The Role of Pharmacognosy in Modern Medicine and Pharmacy

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Abstract: This review details the contribution to modern medicine and pharmacy made by natural products and drugs derived from natural products, with an emphasis on essential medicines and new introductions to the market. Areas covered include recent advances in the development of drugs derived from marine organisms, microbes, terrestrial animals, and vascular plants, and current issues regarding botanical medicines. The role of natural products in drug discovery and development is evaluated, particularly with regard to their value as sources of drug leads with "drug-like" properties. A rationale for the success of natural products research in providing new drugs and drug prototypes is presented, drawing on lines of evidence from chemical informatics and chemical ecology. Several innovative strategies for natural products drug discovery and evaluation of botanical medicines are also reviewed.

Key Words: Pharmacognosy, natural product drugs, botanical medicines, "drug-like" molecules.

1. INTRODUCTION: PHARMACOGNOSY

The word "pharmacognosy" is a combination of the Greek words *pharmakon* and *gnosis*: "drug" and "knowledge". The first use of the term is found in the *Lehrbuch der Materia Medica*, which was published in Vienna in 1811 (cited in Samuelsson [1]). As most drugs of that time were crude preparations of plant and animal origin, pharmacognosy from its beginnings has been associated with natural product drugs. The definition of pharmacognosy has changed over time, reflecting changes in what pharmacognosists do, evolving from a descriptive botanical science to a science chiefly concerned with the chemistry and pharmacology of natural products, including pure compounds obtained from natural sources and synthetic derivatives thereof, as well as crude preparations (e.g., botanical medicines) [1-12]. In this review, pharmacognosy is defined as an interdisciplinary science at the interface of chemistry and biology, charged with the application of natural products research to medicine. As such, it incorporates elements of analytical chemistry, biochemistry, ecology, microbiology, molecular biology, organic chemistry, taxonomy, and related disciplines.

2. THE CONTRIBUTION OF PHARMACOGNOSY TO MODERN MEDICINE

Drugs of natural origin constitute the backbone of the modern pharmacopoeias. The history of the origin of modern drugs is related in large part to the discovery of drugs from nature, and natural products are a major source of modern drug prototypes [13, 14] and pharmacological probes [15-17]. The first pure natural product drug prototypes were identified through the investigation of vascular plants [e.g., atropine (**1**), digitoxin (**2**), ephedrine (**3**), morphine (**4**), quinine (**5**), and salicylic acid (**6**)] and terrestrial animals [e.g., epinephrine (**7**) and various hormones]. Moreover, plants continue to be important sources of new drugs [e.g., artemisinin (**8**), galanthamine (**9**), paclitaxel (**10**)]. Microbial sources started to contribute significant numbers of drugs and drug prototypes in the middle of the 20th century, and marine organisms (primarily animals and their associated microbes) have also begun to make significant contributions to medicine in recent years.

2.1. Natural Product-Related Drugs in Prescription Medicine

The importance of natural products in medicine is evident from an analysis of the number of natural product drugs and drugs derived from natural products that are included in the World Health Organization Model List of Essential Medicines. The 13th revision includes nearly 300 distinct drugs considered to be basic to the practice of medicine, including about 210 small-molecule therapeutic agents [18]. The latter include 44 unmodified natural products (Table **1.1**), 25 semisynthetic derivatives of natural products (Table **1.2**), and over 70 synthetic drugs based on natural product pharmacophores or synthetic mimics of natural products. (In the current review, the delineation of the origins of drugs follows the convention used by Newman, Cragg, and Snader [19], giving consideration to the history of their development and the origins of the relevant drug prototypes [14, 20]).

Another measure of the value of natural products in modern medicine is provided by analysis of national prescription audits. Such audits have been used to determine the number of natural products and natural product-derived drugs among the top-selling drugs based on turnover [21, 22] or frequency [23, 24]. Grifo and colleagues [24] analyzed the origins of the top 150 prescription drugs sold in the United States in 1993 (by number of prescriptions filled), based on figures

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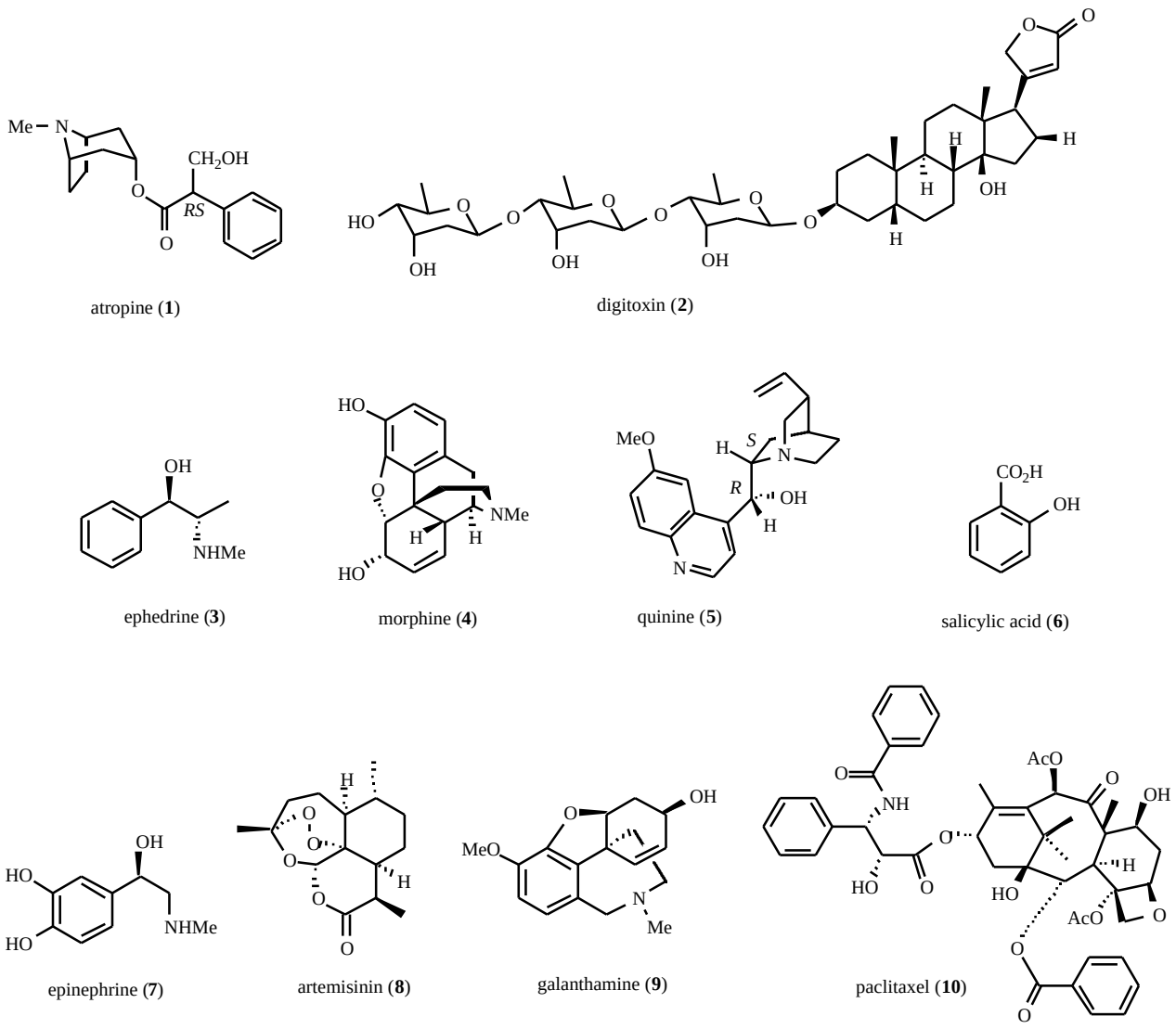


Fig. (1).

from the 1993 Prescription Drug Audit. Of the top 150 prescription drugs, 84 (56%) were natural product-related drugs. Natural products and their derivatives featured prominently in the following disease categories: allergy/pulmonary/respiratory, analgesics, cardiovascular, and infectious disease. In two earlier analyses of the contribution of natural products and their derivatives to prescription medicines, Farnsworth and colleagues reported that the contribution from higher plants alone was consistently about 25% [23, 25], in keeping with the 23% figure reported by Grifo and colleagues [24], and it seems reasonable to assume that there has been little change since 1993.

Natural products and related compounds comprised 59.4% of the turnover of the top 25 drugs in Dutch pharmacies in 1996 [22]. Of the 25 top-selling prescription drugs, one was a natural product (cyclosporin A, **34**) and two were semisynthetic natural product derivatives [ipratropium bromide (**82**) and simvastatin (**86**)]. Additionally, three were synthetic drugs based on natural product pharmacophores [budesonide (**87**), beclomethasone (**88**), and fluticasone propionate (**89**)] and eight were synthetic mimics of natural products [captopril (**90**), enalapril (**91**), cimetidine (**92**), diclofenac (**93**), ranitidine (**94**), salbutamol (**95**), salmeterol (**96**), and sumatriptan (**97**)]. In a similar analysis of the top 25 drugs worldwide in 1991, natural products [augmentin: amoxicillin (**65**) + clavulanic acid (**17**), cyclosporin A (**34**), and lovastatin (**98**)] and semisynthetic derivatives of natural products [cefaclor (**99**) and ceftriaxone (**100**)] accounted for 10.4% and 7% of sales, respectively [21]. In turn, a synthetic drug based on a natural product pharmacophore [acyclovir (**101**)] and eight synthetic mimics of natural products [atenolol (**102**), captopril (**90**), cimetidine (**92**), diclofenac (**93**), enalapril (**91**), piroxicam (**103**), ranitidine (**94**), and salbutamol (**95**)] accounted for sales of 3.5% and 43.9%, respectively. Represented by 14 of the top 25 drugs in 1991, equivalent to 64.9% of the worldwide turnover, natural products and related compounds yielded $16.6 billion in sales [21]. In 2000, nearly a decade later, natural products

and natural product derivatives comprised 14 of the top 35 ethical drugs (based on worldwide sales) [26]. Antineoplastic agents derived from natural products are among the most important drugs used in cancer therapy [27]. Foye and Sengupta consider doxorubicin (**22**) to be "probably the most important anticancer drug available because of its relatively broad spectrum of activity" [28]. In 2004, drugs based on just two plant derived natural products [camptothecin (**104**) and paclitaxel (**10**)] were estimated to account for nearly one-third of the global market for antineoplastic agents, or about $3 billion of $9 billion in total annually [29].

Table 1.1. Selected Natural Product Drugs Included in the WHO Essential Medicines List, 13th Revision

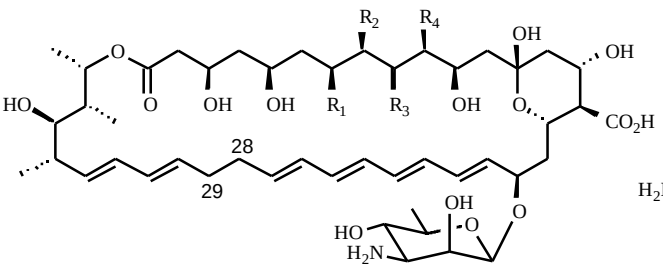
Natural Product Drugs by Source	Natural Product Drugs by Source Contd.
Actinomycete	**Mammalian**
amphotericin B (**11**)	epinephrine (**7**)
bleomycin (A_2, B_2: **12**, **13**)	hydrocortisone (**38**)
capreomycin (1A, 1B: **14**, **15**)	levodopa (**39**)
chloramphenicol (**16**)	
clavulanic acid (**17**)	**Vascular Plant**
cycloserine (**18**)	atropine (**1**) *a*
dactinomycin (**19**)	codeine (**40**) *j*
daunorubicin (**20**)	colchicine (**41**) *g*
deferoxamine (**21**)	digoxin (**42**) *h*
doxorubicin (**22**)	ephedrine (**3**) *i*
erythromycin A (**23**)	mannitol (**43**)
gentamicin C_1 (**24**)	morphine (**4**) *j*
kanamycin A (**25**)	phytomenadione (**44**)
neomycin (B, C: **26**, **27**)	pilocarpine (**45**) *k*
nystatin (**28**)	podophyllum resin: podophyllotoxin (**46**) *l*
spectinomycin (**29**)	quinidine (**47**) *e*
streptomycin (**30**)	quinine (**5**) *e*
tetracycline (**31**)	salicylic acid (**6**) *m*
vancomycin (**32**)	senna: sennosides (A, B: **48**, **49**) *c*
	theophylline (**50**) *b*
Fungal	vinblastine (**51**) *d*
benzylpenicillin (**33**)	vincristine (**52**) *d*
cyclosporin A (**34**)	
ergometrine (**35**) *f*	
ergotamine (**36**) *f*	
griseofulvin (**37**)	

Notes: Ethnopharmacological lead (see text): *a = Atropa belladonna; b = Camellia sinensis; c = Cassia senna; d = Catharanthus roseus; e = Cinchona; f = Claviceps purpurea; g = Colchicum autumnale; h = Digitalis; i = Ephedra; j = Papaver somniferum; k = Pilocarpus; l = Podophyllum; m = Salix* and *Spirea; n = Strychnos toxifera.*

Table 1.2. Selected Semisynthetic Natural Product-Derived Drugs Included in the WHO Essential Medicines List, 13th Revision

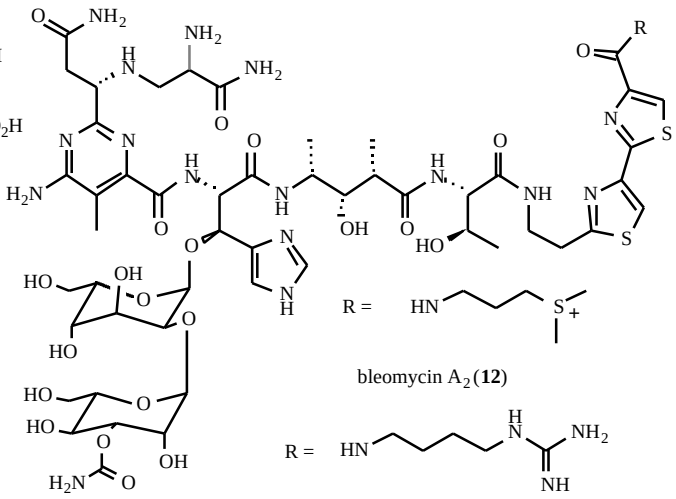
Drug by Source	Lead Structure
Actinomycete	
amikacin (**53**)	kanamycin A (**25**)
azithromycin (**54**)	erythromcyin A (**23**)
clindamycin (**55**)	lincomycin (**56**)
doxycycline (**57**)	oxytetracycline (**58**)
imipenem (**59**)	thienamycin (**60**)
ivermectin (**61**)	avermectin B_{1a} (**62**)
rifampicin (**63**)	rifamycin B (**64**)
Fungal	
amoxicillin (**65**)	benzylpenicillin (**33**)
ampicillin (**66**)	benzylpenicillin (**33**)
phenoxymethylpenicillin (**67**)	benzylpenicillin (**33**)
Mammalian	
carbidopa (**68**)	levodopa (**39**)
dexamethasone (**69**)	hydrocortisone (**38**)
ethinylestradiol (**70**)	estradiol (**71**)
isoprenaline (**72**)	epinephrine (**7**)
methyldopa (**73**)	levodopa (**39**)
prednisolone (**74**)	hydrocortisone (**38**)
Vascular Plant	
acetylsalicylic acid (**75**)	salicylic acid (**6**) *f*
alcuronium (**76**)	toxiferine I (**77**) *g*
aminophylline (**78**)	theophylline (**50**) *c*
artemether (**79**)	artemisinin (**8**) *a*
sodium artesunate (**80**)	artemisinin (**8**) *a*
etoposide (**81**)	podophyllotoxin (**46**) *e*
ipratropium bromide (**82**)	atropine (**1**) *b*
naloxone (**83**)	thebaine (**84**) *d*
p-aminosalicylic acid (**85**)	salicylic acid (**6**) *f*

Notes: Ethnopharmacological lead (see text): *a = Artemisia annua; b = Atropa belladonna; c = Camellia sinensis; d = Papaver somniferum; e = Podophyllum; f = Salix* and *Spirea; g = Strychnos toxifera.*



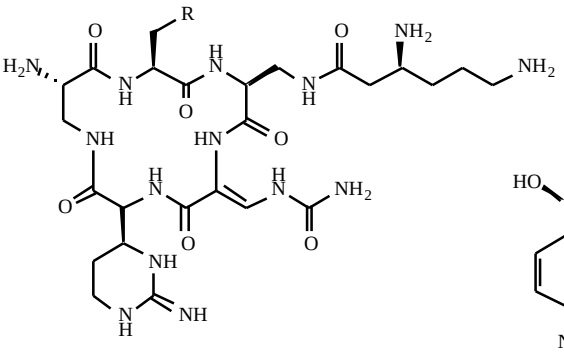
$\Delta^{28(29)}$, $R_1 = R_4 = H$, $R_2 = R_3 = OH$ amphotericin B (**11**)

$R_1 = R_4 = OH$, $R_2 = R_3 = H$ nystatin A1 (**28**)



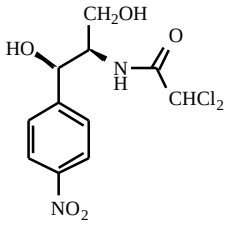
bleomycin A_2 (**12**)

bleomycin B_2 (**13**)

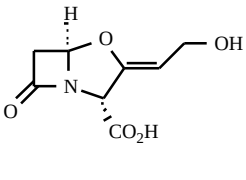


R = OH capreomycin 1A (**14**)

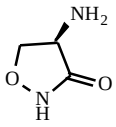
R = H capreomycin 1B (**15**)



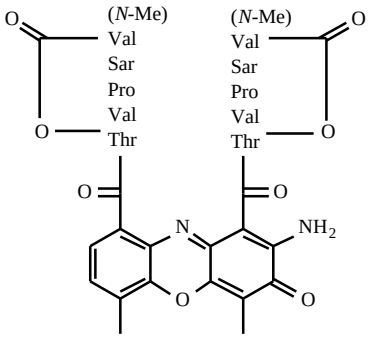
chloramphenicol (**16**)



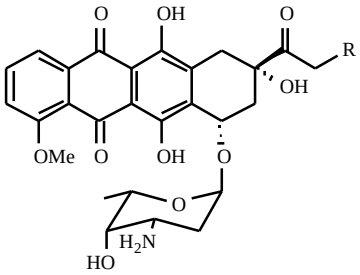
clavulanic acid (**17**)



cycloserine (**18**)

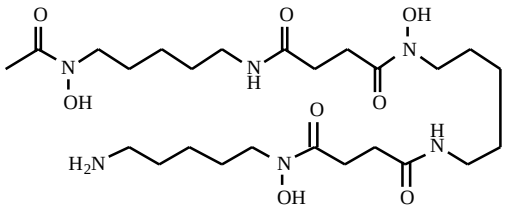


dactinomycin (**19**)

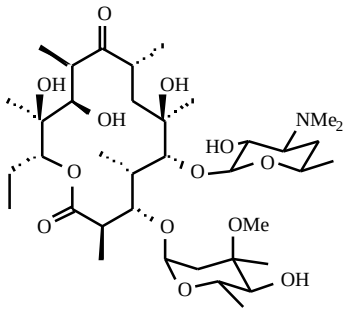


R = H daunorubicin (**20**)

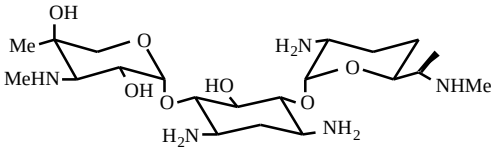
R = OH doxorubicin (**22**)



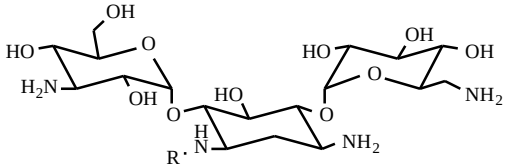
deferoxamine (**21**)



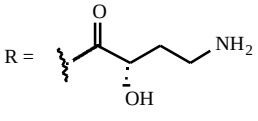
erythromycin A (**23**)



gentamicin C_1 (**24**)

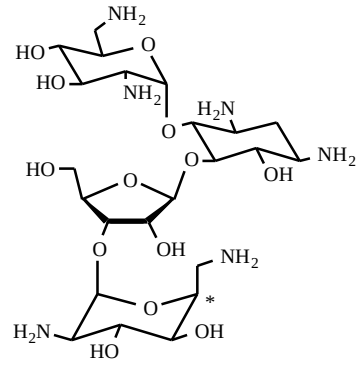


R = H kanamycin A (**25**)



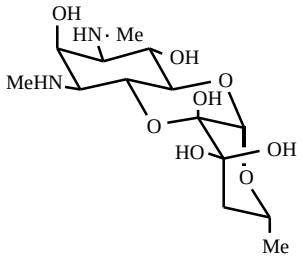
amikacin (**53**)

Fig. (2.1).

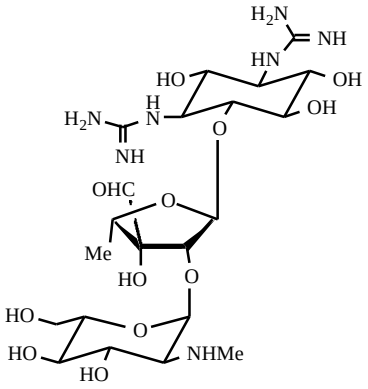


neomycin B (**26**)

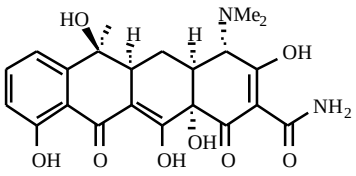
neomycin C (**27**) (epimer is at *)



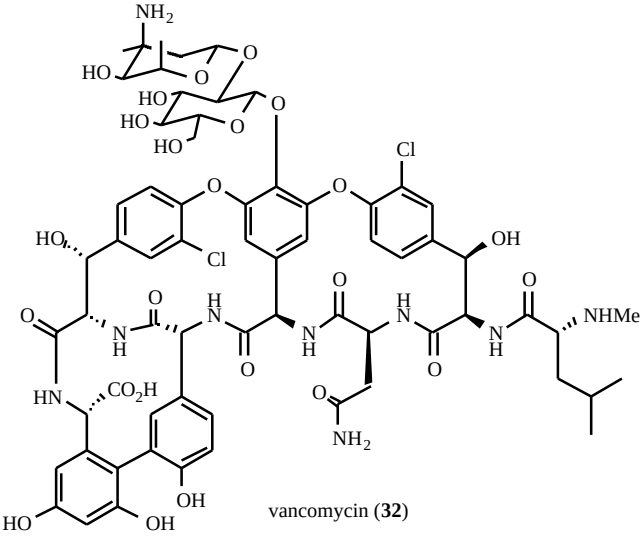
spectinomycin (**29**)



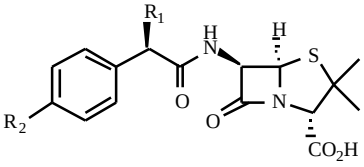
streptomycin (**30**)



tetracycline (**31**)



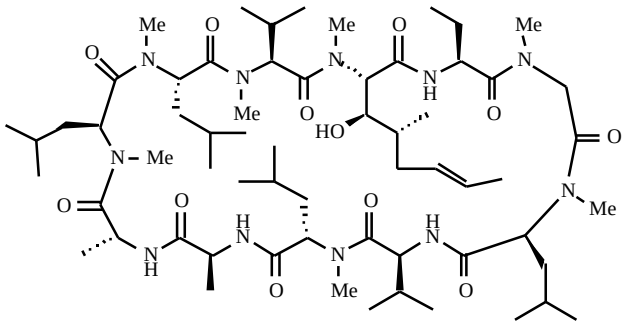
vancomycin (**32**)



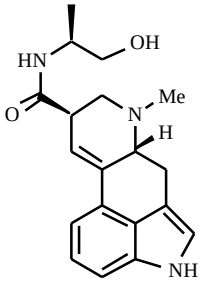
$R_1 = R_2 = H$ benzylpenicillin (**33**)

$R_1 = NH_2$ $R_2 = OH$ amoxicillin (**65**)

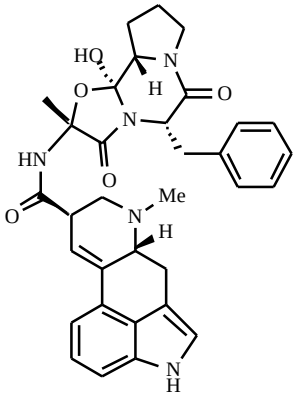
$R_1 = NH_2$ $R_2 = H$ ampicillin (**66**)



cyclosporin A (**34**)

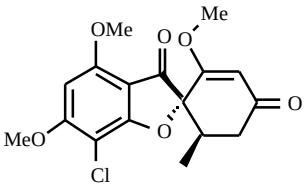


ergometrine (**35**)

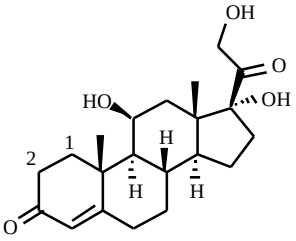


ergotamine (**36**)

Fig. (2.2).

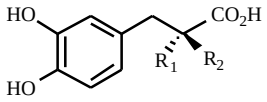


griseofulvin (**37**)



hydrocortisone (**38**)

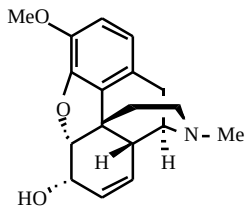
$\Delta^{1(2)}$ = prednisolone (**74**)



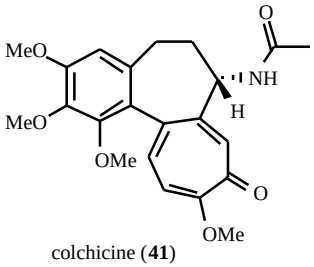
R_1 = H, R_2 = NH_2 levodopa (**39**)

R_1 = CH_3, R_2 = $NHNH_2$ carbidopa (**68**)

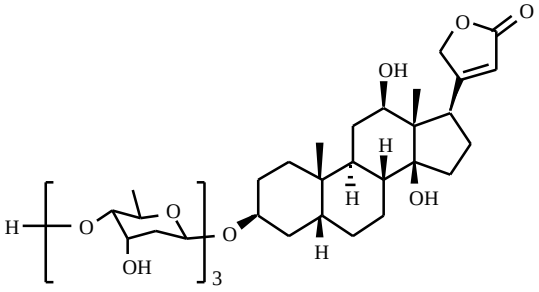
R_1 = CH_3, R_2 = NH_2 methyldopa (**73**)



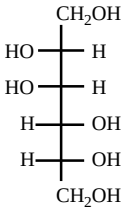
codeine (**40**)



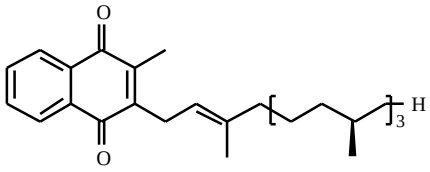
colchicine (**41**)



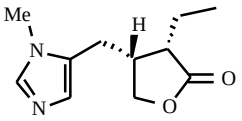
digoxin (**42**)



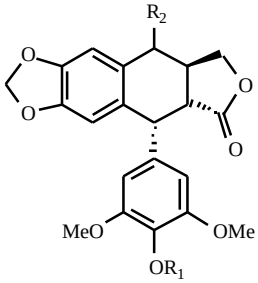
D-mannitol (**43**)



phytomenadione (**44**)

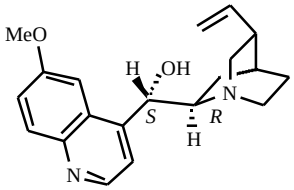


pilocarpine (**45**)

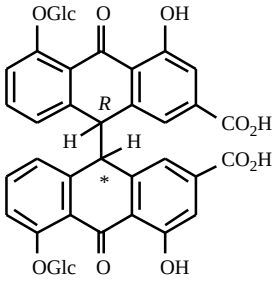


R_1 = CH_3

R_2 = α OH podophyllotoxin (**46**)

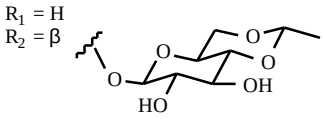


quinidine (**47**)

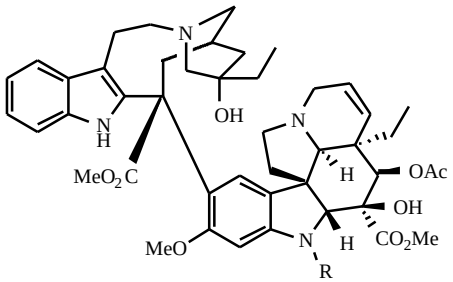


R at * sennoside A (**48**)

S at * sennoside B (**49**)

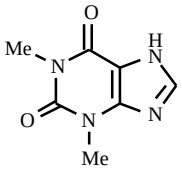


etoposide (**81**)



R=CH_3 vinblastine (**51**)

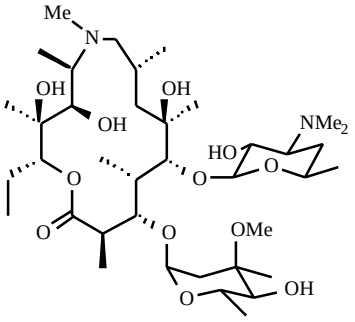
R=CHO vincristine (**52**)



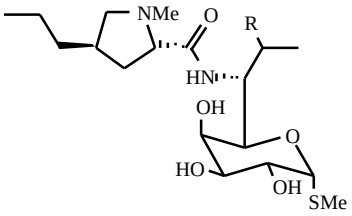
theophylline (**50**)

theophylline-ethylenediamine (2:1) = aminophylline (**78**)

Fig. (2.3).

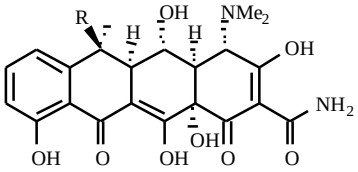


azithromycin (**54**)



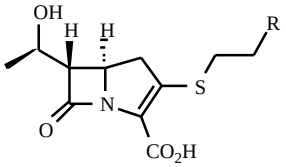
R = β Cl clindamycin (**55**)

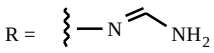
R = α OH lincomycin (**56**)



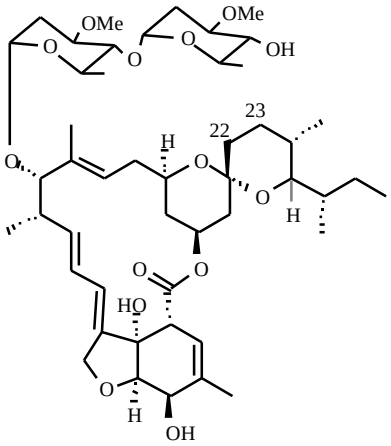
R = H doxycycline (**57**)

R = OH oxytetracycline (**58**)





imipenem (**59**)

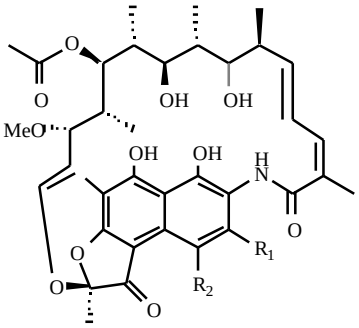


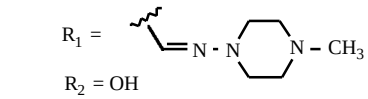
R = NH_2

thienamycin (**60**)

ivermectin (**61**)

$\Delta^{22(23)}$ = avermectin B_{1a} (**62**)





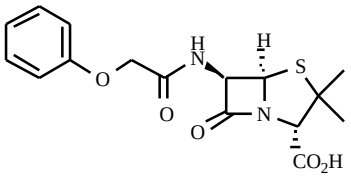
R_2 = OH

rifampicin (**63**)

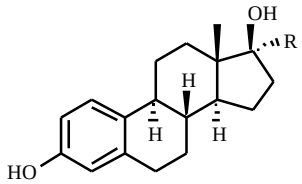
$R_1 = OCH_2CO_2H$

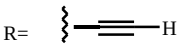
R_2 = H

rifamycin B (**64**)



phenoxymethylpenicillin (**67**)

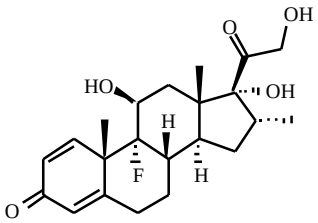




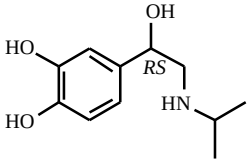
ethinylestradiol (**70**)

R = H

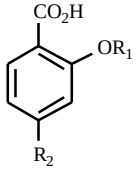
estradiol (**71**)



dexamethasone (**69**)



isoprenaline (**72**)



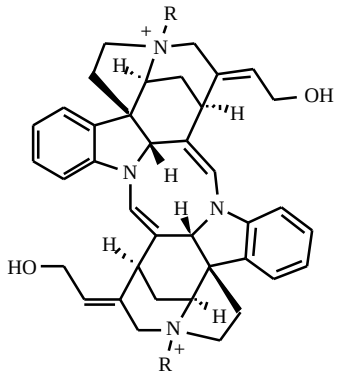
R_1 =Ac R_2 = H

acetylsalicylic acid (**75**)

R_1 =H $R_2 = NH_2$

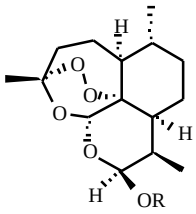
p-aminosalicylic acid (**85**)

Fig. (2.4).

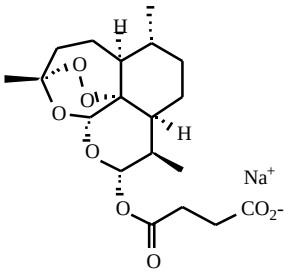


R = alcuronium (**76**)

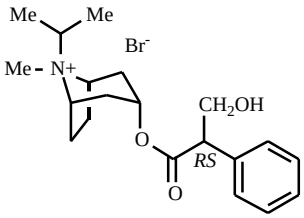
R = CH_3 toxiferine I (**77**)



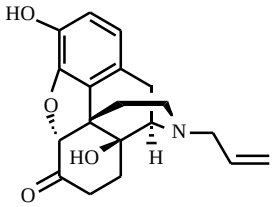
R = CH_3 artemether (**79**)
R = CH_2CH_3 arteether (**132**)



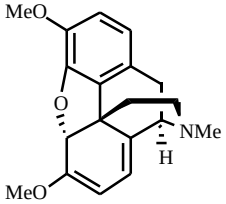
sodium artesunate (**80**)



ipratropium bromide (**82**)



naloxone (**83**)



thebaine (**84**)

Fig. (2.5).

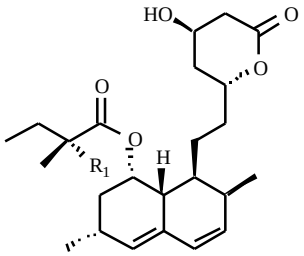
2.2. The Contribution of Pharmacognosy to Drug Discovery

During the period 1981-2002, of the 1031 new chemical entities approved by U.S. Food and Drug Administration, 50 were natural products (4.8%), 240 were semi-synthetic derivatives of natural products (23.3%), and 144 were synthetic compounds based on a natural product pharmacophore (14.0%) [19]. An additional 97 new chemical entities (9.4%) were synthetic compounds that mimic natural substrates for the drug target, or that were designed with knowledge gained from natural products. This category includes peptidomimetics, hormone analogs, and ATP mimics. The total contribution from all these natural product-related categories combined is 531 new chemical entities (51.5%). Note that this excludes vaccines and biologicals (e.g., peptides and proteins), which contributed an additional 154 new chemical entities (14.9%).

In recent years there has been a great deal of concern about the relative slump in new drug applications, the annual numbers of new chemical entities, and the output of first-in-class and blockbuster drugs [19, 26, 30, 31]. The number of natural product-related pharmaceutical patents filed annually over the period 1984 to 2003 grew during the 1980s, then flattened during the 1990s [31]. This time frame roughly coincides with the overall downturn in productivity and the pharmaceutical industry's shift away from natural products in favor of combinatorial chemistry and synthetic libraries as the main sources of chemical diversity for lead discovery. Given that natural products have contributed more than half of the new chemical entities during the last decade and a half of relative neglect by industry, it is interesting to speculate what might have resulted had natural products been more fully explored during this same period.

There are decided physiochemical differences between natural products and synthetic compounds. Chemical informatics comparisons of natural products with synthetic compounds and drugs demonstrate that natural products differ from synthetic molecules in key chemical properties, such as the average number of nitrogen, halogen, oxygen, and sulfur atoms, the degree of steric complexity, and average molecular weight [32]. Compared with synthetic compounds, natural products contain more protonated-amino and free-hydroxy groups, more single bonds, and fewer aromatic rings [33]; natural product libraries provide a greater diversity of ring systems and larger individual ring systems [34]; and natural products are more rigid (probably due to a greater number of fused rings), and contain more chiral centers, fewer rotatable bonds, and shorter exocyclic chains [35].

Many of the chemical differences noted above relate to measures of "drug-likeness". The concept of "drug-like" molecules developed out of lessons learned from early combinatorial chemistry failures [36]. For instance, the "rule-of-5" was first developed because of the need for a simple metric to predict whether a hit/lead identified from screening of library compounds (mainly synthetic) would be orally

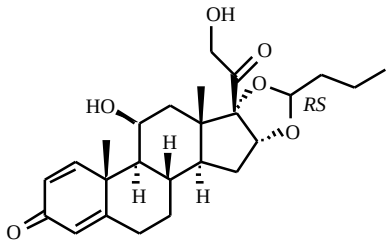


$R_1 = CH_3$

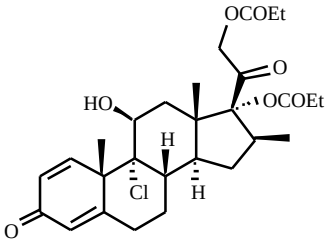
simvastatin (**86**)

$R_1 = H$

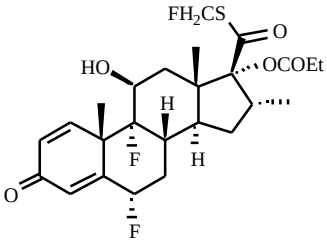
lovastatin (**98**)



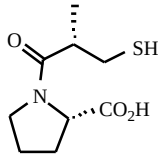
budesonide (**87**)



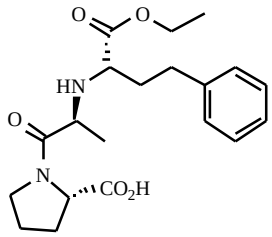
beclomethasone (**88**)



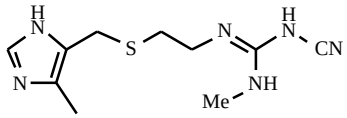
fluticasone propionate (**89**)



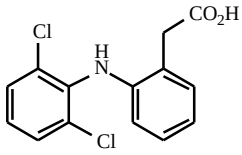
captopril (**90**)



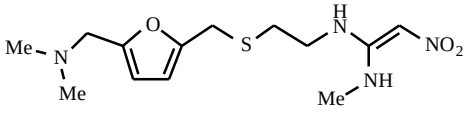
enalapril (**91**)



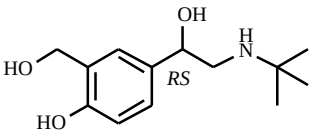
cimetidine (**92**)



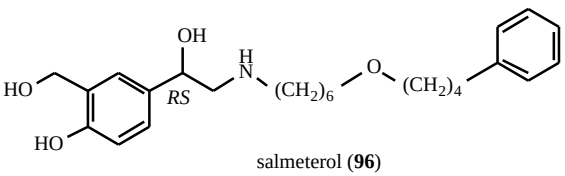
diclofenac (**93**)



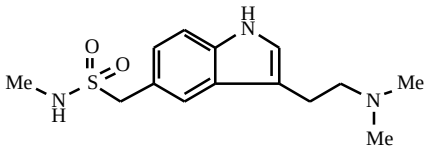
ranitidine (**94**)



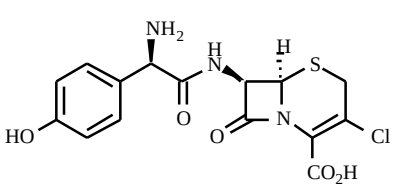
salbutamol (**95**)



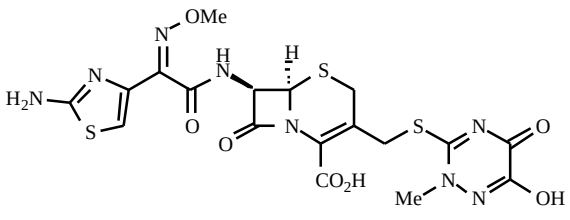
salmeterol (**96**)



sumatriptan (**97**)

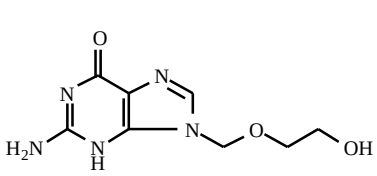


cefaclor (**99**)

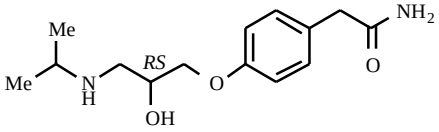


ceftriaxone (**100**)

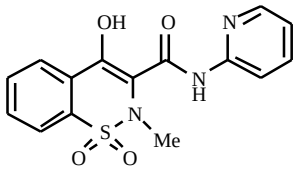
Fig. (3.1).



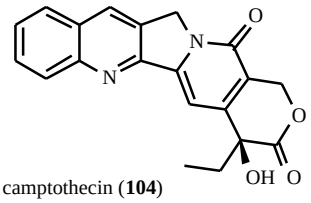
acyclovir (**101**)



atenolol (**102**)



piroxicam (**103**)



camptothecin (**104**)

Fig. (3.2).

available [36, 37]. Lee and coworkers compared rule-of-5 metrics between natural products and trade drugs [34] and found that the average log P, number of nitrogen atoms, and molecular weight were similar between the two groups. Only about 10% of natural products had more than one "rule-of-5 violation", comparable to trade drugs in this regard [34]. Most of the rule-of-5 violations exhibited by natural products were due to high-molecular weight compounds, including many antibiotics. Overall, natural products have a greater degree of drug-likeness than compounds in synthetic and combi-chem libraries [35]. Drug-likeness in lead compounds is important since most recently introduced drugs closely resemble their lead compounds, with very little change in rule-of-5 parameters [38]. Taken together, these studies indicate that natural products and synthetic compounds occupy complementary regions of "chemical space", and that natural products are an important source of chemically diverse, drug-like leads for drug discovery.

The drug-likeness of natural products is probably due to their production in living systems, where they are subject to diffusion and transport within and between cells and tissues. It is thought that natural products (secondary metabolites) serve a function within the producing organism or between organisms (as chemical messengers and defense compounds), and that millions of years of selection and evolution have refined the active natural products of today [39, 40]. Natural products are produced at a biochemical cost to the producing organism, and, because of selection pressure, that cost must be offset by a benefit to the producer ("an increase in fitness"). Firn and Jones note, however, that many natural products are found to be inactive when screened against specific targets, and they have proposed a "screening model" to reconcile the production of large numbers of apparently inactive natural products (in addition to a handful of bioactive natural products) with the concept of evolutionary fitness and cost [40]. Their screening model is based on the hypothesis that inactive compounds produced by an organism constitute a screening library from which some compounds emerge as "hits" when exposed to targets in a predator or competitor. Over evolutionary time, these hits are modified and improved as the well-defended individuals have increased fitness [40]. However, the apparent rarity of biological activity may also be a consequence of screening of single compounds. In the producing organism, compounds occur in complex mixtures, and co-occurring compounds might modify the effects of "inactive" pure compounds (e.g., synergy, see below).

Active secondary metabolites that arise from "chemical arms-races" between predators and prey may appear to be involved in interactions that are quite specific to the context of the interaction. Nonetheless, the biomolecular targets involved are often widely distributed, some of them across kingdoms [41-44]. Furthermore, the same compound can have multiple functions (and, conversely, structurally different compounds can interact with the same target) [45, 46]. When the target is restricted in taxonomic distribution, this also can be exploited, as in the case of many antiinfective agents. Because of the above-mentioned factors, natural products exhibit a significant advantage in drug discovery compared with arbitrary collections of synthetic molecules.

2.3. Biodiversity-Based Drug Discovery

Some interesting trends have begun to emerge from the application of ecological methods in the "lead identification" stage of drug discovery. Indicators of high expression of chemical defenses, such as aposematic coloration ("warning color patterns"), absence of herbivory, and clues from leaf morphology and leaf development pattern have been used to indicate chemically promising source material [47-51]. Systematic, plot-based sampling methods have been borrowed from ecology as well, decreasing sampling bias and improving reproducibility of plant collections [52, 53].

Systematic selection methods are important because, although the pharmacological properties of compounds from plants have been studied for centuries, only a small fraction of the earth's plant diversity has been investigated thoroughly [23]. NAPRALERT^{SM}, a database of pharmacologically active natural products (mainly from plants), contains over 189, 000 compounds, of which just over 50, 000 have been evaluated for biological activity, and less than 5% have been tested for more than three types of pharmacological

activity (Norman R. Farnsworth, University of Illinois at Chicago, personal communication). Given the relatively short history of bioprospecting from marine and microbial sources, it can be assumed that natural products from these sources are also greatly "under-investigated".

3. RECENT DEVELOPMENTS IN DRUG DISCOVERY FROM NATURAL SOURCES

A previous review covered natural product-related drug introductions up to and including 2002 [19] and two other reviews gave updated figures for natural product-related drugs launched in 2003 and 2004 (in the U.S., Europe, and Japan) [26, 54]. Natural products and natural product derived drugs in clinical trials worldwide were extensively reviewed by Butler [54], and the interested reader is referred to this reference for a more thorough treatment of natural products in clinical development, especially many in early phase trials. The new drug approvals for 2003 included two natural products [daptomycin (**105**) and mycophenolate sodium (**106**)] and three semisynthetic derivatives of natural products [miglustat (**107**), pitavastatin (**108**), rosuvastatin (**109**)] [26]. Daptomycin is of particular note because of its potent activity against Gram-positive bacteria, including many antibiotic-resistant strains [55]. The new molecular entities approved by the U.S. FDA during 2004 were recently compiled (online table associated with reference [56]). Among these are one natural product [ziconotide (**110**), see below], several semisynthetic derivatives of natural products [apomorphine hydrochloride (**111**), rifamixim (**112**), telithromycin (**113**), and tiotropium bromide (**114**)] and a number of synthetic compounds based on natural product pharmacophores and synthetic mimics of natural products [e.g., azacitidine (**115**), clofarabine (**116**), and trospium chloride (**117**)].

3.1. Marine Sources

Early marine natural products research was mainly focused on identification of marine toxins [57], but chemical ecology and applications to medical research have been increasingly important [58-60]. First isolated from fish in the family Tetraodontidae [60], tetrodotoxin (**118**) is an example of a promising drug lead from a marine toxin. Tetrodotoxin (Tetrodin™) and a related product based on **118**, Tectin™, are currently being developed for the analgesics market by Wex Pharmaceuticals (Vancouver, BC, Canada). Tetrodotoxin is reported to be in Phase II evaluation for treatment of pain associated with opioid withdrawal, and Tectin™ has completed Phase IIa and is currently in Phase IIb/III (expected to be completed in 2005) for chronic pain in patients with advanced cancer [61].

Interest in the drug applications of conotoxins, neurotoxic peptides from marine snails in the genus *Conus*, has led to their development as potential drugs. Ziconotide [ω-conotoxin MVIIA, (**110**)], a 25-residue peptide discovered from *Conus majus*, selectively binds to N-type Ca^{2+} channels, blocking neurotransmission and producing a potent analgesic effect [62]. Clinical trials using synthetically produced ziconotide began in the 1990s, and in December of 2004, the U.S. Food and Drug Administration granted Elan Pharmaceuticals approval for use of ziconotide in the management of severe, chronic pain in patients with cancer or AIDS [63].

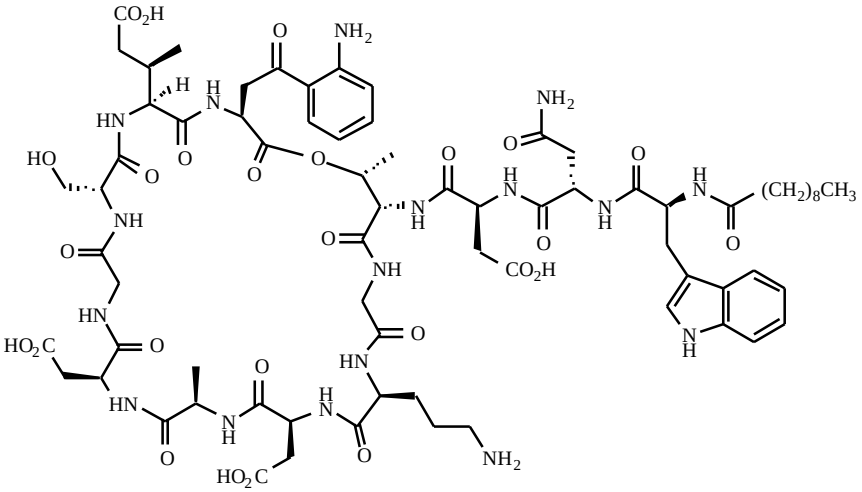
Many of the existing antiviral and anticancer nucleoside-blocking drugs can be traced to spongothymidine (**119**) and spongouridine (**120**), β-D-arabinofuranosides isolated from the marine sponge *Tethya crypta* (*Cryptothelia crypta* in the earlier literature) in the 1950s by Bergmann's group [14, 64-66]. Azidothymidine [AZT(**121**)], cytosine arabinoside [cytarabine (**122**)], ganciclovir (**123**), and related agents including many experimental anti-HIV and anticancer drugs are based on the pharmacophore provided by these marine compounds [19, 67]. A number of other marine natural products are in various stages of drug development (see [54, 68, 69] for recent reviews).

3.2. Terrestrial Sources

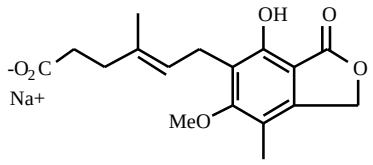
Investigation of the venom of the Brazilian arrowhead viper (*Bothrops jararaca*) led to the discovery of the angiotensin-converting enzyme (ACE) inhibitory activity of teprotide (**124**), a nonapeptide component of the venom [70]. Extensive biochemical investigation of teprotide and related peptide venoms identified several C-terminal tripeptide sequences that retained the antihypertensive activity of the longer peptides [70]. This observation led to a series of molecular modeling experiments and the synthesis of a number of small molecule mimics, which ultimately produced captopril (**90**) and related small-molecule ACE inhibitors [71].

Numerous potent toxins have been reported from frogs and other amphibians (reviewed in [72, 73]). One drug lead that emerged from investigation of natural products from amphibians is the alkaloid epibatidine (**125**), first discovered as a constituent of the brightly colored skin (aposematic coloration) of poison-arrow frogs (*Epipedobates tricolor*). Epibatidine has a potent analgesic effect, acting through nicotinic acetylcholine receptors. A synthetic analog, ABT-594 (**126**) (Abbott Park, North Chicago, IL, USA), was found to be 200 times more potent than morphine (to achieve comparable analgesic efficacy), and lacked opioid-related dependence [74, 75]. Clinical development of ABT-594 apparently has been halted, probably due to a poor therapeutic window [76]. However, there is continued hope for the development of a "next generation" of drugs based on the epibatidine pharmacophore with greater selectivity for nicotinic acetylcholine receptor subtypes specifically related to pain [76] and for potential use against chemotherapy-induced pain [77].

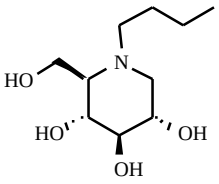
Investigations of the causes of livestock poisonings have led to important medical applications [78], including the discovery of dicoumarol (**127**), an anticoagulant isolated from spoiled hay [79], and the recognition of the estrogenic effects of genistein (**128**) and related isoflavonoids [80]. Swainsonine (**129**), one of the indolizidine alkaloids responsible for "locoweed poisoning" (caused by consumption of certain species of *Astragalus* and *Oxytropis* in North America, and *Swainsona* in Australia), inhibits α-mannosidase, resulting in accumulation of biomolecules in the cell, and leading to eventual cell death [78, 81]. The cytotoxic potential of swainsonine, coupled with pharmacokinetic studies that indicate that swainsonine has an affinity for lymphoid



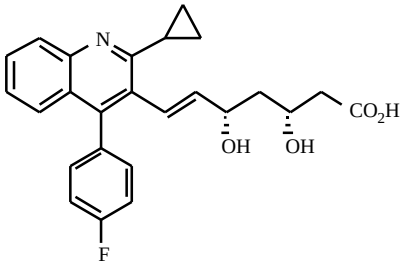
daptomycin (**105**)



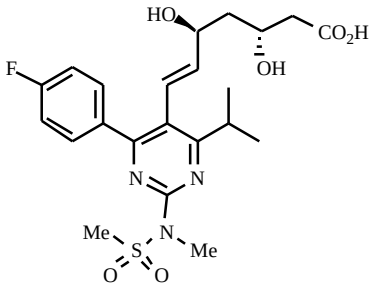
mycophenolate Na (**106**)



miglustat (**107**)

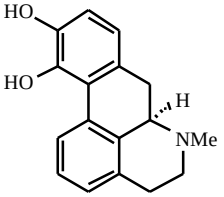


pitavastatin (**108**)



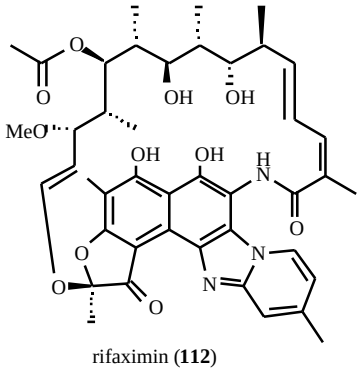
rosuvastatin (**109**)

ziconotide (**110**)

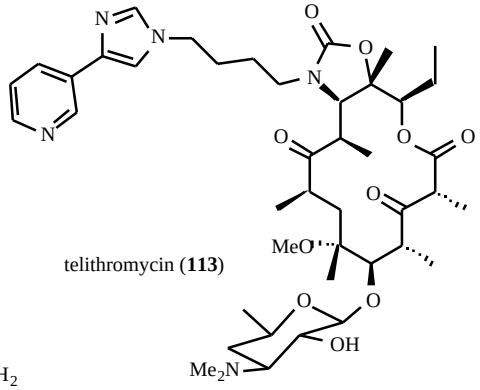


apomorphine (**111**)

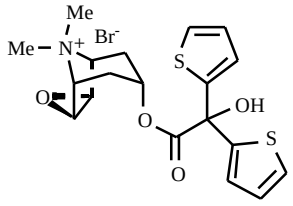
Fig. (4.1).



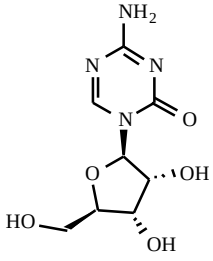
rifaximin (**112**)



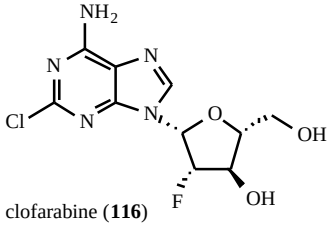
telithromycin (**113**)



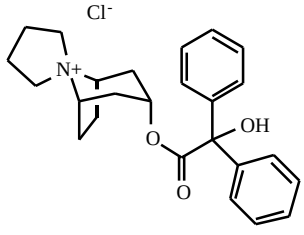
tiotropium bromide (**114**)



azacitidine (**115**)



clofarabine (**116**)



trospium chloride (**117**)

Fig. (4.2).

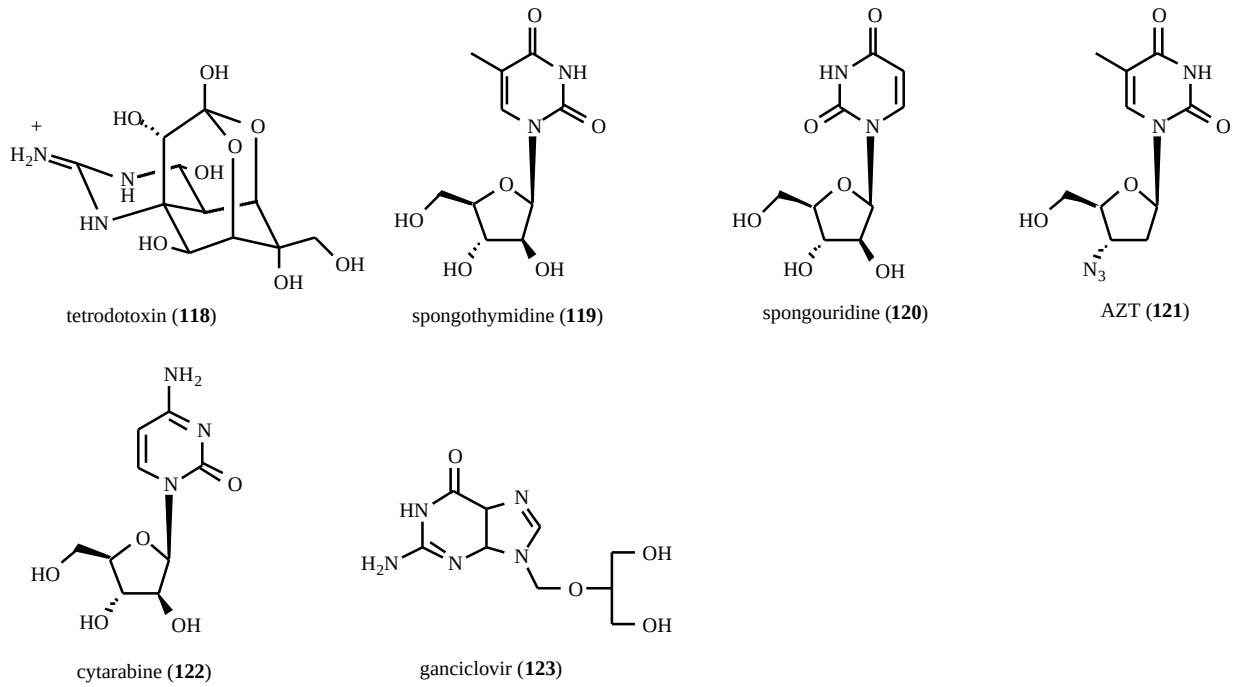


Fig. (5).

tissue, has prompted interest in swainsonine-type compounds as potential antimetastatic agents. However, enrollment for a phase II clinical trial that was planned to begin in 2003 was discontinued, and no further development has been reported [82]. A structurally similar compound, castanospermine (**130**), was isolated from the Moreton Bay chestnut (*Castanospermum australe* Cunn. & Fraser ex Hook.) [83]. The 6-butanoyl derivative [Celgosavir® (**131**)], with improved solubility characteristics, was initially investigated as a potential anti-HIV agent [84]. It is currently being developed by MIGENIX (Vancouver, BC, Canada) as an antiviral agent, and it currently in phase II clinical development for treatment of hepatitis C [85].

3.3. Ethnopharmacology

There is often a correlation between the current medical use of a plant-derived drug and the ehtnopharmacological use of the species from which it was originally discovered [24, 86-88]. For instance, 35 natural product-related drugs originally discovered from vascular plants were among the 150 top-selling prescription drugs in the U.S. in 1993. The majority of these plant-related drugs were discovered by investigation of only ten plant species, nine of which exhibit ethnomedical uses germane to the modern therapeutic indication for the derived drugs [24]. Farnsworth and colleagues reported that 122 natural product drugs derived from plants (94 species) are used in medicine in one or more parts of the world, and of these, 80% (88) can be traced to ethnobotanical uses documented for the plant of origin [24, 86-88]. Of the 26 vascular-plant-derived drugs included in Tables 1.1 and 1.2, fully 21 have uses in modern medicine that correlate with their ethnobotanical use (including traditional medicines and arrow poisons), and two of the fungal natural product drugs have traditional uses that correlate with the modern use. In addition, three of the plant-derived drugs were discovered as an indirect result of investigation of ethnopharmacological uses [i.e., quinidine, used to treat heart arrhythmia, was discovered from *Cinchona*; vinblastine (**51**) and vincristine (**52**), used in oncology, were discovered in a search for antihyperglycemic agents from *Catharanthus roseus* G. Don].

It is often difficult to prove a direct causal relationship between the ethnomedical use of a plant and the development of a drug derived from the plant. Galanthamine (**9**), an alkaloid drug found in *Galanthus woronowii* Losinsk (and many other Amaryllidaceous species), provides a case in point [89]. Galanthamine was approved by the U.S. FDA in 2004 for use as an acetylcholinesterase inhibitor in the treatment of Alzheimer's disease. Circumstantial evidence, including information that the crushed plant was apparently used as a traditional treatment for pain by people in eastern Europe, where the initial drug development occurred, suggests an ethnomedical link for this important new drug [89].

The antimalarial agents obtained from *Artemisia annua* L. ("qinghao" in Chinese and "sweet wormwood" in much of the English-speaking world), provide a clear example of an ethnomedical lead being developed into useful drugs [20]. Qinghao has been used for centuries in Traditional Chinese Medicine to treat fevers and malaria, and the natural product artemisinin (**8**) and its semisynthetic derivatives arteether (**132**), artemether (**79**), and sodium artesunate (**80**) are becoming indispensable antimalarial agents because of their efficacy against chloroquine-resistant malaria [90].

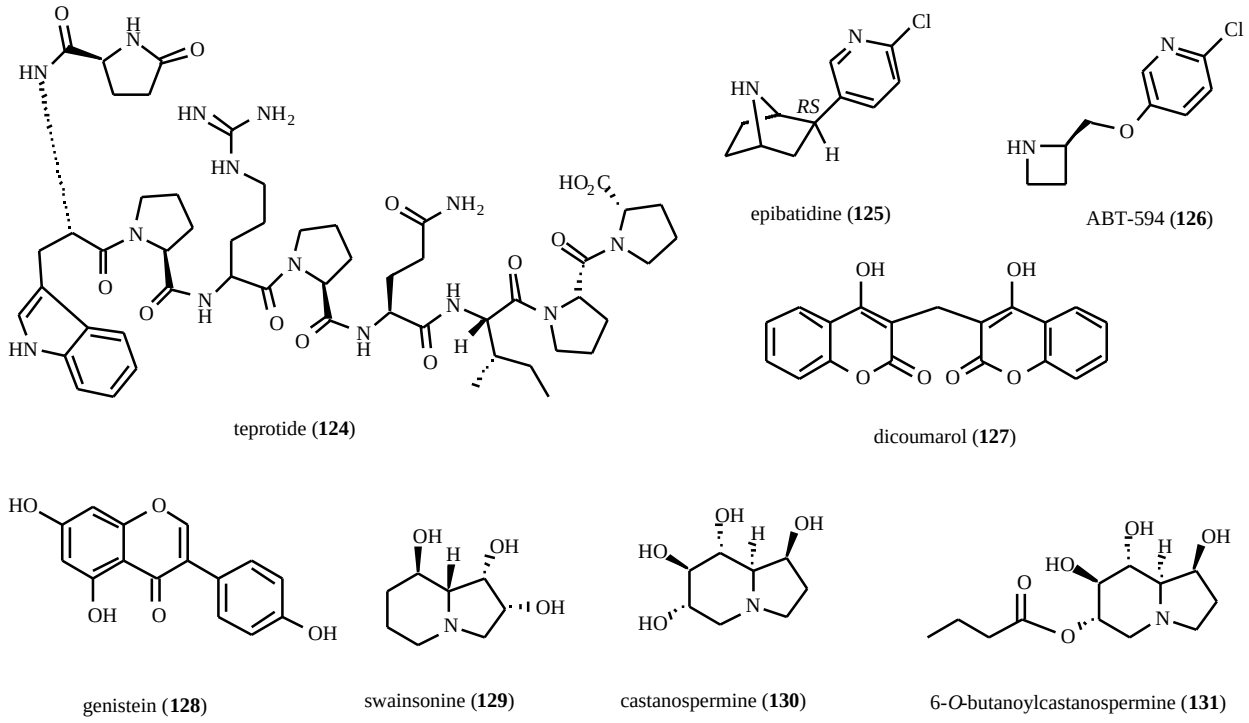


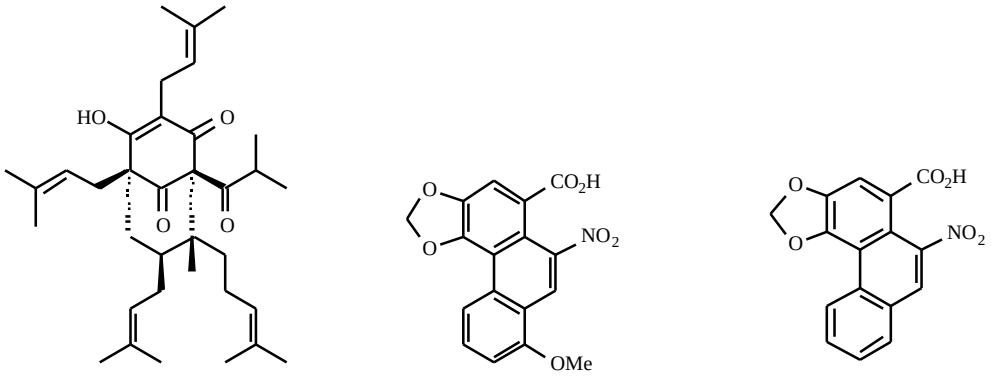
Fig. (6).

4. BOTANICAL MEDICINE

The U.S. botanical dietary supplement market was estimated to be $4.3 billion in 2002 [91]. A recent survey of complementary and alternative medicine use patterns in the U.S. found that 19% of adults used "natural products", primarily botanical supplements, including echinacea, ginseng, ginkgo, garlic supplements, St. John's wort, peppermint, ginger supplements, soy supplements, ragweed/chamomile, kava kava, valerian, and saw palmetto (in order of decreasing frequency of use) [92]. In the U.S., botanicals (herbal products) are regulated as food supplements in accordance with the Dietary Supplement Health and Education Act of 1994 (DSHEA), which provides guidance regarding acceptable health claims and product labeling, and requires manufacturers to maintain records substantiating any health claims made [93]. DSHEA also stipulates that the manufacturer provide to the Food and Drug Administration information related to safety of certain "new dietary ingredients" (ingredients without a history of safe use, especially as foods or food ingredients) [93]. The regulation of botanicals as a subclass of foods rather than as drugs is controversial, and some see DSHEA as inappropriately burdening the Food and Drug Administration with proving that there is a risk of harm to consumers, rather than requiring the manufacturer to provide proof that the product is not harmful prior to marketing the product [94, 95].

There is a critical need for reliable information about the efficacy and safety of botanical supplements. If a supplement lacks efficacy, in addition to any negative financial effect on the consumer, it may indirectly harm the consumer by taking the place of an effective treatment [96]. Proof of efficacy and safety should lead to further investigation of mechanism(s) of action and the identification of active principles, if not already known [11]. Identification of the active principle enables standardization of doses and assurance that a product contains amounts of the active principle comparable with that present in formulations reported in the scientific literature, including published clinical trial reports and official monographs [11, 97].

Many botanical products have uncertain efficacy, lack standardization, or pose safety risks, including potentially harmful herb-drug interactions [94, 95, 98, 99]. For instance, a phloroglucinol derivative, hyperforin (**133**), from St. John's wort (*Hypericum perforatum* L.), interacts with drug metabolizing enzymes, including the cytochrome p450 isozyme CYP3A4 [100]. Furthermore, adulteration (or contamination) with synthetic drugs [101] or misidentified ingredients (e.g., products containing aristolochic acids I and II (**134** and **135**) [102-104] and digitalis glycosides [105]) has proven to be a serious problem. There is concern that harmful products may enter into, and persist in, the marketplace because of poor quality control (non-GMP production methods) and poor mechanisms of post-market surveillance (adverse events reporting) [94, 96, 106]. The U.S. FDA is strengthening its regulatory oversight of dietary supplements, including botanicals (for instance, issuing a ban on ephedrine-containing dietary supplements in early 2004 [107]), and the U.S. FDA is expected to issue good manufacturing practice guidelines for nutritional supplements in 2005 [106]. A number of governments and other agencies (including Australia, Canada, the People's Republic of China, Japan, and the European Union) have already adopted similar regulatory requirements [99, 108].



hyperforin (**133**) aristolochic acid I (**134**) aristolochic acid II (**135**)

Fig. (7).

5. RECENT TRENDS AND FUTURE DIRECTIONS

Despite substantial successes, the traditional bioassay-guided isolation approach to natural products drug discovery has its limitations, particularly in the industrial setting where screening assays tend to be maintained for no more than a few months before they are replaced. This is usually not enough time to complete the multiple iterations of fractionation followed by bioassay that are typically required to isolate pure compounds from an active crude extract. Another liability is the potential for interference with a given assay from "nuisance" compounds that may co-occur with the active principle, and that may cause false readings depending on the nature of the assay [109-114]. These features may put natural product approaches at a disadvantage in the current drug discovery environment. New strategies must be implemented in order for natural products research to be more fully compatible with high-throughput screening.

One approach is to screen pure natural product libraries (or, alternatively, partially purified chromatographic fraction libraries). Although this is not a new approach, it is being pursued in new ways. Recently, the United States National Institutes of Health began a "molecular libraries initiative", in which chemically diverse compounds, specifically including natural products, are being compiled into a shared resource library for high-throughput screening against diverse disease targets. One outcome of such a library approach is that the concept of an "inactive compound" may have to be reconsidered. Echoing Emerson, "inactive compounds" may simply be compounds whose activity has not yet been discovered (i.e., they have not yet been tested against the right pharmacological target). This will have significant bearing on how natural products research is carried out, since structural novelty (chemical diversity) may become more important than biological activity during the isolation process.

Another approach is to accelerate the isolation and structure elucidation process, making use of increases in sensitivity of spectroscopic equipment and biological assays and improvements in chromatographic technologies. Combined chromatographic and spectroscopic methods of mixture analysis (including "hyphenated" techniques such as LC-MS and LC-NMR) employing chromatographic or spectroscopic methods in conjunction with pattern-recognition programs and statistical analysis (phytochemical profiling or "metabolomic" techniques) are beginning to be applied to the investigation of botanical medicines and to natural product drug discovery [115-120].

Computational chemistry methods (*in silico* or "virtual screening") may be used to "assay" the activity of the known chemical constituents of a plant, a mixture, or an entire herbal pharmacopoeia against known targets [121, 122]. Rollinger and colleagues [122] used a virtual screening approach to evaluate the cyclooxygenase (COX) inhibitory activity of compounds with an ethnomedical connection (constituents of plants selected from the works of Dioscorides), arbitrarily selected natural products (from the *Dictionary of Natural Products*), and mostly synthetic compounds (multiple sources). Interestingly, the hit rate for ethnomedically selected compounds was roughly double that of the compounds from other sources [122].

Synergy of activity between components is thought to be an important contributor to the activity of many botanical medicines and natural product extracts. There are, however, very few reported instances of the systematic identification of the exact components in a crude natural product extract that act synergistically. Indeed, there are logistical barriers to conducting bioassay-guided isolation of synergistic components: if all fractions are tested in all possible combinations, the number of samples quickly becomes unmanageable [123]. Nonetheless, there are a number of examples of individual constituents showing synergistic activity after recombination [124-126]. Methods and statistical models for demonstrating synergy between individual components have been described elsewhere [127-129]. Using an innovative sample-pooling method, coupled with automated sample-handling equipment, the systematic evaluation of synergy on a large scale has been shown to be logistically feasible [130, 131], and perhaps it is time for examining synergy more closely in natural products drug discovery.

6. CONCLUSIONS

Drugs derived from natural products (directly or indirectly) constitute roughly half of prescription medicines, and it seems likely that this will continue to be the case in the

future, as about half of the new chemical entities entering the development pipeline are natural products or related compounds. The importance of natural products in modern medicine is not simply a relic of the shared history of medicine and drugs from nature. Natural products are excellent sources of chemically diverse, drug-like lead structures for drug discovery. The search for drugs from nature continues to yield diverse lead compounds from a variety of organisms, and there still remains much to investigate. Furthermore, herbal products are a significant part of modern medicine and pharmacy, and investigation of botanical medicines (particularly with regard to the determination of their active principles and mechanisms of action) by pharmacognosists and other natural product scientists is essential for these products to remain part of the modern healthcare milieu.

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