Anil K. Sharma *Editor*

Bioactive Natural Products for the Management of Cancer: from Bench to Bedside

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Preface

Natural biometabolites have been the mainstay of cancer chemotherapy, being a rich reservoir of candidate compounds for drug discovery. Recent efforts into the research and development of anticancer drugs derived from natural products have led to the identification of a variety of candidate molecules that inhibit cancer cell proliferation and metastasis via various mechanisms. With the advent of new technologies such as combinatorial chemistry and high-throughput screening, next-generation sequencing, and the ease of identifying abnormal genes, it is now possible to consider that natural products would sound the death knell for cancer. Moreover, natural products are likely to provide novel lead molecules which would be used as templates for restructuring them for potential anticancer drug candidates with enhanced biological properties. Moreover, nanomedicine-based natural products have recently shown promising therapeutic effects with better efficacy and target specificity against cancer countering drug resistance as well. Despite the increasing interest in natural product research, to our knowledge, still this area requires attention of the scientific community to explore the wide-scale mechanisms encompassing anticancer therapeutics with natural products being the lead compounds further redressing the growing problem of drug resistance against cancer. In order to fill these gaps and what kind of therapeutic roles natural products especially secondary metabolites play in the treatment and management of cancer, this book titled *Bioactive Natural Products for the Management of Cancer: From Bench to Bedside* has been able to successfully address the remarkable therapeutic potential of bioactive natural products against cancer.

The book has significant contributions in the form of book chapters by renowned authors as follows: Hala Gali-Muhtasib and his group highlighted the potential significance of anticancer alkaloids, underlying action mechanism, and clinical manifestations which were further supported by Batra and Sharma, expanding their studies to emerging alkaloids peeping into various factors and getting insight into the mechanism of action against cancer. Banerjee and his group shed light into the cancer etiology and therapeutic management by natural metabolites. Sharma et al. highlighted the potential anticancer therapeutic role of flavonoids especially flavones. Gajbhiye et al. emphasized the therapeutic properties of dietary polyphenols, flavonoids, terpenoids, and saponins in cancer chemoprevention. The same group further enlightened us with a vast immunogenic potential of natural products. Anshika Singh and S. Krishna further lead us to look into marine flora for their

immunomodulatory and therapeutic potential in the treatment of cancer. Bhattacharrya and her group enlightened us by contributing a chapter on ligand-based designing of natural products paving a way for drug discovery of novel chemical entities. In another chapter, Nag and her group tried to address the mechanism of drug resistance in cancer and the potential role of nanomedicine-based natural products in countering the menace of drug resistance.

The book holds many unique flavors as follows:

1. Recent updates on natural metabolites and their therapeutics use against cancer
2. Unique and distinctive pathways and mechanistic insight into the mode of action of the metabolites
3. The use of these metabolites and nanoparticle-augmented adjuvant therapy to counter the ever-growing problem of drug resistance
4. Ligand-based drug designing of these natural metabolites to enhance their active potential and counter adverse side effects

Once again, my sincere thanks to all the contributing authors who worked as a team to let me complete this book. Special thanks to Dr. Bhavik Sawhney who was available all the time to impart his valuable inputs and assistance. Words of appreciation also go to Mr. Daniel Ignatius Jagadisan, the Production Team, and the Editor as well.

The book is dedicated to my parents and spouse who time and again kept inspiring me to accomplish this task and complete the said manuscript timely.

Ambala, Haryana, India Anil K. Sharma

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About the Editor

Dr. Anil K. Sharma is presently at M.M. (DU), Department of Biotechnology, Mullana, Ambala (India), where he has been a Professor and Head of the department since April 2012. Previously, he worked as a Senior Research Scientist in Health Sciences (UIC Chicago, USA; 2008–2010), Postdoctoral Research Fellow in Molecular Biology (Microbiology and Immunology Department, UIC Chicago, IL, USA; 2003–2008), and Senior Research Scientist at Ranbaxy (R&D, Gurgaon, Haryana, India; 2001–2003). He has authored more than 95 publications in peer-reviewed journals and received many prestigious awards and accolades including an Eminent Scientist Award for Molecular and Microbial Science (2017 and 2018), National Achiever Award (2016), and Bharat Excellence Award (2013). In addition to editing five books, he has been the Editor-in-Chief of two journals, and lead guest editor, editorial board member or reviewer of over 30 more.

Anticancer Alkaloids: Molecular Mechanisms and Clinical Manifestations

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Farah Ballout, Zeina Habli, Alissar Monzer, Omar Nasser Rahal, Maamoun Fatfat, and Hala Gali-Muhtasib

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.

Authors Farah Ballout and Zeina Habli have equally contributed to this chapter.

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Keywords
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)