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Review

Natural Products as a Resource for New Drugs

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Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural products. The aim of this review is to provide an overview of the continuing central role of natural products in the discovery and development of new pharmaceuticals. In this context, selected examples of important natural product-derived drugs are cited, focusing on some of the most recent introductions to the clinical setting, and a brief overview of some of the important recent developments and remaining challenges in the process of discovering and developing bioactive natural products is provided. Interest in natural products research is strong and can be attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structures and biological activities of naturally occurring secondary metabolites, the utility of bioactive natural products as biochemical and molecular probes, the development of novel and sensitive techniques to detect biologically active natural products, improved techniques to isolate, purify, and structurally characterize these active constituents, and advances in solving the demand for supply of complex natural products. Opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products are discussed.

INTRODUCTION

Quinine, theophylline, penicillin G, morphine, paclitaxel, digoxin, vincristine, doxorubicin, cyclosporin, and vitamin A all share two important characteristics: they are cornerstones of modern pharmaceutical care and they are all natural products. Many other similar examples could be cited. The use of natural substances, particularly plants, to control diseases is a centuries old practice that has led to the discovery of more than half of all "modern" pharmaceuticals (1). Documentation of the use of natural substances for medicinal purposes can be found as far back as 78 A.D., when Dioscorides wrote "De Materia Medica", describing thousands of medicinal plants (2). This treatise included descriptions of many medicinal plants that remain important in modern medicine, not because they continue to be used as crude drug preparations, but because they serve as the source of important pure chemicals that have become mainstays of modern therapy. Tyler, Brady, and Robbers (2) wrote that the term "*materia medica (meaning medicinal materials) was synonymous with the substances and products derived from natural sources and employed by the physicians of that era.*" While the term "materia medica" is no longer utilized routinely in Western medicine, the fact remains that the physicians of today continue to use many substances and products derived from natural sources, usually for the same therapeutic benefit as the original crude drug. These single chemical entities, i.e., drugs, form the basis for much of our ability to control disease. While there have been several waves of interest in Pharmacognosy/Natural Products Chemistry, research activity is stronger now than perhaps at any other time. This level of interest can be attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structures and biological activities of naturally occurring secondary metabolites, the utility of novel bioactive natural products as biochemical probes, the development of novel and sensitive techniques to detect biologically active natural products, improved techniques to isolate, purify, and structurally characterize these active constituents, and advances in solving the demand for supply of complex natural products.

This is not intended to be an exhaustive review of natural product-derived pharmaceuticals, but rather is aimed at providing brief overviews of the continuing central role of natural products in the discovery and development of new pharmaceuticals, and advancements in the detection, isolation, characterization, and development of bioactive natural products. In this context, selected examples of important natural product-derived drugs will be cited, focusing on some of the most recent introductions to the clinical setting, and some of the important recent developments (and remaining challenges) in the process of discovering and developing bioactive natural products will be discussed.

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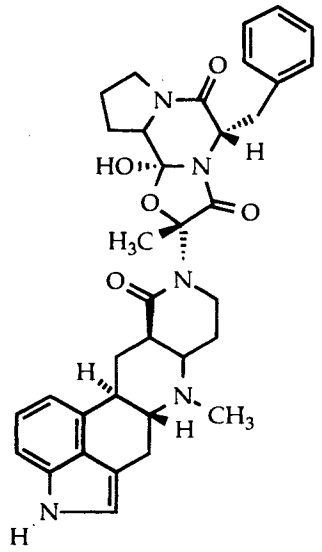
IMPORTANT NATURAL PRODUCT-DERIVED PHARMACEUTICALS

Although the use of plant and animal products to control disease has been well documented for centuries, the biochemical basis for observed efficacies did not come under careful scientific scrutiny until the 18th and 19th centuries, particularly in the early to mid 1800's when a number of important, pharmacologically active natural products such as the cardiac glycosides and a variety of bioactive alkaloids (e.g., morphine, atropine, reserpine, and physostigmine) were discovered. Many of these biologically active natural products became important not only for their use directly as therapeutic agents or as prototype lead compounds for the development of new drugs, but also as biochemical probes to unravel the principles of human pharmacology, a role for natural products which continues today.

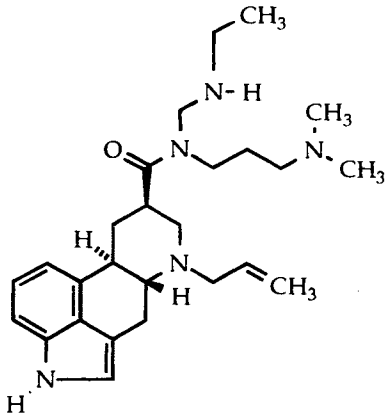
Cardiovascular Drugs

The positive benefits of extracts of two species of *Digitalis* (*purpurea* (Foxglove) and *lanata*) were recognized long before the active constituents were isolated and characterized structurally. The cardiac glycosides, which include digoxin, digitoxin, and deslanoside, exert a powerful and selective positive inotropic action on the cardiac muscle. Digoxin is still produced by mass cultivation and extraction of a strain of foxglove (*Digitalis purpurea*) that has been selected for maximum production of the bioactive glycosides (2). In addition to the cardiac glycosides, a number of naturally-occurring alkaloids are important drugs in the control of various cardiovascular conditions. For example, quinidine, isolated from the bark of the *Cinchona* tree, is an important anti-arrhythmic drug, and was also one of the earliest and most well known examples of the critical role of chirality in drug action. Its diastereoisomer, quinine, has virtually no cardiac activity, but was recognized as one of the first anti-infective agents due to its efficacy against malaria. Other important naturally occurring alkaloids active as cardiovascular drugs include reserpine, once one of the most useful antihypertensive agents known, and papaverine, a non-narcotic peripheral vasodilator. In addition, theophylline, a xanthine alkaloid, is an important bronchodilator used to control asthma in children. Ergotamine, an Ergot alkaloid obtained from a fungus that infects rye grass, is an important central vasoconstrictor that is used therapeutically to treat migraine headaches. One of the newest additions to this class of drugs is the dopamine D_2 receptor agonist, cabergoline, launched in Belgium in 1993 as an antiprolactin. This drug is also being evaluated as a potential therapy for Parkinson's disease and as an anticancer agent for the treatment of breast cancer (3).

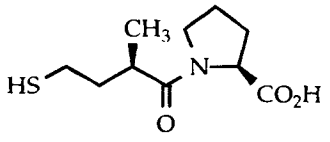
The discovery of the pharmacological effects of components of the venom of the pit viper (*Bothrops jararaca*) ultimately led to the discovery of the role of angiotensin converting enzyme (ACE) in hypertension (4–6). As a result, teprotide, a specific ACE inhibitor, was discovered and a model system for the interaction of small peptides with the enzyme was developed (7). Ultimately, captopril was designed as a specific, orally effective ACE inhibitor and was introduced to the market in 1981 for the control of hypertension (7). The success and utility of captopril led to the design and synthesis of additional ACE inhibitors, such as enapronil. The ACE inhibitors constitute an important class of drugs that has had a major role in the management of cardiovascular disease (8).



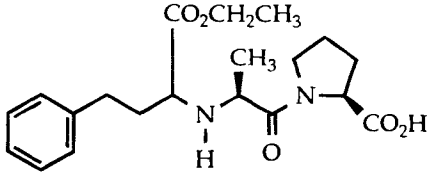
Ergotamine



Cabergoline



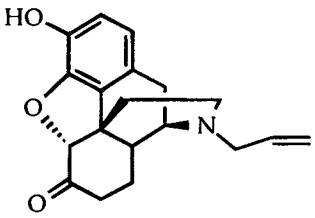
Captopril



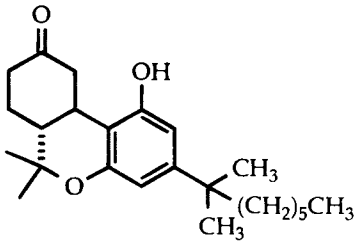
Enalapril

CNS Drugs

One of the most cited examples of important natural product-derived drugs is the neuromuscular blocker, *d*-tubocurarine, derived from the South American plant, curare, which was used by South American Indians as an arrow poison (2). Tubocurarine led to the development of decamethonium, which, although structurally dissimilar to tubocurarine, was synthesized nevertheless based on the presumption at the time that tubocurarine contained two quaternary nitrogens (9). Likewise, the synthetic local anesthetics such as lidocaine, benzocaine, and dibucaine, were synthesized to mimic the nerve blocking activity of cocaine, a natural alkaloid obtained from the leaves of *Coca eroxylum,* but without the adverse side effects that have led to the abuse of cocaine (2). The opium alkaloids, codeine and morphine, served as models for the synthesis of naloxone, an important analog used to treat and diagnose opiate addicts (8), and also led to the discovery of "endogenous opioids" (enkephalins and endorphins). Similarly, delta-9-tetrahydrocannibinol (THC), the component of *Cannibas sativa* responsible for the CNS effects, has also been found to reduce nausea associated with cancer chemotherapy. As a result, efforts to design semi-synthetic or synthetic agents that mimic the desirable anti-emetic effects, while reducing the CNS effects of THC, led to the development and introduction of nabilone as an anti-emetic (8). Although nabilone retains some of the less desirable effects of THC, it is an effective anti-emetic that is widely used.



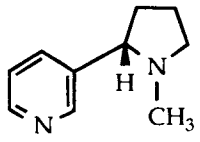
Naloxone



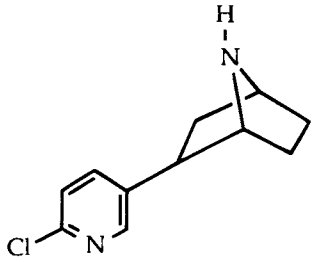
Nabilone

Recently, the recognition of the possibility that a number of vastly different CNS and peripheral nervous system diseases may be therapeutically controlled by selective nicotinic acetycholine receptors (nAChR) agonists has opened a new area of drug design based on the nicotine molecule. Disorders such as Alzheimer's disease, Tourette's syndrome, Parkinson's disease, as well as other cognitive and attention disorders may ultimately be more effectively treated if agonists specific for certain subtypes of nAChRs can be discovered or designed. The characterization and understanding of these receptors was based largely on studies using agonists or antagonists, most of which are natural products, such as acetylcholine, arecoline, anabasine, lobeline, and methyllycaconitine. Recently, reports that the nicotine analog epibatidine, isolated from the skin of poisonous frogs, exhibits exceptional analgesic activity and is a very potent nAChR agonist have led to a number of synthetic studies on this molecule, including the synthesis of both pure enantiomers and the remarkable discovery that both enantiomers are very active (10). While the toxicity of this compound probably precludes its development as a therapeutic agent, SAR studies are likely to be undertaken in an effort to separate its toxic from analgesic effects.

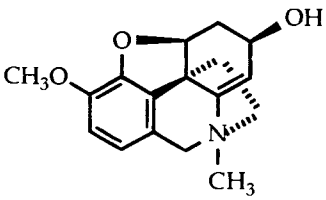
Physostigmine, a naturally-occurring alkaloid, and its carbamate ester, neostigmine are also important acetylcholinesterase inhibitors. The cholinesterase inhibitors are used for the treatment of myasthenia gravis and as antagonists to neuromuscular blockade by nondepolarizing blocking agents. The acetylcholinesterase inhibitor, galanthamine is an alkaloid that occurs in the bulbs of daffodils, and is currently being investigated as a possible therapy for cognitive impairment in Alzheimer's disease (11).



Nicotine



Epibatidine



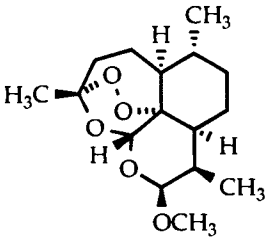
Galanthamine

Anti-infectives

There can be no argument that the antibiotics are among the most important classes of therapeutic agents and have had enormous impact on both life expectancy and quality of life. With the discovery of the natural penicillins as secondary metabolites of species of the fungus *Penicillium,* the course of medical history was dramatically changed and the antibiotic era was introduced. Antibiotics are, by definition, natural products or derivatives of natural products. During the course of some 50 years that followed Alexander Fleming's observations and the subsequent isolation and characterization of the active constituent by Howard Florey and Ernst Chain, hundreds of antibiotics have been isolated from scores of microorganisms (12). On average, two or three new antibiotics are launched each year. Not only do these antibiotics serve as important drugs, but explorations into the mechanisms by which these natural products exert their action have led to an understanding of the biology of the target pathogens that would not likely have been possible without these important biochemical probes. With advances in molecular biology, similar advances in the utilization of natural products to probe specific molecular targets in the pathogens are also being made.

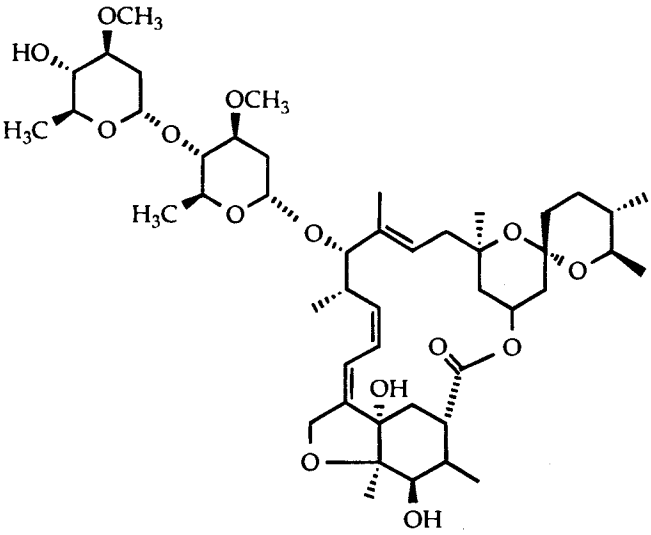
The discovery of important anti-infectives is not limited to antibacterial or antifungal antibiotics from microbial sources. Long before the discovery of penicillin, native Amerindians knew that the bark of the South American "fever tree" *Cinchona succiruba,* was effective in controlling malaria (2). Quinine was ultimately identified as the active antimalarial constituent of the *Cinchona* bark. When the natural source of quinine was threatened during World Wars I & II, massive programs to synthesize multitudes of quinoline derivatives based on the quinine prototype ensued. In fact, it could be said that this effort, if not responsible for the origination, was at the very least a major contributor to the early growth of the discipline of Medicinal Chemistry, which was founded in the synthesis of biologically active compounds modeled after natural products. From this intensive effort emerged the two drugs that remained the therapeutic standards for the treatment of malaria until the past decade: primaquine and chloroquine.

Today, new important anti-infectives are being discovered from microbial, plant, and animal sources. For example, the antimalarial agent, artemisinin, was isolated from the Chinese medicinal plant, *Artemisia annua.* Commonly known as Qinghaosu, this herbal remedy had been used in China for centuries for the treatment of malaria. In 1972, the active constituent was isolated and identified as the sesquiterpene endoperoxide artemisinin. This compound, in addition to having a structure very different from any of the known antimalarial agents (i.e., quinolines), also exhibits antimalarial and pharmacological profiles very different from the clinically useful agents. Specifically, with activity against strains of the parasite that had become resistant to conventional chloroquine therapy and the ability, due to its lipophilic structure, to cross the blood brain barrier, it was particularly effective for the deadly cerebral malaria. For this reason, several major programs were undertaken to produce artemisinin derivatives with more desirable pharmaceutical properties, and much has been published on synthetic and semisynthetic studies, microbial transformations, biological evaluations, mechanism of action studies, and pharmacological profiles of artemisinin and related analogs (13–15). From these studies has emerged artemether, a derivative that is currently approved for the treatment of malaria in much of the world.



Artemether

Another important class of anti-infective natural products to be introduced for human use in recent years are the avermectins, polyketide derived macrolides that were originally isolated from several species of *Streptomyces* (16). The major drug of this class, ivermectin, was originally developed to treat and control nematodes and parasites of livestock. In recent years, however, ivermectin's potential for the treatment of human disease has also been realized, and it is now used to treat onchocerciasis (river blindness) (17,18), a disease that afflicts 40 million people worldwide (19).



Ivermectin

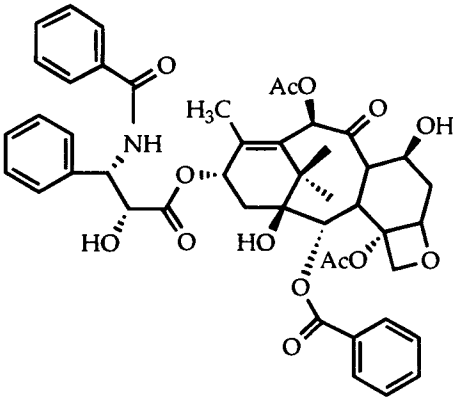
Anticancer

Another therapeutic area where natural products have had a major impact on longevity and quality of life is in the chemotherapy of cancer. In fact, most of the major anticancer drugs are natural products from plants or microorganisms (20). Examples include such important anticancer drugs as bleomycin, doxorubicin, daunorubicin, vincristine, vinblastine, mitomycin, streptozocin, and now, the recent additions of paclitaxel (Taxol™), ironotecan (a camptothecin derivative), and etoposide and tenoposide (podophyllotoxin derivatives).

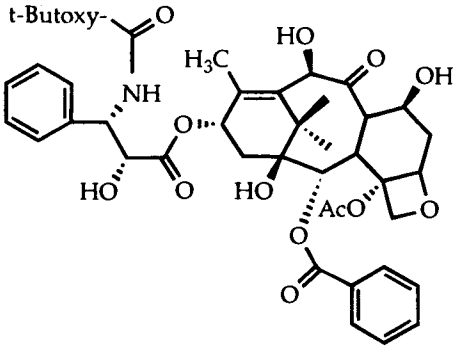
The observation that fractions of the rosey periwinkle, *Catharanthus rosea,* produced severe leukopenia in rats led Gordon Svoboda and his coworkers at Eli Lilly to isolate and develop the two major anticancer drugs vincristine and vinblastine. These two complex, dimeric indole-indoline alkaloids are important therapies for the treatment of acute childhood leukemia (vincristine), Hodgkin's disease (vinblastine) and metastatic testicular tumors (vinblastine), and continue to be manufactured today by mass cultivation and processing of the natural source (2).

Over 40 years ago, the National Cancer Institute initiated a program to explore higher plants as a source of anticancer agents. Although this program went through periods of low productivity and little support, the discovery of one of the most exciting new drugs in recent history, paclitaxel (Taxol®), was a direct result of this effort. This compound, as well as most other anticancer drugs, was discovered using a system of screening large numbers of extracts of plants, microorganisms, and, more recently, marine organisms, for inhibition of cancer cells grown in culture. Recently, a comprehensive account of the discovery and development of paclitaxel was published by the two pioneering natural products chemists who discovered this compound, Monroe Wall and Mansukh Wani (21). Although it took some 15 years for the true benefit of paclitaxel to be fully realized (perhaps a testament, in part, to the unique challenges and difficulties academic/nonindustrial scientists face in drug development), it was approved for the treatment of ovarian

cancer in 1992 and for breast cancer in 1993. Although the total synthesis of paclitaxel has been reported, this drug is a complex natural product with many asymmetric centers and not readily amenable to total synthesis on an economical basis. Although a semisynthetic derivative with improved water solubility, Taxotere™, is now available, the unaltered natural product is approved and used clinically. Studies on the mechanism of anticancer action by paclitaxel revealed that it blocks depolymerization of microtubules (22). Since Taxol™ is the only known compound to exhibit this activity, without its discovery and development this new target for anticancer drug discovery and development would likely not have been identified.

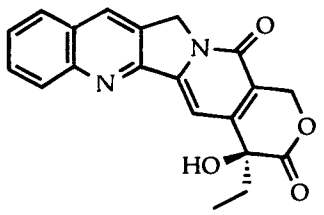


Paclitaxel

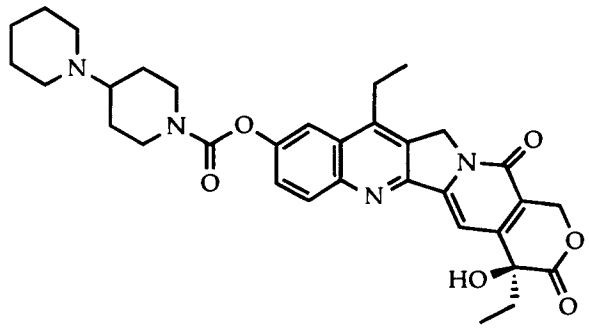


Taxotere™

Another important plant-derived anticancer natural product isolated and identified by Wall and Wani is camptothecin, an alkaloid from the Chinese tree, *Camptotheca acuminata* Descne (23). A semisynthetic water soluble derivative of camptothecin known as Ironotecan (Topotecin™, Campto™) was introduced in Japan in 1994 for the treatment of lung, ovarian, and cervical cancers (10). Unlike Taxol™, camptothecin acts by inhibition of the enzyme topoisomerase I.

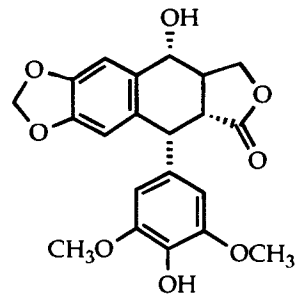


Camptothecin

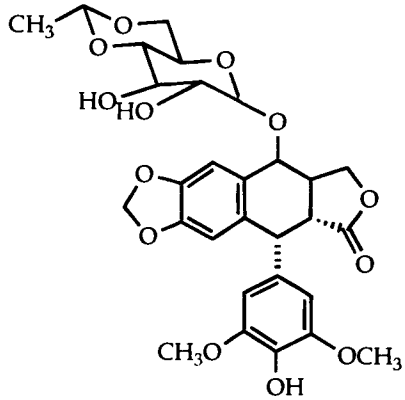


Ironotecan

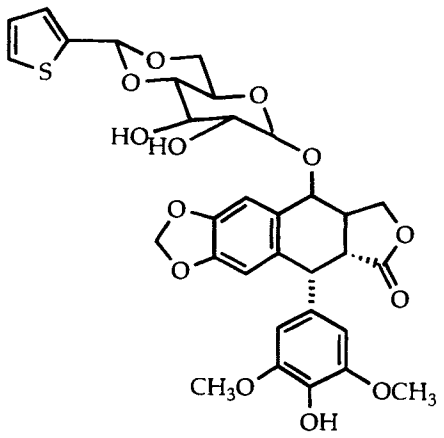
Two important recent additions to the cancer chemotherapeutic arsenal are etoposide and tenoposide (24). *Podophyllum peltatum,* used for years as a folk remedy, is the source of podophyllin, a crude resin used topically to treat condylamata acuminata. Podophyllin contains, among other things, the lignan, podophyllotoxin. Studies directed at preparing a water soluble derivative of podophyllotoxin ultimately led to the discovery of a minor, but very active, constituent of the podophyllin resin, 4′-desmethoxy-1-epipodophyllotoxin glucoside (25). The ability to produce this minor, naturally occurring compound by semisynthetic modification of the more abundant podophyllotoxin was a breakthrough that allowed the preparation and evaluation of a number of analogs, some of which had extraordinary activity. Two of these analogs, etoposide and tenoposide were introduced as anticancer drugs in 1983 and 1992, respectively. Theses compounds act by a mechanism (topoisomerase II inhibitors) different from that of podophyllotoxin (spindle poison), illustrating that structural similarity alone is not always a reliable predictor of similar biological effect. Buss and Waigh (26) give a very nice historical account of the discovery and development of these compounds, as well as many other natural-product derived drugs.



Podophyllotoxin



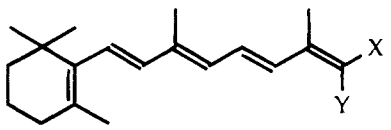
Etoposide



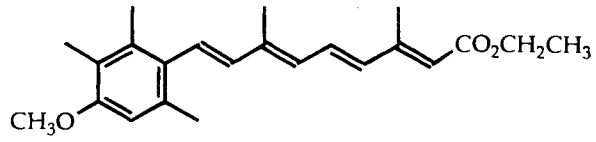
Teniposide

Paclitaxel, camptothecin, vincristine, vinblastine, as well as other compounds currently under development as potential anticancer drugs (i.e., the bryostatins, isolated from marine dinoflagellates, 27) were discovered as result of a broad-based screening program to identify, using a whole cell inhibition assay, natural products that are active against a battery of representative cancer cell lines. The relative merits of this approach and the mechanism-based assay approach that has gained popularity in recent years will be discussed later.

A final example of the importance of natural product drug discovery and development to advances in the chemotherapy of cancer is the growing body of evidence that the retinoids, derived from vitamin A (retinol), may have potential utility in the treatment of cancer. Although several retinoids are already used clinically, i.e., all-*trans*-retinoic acid (ATRA, Retin A™) and 13-*cis*-retinoic acid (13-*cis* RA, Accutane™) are used for the treatment acne and the synthetic analog, etretinate (Tegison™), is used for the treatment of severe psoriasis, it has recently been recognized that these compounds may have significant potential in cancer chemotherapy. Although each of these drugs suffers from significant side effects that diminish its utility, it has been shown that the retinoids exert both their therapeutic and adverse effects through activation of retinoid receptors, for which there are several subtypes (28,29). This data, when coupled with synthetic accessibility, suggest that synthetic retinoids based on the naturally occurring prototypes may be prepared that are more selective for specific receptor subtypes, thus offering the hope of separating the beneficial effects from the undesirable effects. Increasing evidence supports the potential benefit of retinoids in the therapy of cancer and prevention of carcinogenesis, primarily as a result of their ability to regulate cellular growth and differentiation. All-*trans*-retinoic acid, 13-*cis*-retinoic acid, etritinate, and fenretinide have undergone human clinical trials, with varying levels of response (30).



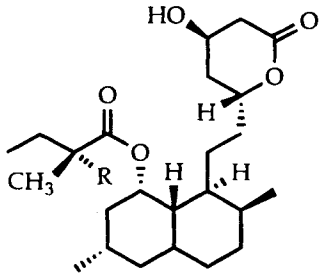
Retinol: X = CH_2OH, Y = H
ATRA: X = CO_2H, Y = H
13-*cis* RA: X = H, Y = CO_2H
Fenretinide: X = CONH-(*p*-hydroxyphenyl); Y = H



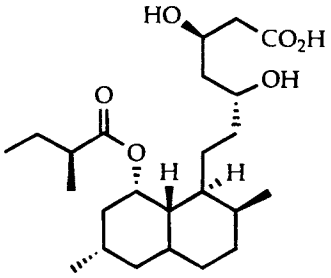
Etritinate

Cholesterol-Lowering Agents [Hypolipaemics]

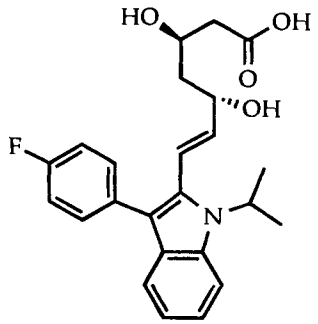
Some of the most exciting natural products discovered in recent years are the cholesterol-lowering agents derived from fungi. These drugs act by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), an enzyme critical in the biosynthesis of cholesterol. The first of the HMG-CoA reductase inhibitors were isolated from *Penicillium* sp. (31,32). Compactin, from *P. brevicompactin,* was first reported as an antifungal agent (32). With the recognition of the mechanism of action of compactin came a search for other naturally occurring HMG-CoA reductase inhibitors that led to the discovery of lovastatin, a secondary metabolite of the fungus *Aspergillus terreus* (33). Although lovastatin was introduced to the market in 1989, many studies were undertaken to prepare improved analogs and led to the development of simvastatin (launched 1991), privastatin (1991), and fluvastatin (1993).



Lovastatin, R = H
Simvastatin, R = CH_3



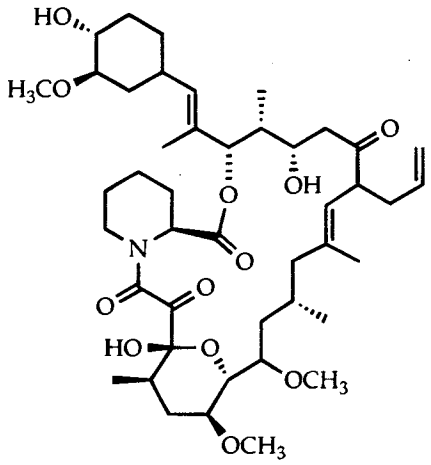
Pravastatin



Fluvastatin

Immunomodulators

The immunomodulator, cyclosporin, was originally isolated from a soil fungus, *Trichoderma polysporum* (34). This compound was a major breakthrough for organ transplantation, since it suppressed immunological rejection of the transplanted organ. Recently, Tacrolimus (FK-506), a secondary metabolite of *Streptomyces tsukabaensis,* was approved in 1994 for use as an immunosuppressant in organ transplantation (3).



Tacrolimus (FK 506)

NEW USES FOR "OLD" DRUGS

It should also be continually recognized and emphasized that as we acquire additional experience with known drugs, it often occurs that new uses for existing agents are identified. For example, it has been shown in recent years that the combination of the antibacterial antibiotic clindamycin (used clinically for years for its relatively narrow spectrum of activity against important gram-positive bacteria and anaerobes) and the antimalarial 8-aminoquinoline primaquine (synthesized after the quinine model) is effective in the treatment of the important AIDS-related opportunistic infection *Pneumocystis carinii* pneumonia (35). This combination therapy is currently undergoing clinical trials for the treatment of AIDS-related PCP, and demonstrates the importance of continuing to explore older, known drugs for new therapeutic applications. The original therapeutic utility of an agent may be expanded as new disease states are recognized and as experience with an agent affords more empirical observations upon which to base recommendations for such new therapeutic uses.

RECENT ADVANCES IN THE DISCOVERY OF BIOACTIVE NATURAL PRODUCTS

One of the consistent challenges for the natural product chemist who aims to identify natural product-derived pharmaceuticals is the issue of how best to determine desirable biological activity. In the beginning, this was largely a trial and error process by native peoples, who, through empirical observation, determined which plant and animal products were effective for a variety of ailments. Through the years this process gave way to an equally random, but more scientifically validated process known as "screening". It is in this area that much of the debate regarding how best to discover a potential new drug rages. There are those who believe the best approach is "biodiversity prospecting" wherein one samples a broad array of plant, microbial, and animal species, searching for compounds with a predefined set of desirable biological activities. The goal is to survey as much diversity as is possible. With estimations of the number of species of plants that inhabit our planet ranging from 300,000 to 500,000, and with a very small percentage of those having been only minimally evaluated, it would take many years of systematic, concerted effort to evaluate all the Earth's plants for a specific biological activity! Nevertheless, this is an important and appropriate undertaking, albeit not likely to be completed in our lifetime!

A second approach to natural product drug discovery is to utilize the impressive quantity and quality of information derived by indigenous cultures that have used plant and animal products to control their disease states. This discipline, referred to as ethnobotany, or ethnopharmacology, is a mix of sociology, medicine, anthropology, and botany, and can provide very useful information to guide the natural products chemist in the search for new therapeutic agents. Supporters of this approach argue that it is unlikely that cultures would have continued to use a material for decades, or even centuries, if it failed to be effective as expected. Given that much of this information is passed from generation to generation through oral history only, there is a sense of urgency to record and validate the knowledge of the "shaman" before the information is forever lost. On the other hand, there are some cultures that have carefully recorded, in written form, the information regarding the use of natural substances to treat illness and injury. The Chinese "Materia Medica" is a centuries-old treatise that documents in impressive detail the classification, description, preparation, and uses of thousands of medicinal plants. Likewise, the Indian Ayurvedic is similar in its level of detail and documentation of plants used in traditional medicine in India.

Much debate has also centered around the most appropriate manner of evaluation of natural products for desirable activities. Prior to the 70's and 80's, when major advancements in molecular biology were made, the discovery of a novel drug other than an antimicrobial relied largely on the use of animal models. However, in the 80's, with major advancements in molecular biology, there was a trend toward the utilization of receptor or enzyme-based assay systems (sometimes referred to as mechanism-based assays) that measure very specific and selective activities. This has led to the development and rapid growth of a subdiscipline of drug discovery dedicated to the rapid evaluation of large numbers of pure compounds and natural product extracts for very specific biological activities, usually based on interaction with selected enzymes or receptors. This approach, known as high throughput screening, relies heavily on robotics and automation and has revolutionized the ability to routinely evaluate tens of thousands of samples. Consequently, new assays using a specific target enzyme or receptor are rapidly developed and adapted for high throughput screening, then making it possible to rapidly screen very large libraries of compounds. These advancements have led to "turnover" of assays about every six months in industry, wherein a new assay is developed, the entire library is evaluated, another new assay developed, the library screened again, and so on. While this approach clearly has a major role in the future of drug discovery,

we should be reminded of two important points. First, the identification of a potential new target for drug discovery must come from somewhere, and this is usually from an understanding of the basic biology of the target system or from an understanding of the mechanism of action of a novel biologically active compound. Most of the latter have been derived from natural products discovered in assay systems that are not mechanism based. The downside of the high throughput mechanism based screening is that it selects only for activity by a specific mechanism. While this is obviously important and useful, it does, nevertheless, restrict the search. Thus, it is critical to recognize the importance of identifying prototype biologically active compounds that are novel not only structurally, but mechanistically as well. A second point to keep in mind is that the need to penetrate a cell or to reach a particular tissue is never circumvented. Thus, there are those who also argue that, given the ultimate goal of using the drug in a whole animal system, complete with complicated cellular and tissue barriers, compounds should be sought that are active in whole cell systems. Clearly, there is a need and a role for both approaches, and when taken in concert and coordinated to compliment one another, the likelihood of identifying useful new drugs is substantially increased.

Finally, an area of much concern in the past, particularly from an industrial viewpoint, is the concern regarding a reliable and sufficient supply of natural products drugs. This, indeed, has been perceived as an almost insurmountable problem in a few cases of compounds from plant or marine sources. It is difficult to know, however, whether there has ever actually been a really good drug candidate that was abandoned for the singular reason that supply was a major concern. Since about half of our clinically useful drugs are natural-product derived, this would seem not to be the case. Clearly, when the source is a cultivable microorganism, the challenges are significantly more manageable, and this fact probably largely accounts for the disproportionate focus on fermentation chemistry in industrial natural products efforts. Nevertheless, there have now been a sufficient number of examples of plant-derived natural products that are used clinically without structural alteration that the concerns regarding supply should not be overriding, i.e., if a drug is useful enough, the challenge of adequate supply will be addressed. One approach that has been quite successful is the development of simpler semisynthetic or synthetic analogs that are designed to incorporate the necessary pharmacophore of the more complex natural product and improve certain "drug" properties such as pharmacokinetics, compatibilities, stability, etc. In these cases, the natural product serves as a prototype lead compound for the design and development of second generation agents with improved characteristics. In such cases, it is unlikely that large quantities of the original prototype natural product are required for mass production of the drug; however, this may occur if the improved agent is a semisynthetic derivative, and issues related to supply are still important. A second approach has been to determine the genetic and environmental factors that influence the production of the critical secondary metabolite, and to couple this information with improved recovery techniques. This has been done successfully in our institution with several important natural products such as paclitaxel, artemisinin, and delta-9-THC (36). A third, largely theoretical, approach to overcoming the supply issue is the use of tissue culture. While in principle this approach is quite appealing, to date the production of important plant-derived drugs by tissue culture has met with limited success (37).

ROLE OF NATURAL PRODUCTS IN THE FUTURE OF DRUG DISCOVERY

The importance of natural products in the future of drug discovery is clear: novel biologically active natural products will continue to serve as lead compounds for drug development and as biochemical probes for the discovery of pharmacological and biochemical processes. There are a number of exciting developments occurring in the general arena of drug discovery for which natural products will play a central or peripheral role. For example, there is substantial interest in the concept of combinatorial chemistry, wherein a molecular scaffold is substituted in a random manner, with a wide variety of substituents (38). Innovation and creativity regarding the molecular scaffolds will be substantially enhanced with the discovery of relatively simple, small molecular weight bioactive natural products. Obviously, to begin a combinatorial approach with a nucleus that is already known to possess exciting biological activity will increase the likelihood of creating interesting drug candidates through this approach. In a similar vein, the "mixing" of genetic information encoding for specific secondary metabolites produces "unnatural" natural products. This approach has been used to produce, by biosynthetic manipulation, "hybrid" antibiotics possessing desirable properties of different naturally occurring compounds (39). Finally, the use of bioactive natural products to probe the molecular and pharmacological processes of living organisms will continue with even greater sophistication, owing to the major advances being made in molecular biology. By coupling the technological capabilities to explore the inner workings of cells that molecular biology offers with the creativity and innovation of nature, in the form of a seemingly infinite supply of natural compounds with biological and chemical diversity, the future of natural product drug discovery is more promising than ever before. Clearly, the natural products discovered to date have played a vital role in improving the human condition, and this role will continue as long as there are unexplored sources of novel natural products.

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