Bioactive Molecules and Medicinal Plants

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(Eds.)

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Preface

Use of medicinal plants is as old as human civilization and continuous efforts are being made to improve medicinal plants or produce their products in high amounts through various technologies. About 200,000 natural products of plant origin are known and many more are being identified from higher plants and microorganisms. Some plant-based drugs have been used for centuries and there is no alternative medicine for many drugs, such as cardiac glycosides. However, natural products research was sidelined to pave the way for combinatorial chemistry, which was expected to produce large numbers of synthetic compounds for high-throughput screening (HTS). This line of work has failed to deliver desirable results. Moreover, it is not possible for all pharmaceutical companies and institutions to adopt costly HTS technology. Therefore, medicinal plants and their bioactive molecules are always in demand and are a central point of research. While planning this book, we endeavored to incorporate articles that cover the entire gamut of current medicinal plants research.

The aim of this book was to review the current status of bioactive molecules and medicinal plants research in light of the surge in the demand for herbal medicine. The chapters focus on bioactive molecules (e.g., stilbenes and phytoestrogens) and on medicinal plants as a whole (e.g., *Bacopa monnierie*). We hope that this book will be useful for researchers in academia, industry, and agriculture planning.

Finally, we would like to acknowledge our contributors, who have made serious efforts to ensure the high scientific quality of this book. We also would like to thank our colleagues at Springer.

June 2007 *K.G. Ramawat and J.M. Mérillon*

About the editors

Professor K.G. Ramawat (born in 1952) received his M.Sc. (1974) and Ph.D. (1978, Plant Biotechnology) from the University of Jodhpur, Jodhpur, India and became a faculty member in January of 1979. He joined M.L. Sukhadia University as an Associate Professor in 1991 and became a Professor in 2001. He served as Head of the Department of Botany (2001–2004), was in charge of the Department of Biotechnology (2003–2004), was a member of the task force on medicinal and aromatic plants at the Department of Biotechnology (Government of India, New Delhi; 2002–2005), and was a coordinator of the UGC-DRS and DST-FIST programs (2002–2007). He did his postdoctoral study at the University of Tours, France (1983–85) and subsequently worked as visiting professor at the University of Tours (1991) and University of Bordeaux 2, France (1995, 1999, 2003, 2006). He visited Poland under the auspices of an INSA-PAN academic exchange program (2005). He has published more than 100 research papers and review articles in reputed journals and books. He has edited two books on the biotechnology of secondary metabolites and of medicinal plants (Scientific Publishers, Enfield, USA). Professor Ramawat has completed several major research projects from UGC, CSIR, ICAR, DBT, and DST, and has supervised the doctoral theses of 16 students. He has been a member of the Plant Tissue Culture Association of India since 1991.

Professor J.M. Mérillon (born in 1953) received his M.Pharma. (1979) and Ph.D. (1984) from the University of Tours, Tours, France. He joined the University of Tours as a faculty member in 1982, became associate professor in 1987, and a full Professor in 1993 at the faculty of Pharmacy, University of Bordeaux 2, Bordeaux, France. He is currently group leader of a "study group on biologically active plant substances" at the Institute of Vine and Wine Sciences, which comprises 20 scientists and research students. He has published more than 80 research papers in internationally recognized journals. He is involved in developing courses and research on phytochemistry and biological properties of compounds from vine and wine in France and has traveled widely as a senior professor. Scientists from several countries are working in his laboratory and his research is supported by funds from the Vinegrowers Association, Ministry of Higher Education and Research, and various private enterprises.

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Chapter 1
Drug Discovery from Plants

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Abstract Many plant-derived compounds have been used as drugs, either in their original or semi-synthetic form. Plant secondary metabolites can also serve as drug precursors, drug prototypes, and pharmacological probes. Recent developments in drug discovery from plants, including information on approved drugs and compounds now in clinical trials, are presented. There are also several plant extracts or "phytomedicines" in clinical trials for the treatment of various diseases. In the future, plant-derived compounds will still be an essential aspect of the therapeutic array of medicines available to the physician, particularly with the availability of new hyphenated analytical methods such as LC-NMR-MS and LC-SPE-NMR to accelerate their future discovery.

Keywords Natural products, Plant-derived drugs, Drug discovery, Drug development, Drug precursors, Drug prototypes, Pharmacological probes, New therapeutic agents, Clinical trials, Accelerated discovery techniques

1.1 The Role of Plants in Human History

Over the centuries humans have relied on plants for basic needs such as food, clothing, and shelter, all produced or manufactured from plant matrices (leaves, woods, fibers) and storage parts (fruits, tubers). Plants have also been utilized for additional purposes, namely as arrow and dart poisons for hunting, poisons for murder, hallucinogens used for ritualistic purposes, stimulants for endurance, and hunger suppression, as well as inebriants and medicines. The plant chemicals used for these latter purposes are largely the secondary metabolites, which are derived biosynthetically from plant primary metabolites (e.g., carbohydrates, amino acids, and lipids) and are not directly involved in the growth, development, or reproduction of plants. These secondary metabolites can be classified into several groups according to their chemical classes, such alkaloids, terpenoids, and phenolics [1].

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Arrow and dart poisons have been used by indigenous people in certain parts of the world with the principal ingredients derived from the genera *Aconitum* (Ranunculaceae), *Akocanthera* (Apocynaceae), *Antiaris* (Moraceae), *Chondrodendron* (Menispermaceae), *Strophanthus* (Apocynaceae), and *Strychnos* (Loganiaceae) [2]. Most compounds responsible for the potency of arrow and dart poisons belong to three plant chemical groups, namely the alkaloids (e.g., strychnine from *Strychnos* species), cardiac glycosides (e.g., ouabain from *Strophanthus* species), and saponins (e.g., a monodesmoside glucoside from *Clematis* species) [2].

In some cultures, toxic plant extracts were also used for murder and "trials by ordeal," where a person accused of a crime was given a noxious brew, and it was believed that if innocent, this suspect would survive this ordeal. Some of the plants well-documented for murder are henbane (*Hyoscyamus niger* L.), mandrake (*Mandragora officinarum* L.), deadly nightshade (*Atropa belladonna* L.), and some *Datura* species, all of which belong to the family Solanaceae [3]. Calabar bean (*Physostigma venenosum* Balf.) was famous for its use in trials by ordeal by people who lived on the Calabar Coast, West Africa [3]. Certain plants formerly used for arrow poisons, such as several *Aconitum* species, have also been used as medicines at lower dosages, for their analgesic and anti-inflammatory properties [4]. In fact, many compounds isolated from poisonous plants were later developed as therapeutic drugs, due to their desirable pharmacological actions [5, 6].

The use of hallucinogens in the past was usually associated with magic and ritual. However, these hallucinogens have been exploited as recreational drugs and accordingly may lead to habituation problems. Several well-recognized plants that contain hallucinogenic or psychoactive substances (the compound names are given in parentheses) include *Banisteriopsis caapi* (Spruce ex Griseb.) Morton (*N,N*-dimethyltryptamine), *Cannabis sativa* L. (Δ^9-*trans*-tetrahydrocannabinol), *Datura* species (scopolamine), *Erythroxylum coca* Lam. (cocaine), *Lophophora williamsii* (Salm-Dyck) J.M. Coult. (mescaline), *Papaver somniferum* L. (morphine), and *Salvia divinorum* Epling & Játiva (salvinorin A) [7, 8]. Several of these plants are also used as drugs due to their desired pharmacological activities, and some of the constituents of these plants have been developed into modern medicines, either in the natural form or as lead compounds subjected to optimization by synthetic organic chemistry [5, 6].

Plants have also been used in the production of stimulant beverages (e.g., tea, coffee, cocoa, and cola) and inebriants or intoxicants (e.g., wine, beer, kava) in many cultures since ancient times, and this trend continues till today. Tea (*Camellia sinensis* Kuntze) was first consumed in ancient China (the earliest reference is around CE 350), while coffee (*Coffea arabica* L.) was initially cultivated in Yemen for commercial purposes in the 9th century [3]. The Aztec nobility used to consume bitter beverages containing raw cocoa beans (*Theobroma cacao* L.), red peppers, and various herbs [3]. Nowadays, tea, coffee, and cocoa are important commodities and their consumption has spread worldwide. The active components of these stimulants are methylated xanthine derivatives, namely caffeine, theophylline, and theobromine, which are the main constituents of coffee, tea, and cocoa, respectively [9].

The most popular inebriants in society today are wine, beer, and liquor made from the fermentation of fruits and cereals. Wine was first fermented about 6000–8000 years ago in the Middle East, while the first beer was brewed around 5000–6000 BCE by the Babylonians [3]. The intoxicating ingredient of these drinks is ethanol, a by-product of bacterial fermentation, rather than secondary plant metabolites. Recent studies have shown that a low to moderate consumption of red wine is associated with reduction of mortality due to cardiovascular disease and cancer [10]. This health benefit has been suggested to be due to the presence of resveratrol, a hydroxylated stilbenoid found in the skin of grapes [11]. Kava, a beverage made from the root of *Piper methysticum* Roxb., has been a popular intoxicating beverage in Polynesia for centuries [3]. Kava is not normally consumed in this manner in the Western world, but has gained popularity as a botanical dietary supplement to ease the symptoms of stress, anxiety, and depression [12]. A study has shown that the anxiolytic activity of kava extract may be mediated in part by the kavalactone, dihydrokavain [13]. The consumption of kava has been associated with liver toxicity, although this is somewhat controversial. Recently, a study has shown that the alkaloid pipermethystine, found mostly in the leaves and stems of *Piper methysticum*, may be responsible for this toxicity [14].

Plants have formed the basis of sophisticated traditional medicine (TM) practices that have been used for thousands of years by people in China, India, and many other countries [9]. Some of the earliest records of the usage of plants as drugs are found in the Artharvaveda, which is the basis for Ayurvedic medicine in India (dating back to 2000 BCE), the clay tablets in Mesopotamia (1700 BCE), and the Eber Papyrus in Egypt (1550 BCE) [9]. Other famous literature sources on medicinal plant include "De Materia Medica," written by Dioscorides between CE 60 and 78, and "Pen Ts'ao Ching Classic of Materia Medica" (written around 200 CE) [9].

Before the realization that pharmacologically active compounds present in medicinal plants are responsible for their efficacy, the "doctrine of signatures" was often used to identify plants for treating diseases. For example, goldenrod with a yellow hue was used to cure jaundice, red-colored herbs were used to treat blood diseases, liverworts were used for liver diseases, pileworts for hemorrhoids, and toothworts for toothache [9]. In 1805, morphine became the first pharmacologically active compound to be isolated in pure form from a plant, although its structure was not elucidated until 1923 [9]. The 19th century marked the isolation of numerous alkaloids from plants (species in parentheses) used as drugs, namely, atropine (*Atropa belladonna*), caffeine (*Coffea arabica*), cocaine (*Erythroxylum coca*), ephedrine (*Ephedra* species), morphine and codeine (*Papaver somniferum*), pilocarpine (*Pilocarpus jaborandi* Holmes), physostigmine (*Physostigma venenosum*), quinine (*Cinchona cordifolia* Mutis ex Humb.), salicin (*Salix* species), theobromine (*Theobroma cacao*), theophylline (*Camellia sinensis*), and (+)-tubocurarine (*Chondodendron tomentosum* Ruiz & Pav.) [9]. Following these discoveries, bioactive secondary metabolites from plants were later utilized more widely as medicines, both in their original and modified forms [5, 6].

The correlation between the ethnomedical usage of medicinal plants and modern medicines discovered from those plants has been studied by Fabricant and Farnsworth [15]. Based on their analysis, 88 single chemical entities isolated from 72 medicinal plants have been introduced into modern therapy, many of which have the same or a similar therapeutic purpose as their original ethnomedical use [15]. Some of these plant-derived compounds, such as atropine (anticholinergic), codeine (cough suppressant), colchicine (antigout), ephedrine (bronchodilator), morphine (analgesic), pilocarpine (parasympathomimetic), and physostigmine (cholinesterase inhibitor) are still being used widely as single-agent or combination formulations in prescription drugs [5].

Nowadays, plants are still important sources of medicines, especially in developing countries that still use plant-based TM for their healthcare. In 1985, it was estimated in the Bulletin of the World Health Organization (WHO) that around 80% of the world's population relied on medicinal plants as their primary healthcare source [16]. Even though a more recent figure is not available, the WHO has estimated that up to 80% of the population in Africa and the majority of the populations in Asia and Latin America still use TM for their primary healthcare needs [17]. In industrialized countries, plant-based traditional medicines or phytotherapeuticals are often termed complementary or alternative medicine (CAM), and their use has increased steadily over the last 10 years. In the USA alone, the total estimated "herbal" sales for 2005 was $4.4 billion, a significant increase from $2.5 billion in 1995 [18]. However, such "botanical dietary supplements" are regulated as foods rather than drugs by the United States Food and Drug Administration (US FDA).

1.2 The Role of Plant-Derived Compounds in Drug Development

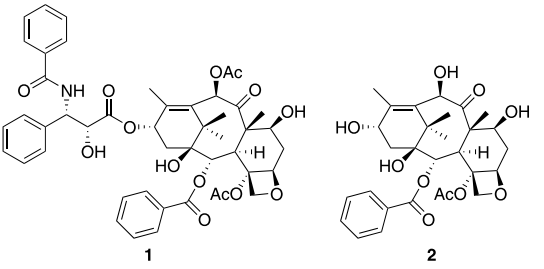
Despite the recent interest in drug discovery by molecular modeling, combinatorial chemistry, and other synthetic chemistry methods, natural-product-derived compounds are still proving to be an invaluable source of medicines for humans. The importance of plants in modern medicine has been discussed in recent reviews and reports [19–22]. Other than the direct usage of plant secondary metabolites in their original forms as drugs, these compounds can also be used as drug precursors, templates for synthetic modification, and pharmacological probes, all of which will be discussed briefly in turn in this section.

1.2.1 Plant Secondary Metabolites as Drug Precursors

Some natural products obtained from plants can be used as small-molecule drug precursors, which can be converted into the compound of interest by chemical

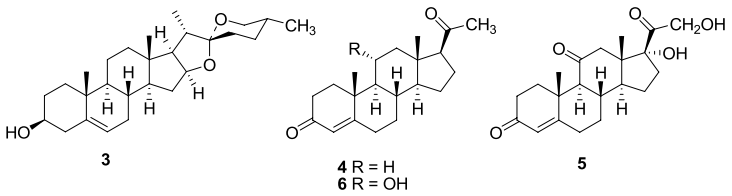
modification or fermentation methods. The semisynthetic approach is usually used to resolve the shortage of supply due to the low yield of compounds from plants and/or the high cost of total synthesis. For compounds with complex structures and many chiral centers, protracted methods may be needed for their synthesis, and thus these methods would not be feasible economically. The following examples indicate that some secondary metabolites from plants are useful drug precursors, although they are not necessarily pharmacologically active in their original naturally occurring forms.

Cropping of the bark of the slow-growing Pacific yew tree, *Taxus brevifolia* Nutt., is not a feasible method to provide sufficient amounts of the antitumor drug paclitaxel (1, Taxol) to meet the market demand (paclitaxel was originally isolated in only 0.014% w/w yield from the bark of *Taxus brevifolia*) [23]. Even though this compound can be produced by total synthesis, this has proven to be inefficient in affording large quantities of paclitaxel [24, 25]. Fortunately, 10-deacetylbaccatin III (**2**) can be isolated in relatively large amounts from the needles of other related yew species, such as *Taxus baccata* L. (a renewable resource), and can be converted chemically in several steps into paclitaxel [26, 27]. During the period 1993–2002, the main pharmaceutical manufacturer, Bristol-Myers Squibb, adopted the semisynthetic method developed by the Holton research group to produce paclitaxel from 10-deacetylbaccatin III [27, 28]. Since 2002, Bristol-Myers Squibb has produced paclitaxel using a plant cell culture method, which will be mentioned in section 1.4 of this chapter [29].

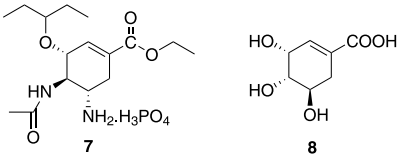


Diosgenin (**3**), a steroidal sapogenin obtained from the tubers of various *Dioscorea* species that grow in Mexico and Central America, can be converted chemically in several steps into progesterone (**4**), a hormone that can be used as a female oral contraceptive [30]. Originally, progesterone was isolated from sow ovaries with a very low yield (20 mg from 625 kg of ovaries), and later was synthesized from cholesterol with very low efficiency [31]. Progesterone is also a key intermediate for the production of cortisone (**5**), an important anti-inflammatory drug. Progesterone can be converted into 11α-hydroxyprogesterone (**6**) by microbial hydroxylation at C-11, followed by chemical reactions, to produce

cortisone (**5**) [32, 33]. Until now, diosgenin (**3**) is still an important starting material for the production of various steroid hormones.



Oseltamivir phosphate (**7**, Tamiflu) is an orally active neuraminidase inhibitor developed for the treatment and prophylaxis of influenza viruses A and B [34, 35]. The starting material for the oseltamivir synthesis is (−)-shikimic acid (**8**), an important biochemical intermediate in plants and microorganisms [36]. Previously, shikimic acid was extracted solely from the fruits of the shikimi tree (*Illicium verum* Hook.f.), also known as star anise, which contains a large amount of this compound [37]. Later on, shikimic acid was obtained from the fermentation of genetically engineered *Escherichia coli* strains, which are deficient in the shikimate kinase gene [38]. Currently, Roche, the drug manufacturer, still relies on both extraction and fermentation methods to obtain ton quantities of shikimic acid [37]. Several routes for the production of oseltamivir independent of shikimic acid have been developed [36, 39], but these alternatives are still not cost efficient [37].

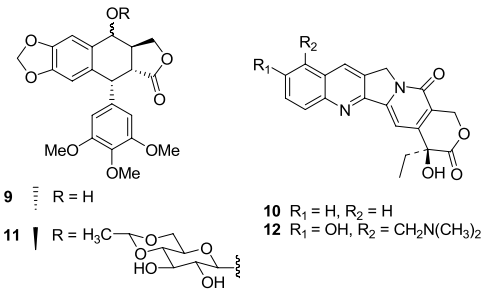


1.2.2 Plant Secondary Metabolites as Drug Prototypes

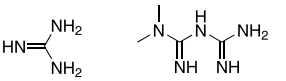
Sneader has defined a drug prototype as "the first compound discovered in a series of chemically related therapeutic agents" [5]. As of 1996, from a total of 244 drug prototypes identified in one analysis from minerals, plants, animals, microbes, and chemical sources, plant secondary metabolites contributed 56 of these (23%) [5]. With advances in organic chemistry, medicinal chemists started preparing analogs from these drug prototypes to provide safer and more potent drugs. Sometimes, new compounds with novel pharmacological properties have

been developed in the process of developing such derivatives. In the following examples, podophyllotoxin, camptothecin, and guanidine have been selected as drug prototypes with analogs having the same pharmacological action as the parent compound, while atropine is a drug prototype that has furnished many analogs that have additional pharmacological properties.

Several antineoplastic compounds isolated from plants, such as podophyllotoxin (**9**) and camptothecin (**10**), are too toxic or not water soluble enough for clinical application, and analogs with higher therapeutic indices such as etoposide (**11**, Vepesid) and topotecan (**12**, Hycamtin) have been developed in consequence [40, 41]. Due to their unique modes of anticancer activities, there is much interest in the clinical development of further derivatives of paclitaxel (**1**) and camptothecin (**10**) as anticancer therapeutic drugs [28, 41–43]. According to a recent review, of the 2255 cancer clinical trials recorded as of August 2003, 310 (or 13.7%) and 120 (or 5.4%) of the trials involved taxane- and camptothecin-derived drugs, respectively [43]. In 2002, it was estimated that the combined sales of paclitaxel and docetaxel (both taxanes), and topotecan and irinotecan (both based on the parent molecule camptothecin) constituted over 30% of the total global sales of cytotoxic drugs [44].



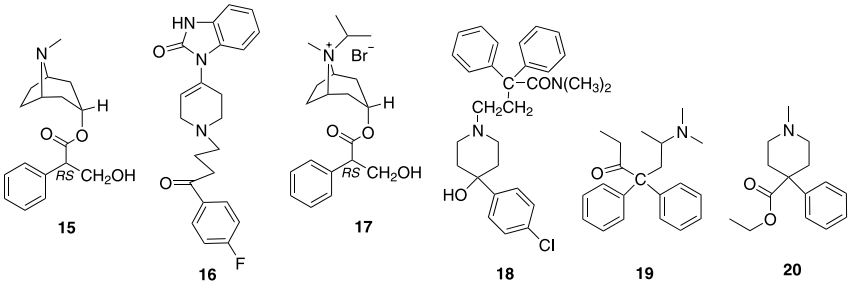
Guanidine (**13**) is a natural product with good hypoglycemic activity isolated from *Galega officinalis* L., but is too toxic for clinical use [45]. Many derivatives of guanidine have been synthesized, and metformin (dimethylbiguanide) (**14**) was later found to be clinically suitable for treatment of type II diabetes [46].



13 **14**

Atropine (**15**) is an artifact of the tropane alkaloid (−)-hyoscyamine, which racemizes during the extraction process from its plant of origin (*Atropa belladonna*). Atropine is a competitive antagonist of muscarinic acetylcholine

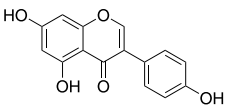
receptors (antimuscarinic agent). Atropine is sometimes used in the ophthalmology area as a mydriatic agent, and has additional therapeutic uses as an antispasmodic. It is also used as a premedication for anesthesia, to decrease bronchial and salivary secretions, and to block the bradycardia (low heart rate) associated with the administration of anesthetic drugs [5]. Biological and physiological studies of a large number of synthetic atropine analogs have led to the introduction of new drugs with different therapeutic applications than the parent compound. Examples of drugs derived from the basic atropine skeleton include droperidol (**16**, antipsychotic), ipratropium bromide (**17**, bronchodilator for the treatment of asthma), loperamide (**18**, antidiarrheal), methadone (**19**, a morphine substitute for addicts), and pethidine (**20**, analgesic) [5].



1.2.3 Plant Secondary Metabolites as Pharmacological Probes

In addition to their direct contribution as drugs or drug protopyes to cure human disease, secondary metabolites of plant origin, such as phorbol esters and genistein, can be used as "pharmacological probes." Pharmacological probes help researchers to understand the mechanism of action of intracellular signal transductions and biological mechanisms related to human disease, which can aid the design of better drugs.

Genistein (**21**), an isoflavone found naturally in soybean (*Glycine max* Merr.), is an inhibitor of various protein tyrosine kinases (PTK), which are essential enzymes involved in intracellular signal transduction [47]. Genistein has been used to probe the interaction between PTK and cyclic nucleotide-gated (CNG) channels, which are important in mammalian olfactory and visual systems [48, 49]. By observing the effect of genistein on the CNG channels containing either homomeric or heteromeric subunits, specific subunits containing binding sites for PTKs can be identified [48]. Furthermore, the mechanism of inhibition of the CNG channels by PTKs has been studied with the aid of genistein as a probe [49].



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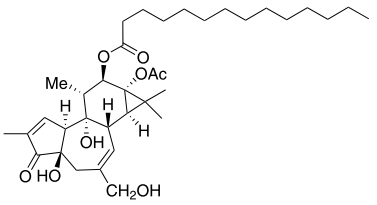
Phorbol is a tetracyclic diterpenoid plant secondary metabolite isolated as a hydrolysis product of croton oil from the seeds of *Croton tiglium* L. [50]. Various 12,13-diesters of phorbol have the capacity to act as tumor promoters, due in part to their role as protein kinase C (PKC) activators [51–53]. The most abundant phorbol ester derivative of croton oil, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (**22**), has been used in biomedical research in standard laboratory models of carcinogenesis promotion [54–56].



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1.3 Recent Developments in Drug Discovery from Plants

Despite the large number of drugs derived from total synthesis, plant-derived natural products still contribute to the overall total number of new chemical entities (NCE) that continue to be launched to the market. Several reviews on drug discovery and development from natural sources (plants, marine fauna, microbes) have been published recently [42, 57–59]. The following sections will cover specifically the plant-derived drugs newly launched since 2001 and examples of some plant-derived compounds currently in clinical trials.

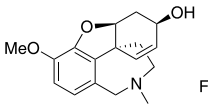
1.3.1 New Plant-Derived Drugs Launched Since 2001

In the past 6 years, five new drugs derived from natural products, namely, apomorphine hydrochloride, galanthamine hydrobromide, nitisinone, tiotropium bromide, and varenicline, have been approved by the US FDA. The following is a brief description of each drug and their therapeutic use.

Galantamine (**23**, Razadyne, Reminyl, Nivalin) was first marketed in 2001 in the USA for the symptomatic treatment of patients with early-onset Alzheimer's

disease [58]. Galantamine (also known as galanthamine) is an alkaloid that was initially isolated from the snowdrop (*Galanthus woronowii* Losinsk.) in the early 1950s, and has since been found in other plants in the family Amaryllidaceae [60]. Galantamine slows the process of neurological degeneration by inhibiting acetylcholinesterase as well as binding to and modulating the nicotinic acetylcholine receptor [60, 61]. Due to the limited availability of the plants of origin of this compound, galantamine is now produced by total synthesis.

Nitisinone (**24**, Orfadin) was approved by the FDA in 2002 for the treatment of hereditary tyrosinemia type 1 (HT-1) [58]. HT-1 is a rare pediatric disease caused by a deficiency of fumaryl acetoacetate hydrolase (FAH), an enzyme essential in the tyrosine catabolism pathway. FAH deficiency leads to the accumulation of toxic substances in the body, resulting in liver and kidney damage [62]. Nitisinone is a derivative of leptospermone (**25**), a new class of herbicide from the bottlebrush plant [*Callistemon citrinus* (Curtis) Skeels]. Both nitisinone and leptospermone inhibit 4-hydroxyphenyl pyruvate dioxygenase (HPPD), the enzyme involved in plastoquinone and tocopherol biosynthesis in plants [63]. In humans, inhibition of HPPD prevents tyrosine catabolism, leading to the accumulation of tyrosine metabolites, 4-hydroxyphenyl pyruvic acid and 4-hydroxyphenyl lactic acid, which can be excreted through the urine [64].



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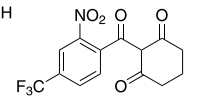

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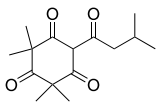

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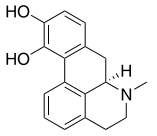
Apomorphine (**26**, Apokyn) was approved by the FDA in 2004 as an injectable drug for the symptomatic treatment for Parkinson's disease patients during episodes of "hypomobility" (e.g., persons unable to move or to perform daily activities) [65]. Apomorphine is a synthetic derivative of morphine (**27**), but unlike morphine, apomorphine does not have opioid analgesic properties, and instead is a short-acting dopamine D_1 and D_2 receptor agonist [66].



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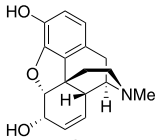

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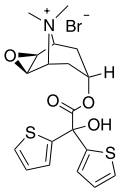
Tiotropium bromide (**28**, Spiriva), an atropine analog, was approved by the FDA in 2005 for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema [67].



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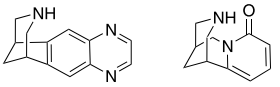
Varenicline (**29**, Chantix), based on the plant quinolizidine alkaloid, cytisine (**30**), has been approved by the FDA since 2006 as an aid to smoking cessation [68–70]. Cytisine (**30**), an alkaloid isolated from *Cytisus laburnum* L., has been used to treat tobacco dependence in Eastern Europe (Bulgaria, Germany, Poland, and Russia) for the last 40 years [71]. Cigarette smoking has been linked to several diseases including cardiovascular disease, COPD, many cancers (particularly lung, mouth, and esophageal), and pregnancy-related complications. Varenicline (**29**) is a partial agonist with a high affinity for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor, and is a full agonist at α_7 neuronal nicotinic receptors [70].



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1.3.2 Examples of Plant-Derived Compounds Currently Involved in Clinical Trials

Although relatively few plant-derived drugs have been launched onto the market the last 6 years, many plant-derived compounds are currently undergoing clinical trial for the potential treatment of various diseases. The majority of such drugs under clinical development are in the oncological area, including new analogs of known anticancer drugs based on the camptothecin-, taxane-, podophyllotoxin-, or vinblastine-type skeletons [42]. Examples of compounds with carbon skeletons different from the existing plant-derived drugs used in cancer chemotherapy will be discussed below, namely, betulinic acid, ceflatonine (homoharringtonine), combretastatin A4 phosphate, ingenol-3-angelate, phenoxodiol, and protopanaxadiol. In the antiviral area, bevirimat and celgosivir are currently undergoing clinical trials for the treatment of human immunodeficiency viral (HIV) and hepatitis C viral (HCV) infections, respectively. Capsaicin is in clinical trial for the treatment of severe postoperative pain, while huperzine is being developed for the treatment of Alzheimer's disease.