF)

Reviews

"*Writing a popular science book is more challenging than writing a professional one for the technical audience. One needs to be scientifically rigorous, yet speak in the language of the school student and the 'lay' public. There can be no threatening equations or complex chemical pathways, yet one should convey the message in a lucid manner. Professor Yuthavong carries it off with ease and elan. He has chosen the word "wilderness" deliberately, to evoke both excitement and awe in the reader. He shows how human creativity is able to chisel molecules from wilderness into useful products, how nature itself has been doing such molecular architecture over evolution, and how we may learn from it. The underlying message, expressed with time honored wisdom, is Gandhian in spirit. Recall what Mahatma Gandhi said: 'Nature provides for man's need, but not his greed', and 'Be the change you want the world to be'. This is a book that needs to be distributed across both the developing and developed worlds.*"

D. Balasubramanian
Professor and Director of Research,
L V Prasad Eye Institute, Hyderabad, India, and
UNESCO Kalinga Prize Laureate in Science Popularization

"*I very much like the idea of writing something that's technically correct but intended for a general audience. The topics would correct an impression that all drug discovery these days comes from high throughput screening of synthetic molecules. I'm very impressed with the variety of topics the writer has managed to touch upon and with how technically accurate the handling of these topics has been.*"

Jon Clardy
Professor, Harvard Medical School and Broad Institute, USA

"*This pioneering book is a powerful source of enlightenment on the vital connections between the diversity world's biological splendour*

and advancement of scientific knowledge. It offers a convincing case as to why the conservation of biological diversity is imperative for human wellbeing. I recommend it to anyone who has an interest in sustainable development in general and environmental protection in particular."

Calestous Juma
Professor, Harvard Kennedy School, USA, and
Former Executive Secretary, United Nations Convention on
Biological Diversity

"*This is an excellent reading not only for researchers and students but also for general readers. The whole book is woven around the key term 'wilderness'. It covers a wide area of subjects, from ancient myth to modern molecular biology and drug design. The book is not only educational but also highly entertaining. I hope in the future it will be available to those people who do not understand English*."

Hisao Masai
Professor, Tokyo Metropolitan Institute of Science
and University of Tokyo, Japan

"*The need to bring together new knowledge in basic sciences, agriculture, anecdotes and cultural norms on a single platform for efforts in prospecting for drugs from natural products cannot be overemphasized. Many have attempted to do this but only a few have the background necessary to succeed in the efforts. Professor Yongyuth brings with him a wealth of knowledge accumulated over thirty years and is probably the best to produce a much needed balanced view in the field.*"

Ayoade Oduola
Former Deputy Director,
UNDP/World Bank/WHO Special Programme for
Research and Training in Tropical Diseases, Geneva, Switzerland

"*Professor Yongyuth Yuthavong has worked for decades at the highest levels of science and government and successfully cross pollinated these worlds. So it's no surprise that his new book,* Tapping Molecular Wilderness: Drugs from Chemistry–Biology–Biodiversity Interface*,*

bridges the worlds of science and nature. Coming at the moment when the world is embarking on a new set of Sustainable Development Goals which also must embrace both science and nature, Prof. Yuthavong's book can be widely recommended for anyone who wishes to think more deeply about these goals—and the future of our world."

Peter Singer
Professor, University of Toronto, and
Chief Executive Officer, Grand Challenges Canada

"*One thing that typifies the writer is his clarity in thinking and presentation: This quality is apparent in this highly readable book. Through hands-on drug research and involvement with related issues, he aims to make us appreciate nature for its cornucopia of simple and complex molecules that are beneficial to mankind. One such benefit is the natural products for combating pathogenic organisms whose drug resistance should be taken seriously by our making sustained and renewed efforts to fight them. After all pathogens must fight for their lives; simplistic and ephemeral efforts by the medical community have constantly proved to be inadequate. In this book the themes of the need to sustain nature for its biodiversity and to combat pathogens by natural and modified biomolecules shine through brilliantly.*"

Bhinyo Panijpan
Former Director, Institute for Innovative Learning,
Mahidol University, Thailand

"*The author beautifully portraits the biodiverse 'molecular wilderness' as the world of wonder, full of treasure to benefit mankind. Complex chemistry of drug discovery and drug design is amazingly made simple. It ends with a strong message that molecular wilderness is powerful. We must respect its balance and coexist with it sustainably. Otherwise it fights back harshly. The book is very educational and inspiring. It is a complex scientific textbook neatly made simple for general readers. We definitely need more science and technology books in this literary style.*"

Khunying Sumonta Promboon
Member of Thai National Legislative Assembly and
Former President of Srinakarinwirote University, Thailand

"*Living organisms produce both toxic compounds to disable their predators and beneficial compounds to protect or heal themselves, so as to enhance their ability to survive. So Nature, or the 'Wilderness', is a rich source of medically important molecules. Thus 'Tapping Molecular Wilderness' has played a crucial role in the discovery of new drugs to combat human illnesses, such as infection and heart disease. The author elegantly discusses the principles of drug discovery, the need for an integrated role of chemistry and biology, novel strategies in research, as well as problems arising from drug resistance. As expert researcher, with success in devising a novel drug for malaria, the author has simplified the scientific concepts, historical perspectives and modern trends in drug discovery in a simplified manner, readily understood by the layman. More books like this are needed to show the importance of research, not only at applied level but also at basic level: Perhaps then governments, especially in developing countries, may invest more in research for the future.*"

M. R. Jisnuson Svasti
Emeritus Professor, Mahidol University and Chulaborn Research Institute, Thailand

"*The author should be admired for his bold effort to write a book on 'natural science' for the general public. As it turns out, this book not only contains a wealth of scientific information but also is very easy to read and to follow from the first page to the last. Readers will benefit from the knowledge given which can be used as a starting point to dig further into the 'beauty of nature'. The author should be congratulated for the beautiful tale of science adventure.*"

Yodhathai Thebtaranonth
Emeritus Professor, Mahidol University, Thailand, and
ASEAN Outstanding Technologist and Technologist Awardee, 1995

"*From the wilderness have come many revelations. Professor Yongyuth Yuthavong now has added chemistry to the list.*"

Prapon Wilairat
Professor, Mahidol University, Thailand, and
Outstanding Scientist of Thailand Awardee, 1997

Contents

Preface

This is a book for general readers with some background in science, concerning the search for drugs, starting from molecular diversity found in nature, which might be called molecular wilderness. The drug molecules may be used as such, or may be used as templates for synthetic or semi-synthetic drugs obtained from the interface of chemistry, biology and biodiversity. In some cases, the active parts from natural molecules may be identified and modified to more effective ones. In other cases, nature provides the targets, such as essential enzymes from infectious microorganisms, from which synthetic drugs can be designed. The mechanisms of action of drugs can be discerned from studying the target-drug interactions. Nature may fight back, as when microorganisms become resistant to drugs, but we can again use the chemistry–biology–biodiversity interface to obtain drugs which overcome the resistance. The battle goes on, hopefully with victory on the human side, but this requires special efforts from wider areas than medical science.

This book offers a bird's eye view on the unifying theme of interface between chemistry and biology as the essence of drug discovery, with focus on "conversation" between science and nature. Examples are taken from successes in discovering useful drugs from the wilderness of biodiversity, from aspirin and quinine to antibiotics and statins. Failures following initial successes due to dynamic nature of molecular wilderness are also highlighted, with examples of eventual successes. The book concentrates on early stage discovery, which requires interdisciplinary approaches combining synthetic with structural chemistry, biochemistry, molecular and cell biology, but also highlights the importance of pharmacology, toxicology, pre-clinical and clinical sciences to complete the chain of drug development. Significantly, the book draws attention on biodiversity as a key to sustainable efforts to discover new drugs from nature.

Most books on natural products and drug development concern mainly or only technical and scientific aspects of the topic. Others on environmental and indigenous knowledge tend to ignore or,

worse still, tend to be hostile to the scientific approaches. This book attempts to bridge the gap between the "two cultures", hopefully resulting in balanced understanding of various issues in development of drugs from nature. It also substantially covers a hitherto little explored topic of plasticity of drug targets and the various ways in which nature "fights back" against our attempts to conquer infectious and other diseases, resulting in drug resistance, or in some cases emergence of other diseases. The conclusion is that brute technological forces alone are insufficient to solve our present problems or prevent new ones, but that science and technology have to be integrated into other aspects of health care, including social science and integrated economic and social development.

The book recalls that biodiversity contains a large number of products, many of which have been used in the form of traditional medicine, and others have been identified as drugs or drug leads for modern medicine. Yet others provide the targets for design of drugs, both based on natural sources and synthetic chemistry. It points out that poor and vulnerable populations still rely substantially on traditional medicine for their health care, the quality of which can be improved by modern science. Conversely, extension of traditional medicine through research can contribute to progress of modern medicine, leading to cheaper and more accessible drugs. The message of the book is that tapping molecular wilderness should be done responsibly, ensuring that fair benefits go back to the indigenous population where the traditional knowledge originated. It also needs to be done in an environmentally sustainable fashion through the help of science as major tools.

The wilderness has been around much longer than we have. Simple cells appeared about 3.6 billion years ago, about a billion years after the formation of our planet. Multicellular life started about a billion years ago. Land plants and animals started to appear from about half that time. In contrast, modern humans only evolved some 100,000 years ago. In this very short history of human beings, we have managed to exert enormous influence on the wilderness, taming many species for agriculture, and condemning many more to extinction by our disregard or ignorance. Until recently, we have tapped the wilderness for our own use as though it is an unlimited reservoir.

Only recently have we come to realize that the wilderness has limits to human insults, with grim consequences for our own

existence. By destroying forests for their products and turning the land to our own use, we have unwittingly created deserts, drained away water resources and contributed to global warming. We have to stop the reckless behaviour, not just to be kind to the wilderness but indeed for the sake of our own survival.

The book deals with the topic of tapping the wilderness for human purposes with three distinct characters. First, it takes chemistry of nature as the essence of wilderness. It considers natural molecules as members of interacting components underlying the phenomena of wilderness. Secondly, it concentrates on tapping this molecular wilderness for drugs, both from the natural molecules themselves and from the use of these molecules as design models for synthetic drugs. Thirdly, it treats the threats of drug resistance of microbes as natural outcomes of interactions of molecular wilderness. Like natural disasters of desertification and flooding, resistance of microbes to drugs is viewed as consequences of disturbance of wilderness.

Just as we need to tap wilderness in the visible world sustainably, so do we need to tap molecular wilderness in a sustainable manner. Both are huge challenges, requiring change of mindset as well as technical progress. The world community is embarking on cooperation, on an unprecedented scale, through United Nations and other world bodies to try to achieve "Sustainable Development Goals". These will cover major issues of development in economic, social and environmental fields. The goals for sustainable tapping of molecular wilderness are different, achieving new effective drugs and overcoming the problems of drug resistance. The goals are more modest, perhaps, but no less worthwhile.