Anticancer Alkaloids: Molecular Mechanisms and Clinical Manifestations

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Abstract

Throughout history, naturally derived molecules have had countless applications in medicine, pharmacy, and biology. This rich reservoir of natural compounds demonstrated great potential in treating various diseases, mainly cancer. Alkaloids, a subfamily of secondary metabolites, are derived from a large variety of organisms including plants, animals, and marine organisms. This group of compounds has exhibited promising anticancer and chemopreventive effects and has been found to chemo-sensitize tumor cells that are resistant to conventional chemotherapy. The remarkable structural diversity of anticancer alkaloids has allowed their use as lead compounds in the treatment of cancer. Chemical derivatization and modifications of alkaloid structures led to the improvement of their therapeutic potential. Many of these second-generation alkaloids are currently commercially available or are in advanced clinical trials, and a major group is still being tested preclinically. Here we provide an overview of alkaloids that are in clinical trials and which are FDA approved. We have classified anticancer alkaloids according to their biological origin and presented an extensive discussion of their mechanism of action and clinical toxicity. The understanding of the mechanism of action and clinical manifestations of anticancer alkaloids is essential for advancing their use and enhancing their efficacy in the clinic.

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Alkaloids · Cancer therapy · FDA approved · Clinical toxicity · Plants · Marine organisms

1.1 Introduction

For millennia, cancer has been a poorly understood disease that is usually fatal. Defined as a relentless growth of cells that are capable of invading surrounding tissues and organs, cancer is an adverse disease with tremendous negative impact on individuals and society. It is one of the most common causes of mortality in developing countries and the second leading cause of death in the United States exceeded only by heart disease (Khazir et al. 2014). The World Health Organization (WHO) projects that the global number of cancer deaths will increase by nearly 80% by 2030 and predicts a rise in the number of cancer patients by 70% in the next two decades. The American Cancer Society expects more than 1.5 million new cancer cases to be diagnosed and more than 600,000 cancer deaths to occur in the United States alone in 2017.

With better understanding of the pathophysiology and natural history of cancer, the field of anticancer therapeutics has gained large popularity among scientist all over the world. At the beginning of the twentieth century, surgery and radiotherapy were solely used to treat malignancies with recovery rates not exceeding 33% (Mukherjee et al. 2001). A major breakthrough in the treatment of cancer occurred in the 1960s when chemotherapy became an adopted approach for treating this deadly disease. The use of chemotherapeutics in conjunction with the aforementioned orthodox treatment approaches opened new opportunities for cancer therapy, and since then chemotherapy became the standard clinical practice (DeVita and Chu 2008).

More than 60% of the currently used cancer chemotherapeutic and chemopreventive drugs are either natural compounds extracted from plants or animals or synthetic compounds derived from natural prototype structures (Amin et al. 2009; Khazir et al. 2014; Newman and Cragg 2016). It all started in 1955 when the National Cancer Institute (NCI) initiated a large-sale preclinical screening mission in the hope of finding promising anticancer compounds and molecules of various origins from plants, marine organisms, microbes, and animals (Nobili et al. 2009). Out of the selected 400,000 molecules, more than 114,000 compounds originating from plant species have been screened and tested (Holton et al. 1994). With this high-throughput screening and combinatorial synthesis, the quest for "safe" and selective anticancer agents was affordable and led to the discovery of compounds having growth inhibitory effects and apoptotic activities against human cancer cells with minimal toxicity to normal ones (Gordaliza 2007). Yet, the search for new improved cytotoxic agents continues to be an important approach to overcome the alarming emergence of chemotherapy resistance along with the annual increasing cancer death rates.

Nature has provided mankind with a wealth of effective agents that have immediate applications in medicine (Gordaliza 2007). Such compounds belong to several structural classes referred to as secondary metabolites (Seca and Pinto 2018). Alkaloids, the largest group of secondary metabolites, are a highly diverse collection of compounds of low molecular weight containing a heterocyclic ring structure and a nitrogen atom. About 17,000 alkaloids have displayed pronounced biological and pharmacological activities with relatively low toxicity and well-documented stability (reviewed in Habli et al. 2017). Alkaloids can be classified according to their structure and other chemical features, biological origin, as well as biogenetic origin. They can be found in a large variety of organisms including plants, especially higher plants, animals, bacteria, and fungi. They have been shown to exhibit a wide range of pharmacological properties including antimalarial, antiasthmatic, anticancer, vasodilatory, antiarrhythmic, analgesic, antibacterial, and antihyperglycemic activities (Lu et al. 2012; Iqbal et al. 2017). Currently, numerous alkaloids are being tested for their cytotoxicity or are undergoing clinical evaluation, and some have received FDA approval for cancer treatment. Their antitumor activity stems from their ability to induce DNA cleavage which is mediated by topoisomerase I and II inhibition, in addition to causing mitotic arrest, mitochondrial permeabilization, and inhibiting key enzymes involved in cell signaling and metabolism (Demain and Vaishnav 2011). In fact, the first series of chemically administered chemotherapeutics included the vinca alkaloid, vincristine, a revolution that increased the curability of children with leukemia and Hodgkin's diseases (DeVita and DeVita-Raeburn 2015). In this chapter, we focus on the various plant- and marine-derived alkaloids that are in clinical trials or that have been FDA approved for the treatment of cancer and discuss their clinical manifestations and adapted strategies to enhance their therapeutic potential.

1.2 Plant-Derived Alkaloids

Plants have played a major role in human life since ancient history. Plants are used for basic needs such as food, shelter, and clothing in addition to being used as dart poisons for hunting purposes and hallucinogens for ritualistic purposes. Plants have also been the basis of traditional medicine in various countries including China and India. Historically, the efficacy of plants was attributed to their color, name, or physiological appearance before the realization and identification of the active compounds mediating these effects (Salim et al. 2008). For example, red-colored herbs were used to treat blood diseases, liverworts were used for liver diseases, and toothworts for toothache (Sneader 2005). Morphine was the first pharmacologically active compound to be isolated from plants. The nineteenth century witnessed the extraction of various alkaloids used as drugs for the treatment of several disease conditions. These are atropine (anticholinergic), codeine (cough suppressant), colchicine (antigout), ephedrine (bronchodilator), morphine (analgesic), physostigmine (cholinesterase inhibitor), and quinine (fever-reducing, antimalarial, analgesic, and anti-inflammatory properties) (Iqbal et al. 2017). The last 200 years have

witnessed the discovery of plant-derived substances (Fridlender et al. 2015). As a result of this undertaking, various plant-isolated alkaloids with anticancer activity have been characterized (Table 1.1). This section focuses on the historical discovery and clinical use of plant-derived anticancer alkaloids that have been FDA approved or that are undergoing clinical trials, their cytotoxicity and mechanism of anticancer activity.

1.2.1 Vinca Alkaloids

Vinca alkaloids were first discovered in the 1950s by the Canadian scientists, Robert Noble and Charles Beer. Vinca alkaloids, namely, vinblastine (VBL) and vincristine (VCR), were the first plant-derived products to be used in clinical oncology. Vinca alkaloids are a versatile group of phytochemicals isolated from *Catharanthus roseus* (Apocynaceae) and are the second-most used class of cancer drugs (Verma and Singh 2010; (Moudi et al. 2013). *C. roseus* is the source of more than 130 different terpenoid indole alkaloids, some of which exhibit pharmacological activities (Mohammad Abu Taher and Ahammed 2017). The anticancer effect of these compounds was discovered by chance during an investigation for hypoglycemic agents. The plant extracts showed minimal effect on glycemia; however, it was noted that they significantly reduced white blood cell counts, caused bone marrow depression in rats, and prolonged the life of mice bearing a transplantable lymphocytic leukemia (Prakash et al. 2013). There are four major vinca alkaloids in clinical use: vinblastine, vinorelbine, vincristine, and vindesine. These alkaloids are used for the treatment of several types of cancer including breast, lung, liver, testes, and leukemia (Table 1.1). Vinca alkaloids mediate their effect by altering microtubule dynamics during mitosis, preventing the formation of the mitotic spindle, and resulting in metaphase arrest and apoptosis (Jordan et al. 1991). Vinblastine and vincristine are naturally occurring active compounds that are present in low amounts in *C. roseus* plants. A series of semisynthetic analogues of vinblastine and vincristine with improved pharmacological properties have been developed. The first semisynthetic vinca alkaloid to enter human clinical trials was vindesine in which the C(23) acetyl group in vinblastine was changed to an amido group (Fig. 1.1) (Jordan and Wilson 2004). Vindesine is used in countries such as Britain, South Africa, and several European countries, but it is not FDA approved (Khazir et al. 2014). Vinorelbine is an FDA-approved semisynthetic derivative of vinblastine in which the bridge linking the indole ring to the piperidine nitrogen has been shortened by one carbon and water has been eliminated from the piperidine ring (Fig. 1.1). This derivative showed lower neurotoxicity when compared to its precursor and has been used in combination with various drugs for the treatment of several types of cancer (Almagro et al. 2015). Vinflunine, a dihydrofluoro derivative of vinorelbine, is the first fluorinated microtubule inhibitor. Unlike other vinca alkaloids, vinflunine binds weakly to tubulin, thus showing lower neurotoxicity and enhanced tolerance. It has not been FDA approved; however, it is being actively studied in patient clinical trials for the treatment of various solid tumors (Almagro et al. 2015; (Khazir et al. 2014). Many other vinca alkaloid derivatives are

Table 1.1 FDA-approved alkaloids

Alkaloid class	Alkaloid name	Type of cancer it is effective against	Mechanism of action	References
Vinca alkaloids	Vincristine (VCR)	Acute leukemia Rhabdomyosarcoma Neuroblastoma Wilm's tumor Hodgkin's disease	Destabilize microtubules by binding to tubulin Inhibit angiogenesis	Moudi et al. (2013)
	Vinblastine (VBL)	Testicular carcinoma Hodgkin and non-Hodgkin lymphomas Breast cancer Kaposi sarcoma		
	Vinorelbine (VRL)	Breast cancer Osteosarcoma Advanced lung cancer		
Taxanes	Taxol/paclitaxel	Ovarian cancer Advanced breast cancer Non-small cell lung cancer	Stabilize microtubules in their polymerized form leading to cell death Inhibit B-cell leukemia2 (Bcl-2)	Barbuti and Chen (2015), Wink (2015) and Seca and Pinto (2018)
	Docetaxel	Breast cancer Prostate cancer Gastric cancer Head and neck cancer Non-small cell lung cancer		
	Cabazitaxel	Hormone-refractory metastatic prostate cancer		

(continued)

Table 1.1 (continued)

Alkaloid class	Alkaloid name	Type of cancer it is effective against	Mechanism of action	References
Camptothecin	Topotecan	Ovarian Small cell lung cancers	Inhibits type I DNA topoisomerase preventing DNA re-ligation during replication	Karthik Mohan (2012)
	Irinotecan	Colorectal cancers		
Homoharringtonine	Omacetaxine mepesuccinate	Chronic myelogenous leukemia	Inhibits protein synthesis by acting on ribosomes of cancer cells	Kantarjian et al. (2013) and Isah (2016)
Tetrahydroisoquinoline	Trabectedine (ET-743)	Soft tissue sarcoma Hematological malignancies Solid tumors	Decreases TAM to modulate TME (i.e., limits numbers of macrophage products promoting tumor growth) Displaces oncogenic transcription factors from their target promoter with high specificity	D'Incalci et al. (2014) and Dybdal-Hargreaves et al. (2015)
	Eribulin mesylate (eribulin) analogue of halichondrin B (E7389)	Metastatic breast cancer Soft tissue carcinoma Breast cancer Ovarian cancer Endometrial cancer Non-small cell lung cancer Prostate cancer	Depolymerizes microtubules	
Purine alkaloids	Cytarabine	Acute myelocytic leukemia Lymphocytic leukemia Meningeal leukemia Blast crisis phase of chronic myelogenous leukemia	Inhibit DNA polymerases	Matthews (2017)

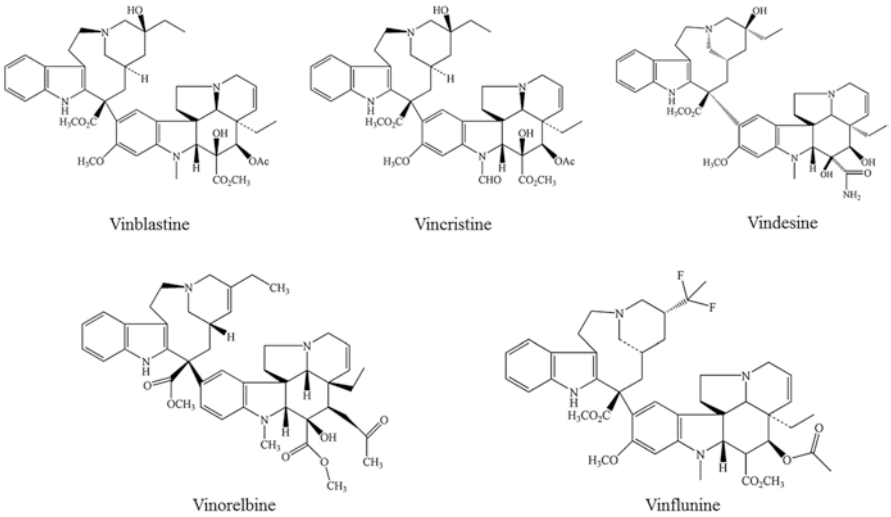

Fig. 1.1 Chemical structures of clinically used vinca alkaloids

being studied for potential use as anticancer drugs including anhydrovinblastine that has been modified from vinblastine by a 3′4′ double bond in the catharanthine moiety (Butler 2008) and is currently in phase I clinical trials. Vinblastine has also been modified by adding amino acid derivatives to facilitate its transport into cells. Vinglycinate and vintripol are examples of such derivatives that showed interesting pharmacological properties; however, they showed toxicity and no marked benefits in clinical evaluation (Khazir et al. 2014). In addition to designing various derivatives, the possibility of vinca alkaloid nanoparticle encapsulation was also tested. In 2012, the FDA approved the use of liposomal formulation of vincristine for the treatment of adult acute lymphocytic leukemia (Douer 2016). This formulation enhances the efficacy and reduces toxicity of vincristine by enabling it to circulate longer in the blood, accumulate in the tumor, and be released over an extended period of time at the tumor site (Shah et al. 2013).

1.2.2 Taxanes

The discovery of paclitaxel was the result of collaboration between the NCI and the US Department of Agriculture on a plant-screening program to identify naturally occurring compounds with anticancer activity. In 1967, Mansukh Wani and Monroe Wall isolated and identified the active ingredient from the bark of the Western yew tree *Taxus brevifolia*, named it taxol, and published its structure in 1971 (Weaver 2014). The pharmaceutical company, Bristol-Myers Squibb, then changed the name to paclitaxel. Paclitaxel entered clinical trials 22 years after its discovery in 1984. Several clinical trials were delayed due to the shortage of taxol. Paclitaxel is present in small amounts in the slow-growing *T. brevifolia*, and its extraction is a

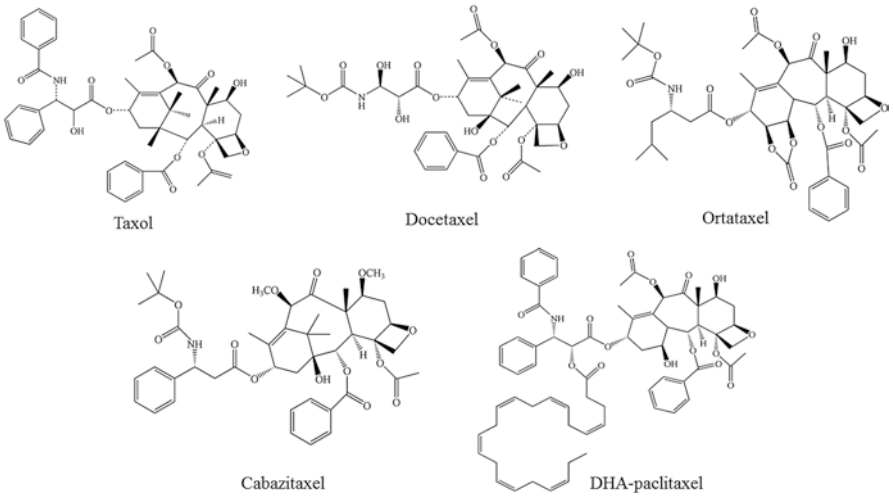

Fig. 1.2 Chemical structures of clinically used taxanes

complicated and expensive process. In addition, bark collection was restricted because the Western yew was an endangered species. Therefore, this method was not feasible to provide sufficient amounts of paclitaxel to meet the market demand. Total synthesis of the compound was established; however, it was inefficient for providing large quantities of paclitaxel (Salim et al. 2008). As the demand for paclitaxel increased, efforts were made by the government and pharmaceutical companies to increase the availability and find alternative sources of production. This led to the production of paclitaxel mimics (Fig. 1.2) including docetaxel, a semisynthetic form of paclitaxel, synthesized from 10-deacetylbaccatin III, which is isolated in large amounts from the needles of the renewable yew tree *Taxus baccata* (Salim et al. 2008; Fridlender et al. 2015). Docetaxel exhibits longer half-life, longer intracellular retention, and more rapid cellular uptake than paclitaxel (Seca and Pinto 2018). Cabazitaxel is another semisynthetic taxane with higher lipophilicity in comparison to doctaxel, which increases its intracellular accumulation, thus enhancing its cytotoxicity and effectiveness in paclitaxel-resistant patients (Seca and Pinto 2018). Bristol-Myers Squibb has also synthesized paclitaxel using plant cell cultures (Amin et al. 2009; Fridlender et al. 2015). Paclitaxel, docetaxel, and cabazitaxel are FDA approved for the treatment of various cancer types (Table 1.1).

Paclitaxel and docetaxel share the same mechanism of action; however, docetaxel has been shown to be more potent in terms of potential patient toxicity possibly due to its more rapid intracellular uptake and is co-administered with dexamethasone to prevent progressive, often disabling, fluid retention in the peripheries, lungs, and abdomen. Unlike vinca alkaloids, taxanes promote the assembly of microtubules and inhibit their depolymerization by binding specifically to the N-terminal 31 amino acids of the beta-tubulin subunit in microtubules rather than to tubulin dimers resulting in cell cycle arrest at the G2/M-phase and apoptosis (Zhang et al. 2014;

Kampan et al. 2015). Paclitaxel has been also shown to mediate its effect by inducing reactive oxygen species and activating multiple signal-transduction pathways associated with pro-apoptotic signaling including c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase, nuclear factor kappa B (NF-KB), and Janus kinase-(JAK-)signal transducer and activator of transcription factor (STAT) pathway. The induction of mitogen-activated protein kinase (MAPK) pathway, for example, results in dephosphorylation of the pro-apoptotic proteins Bad and Bax, phosphorylation of Bcl2, and induction of apoptosis (Kampan et al. 2015; Fridlender et al. 2015). The therapeutic efficacy of paclitaxel is starting to be limited due to the development of multidrug resistance (MDR), the mechanism of which is not fully understood and has been attributed to upregulation of P-glycoprotein (P-gp), alteration in tubulin dynamics, mutations in tubulin gene, changes in signaling pathways, and reduced function of significant apoptotic proteins (such as Bcl-2 and p53) (Barbuti and Chen 2015; Kampan et al. 2015). Paclitaxel is hydrophobic and had to be administrated to patients in a solution containing ethanol and polyethoxylated castor oil (Cremophor EL, CrEL) to enhance its delivery (Seca and Pinto 2018). However, the use of CrEL as drug vehicle has been associated with hypersensitivity reactions and neurotoxicity in patients (Barbuti and Chen 2015). Another issue is the rapid and extensive binding of paclitaxel to plasma proteins and its limited ability to diffuse across the blood brain barrier (Khazir et al. 2014; Kampan et al. 2015). In order to decrease the toxicity, enhance delivery and distribution, and improve efficacy and ease of administration, new paclitaxel formulations have been explored. Abraxane®, also named *nab*-paclitaxel, is an FDA-approved albumin-bound nanoparticle formulation of paclitaxel. It is soluble in saline, thus eliminating the need for the solubilizing agent Cremophor EL responsible for the hypersensitivity reactions. This formulation allows for higher intratumoral drug concentration driven by the ability of albumin to bind to its receptor, glycoprotein gp60 receptor, thus activating caveolin-1 and inducing caveolin formation, which allows nab-paclitaxel to migrate across the endothelial cell membrane into the interstitial space. In addition, Abraxane® can be administered at higher doses than paclitaxel allowing for improved efficacy (Barbuti and Chen 2015; Kampan et al. 2015). Paclitaxel poliglumex (PPX), also known as Xyotax, is a conjugate of paclitaxel and poly-L-glutamic acid developed to enhance the therapeutic index of paclitaxel (Yared and Tkaczuk 2012; Shah et al. 2013). Paclitaxel poliglumex takes advantage of the enhanced permeability of tumor vasculature and lack of lymphatic drainage to accumulate within tumor tissue, thus allowing for direct delivery to the intratumoral microenvironment and prolonged exposure to the active drug while minimizing systemic toxicities (Shah et al. 2013; Kampan et al. 2015). DHA-paclitaxel, also known as Taxoprexin, is another taxol analogue made by linking paclitaxel to the naturally occurring omega-3 fatty acid, docosahexaenoic acid (DHA). DHA is easily taken up by tumor cells, hence increasing intratumoral concentration of paclitaxel (Shah et al. 2013; Khazir et al. 2014). In addition to the abovementioned formulations, several analogues of paclitaxel and taxane derivatives are currently undergoing clinical trials including larotaxel, milataxel, ortataxel, albumin-bound docetaxel, and paclitaxel microspheres (Iqbal et al. 2017).

1.2.3 Camptothecin

Camptothecin is a quinoline alkaloid isolated from the Chinese ornamental tree, *Camptotheca acuminata.* Camptothecin is a type I DNA topoisomerase inhibitor, a critical enzyme in DNA replication and transcription (Khazir et al. 2014; Iqbal et al. 2017). Camptothecin entered clinical trials in the 1970s and was then withdrawn because of its low aqueous solubility and reports of severe bladder toxicity (Prakash et al. 2013). To overcome these limitations, several camptothecin analogues (Fig. 1.3) were synthesized and approved for clinical use including the water-soluble derivatives topotecan and irinotecan (Table 1.1). In addition to these, several analogues are in early stages of clinical trials for the treatment of various types of cancer. These include karenitecin, diflomotecan, gimatecan, elomotecan, and rubitecan. Conjugated camptothecin analogues have also been developed to enhance delivery and increase the exposure of tumor cells to camptothecin while minimizing side effects. One example is linking camptothecin to copolymers such as XMT-1001 in which camptothecin is attached to poly(1-hydroxy methyl ethylene hydroxy methyl formyl) and CRLX-101 in which camptothecin is conjugated to a linear, cyclodextrin-based polymer. These conjugated analogues are in phase I/II clinical trials for the treatment of lung cancer and solid tumors. Nanoparticle encapsulation is also being investigated to optimize delivery and improve safety of camptothecin (Khazir et al. 2014; Iqbal et al. 2017). Irinotecan has been encapsulated in a liposome formulation and is currently in phase I clinical trials for treatment of advanced cancers (https://clinicaltrials.gov/ct2/results?cond=Cancer&term=CPT11+and+liposome&cntry=&state=&city=&dist=).

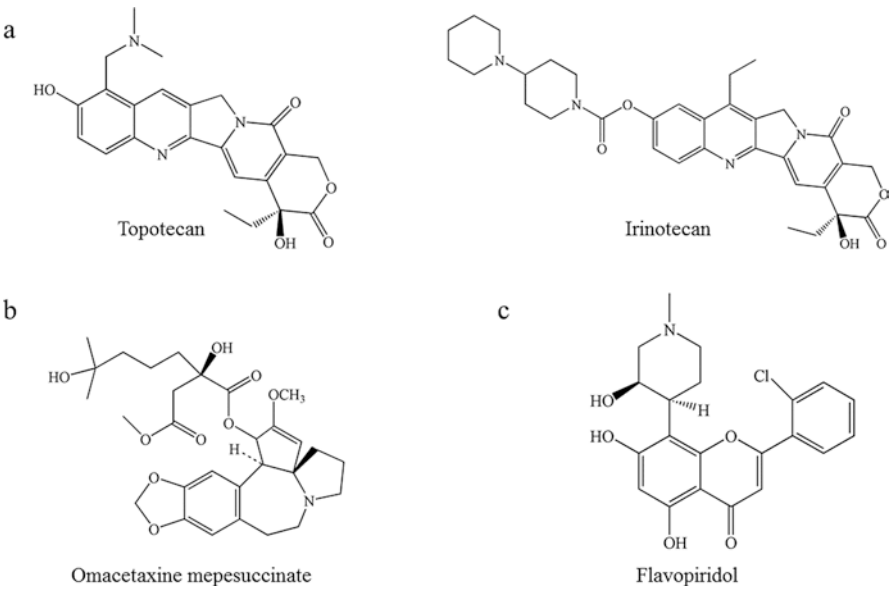

Fig. 1.3 Chemical structures of representative plant-derived alkaloids belonging to the (**a**) camptothecins, (**b**) homoharringtonine, and (**c**) rohitukine

1.2.4 Cephalotaxus

Cephalotaxus alkaloids are a group of phytochemicals originally isolated from the Chinese tree *Cephalotaxus harringtonia* (Cephalotaxaceae) (Prakash et al. 2013). Cephalotaxine itself does not display any biological activity; however, the fractionation of *Cephalotaxus* extracts resulted in the isolation of a series of esters of cephalotaxine with anticancer activity including harringtonine, isoharringtonine, homoharringtonine (HHT), and doxyharringtonine (Quintas-Cardama et al. 2009). They function by inhibiting protein synthesis through targeting initiation of protein synthesis, allowing release of nascent peptide, and polyribosome degradation (Iqbal et al. 2017). Homoharringtonine was considered one of the most effective treatments for chronic myeloid leukemia after failure of interferon-alpha therapy; however, the introduction of the tyrosine kinase inhibitor imatinib mesylate halted its clinical development. In addition, difficult production, toxicity profile of the original dose schedules, and the requirement of large quantities of bulk of cephalotaxus trees for production hampered HHT development (Kantarjian et al. 2013). Omacetaxine mepesuccinate (Fig. 1.3) is a semisynthetic purified HHT compound with 99.7% purity. It is synthesized by direct esterification of cephalotaxine extracted from dry leaves of *Cephalotaxus*, and not from the bark, which reduces the amount of *Cephalotaxus* required for extraction. Omacetaxine inhibits protein translation by preventing the initial elongation step of protein synthesis where it interacts with the ribosomal A-site and prevents the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs. Omacetaxine mepesuccinate showed positive results in patients who have failed imatinib therapy, which established HHT for the second time as a valuable option in the management of CML. Omacetaxine mepesuccinate was approved by FDA in 2012 for the treatment of adult patients with chronic or accelerated phase CML after failure of two or more tyrosine kinase inhibitors. Homoharringtonine-omacetaxine probably holds the record for the longest time of development of an anticancer agent until FDA approval, almost 40 years (Quintas-Cardama et al. 2009; Kantarjian et al. 2013; Khazir et al. 2014; Iqbal et al. 2017).

1.3 Marine-Derived Alkaloids

Covering more than 70% of the earth's surface, the ocean offers a biologically rich ecosystem conferring the largest reservoir of taxonomic variety and wide chemical diversity of secondary metabolites (Huawei Zhang et al. 2017). This massive diversity of secondary metabolites helps marine organisms to withstand extreme conditions of temperature and pressure and consequently offers abundant sources of drugs that could be potential candidates for the treatment of various diseases (Romano et al. 2017). In fact, screening for marine biochemical biodiversity has just began; it is estimated that only 18% of the marine natural products have been discovered so far compared to products of terrestrial origin (Ruiz-Torres et al. 2017); thus, marine organisms represent a promising source of bioactive molecules.

However, in the history of medicine, reference to marine-based drugs is scarce, and a couple of ointments, concoctions, and cataplasms of algae and marine muds have been used for treating endless diseases, especially those involved in traditional Chinese and Japanese medicine (Hayasaka et al. 2012). For example, kainic acid was the first product of marine origin to be commercialized and used as an insecticide and anthelmintic; it was obtained from extracts of the seaweed *Digenea simplex* in 1900 (Colazingari 2013). Marine pharmacology was a new discipline that emerged in the 1950s that aimed to explore drugs and potential pharmaceuticals from sponges and marine microorganisms (Villa and Gerwick 2010). To date, only eight drugs isolated from marine organisms have been FDA approved for the treatment of various diseases. Only three of these eight compounds belong to the alkaloids family and have been approved for use as pharmaceutical drugs in cancer treatment (Table 1.1); on the other hand, two marine-derived alkaloids are in clinical trials (Table 1.2). This section focuses on the historical discovery and clinical use of marine-derived anticancer alkaloids that are undergoing clinical trials or are FDA approved, their cytotoxicity and mechanism of action.

1.3.1 Trabectedin (ET-743)

Trabectedin, ET-743, is a semisynthetic tetrahydroisoquinoline alkaloid that was initially extracted from the Caribbean tunicate *Ecteinascidia turbinata* and was currently prepared by chemical synthesis (Ruiz-Torres et al. 2017). It is the first marine-derived antineoplastic agent approved in Europe for the treatment of patients with advanced soft sarcoma and in combination with pegylated liposomal doxorubicin for the treatment of patients with relapsed platinum-sensitive ovarian cancer (D'Incalci et al. 2014). Its clinical activity is currently being evaluated in phase II/III on patients with advanced breast and hormone refractory prostate cancers. PharmaMar, a Spanish company, was first licensed to develop ET-743 for a large-scale production to provide enough materials for clinical trials. Their chemists performed an extremely elegant semisynthesis reaction by fermenting a marine-derived *Pseudomonas fluorescens* metabolite, safracin B, which led to a cGMP grade ET-743 from a 21-step synthetic process. Ultimately, the production scheme of ET-743 was licensed to Johnson and Johnson in 2001 under the brand name Yondelis, with the generic name of trabectedin (Newman and Cragg 2004). Trabectedin or ET-743 is a novel antitumor agent that has a broad spectrum of activity at pico- and nanomolar concentrations; the mechanism by which it exerts its activity has not been completely elucidated (Zelek et al. 2006). What is known so far is that ET-743 is composed of three tetrahydroisoquinoline rings containing a central carbinolamine moiety (Fig. 1.4) (Le et al. 2015). In contrast to traditional alkylated agents that bind to guanine at N7 or O6 positions, the carbinolamine moiety enables ET-743 to covalently bind to the N2 amino group of guanines in the minor groove of DNA, and through van der Waals interactions, it results in bending of the DNA toward the major groove. This allows the DNA strands to cross-link in a way that seems unique for this molecule, thus creating DNA double-strand breaks

Table 1.2 Plant- and marine-derived alkaloids in clinical trials

Alkaloid class	Alkaloid name	Type of cancer it is effective against	Clinical status	Mechanism of action	References
Taxane derivatives	Paclitaxel poliglumex	Breast Lung cancer Colorectal cancer Ovarian cancer	Phase I/II	Stabilize tubulin, resulting in the inhibition of microtubule depolymerization	Ulukan and Swaan (2002), Jones et al. (2008), Diéras V (2008) and Spigel and Greco (2008)
	DHA-paclitaxel	Non-small cell lung cancer	Phase III		
	Larotaxel	Breast cancer Urothelial tract or bladder cancer	Phase II/III		
	Ortataxel	Non-small cell lung cancer Advanced kidney cancer Refractory non-Hodgkin's lymphoma	Phase II		
Vinca alkaloid derivatives	Vinflunine	Metastatic breast cancer Non-small cell lung cancer Second-line transitional cell carcinoma of the urothelium (TCCU)	Phase I/II Phase II/III	Destabilize microtubules and bind to tubulin heterodimers	Moudi et al. (2013), Khazir et al. (2014), Reddy et al. (2007) and Butler (2008)
	Vindesine	Lung cancer Lymphoma Acute lymphocytic leukemia	Phase II/III		
	Vintafolide	Ovarian cancer Endometrial cancer	Phase II		
	Anhydrovinblastine	Advanced recurrent solid tumors	Phase I		

(continued)

Table 1.2 (continued)

Alkaloid class	Alkaloid name	Type of cancer it is effective against	Clinical status	Mechanism of action	References
Camptothecin derivatives	Rubitecan	Breast cancer Ovarian cancer Lung cancer Prostate cancer	Phase II	Inhibit type I DNA topoisomerase	Shah et al. (2013) and Quesada (2006)
	Karenitecin	Lung cancer Malignant melanoma Brain tumors Ovarian cancer	Phase II/III		
Rohitukine	Flavopiridol	Leukemias Lymphomas Solid tumors	Phase III	Targets cyclin-dependent kinases Downregulates Mcl-1 and other antiapoptotic proteins Induces mitochondrial permeability changes	Newcomb (2004)
Tetrahydroisoquinoline	Lurbinectedin (PM01183)	Relapsed ovarian cancer Breast cancer Pancreatic cancer Hematological tumors Small cell lung cancer	Phase I/II	Binds covalently to minor groove of DNA leading to double-strand break Removes DNA damage by nucleotide excision repair	J. F. M. Leal et al. (2010)
	Zalypsis (PM00104)	Uterine cervical cancer Endometrial cancer Ewing's sarcoma Primitive neuroectodermal tumor Multiple myeloma	Phase II	Binds to DNA and cause DNA double-strand breaks) Arrests cell cycle at S phase Induces apoptosis	Petek and Jones (2014)
Purine alkaloids	Elacytarabine (CP-4055)	Solid tumors (melanoma, ovarian, and lung cancer) Hematological malignancies Patients with refractory AML	Phase I/II	Inhibit DNA polymerases	O'Brien et al. (2012)

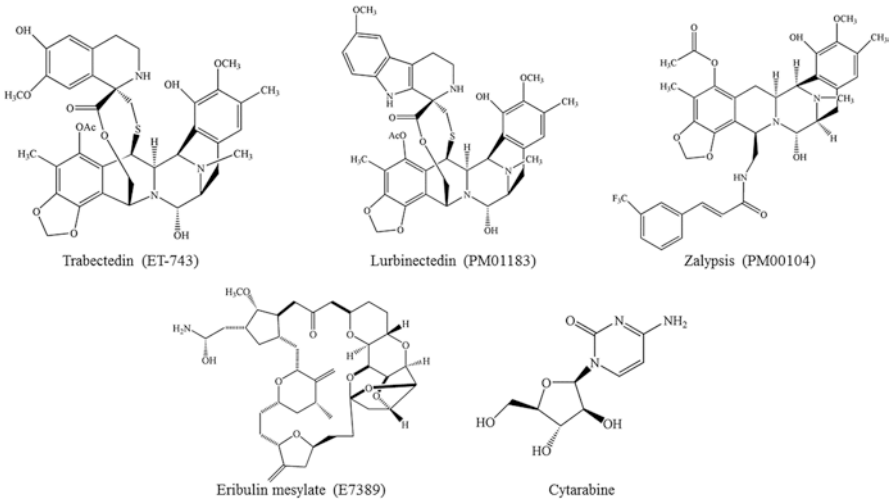

Fig. 1.4 Chemical structures of clinically used marine-derived anticancer alkaloids

(D'Incalci and Galmarini 2010). Furthermore, ET-743 interferes with DNA-binding agents such as transcription factors and DNA repair proteins altering their normal functionality and eventually leading to DNA damage, cell arrest, and cell death (Fayette et al. 2006). At the cellular level, ET-743 effectively blocks the transcription of genes that have been already activated such as HSP-70 and MDR1. It also affects promoters regulated by transcription factors that bind to the major groove such as Sp1. Of interest, ET-743 induces rapid degradation of transcribing RNA polymerase II in cells with normal transcription-coupled nucleotide excision repair, thus modulating transcription regulators (Fayette et al. 2006). It is worth mentioning that at low concentrations in vitro, ET-743 modulates cytokines and chemokines at the transcriptional level. Exceptionally, not only does it regulate tumor growth by affecting the cells directly, but it also plays a role at the tumor microenvironment level where it inhibits the production of pro-inflammatory mediators CCl2 (monocyte recruiter at tumor sites) and interleukin-6 (growth factor for several tumors) by monocytes and macrophages, thus inhibiting tumor growth and progression (D'Incalci and Galmarini 2010). The unique structure of this compound makes it a useful candidate for elucidating the complex mechanisms related to gene transcription regulation and DNA repair.

1.3.2 Lurbinectedin (PM01183)

PM01183 is a synthetic alkaloid structurally related to ecteinascidins that is in phase I clinical development for the treatment of solid tumors (Vidal et al. 2012). Like ET-743, PM01183 has a pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings (subunits A and B) that recognize DNA and bind to it. An additional

third ring (subunit C) in PM01183 makes it a tetrahydro-β-carboline rather than a traditional tetrahydroisoquinoline (Fig. 1.4) (Leal et al. 2010) When it binds to DNA, ring C protrudes from the DNA minor groove, thus causing DNA double-strand breaks and interfering with normal protein machinery at the mRNA level. The accumulated DNA damage delays cell cycle progression at the S-phase and ultimately triggers apoptotic cell death (Casado et al. 2008). Preclinical studies have demonstrated that PM01183 has potent antitumor activities against a wide array of solid and liquid tumors in vitro and in vivo with manageable toxicology profile (Vidal et al. 2012). This has accelerated the clinical trial transition to determine the minimum tolerable doses using various administration methods. Up until 2017, 19 clinical trials with PM01183 have been conducted in patients with various solid and hematological malignancies either alone or in combination with other drugs. Monotreatment and combinations have shown predictable and manageable safety profiles with acceptable tolerance among patients having ovarian, small cell lung metastatic breast, or endometrial cancers. Currently, plans to incorporate PM01183 in pediatric cancers like Ewing sarcoma and neuroblastoma are being designed for future application (https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncolo gicdrugsadvisorycommittee/ucm563559.pdf).

1.3.3 Zalypsis (PM00104)

PM00104 (Zalypsis) is a synthetic tetrahydroisoquinoline alkaloid that mimics natural compounds derived from mollusks. The drug is a novel chemical entity related to jorumycin (isolated from the mantle and mucus of the Pacific nudibranch mollusk *Jorunna funebris*) and ecteinascidins (isolated from the Caribbean tunicate *Ecteinascidia turbinata*) (Fontana et al. 2000; (Ciavatta et al. 2017). The high potent cytotoxic activity of jorumycin at nanomolar concentrations with the clinical success of ET-743 led to intensive chemical modifications of jorumycin's structure and eventually resulted in the development of PM00104. Similar to ET-743, PM00104 has the same cyclic structure (Fig. 1.4) and binds to DNA minor grooves via using its reactive carbinolamine group. However, unlike ET-743, PM00104 covalently binds to guanine residues with preferential affinity to G-rich codons (Leal et al. 2009). In fact, PM00104 differs slightly in one of its rings, and this alteration in structure has conferred its DNA-binding properties and nucleotide excision repair dependencies. Yet, the cytotoxic mechanism of action is similar for both drugs (Guirouilh-Barbat et al. 2009). The interaction between PM00104 and DNA leads to creation of DNA adducts which in turn inhibit early phases of transcription, causes DNA double-strand breaks, and arrests the cell cycle at the S-phase, thus driving the cell toward apoptosis. PM00104 has shown versatile anticancer potential activity in vitro and in vivo in a wide variety of solid and hematological tumors. This has led to moving PM00104 into clinical trial testing. Currently, PM00104 is in phase II clinical trials to treat Ewing sarcoma, urothelial carcinoma, multiple myeloma, and endometrial and cervical cancer (Petek and Jones, 2014).

1.3.4 Eribulin Mesylate (E7389)

Eribulin mesylate (E7389) is a synthetic macrocyclic ketone analogue of halichondrin B that acts as a non-taxane microtubule dynamics inhibitor (Dydal-Hargreaves et al. 2015). The history of this eribulin began when halichondrin B, a marine-derived alkaloid, got extracted from the marine sponge *Halichondria okadai* in 1986 (Hirata and Uemura 1986). Halichondrin B was found to have extraordinary cytotoxic activities in vitro and in murine models of solid tumors and leukemia in vivo (Dydal-Hargreaves et al. 2015). It acted through binding to a region of tubulin referred to as the "vinca domain," thus inhibiting tubulin polymerization and tubulin-dependent guanosine triphosphate (GTP) hydrolysis (Ludueña et al. 1993; Dydal-Hargreaves et al. 2015). The structural complexity made halichondrin B a mechanistically interesting molecule, but its low yield from natural resources limited its potential for clinical development. A breakthrough occurred in 1992 when chemists at Kishi laboratory (Cambridge, Massachusetts) succeeded in synthesizing over 180 analogues of this compound, one of which, eribulin, was produced with a 63-step chemical synthesis process (Yu et al. 2013). Preclinical studies showed that eribulin possessed both in vivo and in vitro antitumor activities against a wide array of solid malignancies, particularly breast and ovarian cancer. Sub- to low-nanomolar levels of eribulin inhibited cancer cell proliferation by disrupting mitotic spindles, blocking cell cycle at the G2/M-phase, and initiating apoptosis (Dydal-Hargreaves et al. 2015). In-depth studies have confirmed that eribulin inhibits microtubule dynamics through a novel mechanism that is distinct from all other tubulin-binding agents. It binds irreversibly to a unique site on tubulin resulting in the repression of microtubule polymerization without affecting the depolymerization process and thus sequestering tubulin into a nonfunctional aggregate (Dydal-Hargreaves et al. 2015). More so, mechanistic studies revealed that eribulin decreased the expression of genes associated with angiogenesis, including genes involved in Wnt, Notch, ephrin, and VEGF signaling pathways (Funahashi et al. 2014). It also triggered the reversal of epithelial-to-mesenchymal transition (EMT) in triple-negative breast cancer cell lines (Yoshida et al. 2014). In fact, drugs with the ability to inhibit or reverse EMT are highly desired as they inhibit the progression of tumors and their metastasis. In 2010 in the United States and in 2011 in Europe and Japan, the antimitotic agent eribulin received FDA approval as a third-line therapy for the treatment of liposarcoma and metastatic breast cancer patients who have been pretreated with a taxane or an anthracycline (Donoghue et al. 2012). Phase III clinical trials have demonstrated that eribulin is also effective in women with human epidermal growth factor 2 (HER2)-negative and triple-negative breast cancer (Dydal-Hargreaves et al. 2015). In addition, the California Cancer Consortium completed a phase I trial of eribulin to determine its pharmacodynamics and pharmacokinetics when administered by bolus injection. So far, results included partial responses of eribulin to several tumors with manageable toxicities, it induced morphological changes in the microtubules of peripheral blood monocytes, and its levels were maintained above the levels required for activity in the plasma for 72 h; however, when administered intravenously, it exhibited a tri-exponential elimination from

plasma of patients (Morgan et al. 2015). Recently phase I clinical trials in which eribulin and gemcitabine were combined showed manageable toxicity in patients diagnosed with advanced tumors (Lheureux et al. 2015). In addition, another phase I clinical trial of combining eribulin with cisplatin against advanced tumors resulted in well-tolerated doses with preliminary anticancer activity (Koczywas et al. 2014). Collectively, considering all the parameters, eribulin is a distinct microtubule inhibitor agent with great potential against cancer, and thus large numbers of clinical trials are still being conducted to decipher its antitumoral potential (https://clinicaltrials.gov/ct2/results?cond=cancer&term=eribulin&cntry=&state=&city=&dist=).

1.3.5 Cytarabine

The synthetic analogue of a C-nucleoside pyrimidine nucleoside cytarabine (arabinosyl cytosine or cytosine arabinoside, Ara-C) was developed from spongothymidine, a nucleoside originally isolated from the Caribbean sponge *Tectitethya crypta* (Mayer et al. 2010). Cytarabine is taken up by cells via nucleoside transporters, mainly the human equilibrative nucleoside transporter 1 (hENT1), and its primary activity stems from its intracellular conversion into cytosine arabinoside triphosphate by several deoxycytidine kinases (Li et al. 2017). Once converted, cytarabine becomes a cytotoxic compound that inhibits DNA polymerases and DNA synthesis via competition with deoxycytidine triphosphate to get incorporated into the DNA. Consequently, it causes cell death by interfering with DNA and RNA synthesis. It is also an S-phase-specific antimetabolite cytotoxic agent and may block the progression of cells from the G1-phase to the S-phase (Galmarini et al. 2002; Wang et al. 2018). Notably, cytarabine was among the first marine-derived compounds to receive FDA approval in 1969 and is still in use today to treat certain classes of leukemia affecting white blood cells mainly acute lymphocytic leukemia, acute myeloid leukemia (AML), and blast crisis phase of chronic myelogenous leukemia and meningeal leukemia (Krug et al. 2011). It is currently commercialized as either the conventional cytarabine under the trade name Cytosar-U1 or as its liposomal formulations under the trade name Depocyt1. Depocyt1 is basically a cytarabine encapsulated into multivesicular nonconcentric lipid-based vesicles that allow the sustainable release of cytarabine. It maintains cytarabine therapeutic drug concentrations in the cerebrospinal fluid for prolonged periods, and thus it has more potent potential to kill tumor cells in the meningeal leukemia (Glantz et al. 1999; (Chhikara and Parang 2010). Depocyt1 is prescribed intrathecally for the treatment of lymphomatous meningitis, whereas commercial presentation of cytarabine is designed to be administered intravenously or subcutaneously. Cytosar-U1 and Depocyt1 are marketed by Bedford Laboratories (http://www.bedfordlabs.com/) and Enzon P Pharmaceuticals (http://www.enzon.com/), respectively. Multiple clinical trials showed that patients with AML demonstrated complete remission rates of 50–60% and overall enhanced survival rates of 30–40% after the administration of cytarabine (Hagop 2016). A novel liposomal formulation of cytarabine in combination with daunorubicin (packed ratio 5:1 molar) is now in phase II clinical trials. It is

known as CPX-351, and it has shown synergistic efficacy when compared with the conventional 7 + 3 treatment of AML (100 mg/m^2 cytarabine and 60 mg/m^2 daunorubicin) (Saygin and Carraway 2017). In fact, high doses of cytarabine had the highest antileukemic efficacy among all used therapies against AML, but the mechanism of high dose of cytarabine therapy remains uncertain and needs further investigation. Although it has been the standard chemotherapy for hematological malignancies, cytarabine resistance has been emerging rapidly especially in patients with reduced expression of hENT1. Therefore, elacytarabine (CP-4055), a lipophilic 5′-elaidic acid ester of cytarabine, has been considered lately for clinical trials. Elacytarabine enters cells independently of hENT1 and has the same mechanism of action as cytarabine. Phase I clinical trials showed that elacytarabine had manageable and transient toxicities in patients with refractory AML and a pharmacokinetic profile that allowed extended exposure of cytarabine and its active metabolites to leukemic cells (O'Brien et al. 2012).

1.4 Modulators of MDR and Chemopreventive Alkaloids

Multidrug resistance (MDR) is a major obstacle in the development of chemotherapeutic agents. Various alkaloids can overcome MDR through several mechanisms including interaction with ABC-transporters and induction of apoptosis, thus enhancing cytotoxicity of chemotherapeutics. Here we provide examples of alkaloids that can serve as promising model compounds for overcoming MDR and that have shown chemopreventive effects.

1.4.1 Cinchona Alkaloids

Cinchona alkaloids are isolated from the bark of several species of cinchona trees. In the early seventeenth century, the antimalarial property of cinchona bark, mainly its active compound quinine, was discovered (Ferreira Júnior et al. 2012). Quinine and cinchonine have the potential of reversing MDR in cancer patients. Phase I/II clinical trials assessing the effect of quinine demonstrated that it could be used safely with a combination of anticancer agents, for instance, mitoxantrone, cytarabine, cyclophosphamide, or paclitaxel, enhancing the treatment of clinically resistant acute leukemias, breast cancer, or non-Hodgkin's lymphomas (Solary et al. 2003; Taylor et al. 1997; Miller et al. 1998). Unfortunately, the use of quinine in phase III clinical trials on patients with acute leukemia showed modest success (Solary et al. 2003). Other preclinical and phase I studies have shown that cinchonine is a more potent and effective anti-MDR agent in comparison with quinine (Ferreira Júnior et al. 2012). Additionally, cinchonine showed MDR-reversing activity in patients with malignant lymphoid disease in combination with cyclophosphamide, doxorubicin, methylprednisolone, and vinblastine (Solary et al. 2000). Lately, dimeric quinine linked by ester bond was also shown to be active in MDR and was capable of totally reversing the P-glycoprotein (P-gp)-mediated

paclitaxel resistance phenotype as well as inhibiting its transport in MCF-7/DX1 cells (Pires et al. 2009).

1.4.2 Dofequidar Fumarate (MS-209)

Dofequidar (MS-209) is a novel, orally active, quinolone-derived inhibitor of MDR and P-glycoprotein (Toshiaki Saeki et al. 2007). In preclinical studies, dofequidar has shown a significant reversal of MDR in P-gp- and MRP-1-expressing cancer cells in vitro. In preclinical models, MS-209 was found to enhance the antitumor activity of various anticancer agents including adriamycin, vincristine, paclitaxel, and docetaxel in multidrug-resistant tumor cell lines (Naito et al. 2002). For instance, compared to adriamycin activity alone, a combination of MS-209 with adriamycin was more effective against transplanted murine tumors, multidrug-resistant murine tumors, and human tumors transplanted to nude mice (Naito and Tsuruo 1997). Phase I clinical trials conducted to assess the safety and tolerability of MS-209 in combination with docetaxel showed no significant differences in docetaxel activity with and without MS-209, which is well-tolerated with no dose-limiting toxicities. Dofequidar in a phase II clinical trial potentiated the anticancer effect of CAF (cyclophosphamide, doxorubicin, and fluorouracil) therapy in patients with advanced or recurrent breast cancer (Saeki et al. 2005).

In addition to their role in overcoming MDR, some alkaloids have chemopreventive potential. A couple of tests done on capsaicin have shown that it inhibits mutagenicity and DNA binding of some chemical carcinogens, possibly by suppressing their metabolic activation which is accompanied with a decrease in NADH oxidase activity. It also caused an alteration in the expression of tumor forming-related genes by stimulating the overexpression of p53 and/or c-myc genes (Lewinska et al. 2015). Additionally, capsaicin inhibited the growth of xenograft prostate tumors in mice. Berberine, which is isolated from the plant *Rhizoma coptidis*, exhibited potential chemopreventive properties against colon tumor formation. It controls colon tumorigenesis by inhibiting the highly expressed enzyme cyclooxygenase-2 (COX2) in colon cancer cells (Wu et al. 2012).

1.5 Clinical Toxicity of Alkaloids

The medical adverse effects and toxicities of chemotherapeutic drugs provide insights about the unique activity of each drug and its function in the human body system. The choice of the appropriate chemotherapeutic drug is based on several considerations which include the type, size, and grade of the tumor in addition to the patients' comorbidities, age, and health status at the time of chemotherapeutic administration.

The different drugs within the vinca alkaloid family have a variable toxicity profile. Vinflunine is the latest member of the vinca alkaloid, which is evaluated in multiple trials for the treatment of metastatic and advanced urothelial cancer. A

systematic review and meta-analysis to examine the toxicity profile of vinflunine showed that fatigue (40.1%), nausea (33.9%), constipation (34.1%), and alopecia (26.0%) are the most prevalent non-hematological adverse effects, whereas anemia (56.6%), neutropenia (46.0%), and thrombocytopenia (25.5%) are the most common hematological adverse effects (Brousell et al. 2018). Neurotoxicity and axonal neuropathy are most notable with vincristine treatment, a dose-dependent toxicity that is caused by interrupting microtubules within axons (Quant 2014). However, neurotoxicity is usually reversible requiring few months for recovery (Quant 2014). Nearly all patients have neurotoxicity following vincristine treatment which is manifested as paresthesia in the feet and fingertips, cramps, and weakness often occurring weeks post treatment (Quant 2014). Vincristine-induced autonomic neuropathy is commonly displayed as abdominal pain, constipation, and paralytic ileus (Quant 2014). Vinblastine, another vinca alkaloid, is associated with less neurotoxicity but results in a dose-dependent hematological toxicity; in the same token, vinorelbine has less neurotoxicity that is reversible post treatment (Quant 2014).

Paclitaxel showed many adverse effects that were manifested during clinical trials. These include myelosuppression, neurotoxicity, musculoskeletal, and dermatological adverse effects (Walker 1993). Myelosuppression, neutropenia, and/or leukopenia was considered a major dose-limiting toxicity. In fact, results from phase I and II clinical trials showed that the administration of a recommended drug dose intravenously for 24 h every 3 weeks caused neutropenia and leukopenia in 68% and 26% of patients, respectively (Walker 1993). Thrombocytopenia was not significant when compared to leukopenia and neutropenia in paclitaxel-induced myelosuppression. Paclitaxel-induced severe neurological toxicity occurred at higher doses. Initial signs of neurotoxicity are paresthesia manifested as a burning sensation in the feet tailed by a sensation loss in a stocking-and-glove distribution followed by loss of pain sensation, vibration, temperature, and reflexes (Walker 1993). Arthralgias and myalgias are dose-dependent effects that are displayed at high paclitaxel doses causing bone and joint pain (Walker 1993). Alopecia was abrupt involving facial and body hair loss and occurred in almost all patients 2 weeks post treatment (Walker 1993).

Docetaxel can cause both acute and chronic adverse effects. Myelosuppression, cardiovascular toxicity, gastrointestinal, and dermatological side effects are some of the acute toxicities of docetaxel. On the other hand, neurotoxicity is one of the chronic side effects that can persist after the completion of the drug regimen (Ho and Mackey 2014). Unlike other chemotherapeutic regiments, febrile neutropenia could develop in patients receiving chemotherapeutic regimen containing docetaxel (Ho and Mackey 2014). Febrile neutropenia usually requires hospitalization and is associated with increased risk of developing serious infections in addition to high morbidity and mortality (Ho and Mackey 2014). In terms of the cardiovascular system, patients taking docetaxel experience fluid retention manifested as swelling in their extremities, ascites, and pericardial and pleural effusions, likely due to docetaxel-induced increase of capillary permeability and fluid leakage into the tissues (Ho and Mackey 2014). Fluid retention is a dose-dependent side effect and can be decreased by co-administration of steroids or symptomatically treated by

diuretics (Ho and Mackey, 2014). Docetaxel-induced nail toxicity consists of hyperkeratosis, subungual and splinter hemorrhages, nail growth cessation, and separation of the nail from the nail bed (Ho and Mackey 2014). Nail toxicity can be slowed down using frozen gloves and socks and can be resolved 6–12 months post treatment (Ho and Mackey 2014). Long-term neurotoxicity induced by docetaxel includes motor and sensory peripheral neuropathy, which is however less severe than paclitaxel and can be manifested as tingling, numbness, and loss of reflexes (Ho and Mackey 2014).

Irinotecan and topotecan are two camptothecin analogues that show variability in their profile toxicity. Irinotecan is used in the management of gastrointestinal tumors and therefore has mainly gastrointestinal adverse effects. On the other hand, topotecan has predominantly hematological profile toxicity (Seiter 2005). Seiter compared the toxic effects of the two drugs showing that irinotecan caused diarrhea in 20–40% of patients, while neutropenia occurred in 20–40% and 70–80% in irinotecan and topotecan, respectively (Seiter 2005). Anemia and thrombocytopenia are the other hematological toxicities occurring in patients receiving topotecan in 20–40 and 2–30%, respectively (Seiter 2005).

Omacetaxine mepesuccinate is a semisynthetic homoharringtonine approved by FDA in 2012. Clinical trials that included patients with chronic myeloid leukemia showed that hematological toxicity was the most common adverse effect of omacetaxine including thrombocytopenia, anemia, and neutropenia, in addition to other toxicities such as nausea, diarrhea, fatigue, and fever (Damlaj et al. 2016). Hematological toxicities were predictable and manageable where the highest toxicity occurred in the initial three cycles following improvement during the maintenance phase (Damlaj et al. 2016). Of note, it was impossible to conclude that the adverse effects were completely related to the omacetaxine drug versus the underlying chronic myeloid leukemia disease due to the lack of a control arm (Damlaj et al. 2016).

Trabectedin's predominant dose-dependent toxicity is neutropenia and abnormal liver function, namely, an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as bilirubin and alkaline phosphatase probably because trabectedin is cleared by hepatic metabolism (Jordan et al. 2015). Importantly, liver biopsies post phase I trial treatment did not show serious liver damage, and thus many studies showed that liver enzyme abnormality was reversible and was not associated with significant liver dysfunction (Jordan et al. 2015). Furthermore, neutropenia was the predominant manifestation of trabectedin-induced myelosuppression during clinical studies ranging between 24% and 100% (Jordan et al. 2015). Moreover, nausea and vomiting have been reported in trials, and thus trabectedin can be best described as a moderately emetogenic agent (Jordan et al. 2015). Interestingly, rhabdomyolysis, muscle breakdown, has been described as an uncommon toxicity of trabectedin treatment with no clear mechanism of this adverse effect (Jordan et al. 2015). In contrast to other cytotoxic chemotherapeutic agents, dermal toxicity, alopecia, and diarrhea are uncommon (Jordan et al. 2015).

Eribulin is a halichondrin analogue that was approved by the FDA in 2010 for cancer treatment. Multiple studies assessed the safety profile of eribulin as a single agent, and the most common dose-limiting drug toxicity was fatigue, anorexia, and

febrile neutropenia, in addition to other toxicities such alopecia, hypophosphatemia, and hypoglycemia (Preston and Trivedi 2012). Patients with underlying renal impairment experienced liver function test abnormalities and sensory neuropathy (Preston and Trivedi 2012).

Cytarabine, a pyrimidine analogue, is used to treat many types of cancer including lymphomas, leukemias, and neoplastic meningitis when used intrathecally (Quant 2014). Little neurotoxicity is manifested when cytarabine is used in conventional doses; however, higher doses can cause acute cerebellar syndrome; the underlying pathogenesis of cerebellar syndrome is still unknown even though loss of Purkinje cells in the cerebellum is known (Quant 2014). This syndrome is likely to occur in patients who have abnormalities in their renal or liver function or if they are above the age of 40. It is characterized by somnolence and encephalopathy post few days of treatment followed by cerebellar signs such as ataxia (Quant 2014). Peripheral neuropathy such as optic neuropathy, lateral rectus palsy, Guillain-Barre syndrome, and brachial plexopathy can be occasionally caused by high doses of cytarabine (Quant 2014).

1.6 Discussion

Nature has provided mankind with many invaluable benefits mainly through its chemical products that are used as medicine to cure human diseases. The discovery of natural bioactive molecules and assessing their biological activities has been a basic scientific endeavor aimed at treating the countless maladies, specifically malignancies. The most significant challenge of all times was turning these natural products into commercialized medicines and effectively using them to eradicate tumors. In fact, the cost of moving a new drug from bench to bedside has been the main limiting factor for commercializing natural products. Developing a drug currently costs more than 2500 million dollars and only 11.8% of the drugs tested in clinical trials will eventually get FDA approved according to a new study performed by the Tufts Center for the Study of Drug Development (http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study). Another major challenge is the lag time needed for these molecules to be discovered, then researched for usefulness in human trials, and later marketed, a time which is estimated to be more than 10 years of thorough testing and investigation. A further complication is related to the legislation protocols to access and utilize these natural products for human trials. All these factors have hampered the pharmaceutical industry to invest in the quest for finding natural products with anticancer potential.

Notwithstanding these obstacles and difficulties, alkaloids, being the largest subunit of naturally derived secondary metabolites, have been extensively studied and shown to carry promising antitumor potential for the treatment of cancer. Since their discovery, alkaloids have shown a rich history of pharmacological activities (Iqbal et al., 2017), which promoted their translation to clinical trials. More than 10 alkaloids are currently undergoing clinical evaluation (Table 1.2), and more than 14 survived clinical trial testing and received FDA approval for the treatment of various

diseases including but not limited to cancer (Table 1.1). The majority of FDA-approved and clinically tested alkaloids are derived from plants, with few derived from marine organisms. Alkaloids serve diverse purposes in plants including storage and transport of acids, antioxidant protection, anti-predation effects, end products of metabolism, waste products, and source for energy and reserve of nitrogen. In marine organisms, the soft bodies and sedentary lifestyle of these organisms caused the evolution of mechanisms for synthesizing or extracting toxic compounds and releasing them into surrounding environments for protection. Once released to the water, these compounds become diluted rapidly; thus, they must be very potent to mediate the desired effect (Hussain 2012). The protective role of alkaloids in both plants and marine organisms underlies to some extent their therapeutic potential. The cytotoxicity of some of these compounds resulted in their limited use in human trials; however, extensive structural modifications have and are still being developed to overcome toxicity, solubility, and availability problems and enhance potency. In fact, almost all clinically used alkaloids have been synthesized and are referred to as hybrid molecules or semisynthetic (Kaur 2015). Another limitation is the slow growth and endangered status of the majority of alkaloid-yielding plants, which necessitates the adoption of alternative approaches for the supply of these molecules. The workable alternatives include the application of biotechnology in plant cell and tissue culture or fermentation technology of alkaloid-producing microbes and metabolic engineering (Isah 2016). The generation of an adequate biomass of marine-derived molecules is still a drawback for translating marine-based drugs into the market.

Unlike plant-derived molecules, the structural complexity of marine molecules limits their total chemical synthesis by economically feasible strategies. Aquaculture of the source organisms including sponges and tunicates has succeeded in providing a supply of drug products; however, this supply is still far short from what is required for marine-based drugs to enter the market. In addition, these cultures are subject to uncertainties such as destruction by ocean pollution and improper exploitation of the undersea world. One interesting strategy for overcoming this issue is to identify the true leading producers of these bioactive compounds. To do so, maximizing the search for botanical and marine diversity is a must to find new sources from newer and hitherto unexplored areas. This plan is expected to deliver a number of new or analogous molecules with high activity and less toxicity. Development of high-throughput isolation of components from a crude natural product extract using highly automated separation techniques will enable chemists to speed up the isolation, purification, and characterization processes. These modern techniques coupled with high-throughput screening systems and the combination of complementary technologies, such as genomics, proteomics, metabolomics, metagenomics, metabolic and genetic engineering, and synthetic biology, are expected to yield a much larger number of lead structures in the near future with lower investment of time and money (Demain and Vaishnav 2011).

Unlike the long-standing historical medical uses of plants, marine organisms have a shorter history for the treatment of human diseases. In fact, it was not until the middle of the twentieth century that scientists began to systematically probe the

oceans for medicines. Advancement in drug discovery research resulted in the identification of many bioactive molecules from marine organisms. Despite that, the rich marine biodiversity has so far been explored to an extremely limited extent. This diversity is most likely capable of delivering a great abundance of secondary metabolites for research use (Hussain 2012) and might exceed those derived from plants. The extensive research on plant-derived alkaloids has deciphered major mechanisms of action of these molecules including topoisomerase inhibition, mitotic arrest, and inhibition of protein synthesis. On the other hand, most marine-derived alkaloids discovered so far have been shown to mediate their effect through inhibition of DNA polymerase and induction of double-strand breaks (Demain and Vaishnav 2011). A major problem with antimitotic drugs is that they only target cells in M-phase, leaving G1- or S-phase tumor cells refractory to the drug's cytotoxic effect. These cells can then repopulate the tumor mass once the drug is cleared. In addition, the underestimation of the human tumor doubling time in comparison to cell lines and animal models was a major challenge for advancing many of these agents into human testing. The considerable clinical efficacy of taxane, an antimitotic agent, is explained by the drug retention issue, where paclitaxel has been shown to linger in the tumor cells for a week and is thus able to exert its cytotoxicity unlike other agents that have a median half-life of approximately 13 h. In addition, paclitaxel is likely to target quiescent cancer cells because of the importance of microtubule dynamic trafficking in cells not undergoing mitosis (Chan et al. 2012). The fact that very few marine-derived alkaloids act as antimitotic agents provides an advantage for these drugs over plant-derived alkaloids. Although creating DNA double-strand breaks is an effective and a powerful mechanism by marine-derived alkaloids, there are three principal underlying factors of their bioactivities that are still not fully understood. First, what is the precise molecular link between the DNA repair systems, cell response to such DNA damage, and its effects on transcription regulation? Second, what is the role of tumor stroma interactions with the DNA-damaging alkaloids? And finally, how can we explain the context-specific induction of DNA damage in different tumor types? For example, in some tumors, the DNA-damaging anticancer activity of trabectedin stems mainly from its ability to modulate the tumor microenvironment by inhibiting tumor-associated macrophages (TAMs) that display several pro-tumoral functions such as on/off switching of neo-angiogenesis, whereas, in other tumors, the high activity of trabectedin can be related to its negative regulation of common cancer hallmark genes. It has the capacity to displace the oncogenic fusion protein FUS-CHOP (an abnormal transcription factor) from its target promoter, thus inhibiting its trans-activating ability (D'Incalci et al. 2014). Further investigations on the mechanism of action of these drugs in different tumor types could lead to a better understanding of the key molecules targeted by these drugs and ultimately allow the development of personalized treatments for cancer patients.

In terms of alkaloid toxicity, research has shown that compounds belonging to the same family have almost similar clinical manifestations probably due to structural similarity. Interestingly, both plant- and marine-derived alkaloids cause gastrointestinal adverse effects (Table 1.3). Abnormal liver function is a major manifestation

Table 1.3 Common adverse effects of clinically approved alkaloids

Alkaloid	Neurotoxicity	Cardiotoxicity/ other	Gastrotoxicity	Hematology-oncology	Musculoskeletal	Dermatotoxicity	References
Paclitaxel	Peripheral neuropathy	N/A	Diarrhea Nausea Vomiting Inflammatory disease of mucous membrane	Anemia Leukopenia Neutropenia Thrombocytopenia	Arthralgia Myalgia	Alopecia	www.dynamed.com
Docetaxel	Asthenia Neuropathy	Fluid retention Vasodilation *Reproductive:* Amenorrhea	Diarrhea Nausea Vomiting Stomatitis Inflammatory disease of mucous membrane	Anemia Leukopenia Neutropenia	N/A	Alopecia Nail changes Pruritus Rash	www.dynamed.com
Vincristine sulfate	N/A	N/A	Constipation Nausea Vomiting	N/A	N/A	Alopecia	www.dynamed.com
Vinblastine	N/A	Hypertension	Constipation	N/A	Bone pain Jaw pain	Alopecia	www.dynamed.com
Vinorelbine	Asthenia Neuromyopathy	N/A	Diarrhea Nausea Vomiting	N/A	N/A	Alopecia Injection site reaction	www.dynamed.com

Vinflunine ditartrate	Asthenia	*Endocrine:* Hyponatremia Weight loss	Abdominal pain Constipation Diarrhea Appetite loss Nausea Vomiting Stomatitis	Anemia Leukopenia Neutropenia Thrombocytopenia	Arthralgia Myalgia	Alopecia Injection site reaction	www.dynamed.com
Topotecan	Asthenia Headache	*Respiratory:* Cough Dyspnea	Abdominal pain Constipation Diarrhea Nausea Vomiting Stomatitis	Anemia Neutropenia Thrombocytopenia	N/A	Alopecia Rash	www.dynamed.com
Irinotecan	Asthenia Dizziness Parasympathomimetic	*Respiratory:* Cough Dyspnea *Endocrine:* Weight loss *Hepatic:* Increased bilirubin level	Abdominal pain Constipation Diarrhea Appetite loss Nausea Vomiting	Anemia Eosinophilia Leukopenia Neutropenia Thrombocytopenia	N/A	Alopecia	www.dynamed.com
Omacetaxine		*Endocrine:* Increase uric acid	Diarrhea Nausea	Anemia Neutropenia Thrombocytopenia	N/A		www.dynamed.com

(continued)

Table 1.3 (continued)

Alkaloid	Neurotoxicity	Cardiotoxicity/ other	Gastrotoxicity	Hematology-oncology	Musculoskeletal	Dermatotoxicity	References
Trabectidin	Headache	*Endocrine:* Hypoalbuminemia *Respiratory:* Dyspnea *Hepatic:* Increased (ALK, ALT, AST)[a]	Constipation Decrease appetite Diarrhea Nausea Vomiting	Anemia Neutropenia Thrombocytopenia	Increased creatine kinase		www.dynamed.com
Eribulin	Peripheral neuropathy	*Endocrine:* Hypocalcemia Hypokalemia	Constipation Nausea	Anemia Neutropenia	N/A	Alopecia	www.dynamed.com
Cytarabine		Thrombophlebitis *Hepatic:* Decreased liver function	Anal inflammation Diarrhea Appetite loss Stomatitis Anus ulcer Mouth ulcer Nausea Vomiting	N/A	N/A	Rash	www.dynamed.com

[a]*ALK* alkaline phosphatase, *AST* aspartate Aminotransferase, *ALT* alanine aminotransferase, *N/A* not available

in marine-derived alkaloids, most likely because these compounds are cleared by hepatic metabolism (Jordan et al. 2015).

Despite their clinical manifestations, alkaloids are valuable lead compounds for drug discovery. In addition to their anticancer activity, alkaloids have been shown to act as chemopreventive agents through modulation of various pathways and gene expression. Importantly, alkaloids have been shown to modulate MDR, which is a major reason for cancer treatment failure by chemotherapy, by restoring drug sensitivity. The combination of alkaloids with various chemotherapeutic drugs has been shown to restore chemosensitivity through various mechanisms including suppression of ABC-transporters such as P-gp, MRP1, and ABCG2 and induction of apoptosis (Aung et al. 2017). The best possible drug combinations are based on the understanding of the cancer-specific context of mutated oncogenes, tumor suppressor genes, and their regulatory pathways. This suggests that alkaloids merit further investigation as anticancer and chemo-sensitizing cancer therapeutics to improve our understanding of the molecular changes in cancer cells and provide clues about how the disease can be controlled.

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