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ISBN 978-981-99-9182-2 ISBN 978-981-99-9183-9 (eBook)
https://doi.org/10.1007/978-981-99-9183-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

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Prof. Tej Pal Singh

Prof. T. P. Singh is a scientific leader who has made overwhelming contributions to structure-based rational drug design. His contributions in the structural biology of transferrin family proteins and anti-inflammatory drug targets are pioneering. His protein structure investigations have thrown new light on mammalian innate immunity and the role of non-immunoproteins in innate immunity. This has provided new ideas for combating microbial infections. The editors of this book dedicate it to Prof. Singh for his internationally recognized, immense research findings and consistent encouragement showered on generations of scientists, including the editors of this book.

Editors

Foreword

As biological entities, human beings are inevitably vulnerable to diseases that disrupt the complex mechanisms we depend on for life. During evolution we have developed sophisticated protective mechanisms such as the human immune system, but the threat of new diseases is ever-present. The recent Covid-19 pandemic is but one example. Modern science has led to unprecedented understanding of disease processes, and as each new tool arises, such as whole-genome sequencing and artificial intelligence (AI), our ability to combat disease increases.

But is our collective imagination sufficient in itself to rely on these tools to come up with the new medicines we need? In the past 20 years, the revolution in genome sequencing has led to the discovery of many genes whose protein products appear to be attractive targets for the development of new drugs. While there have been some outstanding successes, it is still the case that the majority of these appear to be 'undruggable', at least with current approaches.

Could we benefit from more help from Nature? There is much debate today on the merits of so-called 'alternative therapies'. Many of these have been adopted over time by human societies from close scrutiny of the natural world in which they live, primarily using plants and their products. Others come from cultural beliefs. Few have yet been subjected to the rigour of today's scientific methods. Can we learn from them by delving more deeply into their basis?

This book, comprising 20 chapters written by a group of scientists from Kerala, India, provides a unique perspective on this important question. Indian science has a fascinating cultural history that has evolved over a longer period and in a different environment from Western science. Much of this has been dependent on the rich and diverse ecology of India that has seen the emergence of many traditionally based therapies. A prime example is the practice of Ayurvedic medicine, which utilizes mostly plant materials, from roots, leaves, fruits, bark or seeds, together with dietary, exercise and lifestyle protocols. The lead editor, Dr. M Haridas, has made it his mission to explore the basis and efficacy of traditional Indian practices utilizing the sophisticated tools of Western science (structural biology, genomics, computational modelling). He is well qualified to do so, being a biologist who subsequently trained in structural biology both in India and abroad. In this book he has collected together articles from a number of different contributors, many of them his former students, a strategy that gives the work a nice coherence.

The book begins with an introductory chapter that discusses the fundamental question that provides the rationale for the book: whether the era of drug discovery from natural products is over, having been superseded by the target-based approaches of reverse pharmacology. The answer is a resounding 'No'. This is followed by an interesting chapter by Kumar et al. that discusses the history of the development of therapeutic medicines from its origins in the discovery of the properties of local plants by early human societies, to its place in the present day. The following chapters then give overviews of some of the key approaches that are, or can be, applied today. These include the approaches involved in the discovery of new drug targets from genomics, including the challenges inherent in developing these further towards actual drug candidates; new technologies that could accelerate progress, such as CRISPR-Cas9; and the computational tools that now play such a critical role in the design of novel drugs. Turning next to the use of natural products for medicinal development, there are chapters on the use of plants as a source of the secondary metabolites that are such important components of many current medicines, and on the value and applicability of peptides from marine organisms. Following these chapters, the applicability of Nature-based methods to some of the key challenges in human health—cancer, cardiovascular disease, infectious disease, inflammatory conditions, and Alzheimer's disease—is documented. Probably the most intriguing parts of this book, and the most original, are in the discussions of Ayurvedic medicine. This therapeutic system will be new to many readers, and because of its complexity it is so far under-explored by Western science.

As the use of natural resources returns to take its proper place in the pantheon of drug discovery approaches, and both methods and findings can be subjected to the new tools of exploration and utilization, it is hoped that this book will provide a significant step forward. In particular, the use of AI to help unravel the wealth of knowledge inherent in a traditional medical system such as Ayurveda may be of immense benefit.

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Edward N. Baker,

Preface

Modern drug discovery draws upon the wealth of knowledge in traditional healthcare practices and folk wisdom regarding the therapeutic applications of natural substances. Many natural remedies used in traditional medicinal practices have made their way into the modern pharmaceutical industry, often in the form of refined bioactive compounds. A classic example is aspirin, or acetylsalicylic acid, the blockbuster analgesic, anti-inflammatory and antithrombotic drug introduced by Bayer in 1899 and still popular as an over-the-counter medication worldwide. Ancient Sumerians and Egyptians used the barks of willow and poplar trees, rich in salicylates, for pain relief. The age-old Egyptian practice of using a poultice of mouldy bread to treat infected wounds received rational backing when Alexander Fleming discovered penicillin in an act of serendipity. Many modern drugs have their origins either directly or indirectly in natural sources. Although only a few are natural products in an unaltered form, many are semisynthetic derivatives of natural products or synthetic drugs designed based on natural pharmacophores. Out of the 1394 molecule drugs approved between 1981 and 2019, 1% (14) are defined botanical mixtures, 5% (74) are unaltered natural products, 27.5% (356) are semisynthetic derivatives of natural products, and 19.5% (272) are synthetic drugs designed based on natural pharmacophores. These statistics underscore the significant contribution of the natural world, accounting for nearly half of modern drug development. Further, out of the approximately 175 small molecules approved since 1940 in cancer therapeutics, about 85 are natural products or their derivatives.

In the initial years of modern pharmacology, many traditional therapeutic formulations and natural sources were explored systematically to identify the pharmaceutically active molecules to develop them into refined drugs. This approach has led to the discovery of important drugs such as morphine, ephedrine and quinone. In addition, the enormous diversity of the natural world is constantly exploited for identifying novel drug leads. Drug discovery relies on three major components, especially in the preclinical stages. A drug target, which is the biological macromolecule with which the drug interacts to exert its effects. An assay system, which can be in vitro (in a controlled laboratory environment), in vivo (in living organisms), or in silico (computer-based) experimental system used to analyse the effect of a small

molecule on the drug target or the disease phenotype. The third component is the drug lead, a molecule showing promising biological activity in the screening assays.

The edited volume, titled 'Drugs from Nature: Targets, Assay Systems, and Leads,' offers a comprehensive overview of the drug discovery process from natural sources such as plants and microbes. The volume was conceptualized to pay tribute to the contributions of the lead editor, Professor Madathilkovilakathu Haridas, a pioneer in structural biology and drug discovery with a keen interest in natural and nature-inspired drugs. His illustrious four-decade-long scientific career has resulted in substantial contributions to medicinal chemistry. Moreover, he has inspired a generation of young scientists to embark on careers in this domain, and some have contributed to this volume. The book comprises 20 chapters contributed by distinguished biologists from around the world, focusing on various aspects of nature-inspired drug discovery. The book delves into state-of-the-art approaches for target identification, assay system development, and lead identification. It also discusses targets and leads associated with various disease conditions, such as inflammation, cancer, reproductive disorders, cardiovascular issues, neuromuscular disorders, and infectious diseases. As the editors, we are confident that this book will serve as a valuable reference for scientists and scholars in phytochemistry and drug discovery. We also hope it will facilitate the practical integration of traditional medicinal practices with modern medicine by revealing the common ground between these seemingly distinct schools while highlighting their differences.

Madhathilkovilakathu Haridas
Sabu Abdulhameed
Dileep Francis
Swaroop S Kumar

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About the Editors

Madhathilkovilakathu Haridas did his doctoral and postdoctoral studies in structural biology at AIIMS, New Delhi, and Massey University, New Zealand, respectively. He was the first biologist to get trained in X-Ray crystallography of single crystals of proteins. He has solved several animal and plant protein crystal structures. He has more than 150 international publications and more than 30 chapters in edited volumes. He has one international and two Indian patents. He has guided 26 students for their Ph.D. He is the founding honorary director of the Inter-University Centre for Bioscience, Kannur University. He has served in various academic bodies at all tiers of all universities in Kerala. Currently, he is a serving member of the Biotechnology Commission Kerala, Biodiversity Board Kerala, Research Council Amrita School of Ayurveda Kollam, Research Committee Arya Vaidya Pharmacy Coimbatore, and Research and Ethical Committee of MVR Cancer Centre & Research Institute, Kozhikode.

Sabu Abdulhameed is a Professor in the Department of Biotechnology and Microbiology at Kannur University, India, and is serving as Pro-Vice Chancellor of the University since January 2021. He received his Ph.D. from Cochin University of Science and Technology and served as a Scientist Fellow at CSIR-NIIST, Thiruvananthapuram. He did his postdoctoral research in microbial fermentation and biotransformation in the USA and France. His research interests are in microbial fermentation, therapeutic enzymes, and the biotransformation of bioactive molecules. He has contributed extensively to fermentation and biotransformation in medicated wines and has three patents to his credit. Dr. Sabu has published six books and nearly 100 research papers in international journals. He is a recipient of a postdoctoral fellowship from the Institute for Research and Development (IRD, France) and a Visiting Professorship from the Mexican Agency for International Cooperation and Development. He is also a member of many academic bodies and expert panels and serves on the editorial boards of numerous research journals.

Dileep Francis, an Assistant Professor in the Department of Life Sciences at Kristu Jayanti College, Bengaluru, earned his Ph.D. in Life Sciences from Kannur University, India. Achieving an impressive all India rank of 60 in the CSIR-NET

exam, he received research fellowships from the Council for Scientific and Industrial Research (CSIR) during his doctoral studies. Dr. Dileep's research accomplishments include identifying a vaccine candidate for Methicillin-resistant *Staphylococcus aureus* infections. Currently, his focus extends to interventions in diagnosing and treating infectious diseases, with recent explorations in material sciences for biomedical applications. With a robust publication record encompassing high-impact journals, book chapters, and popular science articles, Dr. Dileep also serves as the editor of the *Kristu Jayanti Journal of Core and Applied Biology*. He is a life member of the Kerala Academy of Sciences, a research advisory committee member at Kristu Jayanti College, and coordinates the Star College Scheme of the Department of Biotechnology, Government of India, at the college.

Swaroop S Kumar is currently working as Assistant Professor, Department of Food Technology, Amal Jyothi College of Engineering, Kanjirappally, Kerala, India. He earned his Ph.D. in Biotechnology from Kannur University, Kerala, India. He has eight years of experience and published several papers in reputed national and international journals with an h-index of 9 and 225 citations. He also has one patent to his credit. He has been an invited speaker in many seminars and workshops and mentored several undergraduate student projects. He is also a member of various institutional academic bodies. He has also been an external evaluator for the young investigator program conducted by Kerala Development and Innovation and Strategic Council (K-DISC). He is a life member of the Biotech Research Society of India. His current research interest includes the production, purification, and characterization of therapeutic enzymes, protein engineering, and the characterization of bioactive molecules.

Chapter 1
Drugs from Nature: Targets, Assay Systems, and Leads

Madhathilkovilakathu Haridas and Sabu Abdulhameed

Abstract The overview is done to determine whether the era of natural products for drug discovery is over or not over. Though the drug discovery process is considered scientific, the study reveals that it may be considered highly inefficient in the infant stage, and it is hard to distinguish between natural products and systematically prepared synthetic compounds. The inference is that the era of natural products is not over. A few decades ago, it was speculated that the number of new natural product-derived drugs could go to zero. However, this analysis has proved a fact contrary to the speculation. It shows that the era of natural product drug discovery is not over, but it is with an endless frontier.

1.1 Why This Overview?

The evolution of the concept of medicine, as an exception to food, must be clarified. The sources of medicines or medicinal raw materials were directly from nature until the synthetic chemicals got into the streams by experimentation. Till the nineteenth century, this was the scenario. The importance and dependence on natural sources for finding new drugs shifted to synthetic chemistry. The natural sources were never completely thrown down, but their role was minimal.

Historically, natural sources have been the reservoirs of medicinal compounds or compounds for drug development. However, this past has been increasingly challenged as future resources must still be abandoned in the pharmaceutical industry. There are many reasons why natural sources are facing challenges in the field of drug development. The above challenges are summarized as follows: The natural sources supply complex compounds of intricate structures, and their total synthesis is challenging in case such compounds win the approval of regulatory authorities.

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M. Haridas et al. (eds.), *Drugs from Nature: Targets, Assay Systems and Leads*,
https://doi.org/10.1007/978-981-99-9183-9_1

Even if the pharmaceutical industry bends upon utilizing natural sources for procuring drugs, their supply would be limited by various factors like season, geography, farming, and other similar constraints. Other factors like environment, genetic variations, and extraction methods would be the constraints affecting the purity of the prospective drugs and the standardization. Since patenting issues may affect natural products, entrepreneurs may be less willing to invest in such projects. Developing drugs from natural sources may be more taxing in time and less cost-effective in mission-mode operations. Most of the time, entrepreneurs need to be more optimistic about solving the problems related to regulatory issues. The most important of all the challenges faced by drug discovery from natural sources is the advancement in synthetic chemistry.

Despite the above disincentives, the natural sources hold the significant promise of outcomes from drug discovery and development endeavors. However, there is a growing interest in exploring natural products as a source of inspiration for drug design and in harnessing modern techniques to enhance the production and consistency of natural product-derived drugs. Also, the demand for sustainable and environment-friendly drug development shows renewed interest in natural sources.

Traditional medicines may face challenges like less acceptance among culturally alienated people and skepticism in people looking for evidence and drug action mechanisms. The following are reasons why traditional medicines may be looked down upon or face rigorous scrutiny in contemporary drug development. Because many traditional medicines lack rigorous scientific evidence to support their safety, efficacy, and mechanisms of action, there may not be any record of testing the efficacy of such drugs or the toxicity due to them. They may need to find out whether such tests and evaluations had been performed for them in the past. Unless they are in pure form, and most of them are not, the drugs from natural sources may not be amenable to standardization and quality control. In modern medicine, strict quality control and standardization are essential for regulatory approvals. Since traditional drugs are massive mixtures of many compounds, assessing adverse effects and interactions with other drugs may be nearly impossible. Owing to the same settings, there will be considerable problems in understanding the mechanism of drug action. However, there may be cases in modern medicine where the exact mechanism of action might not be made available at the time of statutory approval as a drug. Like drugs from natural sources, traditional medicines may also face patentability hurdles. If patents are not allowed, private R&D investments may not be attracted.

Despite these challenges, there is a growing recognition of the value of traditional medicines in drug development. Some researchers and pharmaceutical companies are exploring traditional remedies as sources of new drug leads. Traditional medicines serve as inspirations for drug design and development. They work to bridge the existing, sometimes imaginary, gap between traditional and modern medicines.

Many factors influence the functioning of drug molecules; consequently, any medicine has never achieved absolute predictability of the therapeutic effect. It may be because many factors play at medicines' function and often produce conflicting and contradicting results. Also, though the drug discovery process is considered to

be scientific, Fig. 1.1 reveals the fact that the process may be considered highly inefficient as the infant stage and it is hard to distinguish between natural products and systematically prepared synthetic compounds, as reviewed by Hay et al. (2014). The inference is that the era of natural products is not over.

A later report (Wong and Siah 2020) also concludes with similar results, as shown in Fig. 1.2.

All the critical analyses suggest that there is little difference in success rates of obtaining drug-regulatory approvals regarding the drug leads inspired and obtained from natural sources or traditional medicines and drug leads supported by contemporary scientific investigations of chemicals from synthetic laboratories. Also, it is to be seen that the success of natural and traditional medical drugs leads in all branches of modern medicine, the most recent being the success story of artemisinin. Hence, natural sources and traditional medicines will remain as sources of drug leads for modern medicine for a long time. The choice depends on factors such as the target specifications, the availability of resources, the desired properties of drugs to be developed, and the stage of drug development. In many cases, combining both approaches would give the best results by exploiting the advantages of both natural and synthetic molecules. It is the "bioinspired drug development." Currently, the argument is that the era of natural product research is still ongoing. On the contrary, it is an endless research frontier for drug discovery and development.

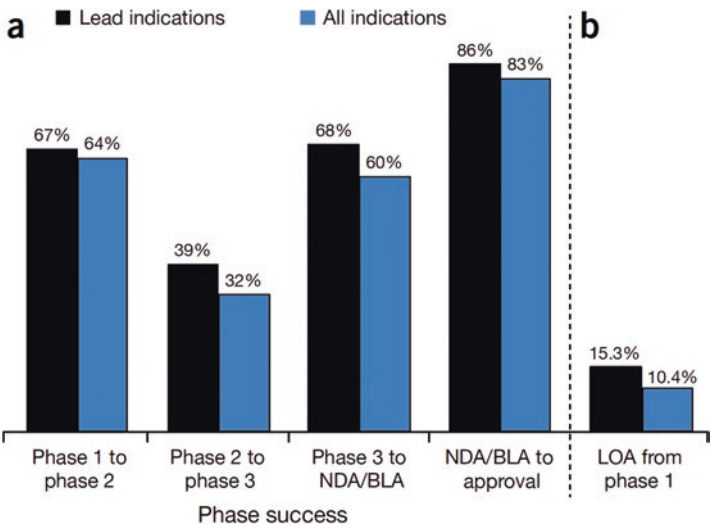

Fig. 1.1 Clinical development success rates for investigational drugs (Courtesy: Hay, M., Thomas, D., Craighead, J. et al. (2014) *Nat Biotechnol* 32(1), 40–51)

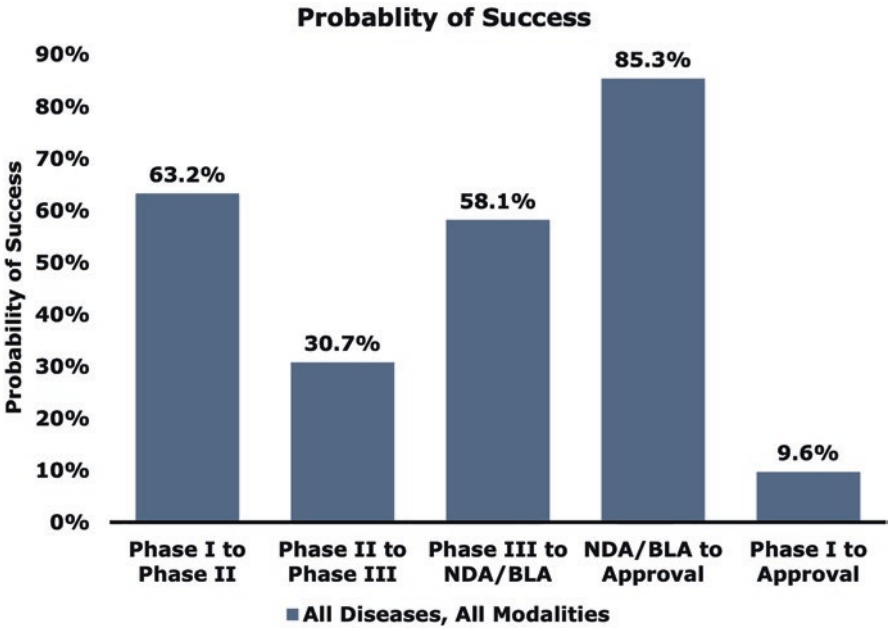

Fig. 1.2 Estimation of clinical trial success rates and related parameters (Courtesy: Wong, C. H., Siah, K. W., (2019) *Biostatistics*, 20(2), 273–286, doi: https://doi.org/10.1093/biostatistics/kxx069)

1.2 Developmental History of Drugs

Linking man, medicine, and nature involves exploring their interactions (Kushner 2008). It explores how nature or products from nature interfere with the sick human body. The point from which man started using natural products to cure human sickness is obscure. Physical anthropology has indirectly contributed to our understanding of the history and evolution of medicine. However, the origin of medicine is more obscure than the origin of life, though the studies in physical anthropology could propose a form of evolution of medicine. No single theory is found convincingly explaining the origin of the use of medicine and medical practice. However, the picture of the evolutionary developments of medical practice could be completed by the jigsaw pieces of cultural practices and scientific discoveries. The scientific discoveries of the development of medical practice have been embedded in the development of traditional medicines (Hardy 2020). The development of medicine is seen in ancient civilizations such as Indian, Egyptian, Mesopotamian, Chinese, and Greek; also, civilizations originated in Africa and America. The development of modern medicine has come through the following stages (Shryok 1936; Silvano 2020):

Ancient civilizations such as Indian, Egyptian, Mesopotamian, Chinese, and Greek
Renaissance and scientific revolution

Age of enlightenment (eighteenth and nineteenth CE centuries)
Twentieth century to the present

The pharmaceutical industries, drug discovery and design operations, biotechnology and molecular biology, combinatorial chemistry and drug optimization, personalized medicine and targeted therapies, and other emerging technologies are the contributing experimental sciences toward the continuing development of modern medicine (Boudoulas et al. 2017). It is interesting to see the argument of Teppone (2019) that medicine has always been "modern" and "scientific" from ancient times to the present day (Teppone 2019). It only means that the system was developing based on experience/results. It may be considered overlooked or not significant if the contributions from traditional or herbal medicines would be worthwhile in the future. Natural products and traditional medicines, developed as orderly regulated systems, have an incredible repertoire of clinical experience and a unique diversity of chemical structures. If they are addressed, developing new drugs would tend to be better. It needs to be remembered that most antihypertensive, anticancer, and antimigraine medicines are directly linked to natural products and knowledge of traditional medicine (Joo 2014; Newman et al. 2003). The social significance of traditional medicines and natural products is excellent, so the validity of those systems may be relevant for the future (Ngo et al. 2013; Zhu et al. 2012; Galm and Shen 2007). Some drugs initially derived from natural sources are still in use (Newman et al. 2003; Li-Weber 2009). The most crucial contemporary contribution to modern medicine from a natural source is artemisinin (Muschietti et al. 2013; Cragg and Newman 2013).

1.3 Drugs from Nature

Discovering new drugs from natural products has a fascinating history that dates back thousands of years, starting with prehistoric societies and progressing to the sophisticated realm of contemporary pharmaceutical research. Humans have depended on the therapeutic benefits of plants and other natural resources to treat various diseases throughout history. Ancient cultures like the Egyptians, Greeks, Mayans of Central America, and Chinese left the first traces of using natural products for medical purposes. These societies acquired a profound grasp of the healing potential of plants and other natural resources, which served as the foundation for their medical systems. In 2735 BC, the emperor Shen Nung compiled a pharmacopoeia that included details on ephedrine's origins and antimalarial drugs. Chaulmoogra fruit was known to Native American Indians, while emetine-containing ipecacuanha root was used in Brazil to cure diarrhea and amoebiasis. Indians from South America used coca leaves, which contain cocaine, and mushrooms, which contain methylated tryptamine, as hallucinogens. Herbs, including opium, squill, *Hyoscyamus*, poisons like viper toxin, and metallic medicines like copper and zinc ores, iron sulfate, and cadmium oxide were all available in ancient

Greek pharmacies. These ancient customs show the long history of harnessing natural resources for therapeutic, ceremonial, and medicinal purposes among various civilizations and geographical areas.

The fundamental disciplines of chemistry and physics underwent a profound change as the Greco-Roman age gave way to the Arabian alchemists' era, which lasted from the thirteenth to the sixteenth centuries. One notable figure from this era was Paracelsus (1493–1541), who was crucial in shaping the understanding of chemistry and medicine. In the nineteenth century, the great scientists Antoine Lavoisier, Adolph Kolbe (acetic acid synthesis, 1845), and Pierre Berthelot (methane synthesis, 1856) seed stage for organic chemistry. Friedrich Sertürner (Morphine isolation) and Pierre-Joseph Pelletier (emetine from ipecacuanha and other compounds like caffeine, quinine, and colchicine isolations) significantly contributed to the chemical world regarding phytochemistry, pharmacognosy of medicinal compounds from plants, microbes, and marine organisms. In the late nineteenth century, there was a prominent hype in the isolation of pure compounds from plants. Albert Niemann isolated and purified the substances which were used by William Withering, an English physician and botanist, in his experiments to reduce edema. These substances included digitalis, cocaine, and physostigmine. These discoveries made significant milestones in drug discovery, leading to the emergence of the pharmaceutical industry by the end of the nineteenth century (Newman and Cragg 2020a).

In the realm of diseases caused by protozoa and spirochetes, the development of synthetic chemotherapeutic agents gained momentum, particularly with the groundbreaking discovery of prontosil, a red dyestuff containing 2,4-diaminoazobenzene-4′-sulfonamide, by Gerhard Domagk. Prontosil effectively treated systemic Gram-positive bacterial infections. Additionally, the observation by Woods and Fildes in 1940 that sulfonamide-like drugs' bacteriostatic action could be countered by *p*-aminobenzoic acid illustrated the role of chemical structure in their function. Furthermore, the discovery of penicillin by Alexander Fleming in 1929, followed by its refinement by Howard Florey and Ernst Chain in 1941, ushered in a new era of water-soluble, highly potent, and less toxic antibacterial agents, fundamentally transforming medical practice (Neumeyer et al. 1997).

The proper drive for discovering natural and synthetic therapeutic agents started when it was realized that microbes brought on many infectious disorders. Significant developments in synthetic organic chemistry and biochemistry were made simultaneously with discoveries in medical microbiology, which gave the field of therapeutic agents more vigor. The natural antibiotic penicillin from *Penicillium notatum*, the semi-synthetic antibiotic tetracycline made from natural chlortetracycline elaborated by *Streptomyces aureofaciens*, and the anti-tubercular aminoglycoside streptomycin from *Streptomyces griseus* were all significant discoveries of the 1930s and 1940s. During this time, the significance of vitamins and the illnesses brought on by vitamin deficiencies were also revealed. In the ensuing decades, developments in X-ray crystallography, NMR spectroscopy, mass spectrometry, electrophoresis, ultracentrifugation, HPLC, and other technologies helped uncover more chemical compounds with therapeutic properties. They helped with some vaccine

development, including poliomyelitis vaccinations (Salk and Sabine), tranquilizers (such as Valium), and oral contraceptives (Dhont 2010).

1.4 Classical Drugs from Nature

The classical drugs have been derived/developed from natural sources such as plants and microorganisms, both terrestrial and marine. They include the following:

1. **Aspirin**: Salicylic acid was purified from willow bark, a natural remedy for pain and fever that has been used for thousands of years. Willow bark contains salicin, a natural compound with pain-relieving and anti-inflammatory properties. Greeks and Egyptians used willow bark preparations to alleviate various ailments, which continues in its avatar as aspirin as a solitary drug or in combination with other drugs (Ugurlucan et al. 2012).
2. **Morphine**: Morphine has a very long history and has played various roles. It has been used as a valuable medication for pain relief, with the potential danger of addiction and, hence, misuse. Still, its different forms remain potent modern medicines to manage severe pain of various origins, especially in cancer patients, post-surgery, or palliative care (Brook et al. 2017).
3. **Quinine**: Quinine is a natural alkaloid with a long history of antimalarial use. However, its use is limited today due to the development of more effective and safer antimalarial drugs like artemisinin and its side effects (Achan et al. 2011).

1.5 Modern Drugs from Nature

1. **Artemisinin**: Purified from *Artemisia annua*, a traditional Chinese medicine herb.
2. **Taxol:** Taxol was first purified from *Taxus brevifolia* (Pacific yew's bark), and later, it was found to be a product of an endophytic bacteria. Taxol binds to microtubules, prevents cell division, and arrests the growth of cancer cells; thus, it is anti-cancerous (Weaver 2014).
3. **Erythromycin**: Erythromycin is a macrolide, ribosome-binding antibiotic obtained from *Saccharopolyspora erythraea* (Cyphert et al. 2017).
4. **Penicillin**: Penicillin is one of the oldest antibiotics, obtained from *Penicillium chrysogenum* (Wiegand 2023).
5. **Digoxin**: Digoxin is used for treating heart failures and arrhythmias and is obtained from *Digitalis lanata*, a cardiac glycoside. It helps the heart work better (Grubb and Mentz 2020).
6. **Statins**: Statins obtained from *Aspergillus terreus* control atherosclerosis by lowering blood cholesterol. HMG-CoA-reductase is the target (Ramkumar et al. 2016).

7. **Tamoxifen**: Tamoxifen is a well-tolerated drug for treating primary and recurrent breast cancer (Brufsky and Dickler 2018).

Medicinal plants are the sources of many other critical active principles that have been approved as drugs that are not listed above. They are atropine (muscarinic antagonist), isolated from *Atropa belladonna*; caffeine, obtained from *Coffea arabica*; digoxin (Digitalis); and curare (muscle relaxant), isolated from the South American plant *Chondrodendron tomentosum*.

The global medicine market is worth about a trillion US dollars. About 35% of these medicines have natural products as their origins. It has been estimated that such medicines have been directly or indirectly sourced from plants (25%), microorganisms (13%), and animals (about 3%). They are used as follows:

(a) Directly as the source of therapeutic agents, such as drugs or herbal medicines
(b) A source of raw material for the development of complex, semi-synthetic drugs
(c) Scaffolds for the design of novel lead molecules
(d) Indicators or inspiration for the discovery of new drugs

About one-third of the pharmaceutical industry's revenue worldwide is from natural products or their derivatives. The Food and Drug Administration (FDA, USA) approved over 500 products between 1983 and 1994. It has been observed that there has been a decline in natural products getting approved as drugs for a long time (Li and Vederas 2009). In contrast to the earlier scenario, most new drugs have been generated from the secondary metabolites of plants or microorganisms. Pharmaceutical industry research into natural products has declined during the period 1990–2005 because of an emphasis on deviating from natural product research and moving on to high-throughput screening of synthetic libraries. It caused a substantial decline in new drug approvals, which caused a loss of patent protection for essential medicines. However, the fact remains that natural products or products derived from natural products form about 40% of them. About 60–80% of antibiotics and anticancer drugs are derived from natural products. Newman and Cragg (2016) assessed the natural products that got into the drugs approved by the FDA between 1/1981 and 9/2019. They found that in this period, the FDA approved 1562 drugs, 64 (4%) were unaltered natural products, 141 (9.1%) were botanical drugs (mixture), 320 (21%) were natural product derivatives, and 61 (4%) were synthetic drugs but with natural product pharmacophores (Newman and Cragg 2020b).

1.6 Targets of Drugs from Nature

Drug targets operate positively or negatively. They may operate at structural, transcriptional, translational, or functional levels. Their number in the human body cannot be exact, and it depends on the state of health, metabolism, or disease. A drug target is typically a specific biomolecule with which the "drug" interacts by which

the diseased state would be recovered or well-being is re-established. Many thousands of proteins or other biomolecules are potential drug targets. The treasure of drug targets is with a dynamic number of potential targets. Many thousands of proteins, receptors, enzymes, or other biomolecules are potential drug targets in the human system. The human genome project, completed in 2000, and the development in bioinformatics and next-generation sequencing have identified more than 40,000 potential genes of the human system. Its vastness is continuously expanding by the expanding knowledge of human physiology due to advancements in genomics, proteomics, and other scientific disciplines. No characteristic difference exists between the drug targets of naturally derived drugs or synthetically developed drugs. In other words, drug targets are defined by the disease physiology. It only means that the uniqueness of the drug target of a synthetic drug is only in the fact that a naturally derived drug molecule has not been found to date. A prospective finding of a naturally derived molecule exists when we consider the vastness of the secondary metabolites of plants or microorganisms. The innovativeness of novel drug target finding of unique synthetic drugs may be extended to exploring natural resources to procure naturally occurring, synthetic-drug-like molecules.

The targets of drugs, either the natural and their derived forms or synthetically made drugs, may be classified together in the following scheme. They are as follows:

Proteins: Most of the drug targets are proteins. Any functional or structural protein that gets deranged in disease, and if it has a critical role in health and could be structurally/functionally corrected by a natural or synthetic compound, that compound would be named a drug. The protein would be known as the drug target. There are many unique proteins in the human body, and many of these can function as drug targets. They are enzymes, receptors, transporters, transducers, and structural proteins.

Genes: There may be many thousands of genes, similar to their product proteins, which could serve as drug targets. Additionally, noncoding RNAs and other regulatory molecules that function with the DNAs are potential drug targets.

Cell signaling pathways: The proteins/signaling molecules are also potential drug targets. Such drugs break the signal transduction specific to disease conditions. These pathways may involve multiple proteins and interactions.

Targets specific to diseases: Drugs could be found regulating specific receptor molecules of the diseased state, like the receptors found in many cancers. In most cases, there will be differences between the healthy and diseased states in having or not having such receptors.

Personalized medicine targets: This depends on the individual molecular differences about the disease or healthy state. Such differences may be due to the individual differences governed by individual genetic differences. Ayurveda is the only medicine that targets personal traits for considering the specific treatment protocols. They call the category of individuals specific to various combinations of "tridosha" so that people could be categorized for prescribing specific drugs when there was no knowledge of genes. The categorization based on tridosha was quite scientific to categorize based on several observable features thousands of years ago. Now, it has been proven that Ayurvedic characterization of people has support of contemporary

scientific analyses. It needs to be considered that all proteins or genes may not be effective drug targets. In such cases, regulating relevant, disease-specific proteins and genes must be left untouched. The following are some examples of human drug targets and the drugs derived from nature that target them.

Acetylcholinesterase is the target of the drug, galantamine derived from the snowdrop plant. It is used to treat Alzheimer's disease by inhibiting the breakdown of acetylcholine.

HMG-CoA-reductase: Statins (obtained from red yeast rice) are used to lower cholesterol levels. Inhibition of HMG-CoA-reductase means the inhibition of cholesterol synthesis. The drug lovastatin or other statins need to be administered in a controlled manner since the cholesterol synthesis cannot be shut down.

Opioid receptors: One of the most ancient drugs from nature, morphine (from the poppy plant), and its derivatives act on opioid receptors of the brain to relieve pain. However, morphine is not good to continue to use for long due to its addictive characteristics. It is a great relief to patients in trauma and palliative care.

Cannabinoid receptors: The blockage of these receptors would result in pain relief, as in the case of morphine, though not to that extent. Cannabidiol and tetrahydrocannabinol from the cannabis plant have various therapeutic uses since they suppress the cannabinoid receptors. Cannabidiol is given for pain management and seizure control. Tetrahydrocannabinol is applied for psychoactive effects.

Microtubules: Taxol (derived from Pacific yew tree endophyte), a chemotherapeutic agent, inhibits microtubule depolymerization, disrupts cell division, and arrests growing cells fast. Hence, it inhibits cancer growth.

Topoisomerases: Camptothecin (from the *Camptotheca* tree) and its derivatives inhibit topoisomerases and DNA replication enzymes, are used in cancer therapy.

Dihydrofolate reductase: Bio-derived methotrexate inhibits the enzyme dihydrofolate reductase to arrest the formation of tetrahydrofolate and nucleic acid synthesis.

Proinflammatory enzymes: Phospholipase A2, cyclooxygenase, lipoxygenase, and trypsin are inhibited by aspirin and many other bio-derived compounds to act as anti-inflammatory.

The following are some other natural drugs and their targets in humans. They are digitalis (sodium-potassium pump in cardiac cells), ephedrine (adrenergic receptors), atropine (muscarinic acetylcholine receptors), quercetin (various receptors involved in inflammation), curcumin (multiple molecular targets and inflammatory and transcription factors), and resveratrol from grapes giving red wine and red wine (various signaling pathways). Certain drugs are administered into the human body for which targets may be alien. Such drugs are directed to targets of pathogens like bacteria, fungi, or other organisms. Artemisinin, quinine (both with targets in *Plasmodium*, causing malaria), and penicillin (various bacteria) are directed to non-human targets. All the drugs directed to pathogens are of this class, with no drug target in humans. Their binding to human structures may appear as side effects of drugs.

The above examples show how nature has been used as a source of valuable compounds that target biomolecules in the human body as drug targets. The

contextual consideration is that the unidentified drug targets in the human system form a massive fold of the identified drug targets. It is relevant when poly drugs and polyherbal drugs are considered. The concept and practice of poly drugs are firmly rooted. As the term suggests, polydrugs are a combination of drugs that can act in tandem on several drug targets. However, the combination drugs should act toward the same goal, and they may act synergistically. Although this system of poly drugs appears novel to modern medicine, it need not be considered novel. The traditional medicines, more rigorously in Ayurveda, have poly-herbal drugs, which are supposed to operate in the same way as the drugs are supposed to do. The poly-herbal drugs will have many drug compounds that would act upon many targets. From millennia of clinical experience and therapeutic results, herbal drugs existed with traditional medicines and continued to serve positive results.

1.7 Drug-Target Assay Systems

The interaction between the drug and its target needs to be assayed to understand its mechanisms of action and identify potential off-target effects or toxicities. Interaction testing is essential for small molecules or biologicals. This system is critical in drug discovery and development. Such assay systems evaluate the interaction between candidate drug compounds and their specific molecular targets, such as proteins, enzymes, receptors, or nucleic acids. The drug targets may beat different loci in the cells. These assays help researchers identify and characterize drug candidates. It also helps determine their efficacy and safety profiles. Drug-target assay systems are suitably designed to the specific characteristics of the drug target. It should also be specific to the disease being studied so that the testing can prove that recovery from the disease or amelioration of disease symptoms is due to the administration of the candidate drug. They may be used to identify lead compounds. They are essential for optimizing drug candidates and ensuring their safety and efficacy. Such tests will be conducted before candidate drugs are proposed to proceed with clinical trials.

The following are some standard drug-target assay systems.

1.7.1 Enzyme Assays

Enzyme inhibition assays: The assay assesses drug candidates' ability to inhibit specific enzyme activity. These data are crucial for identifying the enzyme inhibitors as drug candidates.

1.7.2 Enzyme Kinetics Assays

The assay for collecting enzyme kinetics data determines the kinetic parameters of enzyme–substrate interactions in the presence of drugs. They provide insights into the mechanism of action of the drug.

1. **Binding assays:** The two types of binding assays are receptor binding assays and assays to measure the interaction between drug candidates and specific biomolecules, such as DNA or RNA. These assays are significant for the assessment in areas like anticancer drug development to have any indication of probable side effects. Since the antimicrobial drug targets mainly belong to the microbe, the binding assays with the biomolecules of the host system are crucial.
2. **Binding kinetic assays:**

   Radio ligand binding assays: These assays use a radio-labeled ligand to measure the binding affinity between a drug candidate and its target receptor. This assay helps determine the drug's binding kinetics and affinity constants.

   Fluorescence-based binding assays: Fluorescent labels are attached to either the drug candidate or the target molecule. Changes in fluorescence signal upon binding are used to quantify binding affinity.

   Surface plasmon resonance assay: Surface plasmon resonance measuring assesses the changes in refractive index near a sensor surface when molecules bind. It is widely used to study drug–protein interactions in real-time. Isothermal titration calorimetry would also give similar, real-time data.
3. **Cell-based assays:**

   Gene assays: Gene assays use genetically modified cells that express a reporter gene when a drug binds to its target receptor. It allows for high-throughput screening of drug candidates.

   Viability assays: Cell viability assays are for measuring the effect of a drug on cell viability, helping to assess drug toxicity and potential side effects.
4. **Ion-channel assays:** Drugs targeting ion channels in the heart tissue or the nervous system are evaluated using ion-channel assays. These assays measure changes in ion flow across the cell membrane in response to the exposure of drug candidates. These assays may be done concurrently with electrophysiology assays.
5. **Biomarker assays:** They identify and measure specific biological markers associated with diseases or drug responses. They play a crucial role in personalized medicine and drug development since they are highly affected by mutations.
6. **Functional assays:**

   Electrophysiology assays: Electrophysiology assays measure changes in ion currents across cell membranes in response to drug–receptor interactions. They are often used for studying ion channel targets.

   Radio-labeled ligand uptake assay: It assesses the drug's ability to affect the uptake of radio-labeled ligands by cells expressing the target receptor.
7. **Proteomics and genomics assays:**

Proteomics assay: Proteomics study is performed with mass spectrometry and other proteomics techniques to monitor protein expression changes and post-translational modifications in response to drug administration.

RNA sequencing: It can be used to analyze changes in gene expression in response to drug treatment to elucidate mechanisms of drug action.

8. **High-throughput screening assays**: These assays are designed for rapid testing to quickly assess thousands to millions of compounds for their potential drug nature.
9. **Organoid models:** 3D cell cultures and organoids mimic the in vivo environment better than traditional 2D cell cultures, providing more physiologically relevant data in drug–target interaction studies.
10. **Animal models:** Disease-animal models assess drug action and toxicity in vivo.
11. **In silico models**: Computer-based simulation studies are inexpensive, and avoidable cruelty toward animals is minimized. Such studies may indicate the results of wet lab experiments.

1.8 Prospects of Natural Drug Leads

Anti-infective, anti-tumor, and anti-metabolic diseases are the main categories of drugs into which naturally derived drug leads have contributed immensely. Newman and Cragg (2020b) produced a remarkable review of the products as a source of new drugs over the nearly four decades in the immediate past. Their sixth review on natural products appeared in the *Journal of Natural Products* in 1997, 2003, 2007, 2012, and 2016 (Cragg et al. 1997; Newman et al. 2003; Newman and Cragg 2007, 2012, 2016). All these reviews appeared in the same journal, with almost the same title, having only variations of the review period. Their review has shown that natural products have got into almost all areas of different lines of medicines and types of diseases. However, the review shows that no drugs from natural products are found in specific disease areas for which no drugs derived from natural products are found. Combinatorial chemistry techniques have succeeded as methods of optimizing structures. However, only two de novo combinatorial compounds have been approved as drugs. All other synthetic compounds that got drug approval were only for modifications of approved drugs. It means the natural products or their derived forms rule the roost of the drug approval scenario. Presently, many natural product drugs/leads are produced by microbes (Newman and Cragg 2020a). Many microbial products approved as drugs are from endophytic or epiphytic microbes. It has been found that Lipinski's rule of five is violated by 50% of the drugs based on natural products that got approval in the previous decades (Koehn 2012).

A few decades ago, it was speculated that the number of new natural product-derived drugs could go to zero. It was mainly from the viewpoint of the pharmaceutical industry based on the profit they could make. However, this may be temporary by disproving the potential for discoveries in the long term. Developments in scientific methods may charter new vistas and methods by fully enabling metagenomics

for unculturable organisms to facilitate hitherto unknown natural resources. Hence, the number of biosynthetic products and enzymes remaining to be examined would be huge. Even with the recent advances in scientific methodologies, including various omics, the data of natural products still needs to be completed. Systems biology will predict the likely metabolism for novel species procured from metagenomic-empowered methods. Network pharmacology would be a handy tool to propose novel drug leads, as proposed by Hopkins (2007, 2008). Such a library of biochemical transformations could be an excellent tool for designing and generating new products. Synthetic biologists can utilize the vast array of novel metabolites and bio-reagents to make complex molecules rationally. Future with more research methods, both experimental and computational, may facilitate more overall and more accurate data to enable drug discovery. Hence, personalized medicine may enter into an individual's DNA sequence as a basis for drug selection. It would lead to the present expectations of the future that high levels of safety could be achieved by predicting side effects and proposing the correct method to give a choice of therapeutic drugs.

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Chapter 2
The Process of Drug Development from Natural Sources

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Abstract The history of drug discovery and development is deeply knotted with human civilization. Early humans, driven by curiosity and the need for survival, closely observed nature. They not only identified plants for food and nutrition but also recognized those with medicinal, toxic, or harmful properties. For a long time, natural products have been the go-to for developing new medicines. There are a number of known methods for locating natural medications. Significant breakthroughs in medicinal research have come from natural ingredients, with much of the information about their medicinal characteristics coming from traditional and indigenous drugs. Because of the possibility of adverse reactions and other peculiarities, medicinal plants have inspired scientists to develop novel smaller molecules. This chapter places the significance of pharmacology within the context of contemporary methodologies utilized in the process of discovering and developing drugs. In addition, drug development methodologies, application of computational chemistry principles, and modern techniques utilized for structural elucidation are discussed.

Keywords Bioprospecting · Reverse pharmacology · Ethnobotany · Mass spectrometry · HPLC

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M. Haridas et al. (eds.), *Drugs from Nature: Targets, Assay Systems and Leads*,
https://doi.org/10.1007/978-981-99-9183-9_2

2.1 Introduction

Fundamental needs of mankind such as food, shelter, clothing, and medicines have always been counted on natural resources. The basis of traditional medical practices is built on plant resources over thousands of years. The earliest records of plant-derived medical practices date back to 2600 BC in Mesopotamia. They were known to use nearly thousands of plant derivatives from cedar, licorice, poppy, etc. The majority of them still find their usage during current holistic medical practices for the treatment of inflammations and infections. "Ebers Papyrus" written in 1550 BC documents nearly seven hundred formulations of ancient Egyptian medical practices. Most among them were plant origins, although some animal-origin medications were also documented. Another ancient medical tradition with well-documented origins includes Chinese Materia Medica, tracing its roots to around 1100 BC, and the Indian Ayurvedic system, which dates back to approximately 1000 BC. Most of these practices as discussed were laid upon the foundations of natural resources such as plants. WHO estimates that roughly 80% of the global population depends on conventional medical practices for primary healthcare (Newman et al. 2000). However, the remaining 20% also depend on plant-derived chemical entities or natural products as active constituents of their drug formations (Newman et al. 2000).

Natural products (NPs) encompass a vast array of chemically diverse compounds, exhibiting a wide range of biological activities, and have been extensively utilized in various fields, including human and veterinary medicine, as well as agriculture (Demain 2014; Newman and Cragg 2012). They may originate from microbial sources such as bacteria and fungi, plants, animals, and even marine creatures. The exploration of secondary metabolites sourced from plants can be traced back to 1806 when Friedrich Wilhelm Sertürner isolated morphine (referred to as *principium somniferum*) from the plant *Papaver somniferum*. This pivotal discovery, demonstrating that the potent component of a plant-based medicine could be isolated and pharmacological characteristics might be attributed to a single chemical compound, marked the inception of natural product chemistry (Hartmann 2007). Subsequently, there was a rapid succession of isolating various active compounds from plants. Quinine was extracted from the cinchona tree bark in 1820 and became the standard treatment for malaria (Rosenthal 2001). Nicotine, the principal alkaloid in tobacco leaves, was first isolated from the tobacco plant in 1828 (Zhang et al. 2020). Along with the separation techniques of active compounds from natural products progresses, structural identification became a new direction for finding drugs from natural products. Robert B. Woodward introduced Woodward's rules for determining molecular structure by ultraviolet spectroscopy during 1940s. The molecular structure of penicillin was revealed in 1945 followed by many natural products such as quinine and vitamin B_{12} (Seeman 2017). The swiftness with which this field progressed significantly influenced and guided significant realms of organic chemistry. The process of drug discovery and development advances through multiple stages, as illustrated in Fig. 2.1.