4

Drugs in Clinical Practice from Toxic Plants and Phytochemicals

Tadele Mekuriya Yadesa[1,2], Patrick Engeu Ogwang[1,2], and Casim Umba Tolo[2,3]

[1] *Department of Pharmacy, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda*
[2] *Pharmbiotechnology and Traditional Medicine Center (PHARMBIOTRAC), Mbarara University of Science and Technology, Mbarara, Uganda*
[3] *Department of Biology, Faculty of Science, Mbarara University of Science and Technology, Mbarara, Uganda*

CONTENTS

Poisonous Plants and Phytochemicals in Drug Discovery, First Edition.
Edited by Andrew G. Mtewa, Chukwuebuka Egbuna, and G.M. Narasimha Rao.

4.1 Introduction

The use of natural products as medicines is assumed to have presented a great challenge to early humans. Despite the potential adverse outcomes, perhaps early humans often used poisonous plants on themselves to ultimately discover natural medicines [1]. Traditionally, a single herb or formula may contain many phytochemical constituents, such as alkaloids, terpenoids, or flavonoids. Generally, these chemicals function alone or in conjunction to effect the desired medicinal outcome [2]. However, with advances in the theoretical background, therapeutic principles, associated technologies, and understanding of the life sciences, a deeper understanding of the active compounds of traditional and complementary medicine has been reached [3].

Shortly after the beginning of the era of "modern" drugs in the nineteenth century, a German pharmacist, Friedrich Sertürner, isolated the first pharmacologically active compound, morphine, from the opium plant in 1805. Subsequently, numerous active compounds have been separated from natural products. Despite the fact that the development of synthetic techniques has led to a significant reduction in their importance, natural products still continue to be crucial for the development of new drugs. To this effect, categories of medicines, such as anticancer, antihypertensive, and antimigraine medication, have benefited greatly from natural products [4–6]. The acceptability, convenience, and accessibility of traditional medicine has been, and will continue to be, helpful for new drug research [7].

The toxicity of medicinal plants derives primarily from the fact that they contain diester diterpene alkaloids such as aconitine, mesaconitine, and hypaconitine [8]. Poisoning as a result of taking homemade medicated liquor containing aconite and traditional medicine containing *Aconitum carmichaelii* was reported in China between 1999 and 2008 [9]. Severe cases of cardiac toxicity from the consumption of aconitine-containing herbal preparations manifesting as ventricular tachycardia and fibrillation and eventually leading to death have also been reported [10, 11].

Venoms have been included in numerous systems of traditional healing since prehistoric times, but the modern translation of toxins into medicines began only in the 1940s with the introduction of tubocurarine, a vegetal compound, into anesthetic practice as a selective muscle relaxant. Generally speaking, plant toxins are representative of a large group of structurally diverse small molecules that result from plant secondary metabolism, whereas most animal toxins are peptides and proteins that are often resistant to protease owing to their disulfide-rich architectures [12, 13]. In this chapter, the drugs in clinical practice obtained from toxic plants and their chemistry will be discussed.

4.2 Drugs in Clinical Practice from Toxic Plants

4.2.1 Curare

Curare is the common name for various plant alkaloid toxins originating from Central and South America. Originally, it was familiar as an "arrow poison" because the indigenes used it for hunting; it was traditionally produced by boiling diverse plants (e.g. *Chondrodendron tomentosum*, *Menispermaceae*, or *Strychnos*). In the 1860s, the scientists Thomas Richard Fraser and Alexander Crum Brown, working on the relationship between chemical structure and biological activity, discovered that when alkaloids such as atropine, brucine, codeine, morphine, and nicotine had their nitrogen atoms changed from the tertiary to the quaternary form they acquired curare-like activity. Harold King isolated D-tubocurarine from a museum sample of curare, and in 1942 Oscar Wintersteiner and James Dutcher isolated the alkaloid D-tubocurarine from the plant *C. tomentosum*. Its first clinical use as a muscle relaxant during an operation was in the same year [14, 15].

In addition, the molecular mechanism of curare as a competitive antagonist of nicotinergic neuromuscular synaptic junctions was finally elucidated in the twentieth century. This non-depolarizing muscle relaxant acts by paralyzing skeletal musculature, including respiratory muscles. Tubocurarine is a long-acting benzylisoquinoline that is eliminated by both renal excretion and hepatic metabolism. It also causes the release of histamine, which is associated with a significant reduction in blood pressure following rapid infusions of large doses [16, 17]. Histamine-associated hypotension can be minimized by slow injection, incremental dose increases, and co-administration of histamine-1 and histamine-2 receptor blockers [18].

With the ongoing rapid development of medical science, new derivatives, such as atracurium, succinylcholine, gallamine, pancuronium, rocuronium, vecuronium, and mivacurium, have been synthesized with an excellent effectiveness to safety ratio and thus the original tubocurarine is no longer used clinically in most countries around the world. The most successful of the new muscle relaxants is atracurium [15].

4.2.2 Drugs Acting on the Central Nervous System

4.2.2.1 Morphine

Morphine's history begins with the use of opium poppy plants (*Papaver somniferum*), which are native to Eurasia and have been cultivated for more than 5000 years. Opium was used for its analgesic and sedative effects, whereas its poisonous effects were characterized by lethal respiratory depression at high doses. The molecule was discovered in 1805 by Friedrich Wilhelm Adam Sertürner

(1783–1841), a pharmacy pupil in Germany who was working on active opium compound isolation. Morphine is a morphinan isoquinoline alkaloid. Later, a number of other alkaloids, such as codeine and papaverine, were isolated from opium. Currently, codeine is obtained from morphine and is used as an analgesic and antitussive drug. Papaverine formed the basis for developing verapamil, a calcium channel blocker that is used to treat hypertension [19, 20].

Currently, morphine is approved by the US Food and Drug Administration (FDA) in sulfate form and is still accepted as the gold standard treatment for severe pain. Morphine was also the prototype for several opioid receptor agonists in clinical use, such as fentanyl, oxycodone, and methadone [20]. Nowadays, codeine is used in the management of mild to moderately severe pain and short-term relief of cough in select patients. Recently, the FDA has issued a drug safety communication after reviewing reports of children who developed serious adverse effects, including death, after receiving codeine in the usual dosage range for pain relief following tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome [21, 22].

Papaverine is currently indicated in various vascular spasms associated with smooth muscle spasms, such as myocardial infarction, angina, peripheral and pulmonary embolism, peripheral vascular disease, cerebral angiospastic states, and visceral spasms (ureteral, biliary, and gastrointestinal colic). However, because of the availability of safer and more effective alternative medications, these uses of papaverine have recently declined. Papaverine is also occasionally used in the prevention of vasospasm during harvesting of mammary arteries for coronary artery bypass graft surgery [23, 24].

4.2.2.2 Cocaine

Cocaine (benzoylmethylecgonine), supposed to be the most potent stimulant of natural origin, is extracted from the leaves of the coca plant (*Erythroxylum coca*), which is indigenous to the Andean highlands of South America. Natives in this region chew or brew coca leaves into a tea for refreshment and to relieve fatigue, similar to the customs of chewing tobacco and drinking tea or coffee in other cultures. Cocaine acts mainly by increasing dopamine levels by binding to the dopamine transporter and blocking the reuptake of dopamine into presynaptic cells. The therapeutic use of cocaine dates back to 1884, when Carl Koller used it in ophthalmic surgery. Despite legislative attempts dating from the early twentieth century to eradicate its use, cocaine remains a common and dangerous drug of abuse. The alkaloidal form of cocaine is extracted from the coca leaf by mechanical degradation in the presence of a hydrocarbon solvent. The resultant product is converted into a hydrochloride salt and extracted into an aqueous phase, from which water is subsequently evaporated to yield a white powder (cocaine hydrochloride) [25, 26].

Currently, its toxicity and potential for addiction have stringently limited cocaine's therapeutic purposes to topical anesthesia in ophthalmological and nasal surgery. However, the identification of the benzoyl moiety of cocaine enabled the synthesis of different molecules, such as: in 1890 benzocaine, which is the cocaine benzoic acid ester; in 1905 procaine, which is the cocaine para-aminobenzoic acid; and, finally, in 1943 lidocaine, which is the diethyl-aminoacetic acid derivative of cocaine that started the amide-type local anesthetic age. These drugs are now most commonly used for local anesthesia. Lidocaine is also often used in cardiac arrhythmias [26–28].

4.2.2.3 Ergot Alkaloids

Being primarily responsible for ergotism, or St. Anthony's fire disease, ergot alkaloids are currently used in the management of various medical conditions, particularly through their psychoactive and vasoconstrictive effects. This class of molecules belongs to the indole alkaloid group and can be classified according to their structures; namely, clavines, lysergic acid amides (ergoamides), and peptides (ergopeptines). Ergot alkaloids lead to the formation of the tetracyclic ergoline ring system, except the simplest one, the tricyclic compound. Convolvulaceae, Poaceae, and Polygalaceae are the three families of higher plants in which these metabolites are found, but their production is often dependent on the presence of plant-associated fungi. Moreover, fungi from the phylum Ascomycota, such as *Claviceps*, *Epichloë*, *Penicillium*, and *Aspergillus* spp., are the main producers of ergot alkaloids. *Claviceps purpurea* is the most studied species related to ergotism [29].

The ergot alkaloids have a strong affinity for the 5-hydroxytryptamine, dopamine, and adrenergic receptors in the central nervous system and also the adrenergic receptors in blood vessels. Owing to its specific uterotonic action, ergometrine started to be used for the prevention and treatment of postpartum hemorrhages. At the beginning of the nineteenth century, because of repeated cases of associated intrapartum ergometrine use and tetanic uterine contractions that led to fetal asphyxia, stillbirth, and uterine rupture, the role of ergometrine changed from *pulvis ad partum* (the powder of birth) to *pulvis ad mortem* (the powder of death), and its use was restricted to the management of postpartum hemorrhage. Additionally, ergot alkaloids were the first antimigraine drug available [29, 30].

Currently, ergotamine is indicated for the prevention and treatment of vascular headaches, such as migraine, migraine variants, or so-called "histaminic cephalalgia." Natural and semisynthetic ergot alkaloids are used as a second-line intervention if uterine atony persists after oxytocin administration during cesarean delivery. These are used as blood pressure modulators and pituitary hormone regulators for migraine prevention and as dopaminergic agents.

The cardiovascular adverse reactions of the class include: absence of pulse, bradycardia, cardiac valvular fibrosis, cyanosis, edema, electrocardiograph changes, gangrene, hypertension, ischemia, precordial distress and pain, tachycardia, and vasospasm. The contraindications of the class include hypersensitivity to ergotamine or any component of the formulation; peripheral vascular disease; hepatic or renal disease; coronary artery disease; hypertension; sepsis; coadministration with CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); and pregnancy [30, 31].

4.2.3 Atropine, Scopolamine, and Hyoscyamine

Atropine, scopolamine, and hyoscyamine are alkaloids found in plants of the Solanaceae botanical family, such as *Atropa belladonna*, *Datura stramonium*, *Hyoscyamus niger*, and *Hyoscyamus muticus*. Atropine and scopolamine are esters derived from the reaction of an aromatic acid (tropic acid) with tropine (tropanol) or scopine. Scopine differs from tropine only in having an oxygen bridge between C6 and C7. On the other hand, hyoscyamine is the tropine ester of tropic acid. It is an asymmetric molecule and forms atropine when (−)-hyoscyamine is racemized into the (±)-compound. During the Roman Empire and in the Middle Ages, *A. belladonna* (also called deadly nightshade) was frequently used to poison people by ingestion. To date, it is the major cause of poisoning [32].

Atropine and scopolamine work by blocking the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and the central nervous system, increasing cardiac output and drying secretions. Atropine reverses the muscarinic effects of poisoning by acetylcholinesterase inhibitors by acting as a competitive antagonist. Owing to their mechanisms of action, atropine and scopolamine are used as preoperative medications to inhibit salivation and secretions; in the treatment of symptomatic sinus bradycardia; as an atrioventricular block (nodal level); as an antidote for anticholinesterase poisoning (carbamate insecticides, nerve agents, organophosphate insecticides); and as an adjuvant to anticholinesterases (e.g. edrophonium, neostigmine) to decrease their side effects during reversal of neuromuscular blockade [33].

Significant adverse reactions of these drugs include cardiovascular (arrhythmia, flushing, hypotension, palpitation, tachycardia), central nervous system (ataxia, coma, delirium, disorientation, dizziness, drowsiness, excitement, fever, hallucinations, headache, insomnia, nervousness), dermatological, gastrointestinal, genitourinary, neuromuscular and skeletal weakness, ocular, and respiratory effects as well as anaphylaxis [34].

4.2.4 Physostigmine and Other Acetylcholinesterase Inhibitors

Physostigmine is a tertiary amine belonging to the indole alkaloid class. It is a highly unstable white powder that becomes red upon exposure to light, air, and heat. Physostigmine is present in the ripe seeds of *Physostigma venenosum* from Western Africa [35].

The first therapeutic use of the drug dates from 1877, when Ludwig Laqueur used it in the treatment of glaucoma. Further studies in 1929 led Edgar Stedman to identify the mechanism of its parasympathomimetic effect through acetylcholinesterase inhibition, thus acting as a substrate and facilitating carbamylation of the enzyme. Currently, physostigmine is indicated to reverse toxic, life-threatening delirium caused by atropine, diphenhydramine, dimenhydrinate, *A. belladonna* (deadly nightshade), or jimson weed (*Datura* spp.). Significant adverse reactions include cardiovascular (asystole, bradycardia, palpitation), central nervous system (hallucinations, nervousness, restlessness, seizure), gastrointestinal (diarrhea, nausea, salivation, stomach pain), genitourinary (urinary frequency), neuromuscular and skeletal (twitching), ocular (lacrimation, miosis), and respiratory (bronchospasm, dyspnea, pulmonary edema, respiratory paralysis) effects as well as diaphoresis [36–39].

The chemical structure of physostigmine has provided a template for the development of other molecules with highly significant anticholinesterase activity, such as rivastigmine, galantamine, and huperzine, all of which have demonstrated efficacy in Alzheimer's disease. Currently, rivastigmine is used for the treatment of mild to moderate dementia associated with Alzheimer's disease or Parkinson's disease as well as for the relief of severe dementia associated with Alzheimer's disease, including Lewy body dementia [35, 38].

4.2.5 Antitumor Agents

4.2.5.1 Podophyllotoxin and Etoposide

Podophyllotoxin is an aryltetralin-type lignan isolated from podophyllin, a resin produced by species belonging to the *Podophyllum* genus, such as *Podophyllum emodi* and *Podophyllum peltatum*. Because of its tremendous cytotoxicity, podophyllin is nowadays indicated topically in the treatment of genital warts and condylomata. Among the numerous compounds of the resin, podophyllotoxin is the main cause of the associated cytotoxic and neurotoxic effects. The manifestations of podophyllotoxin intoxication include vomiting, diarrhea, abdominal pain, and abnormal hepatic functions, in addition to neurological disturbance. Podophyllotoxin exerts its pharmacological actions by irreversibly binding to tubulin; therefore, inhibiting its polymerization and inducing cell cycle arrest at the G2/M phase. Podophyllotoxin (podofilox) is included in many pharmacopoeias and is

used as an antiviral agent against the human papillomavirus, cytomegalovirus, Sindbis virus, molluscum contagiosum, and venereal warts. Additionally, the antitumor activity of podophyllotoxin has been demonstrated: it is effective in the treatment of some types of genital tumors and in non-Hodgkin's and other lymphomas, as well as in lung cancer. The limiting factors of the clinical uses of podophyllotoxin include its non-selectivity against tumor cells and its narrow therapeutic window. Consequently, derivatives of podophyllotoxin, such as the semisynthetic derivative etoposides synthesized in 1963, were developed. These compounds present good clinical effects against several types of neoplasms [40, 41].

Etoposide has been shown to delay the transit of cells through S phase and arrest cells in late S or early G2 phase. The drug may inhibit mitochondrial transport at the protonated nicotinamide adenine dinucleotide dehydrogenase level or inhibit the uptake of nucleosides into HeLa cells. It is a topoisomerase II inhibitor and appears to cause DNA strand breaks. Etoposide is used in combination with other chemotherapeutic agents for the treatment of non-Hodgkin's lymphomas, refractory testicular tumors, small cell/non-small cell lung cancer (NSCLC), lymphoma, non-lymphocytic leukemia, and glioblastoma multiforme as well as many other cancers. The most common adverse reactions of etoposide include dermatological (alopecia), gastrointestinal (nausea, vomiting, anorexia, diarrhea), and hematologic (leukopenia, thrombocytopenia, anemia) effects [42–45].

4.2.5.2 Taxanes

Taxanes are modified diterpenes, which are also known as non-heterocyclic pseudo-alkaloids. These chemicals are synthesized by the yew tree, which belongs to the *Taxus* spp. The noxious nature of yew has been quoted since the second century BCE, when the "juice" was used for poisoning and in ritual suicides and as emmenagogues. Taxanes gained popularity in the 1980s and 1990s as an innovation against cancer; at the time, they were considered to be the most promising new chemotherapeutic agents developed for cancer treatment, particularly paclitaxel and docetaxel. To date, several taxanes have been isolated and their structural analogs described. Chemical features of this class of compounds include a taxane ring with a four-member oxetane ring attached at positions C4 and C5 and a bulky ester side chain at C13. The configuration of this ester chain is essential for the antitumor activity through a special mechanism of action. The prototype of taxanes, paclitaxel, was discovered as part of a National Cancer Institute program in which extracts of thousands of plants were screened for anticancer activity. Paclitaxel was initially supplied from the bark of the Pacific yew, *Taxus brevifolia*, which is not a sustainable source because of plant scarcity. Further investigations led to an approved semisynthetic molecule, 10-deacetylbaccatin III, being derived from the needles of a readily available precursor, *Taxus baccata*,

which is the European yew species; the European species is more abundant than the Pacific one and is able to meet commercial demands [46, 47].

Taxanes act by microtubule stabilization, interfering with the normal mitotic process as a result of induced resistance to cell division. Both paclitaxel and docetaxel bind to the β-subunit of tubulin, but higher activity for tubulin has been observed with docetaxel, which results in a longer intracellular period than with paclitaxel. This may explain why docetaxel appears to be two to four times more potent than paclitaxel. The transition between microtubule stabilization and cell death that is effected by taxanes is not well understood [48].

Currently, the common indications of taxanes include breast cancer (locally advanced/metastatic), NSCLC, metastatic prostate cancer, advanced gastric adenocarcinoma, locally advanced squamous cell head and neck cancer, and metastatic ovarian cancer. Paclitaxel is also used for the treatment of AIDS-related Kaposi's sarcoma. Significant adverse reactions include fluid retention, neurosensory events including neuropathy, fever, neuromotor events, alopecia, cutaneous events, nail disorders, stomatitis, diarrhea, nausea, vomiting, neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia, muscle weakness, pulmonary events, and hypersensitivity [49–51].

4.2.5.3 Vincristine and Vinblastine

The vinca alkaloids are indole alkaloid molecules primarily encountered in the pink periwinkle (*Catharanthus roseus*). This is known as the vinca plant; it is native and endemic to Madagascar and also encountered in Europe, Northwest Africa, Southwest Asia, and Southern USA. These have dimeric chemical structures containing an indole (catharanthine) and a dihydroindole nucleus (vindoline) joined together with other complexes. The earlier therapeutic use of vinca is related to diabetes treatment in the population of Madagascar. Further evaluation of the hypoglycemic activity of its extracts evidenced a granulocytopenia produced as a result of bone marrow suppression in animals, directing studies to model leukemia and lymphoma treatment. Identification of their bone marrow suppression activity led to the isolation of vinblastine and vincristine alkaloids, which today are widely used in the treatment of Hodgkin's and non-Hodgkin's lymphoma, testicular cancer, breast cancer, mycosis fungoides, Kaposi's sarcoma, histiocytosis (Letterer–Siwe disease), and choriocarcinoma. Vincristine is also used for the treatment of Wilms' tumor, neuroblastoma, and rhabdomyosarcoma. Though wide in range, the frequency of adverse reactions is not well established for these drugs. The toxicity of vincristine and vinblastine is mainly characterized by peripheral neuropathy and neutropenia. Despite being less neurotoxic, vinblastine presents similar side effects to vincristine, particularly when it is combined with or follows other neurotoxic agents such as taxanes [52–59].

Structurally, vinblastine and vincristine are identical except for the substituent found on the indoline nitrogen in the lower vindoline portion of the molecule. This single structural difference distinguishes both the clinical activities and toxicity profiles of these molecules. This modification, however, does not affect their mechanism of action, which is through binding to tubulin and inhibiting microtubule formation, thus arresting the cell at metaphase by disrupting the formation of the mitotic spindle; this is specific for the M and S phases [53]. The vinca alkaloids vincristine and vinblastine are structurally identical apart from the substituent attached in the indoline nitrogen in the lower vindoline portion of the molecules; these substituents are an aldehyde and a methyl group, respectively.

Knowledge of the structure and functional groups as well as the toxicity of vinca alkaloids guides studies in a natural direction: the search for new analogs that are more active, less toxic, and exhibit a broader spectrum of anticancer efficacy. To this effect, there are two other major vinca alkaloids in clinical use based on vincristine and vinblastine: vinorelbine and vindesine.

4.2.6 Other Drugs

4.2.6.1 Cardiac Glycosides

Cardiac glycosides are perfectly individualized chemical groups with excellent structural homogeneity. They possess a β-lactone unsaturated ring at C17 and are divided into cardenolides, such as ouabain and digoxin, and bufadienolides, such as bufalin. Although historical records indicate that extracts of the common foxglove *Digitalis purpurea* were used (mainly as poisonous preparations) as early as Egyptian and Roman times, the first scientific reports on the medical application of cardiac glycosides date back to 1785. In the nineteenth century, the cardiac glycosides began to be used in the control of tachyarrhythmia, despite being considered tremendously toxic [60, 61].

The fundamental cardiac glycoside digoxin is well known to have a complex mechanism of action. It remains the only positive ionotropic drug for chronic heart failure. Digoxin acts by inhibiting the sodium pump, which indirectly promotes calcium influx by sodium–calcium exchange. One of the major concerns related to the medical use of cardiac glycosides originates from their rather narrow therapeutic index, with the most prominent adverse effects including anorexia, nausea, vomiting, diarrhea, and life-threatening alterations of cardiac rhythm. Nevertheless, the prototypical cardiac glycosides digoxin and digitoxin were approved by the FDA for the treatment of atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia prior to 1982. In 1998, the FDA extended the indications of digoxin to congestive heart failure. Currently, digoxin is indicated for the treatment of congestive heart failure, atrial fibrillation, and

atrial flutter with rapid ventricular response, whereas the use of digitoxin has been discontinued in several Western countries. The significant adverse reactions of digoxin include cardiovascular, central nervous system, and dermatological reactions [61–64].

4.2.6.2 Colchicine

Colchicine is an alkaloid originally extracted from the meadow saffron *Colchicum autumnale* (L.). Because of its feared toxicity, preparation of the plant was not recommended for pain treatment until the sixth century CE [65]. Colchicine was approved in 2009 by the FDA as a monotherapy drug to treat familial Mediterranean fever and acute gout flares.

Colchicine disrupts cytoskeletal functions by inhibiting β-tubulin polymerization into microtubules and preventing the activation, degranulation, and migration of neutrophils associated with mediating some gout symptoms. The uses of colchicine include the prevention and treatment of acute gout flares and the treatment of familial Mediterranean fever. Unlabeled uses for primary biliary cirrhosis and pericarditis are also significant. In addition, colchicine is being investigated as an anticancer drug. However, the therapeutic value of colchicine against cancer is restrained by its low therapeutic index. Its toxicity includes dose-dependent gastrointestinal toxicity, neutropenia, bone marrow damage, and anemia [66–69].

4.2.6.3 Coumarins

Previously unseen hemorrhagic disease in cattle was associated with the sweet clover recently imported from Europe as cattle feed in the early twentieth century. When fresh, the plant appeared to be harmless. The problem arose when sweet clover was fed to cattle in the form of hay or silage, which when spoiled as a result of mold caused spontaneous and uncontrollable bleeding. It took many years for the active compound in spoiled sweet clover to be identified as the toxin dicoumarol, which had been converted from coumarin in the plants during the spoiling process. The most potent compound was patented in 1948 under the name of warfarin; it was initially marketed and used as a rat poison, the belief being that it was too poisonous to be used in humans. Warfarin later became the standard treatment for long-term thrombotic conditions. Currently, warfarin is used in the prophylaxis and treatment of thromboembolic disorders (e.g. venous, pulmonary) and embolic complications arising from atrial fibrillation or cardiac valve replacement and as an adjunct to reduce the risk of systemic embolism (e.g. stroke) after myocardial infarction. Bleeding is the major adverse effect of warfarin. Hemorrhage may occur at virtually any site. The risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility [70–73].

4.2.6.4 Nicotine and the Neonicotinoids

Nicotine is an alkaloid found in the Solanaceae family (nightshade) of plants, predominantly in tobacco and in lower quantities in some vegetables and the coca plant. Nicotine, which is well known as the addictive compound in cigarettes, has been used both as a pesticide and as the model for a series of synthetic insecticides called neonicotinoids. Because of their preferential binding to receptors in the nervous systems of insects and not to those in mammals, the neonicotinoids are considered to be safer options than nicotine itself. Currently, the clinical uses of nicotine are to aid smoking cessation by relieving nicotine withdrawal symptoms and the management of ulcerative colitis. The most significant adverse reactions of nicotine include headache, mouth/throat irritation, dyspepsia, cough, and rhinitis [74–77].

References

1 Gao, X.M., Zhang, T.M., Zhang, J.R. et al. (2007). *Chinese Materia Medica*. Beijing, China: China Press of traditional Chinese Medicine.

2 Parasuraman, S., Thing, G.S., and Dhanaraj, S.A. (2014). Polyherbal formation: concept of ayurveda. *Pharmacogn. Rev.* 8: 73–80.

3 Dong, J.C. (2013). The relationship between traditional Chinese medicine and modern medicine. *Evid. Based Complment. Altern. Med.* 2013.

4 Joo, Y.E. (2014). Natural product-derived drugs for the treatment of inflammatory bowel diseases. *Intest. Res.* 12: 103–109.

5 Hamilton, G.R. and Baskett, T.F. (2000). In the arms of Morpheus the development of morphine for postoperative pain relief. *Can. J. Anaesth.* 47: 367–374.

6 Newman, D.J., Cragg, G.M., and Snader, K.M. (2003). Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.* 66: 1022–1037.

7 Ngo, L.T., Okogun, J.I., and Folk, W.R. (2013). 21st century natural product research and drug development and traditional medicines. *Nat. Prod. Rep.* 30: 584–592.

8 Xu, T.X., Liang, X.L., and Lu, Z. (2005). Prevention and management of aconitum poisoning. *Henan Trad. Chin. Med* 25: 65.

9 Liu, Q., Zhuo, L., Liu, L. et al. (2011). Seven cases of fatal aconite poisoning: forensic experience in China. *Forensic Sci. Int.* 212: e5–e9. https://doi.org/10.1016/j.forsciint.2011.05.009.

10 Tai, Y.T., But, P.P., Young, K., and Lau, C.P. (1992). Cardiotoxicity after accidental herb-induced aconite poisoning. *Lancet* 340: 1254–1256. https://doi.org/10.1016/0140-6736(92)92951-B.

11 Fujita, Y., Terui, K., Fujita, M. et al. (2007). Five cases of aconite poisoning: toxicokinetics of aconitines. *J. Anal. Toxicol.* 31: 132–137. https://doi.org/10.1093/jat/31.3.132.

12 Rates, S.M.K. (2001). Plants as source of drugs. *Toxicon* 39 (5): 603–613.

13 Ibanez, S., Gallet, C., and Després, L. (2012). Plant insecticidal toxins in ecological networks. *Toxins* 4 (4): 228–243.

14 Czarnowski, C., Bailey, J., and Bal, S. (2007). Curare and a Canadian connection. *Can. Fam. Physician* 53 (9): 1531–1532.

15 Raghavendra, T. (2002). Neuromuscular blocking drugs: discovery and development. *J. R. Soc. Med.* 95 (7): 363–367.

16 Durbin, C.G. Jr. (1991). Neuromuscular blocking agents and sedative drugs. Clinical uses and toxic effects in the critical care unit. *Crit. Care Clin.* 7: 489.

17 Basta, S.J., Savarese, J.J., Ali, H.H. et al. (1983). Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. *Br. J. Anaesth.* 55 (Suppl 1): 105S.

18 Scott, R.P., Savarese, J.J., Basta, S.J. et al. (1985). Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br. J. Anaesth.* 57: 550.

19 Rinner, U. and Hudlicky, T. (2012). Synthesis of morphine alkaloids and derivatives. *Top. Curr. Chem.* 309: 33–66.

20 Heydari, M., Hashempur, M.H., and Zargaran, A. (2013). Medicinal aspects of opium as described in Avicenna's canon of medicine. *Acta Med. Hist. Adriat.* 11 (1): 101–112.

21 Cardan, E. (1981). Fatal case of codeine poisoning. *Lancet* 1 (8233): 1313.

22 Irwin, R.S., Boulet, L.P., Cloutier, M.M. et al. (1998). Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. *Chest* 114 (2): 133–181.

23 Girard, D.S., Sutton, J.P., Williams, T.H. et al. (2004). Papaverine delivery to the internal mammary artery pedicle effectively treats spasm. *Ann. Thorac. Surg.* 78 (4): 1295–1298.

24 Heulitt, M.J., Farrington, E.A., O'Shea, T.M. et al. (1993). Double-blind, randomized, controlled trial of Papaverine-containing infusions to prevent failure of arterial catheters in pediatric patients. *Crit. Care Med.* 21 (6): 825–829.

25 Alañón, F., Alañón, M.A., Jiménez, J.A. et al. (2014). Comparison between topical anesthesia with cocaine versus lidocaine plus adrenaline for outpatient laser dacryocystorhinostomy. *Arch. Soc. Esp. Oftalmol.* 89 (2): 53–57.

26 Keck, T.M., John, W.S., Czoty, P.W. et al. (2015). Identifying medication targets for psychostimulant addiction: unraveling the dopamine D3 receptor hypothesis. *J. Med. Chem.* in press. doi: https://doi.org/10.1021/jm501512b.

27 Jatlow, P.I. (1987). Drug of abuse profile: cocaine. *Clin. Chem.* 33: 66B.

28 Jeffcoat, A.R., Perez-Reyes, M., Hill, J.M. et al. (1989). Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking. *Drug Metab. Dispos.* 17: 153.

29 Gerhards, N., Neubauer, L., Tudzynski, P., and Li, S.M. (2014). Biosynthetic pathways of ergot alkaloids. *Toxins* 6: 3281–3295.

30 McGuigan, M.A. (1984). Ergot Alkaloids. *Clin. Toxicol. Rev.* 6: 1–2.

31 Orton, D.A. and Richardson, R.J. (1982). Ergotamine absorption and toxicity. *Postgrad. Med. J.* 58 (675): 6–11.

32 Grynkiewicz, G. and Gadzikowska, M. (2008). Tropane alkaloids as medicinally useful natural products and their synthetic derivatives as new drugs. *Pharmacol. Rep.* 60 (4): 439–463.

33 Renner, U.D., Oertel, R., and Kirch, W. (2005). Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. *Ther. Drug Monit.* 27 (5): 655–665.

34 Mokhlesi, B., Leikin, J.B., Murray, P. et al. (2003). Adult toxicology in critical care: part II: specific poisonings. *Chest* 123 (3): 897–922.

35 Čolović, M.B., Krstić, D.Z., Lazarević-Pašti, T.D. et al. (2013). Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr. Neuropharmacol.* 11 (3): 315–335.

36 Moore, P.W., Rasimas, J.J., and Donovan, J.W. (2015). Physostigmine is the antidote for anticholinergic syndrome. *J. Med. Toxicol.* 11 (1): 159–160.

37 O'Donnell, S.J., Burkhart, K.K., Donovan, J.W. et al. (2002). Safety of Physostigmine use for anticholinergic toxicity. *J. Toxicol. Clin. Toxicol.* 40 (5): 684.

38 Emre, M., Aarsland, D., Albanese, A. et al. (2004). Rivastigmine for dementia associated with Parkinson's disease. *N. Engl. J. Med.* 351 (24): 2509–2518.

39 van Eijk, M.M., Roes, K.C., Honing, M.L. et al. (2010). Effect of Rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 376 (9755): 1829–1837.

40 Canel, C., Moraes, R.M., Dayan, F.E., and Ferreira, D. (2000). *Podophyllotoxin. Phytochemistry.* 54 (2): 115–120.

41 Gordaliza, M., Garcia, P.A., Miguel del Corral, J.M. et al. (2004). Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. *Toxicon* 44 (4): 41–459.

42 Albain, K.S., Swann, R.S., Rusch, V.W. et al. (2009). Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 374 (9687): 379–386.

43 Joel, S.P., Shah, R., Clark, P.I. et al. (1996). Predicting etoposide toxicity: relationship to organ function and protein binding. *J. Clin. Oncol.* 14 (1): 257–267.

44 Saito, H., Takada, Y., Ichinose, Y. et al. (2006). Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan thoracic oncology group 9902. *J. Clin. Oncol.* 24 (33): 5247–5252.

45 Sundstrom, S., Bremnes, R.M., Kaasa, S. et al. (2002). Cisplatin and etoposide regimen is superior to Cyclophosphamide, Epirubicin, and Vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 Years' follow-up. *J. Clin. Oncol.* 20 (24): 4665–4672.

46 Wang, S., Qiu, J., Shi, Z. et al. (2015). Nanoscale drug delivery for taxanes based on the mechanism of multidrug resistance of cancer. *Biotechnol. Adv.* 33 (1): 224–241.

47 Yared, J. and Tkaczuk, K.H.R. (2012). Update on taxane development: new analogs and new formulations. *Drug Des. Devel. Ther.* 6: 371–384.

48 Garcia, A.A., Blessing, J.A., Vaccarell, L. et al. (2007). Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a gynecologic oncology group study. *Am. J. Clin. Oncol.* 30 (4): 428–431.

49 Ajani, J.A., Moiseyenko, V.M., Tjulandin, S. et al. (2007). Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 study group. *J. Clin. Oncol.* 25 (22): 3205–3209.

50 Mukai, H., Katsumata, N., Ando, M. et al. (2010). Safety and efficacy of a combination of docetaxel and cisplatin in patients with unknown primary cancer. *Am. J. Clin. Oncol.* 33 (1): 32–35.

51 Smyth, J.F., Smith, I.E., Sessa, C. et al. (1994). Activity of docetaxel (Taxotere) in small cell lung cancer. The early clinical trials group of the EORTC. *Eur. J. Cancer* 30A (8): 1058–1060.

52 Magge, R.S. and De Angelis, L.M. (2015). The double-edged sword: neurotoxicity of chemotherapy. *Blood Rev.* 29 (2): 93–100.

53 Moudi, M., Go, R., Yien, C.Y.S., and Nazre, M. (2013). Vinca alkaloids. *Int. J. Prev. Med.* 4 (11): 1231–1235.

54 Bowman, W.P., Shuster, J.J., Cook, B. et al. (1996). Improved survival for children with B-cell acute lymphoblastic leukemia and stage IV small noncleaved-cell lymphoma: a pediatric oncology group study. *J. Clin. Oncol.* 14 (4): 1252–1261.

55 Eiden, C., Palenzuela, G., Hillaire-Buys, D. et al. (2009). Posaconazole-increased vincristine neurotoxicity in a child: a case report. *J. Pediatr. Hematol. Oncol.* 31 (4): 292–295.

56 McCune, J.S. and Lindley, C. (1997). Appropriateness of maximum-dose guidelines for vincristine. *Am. J. Health Syst. Pharm.* 54 (15): 1755–1758.

57 Bartlett, N.L., Rosenberg, S.A., Hoppe, R.T. et al. (1995). Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J. Clin. Oncol.* 13 (5): 1080–1088.

58 Chong, C.D., Logothetis, C.J., Savaraj, N. et al. (1998). The correlation of vinblastine pharmacokinetics to toxicity in testicular cancer patients. *J. Clin. Pharmacol.* 28 (8): 714–718.

59 Pronzato, P., Queirolo, P., Vidili, M.G. et al. (1991). Continuous venous infusion of vinblastine in metastatic breast cancer. *Chemotherapy* 37 (2): 146–149.

60 Opie, L.H. (2013). Digitalis, yesterday and today, but not forever. *Circ. Cardiovasc. Qual. Outcomes.* 6 (5): 511–513.

61 Kirilmaz, B., Saygi, S., Gungor, H. et al. (2012). Digoxin intoxication: an old enemy in modern era. *J. Geriatr. Cardiol.* 9 (3): 237–242.

62 Cheng, J.W. and Rybak, I. (2010). Use of digoxin for heart failure and atrial fibrillation in elderly patients. *Am. J. Geriatr. Pharmacother.* 8 (5): 419–427.

63 Lindenfeld, J., Albert, N.M., Boehmer, J.P. et al. (2010). HFSA 2010 comprehensive heart failure practice guideline. *J. Card. Fail.* 16 (6): e1–e194.

64 Ujhelyi, M.R. and Robert, S. (1995). Pharmacokinetic aspects of digoxin-specific fab therapy in the Management of Digitalis Toxicity. *Clin. Pharmacokinet.* 28 (6): 483–493.

65 Slobodnick, A., Shah, B., Pillinger, M.H., and Krasnokutsky, S. (2015). Colchicine: old and new. *Am. J. Med.* 128 (5): 461–470.

66 Dalbeth, N., Lauterio, T.J., and Wolfe, H.R. (2014). Mechanism of action of colchicine in the treatment of gout. *Clin. Ther.* 36 (10): 1465–1479.

67 Borstad, G.C., Bryant, L.R., Abel, M.P. et al. (2004). Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J. Rheumatol.* 31 (12): 2429–2432.

68 Majeed, H.A., Rawashdeh, M., el-Shanti, H. et al. (1999). Familial Mediterranean fever in children: the expanded clinical profile. *QJM* 92 (6): 309–318. [PubMed 10616706].

69 Terkeltaub, R.A. (2009). Colchicine update: 2008. *Semin. Arthritis Rheum.* 38 (6): 411–419.

70 Bennett, J.D. and Ferneini, E.M. (2016). Coagulopathy management: the balance between thromboembolism and hemorrhage. *Oral and Maxillofacial Surgery Clinics of North America: Coagulopathy* 28 (4): 443–576.

71 Ageno, W., Gallus, A.S., Wittkowsky, A. et al. (2012). Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141 (2 Suppl): e44–e88.

72 Baillargeon, J., Holmes, H.M., Lin, Y.L. et al. (2012). Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am. J. Med.* 125 (2): 183–189.

73 Bates, S.M., Greer, I.A., Middeldorp, S. et al. (2012). VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141 (2 Suppl): e691–e736.

74 Skanes, A.C., Healey, J.S., Cairns, J.A. et al. (2012). Focused 2012 update of the Canadian cardiovascular society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can. J. Cardiol.* 28 (2): 125–136.

75 Blanchard, J. (1993). Nicotine. *Clin. Toxicol. Rev.* 15: 11–12.

76 Sandborn, W.J. (1999). Nicotine therapy for ulcerative colitis: a review of rationale, mechanisms, pharmacology, and clinical results. *Am. J. Gastroenterol.* 94 (5): 1161–1171.

77 Wynn, R.L. (1994). Nicotine patches in smoking cessation. *AGD Impact* 22: 14.