Medicinal Plants: A Potential Source of Compounds for Targeting Cell Division

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ABSTRACT: Modern medicinal plant drug discovery has provided pharmacologically active compounds targeted against a multitude of conditions and diseases, such as infection, inflammation, and cancer. To date, natural products from medicinal plants remain a solid niche as a source from which cancer therapies can be derived. Among other properties, one favorable characteristic of an anticancer drug is its ability to block the uncontrollable process of cell division, as cancer cells are notorious for their abnormal cell division. There are numerous other documented works on the potential anticancer activity of drugs derived from medicinal plants, and their effects on cell division are an attractive and growing therapeutic target. Despite this, there remains a vast number of unidentified natural products that are potentially promising sources for medical applications. This mini review aims to revise the current knowledge of the effects of natural plant products on cell division.

KEYWORDS: cell division, cancer, medicinal plants, microtubule, natural products

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Introduction

Human beings have long used plants as a medicinal source. Their use has grown more sophisticated with modern chemists using compounds isolated from plants as a basis for generating novel compounds with additional benefits, such as its lower toxicity and potential for combating drug-resistant diseases. Between 1981 and 2010, naturally derived products and their mimics composed an estimated 70% of new chemical compounds reported.[1] Naturally derived compounds with anticancer activity have also been used as the basis for original synthetic analogs, forming their own novel class of chemical compounds.[2]

Mammalian microtubules appear to be a common target for naturally occurring toxic molecules produced by a large number of flora, presumably with the original intent of self-defense. Microtubules are a component of the cytoskeleton, found throughout the cell cytoplasm, which is important in the process of mitosis (ie, cell division). Most microtubule-targeting compounds have been discovered in large-scale screens of natural products[3,4] (Table 1). Approximately 75% of the available anticancer drugs between 1940 and 2010 were naturally derived products or their mimics. Additionally, of the seven anticancer drugs approved in 2010, almost half of them exert their effects by binding onto microtubules.[1]

One of the biggest success stories of microtubule-targeted compounds from a naturally derived source is Paclitaxel (commercially known as Taxol), a member of the Taxane family. Paclitaxel is extracted from the bark of the Pacific yew tree (*Taxus brevifolia*) and acts as an antimitotic drug, by binding to microtubules, thus stabilizing them and arresting cells in mitosis.[5–9] Taxol and its derivatives have successfully been used clinically to treat ovarian cancer, breast cancer, and non-small cell lung cancer for almost 40 years, making Taxol the best-selling anticancer drug currently manufactured. Its success has sparked the search for similar microtubule-stabilizing compounds.

Another class of microtubule-targeted compounds from a naturally derived source is the vinca alkaloids, vincristine and vinblastine, which were initially isolated from the Madagascar periwinkle plant (*Catharanthus roseus*).[10] The vinca alkaloids are microtubule destabilizers and have proven to be particularly effective against hematological malignancies,[11] and their success has generated several semisynthetic derivatives. Semisynthetic and synthetic derivatives may offer advantages over a fully natural source, as the bioactive natural compound may be present only in trace amounts. Natural compounds may instead act as lead compounds, where analogs with higher potencies and lower toxicities may be developed[12,13] (Table 2). Natural products are ideal as lead compounds as their chemical structures are complex and diverse (Table 3). The biggest study looking into the isolation of compounds with clinical bioactivity, specifically anticancer activity, from natural sources was done by the National Cancer Institute (NCI) of the National

Table 1. Selected compounds originally isolated from natural sources that act on microtubules.

BIOLOGICALLY ACTIVE COMPOUND(S) AND THEIR STRUCTURE	SCIENTIFIC NAME(S) OF NATURAL SOURCE	MECHANISM OF ACTION ON MICROTUBULES	STATUS AS ANTI-CANCER DRUG	TESTED CANCER TYPES	REFERENCES
Paclitaxel	*Taxus brevifolia*	Stabilizes microtubules	In clinical use	Ovarian cancer, breast cancer, non-small cell lung cancer, advanced Kaposi sarcoma	47,48
Vinblastine Vincristine	*Catharanthus roseus*	Destabilizes microtubules	In clinical use	Acute lymphoblastic leukaemia, breast cancer, choriocarcinoma, Hodgkin lymphoma, Kaposi sarcoma, Mycosis fungoides, Hodgkin and non-Hodgkin lymphoma, testicular cancer, neuroblastoma, rhaddomycosarcoma, Wilms tumour, bladder cancer, testicular cancer, breast cancer, choriocarcinoma, lung cancer, multiple myeloma, soft tissue sarcoma, brain tumours. Leukaemia, head and neck cancers	10,11,49,50
Colchicine	*Colchicum autumnale*	Destabilizes microtubules	Failed anti-cancer trials due to toxicity; in clinical use for gout therapy	Hepatocellular carcinoma, multiple myeloma, Hodgkin's lymphoma, chronic lymphatic leukaemia, breast cancer, lung cancer, chronic lymphocytic leukaemia	51–53
Podophyllotoxin	*Podophyllum* spp.	Destabilizes microtubules	In use for the topical treatment of external genital warts	None	43,54,55
Combretastatins	*Combretum caffrum*	Destabilizes microtubules	Phase I, II clinical trials; Semi-synthetic derivative in Phase III clinical trials	Acute myeloid leukaemia, myelodysplastic syndrome, thyroid cancer, non-small cell lung cancer, various solid tumours	56
Noscapine	*Papaveraceae* spp.	Suppresses microtubule dynamics	Phase II clinical trials	Multiple myeloma	57

Note: Data in this table were obtained from a combination of NCI Drug Dictionary (http://www.cancer.gov/drugdictionary), published literature, and company web sites.

Table 2. Selected synthetic and semisynthetic compounds originally isolated from natural sources that act on microtubules.

COMPOUND AND STRUCTURE	ORIGINAL COMPOUND	MECHANISM OF ACTION ON MICROTUBULES	STATUS AS ANTI-CANCER DRUG	TESTED CANCER TYPES	REFERENCES
Vindesine	Vinca alkaloids	Destabilizes microtubules	In clinical use	Various lung cancers, various haematological malignancies, melanoma, renal cancer, colorectal cancer and breast cancer. Currently in clinical trials for other cancer types	58
Vinorelbine	Vinca alkaloids	Destabilizes microtubules	In clinical use	Non-small cell lung cancer, metastatic breast cancer, renal cancer	42,59,60
Vinflunine	Vinca alkaloids	Destabilizes microtubules	In clinical use	Bladder cancer, urethral cancer, ureteral cancer, cancer of the renal pelvis	42
Docetaxel	Paclitaxel	Stabilizes microtubules	In clinical use	Breast cancer, gastric cancer, non-small cell lung cancer, prostrate cancer, squamous cell carcinoma of the head and neck, stomach cancer	61
Cabazitaxel	Paclitaxel	Stabilizes microtubules	In clinical use	Metastatic prostrate cancer	62,63
Larotaxel	Paclitaxel	Stabilizes microtubules	Phase III clinical trials	Breast cancer, pancreatic cancer, urothelial tract cancer, bladder cancer, various solid tumours	63
Tesetaxel	Paclitaxel	Stabilizes microtubules	Phase II clinical trials	Gastric cancer, melanoma, bladder cancer, breast cancer, prostate cancer, various solid tumours	63
Ombrabulin	Combrestatin	Destabilizes microtubules	Discontinued, due to insufficient clinical benefit	Soft tissue sarcoma, non-small cell lung cancer, ovarian cancer, various solid tumours	55,64
Fosbretabulin	Combrestatin	Destabilizes microtubules	Phase I and phase II clinical trials	Ovarian cancer, gastrointestinal neuroendocrine tumours, ovarian epithelial, fallopian tube, and primary peritoneal cancers, gliomas, thyroid cancer	65
Crolibulin	Combrestatin	Destabilizes microtubules	Phase I and phase II clinical trials	Thyroid cancer	66
Verubulin	Combrestatin	Destabilizes microtubules	Phase I and phase II clinical trials	Glioblastoma	66–68

Note: Data in this table were obtained from a combination of NCI Drug Dictionary (http://www.cancer.gov/drugdictionary), published literature, and company web sites.

Institute of Health in USA from 1960 to 1980.[14] However, it is estimated that >90% of plant species worldwide remain understudied. Discovery of drug molecules has been limited because of genomic instability and drug resistance characteristics in certain cancer cells.[15] Therefore, modern drug discovery has shifted to personalized treatment of patients, where drugs are selected for specific molecular targets, taking advantage of the vulnerabilities of cancer in a particular patient, leading to increased interest in studying traditional herbs as an alternative source of anticancer drugs because of its multitargeted characteristic.[16]

The Role of the Microtubule in Cell Division

Microtubules are a class of the cytoskeletal proteins present in all eukaryotic cells. They form long, filamentous, polymeric structures within the cell, composed of α- and β-tubulin heterodimers, of which there are several isotypes.[17] The different isotypes of tubulin in human beings are summarized in Table 4. Microtubules play many roles in eukaryotic cells, including development and maintenance of cell shape,[18] intracellular transport,[19] cell motility,[20,21] cell signaling,[22] and cell division.[23]

Cell division, or mitosis, is a crucial event in the cell cycle that results in the division of a single cell into two identical daughter cells with the equal distribution of genetic materials (Fig. 1). During mitosis, the cytoskeleton forms a superstructure called the mitotic spindle, which facilitates many of the cell division processes. Mitosis involves a series of stages. The initial prophase and prometaphase stages are where there is condensation of chromosomes, which then attaches to the mitotic spindle. The chromosomes then align at the equator of the mitotic spindle (metaphase) before the sister chromosomes segregate into daughter cells (anaphase). The final stage is where the chromosomes decondense and the cells divide fully into two daughter cells (telophase). All the stages of mitosis must be regulated for the proper development and function of a multicellular organism. Central to the function of microtubules is the regulation of microtubule dynamics. Microtubule filaments are able to polymerize and depolymerize stochastically within a cell, in what is termed

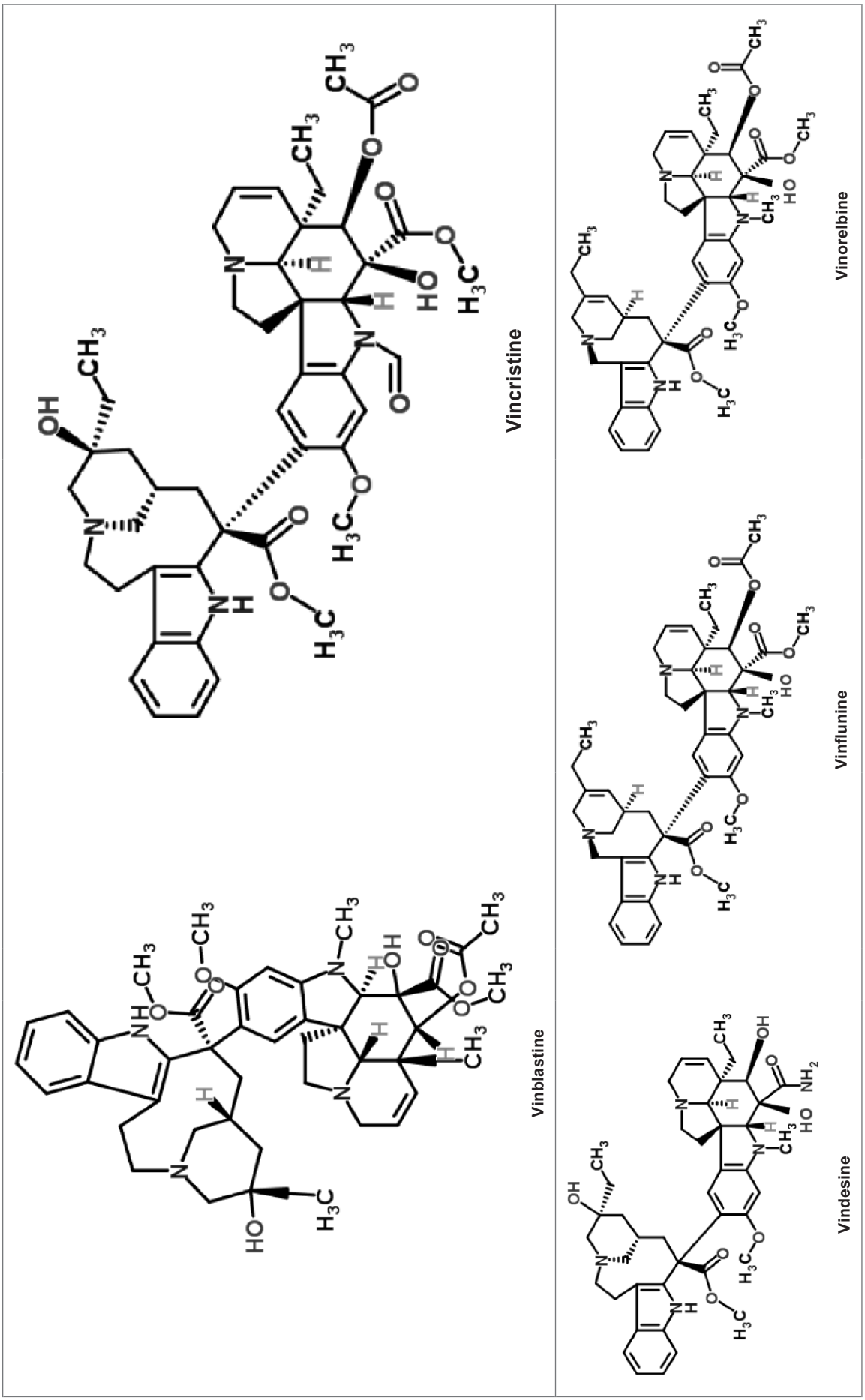
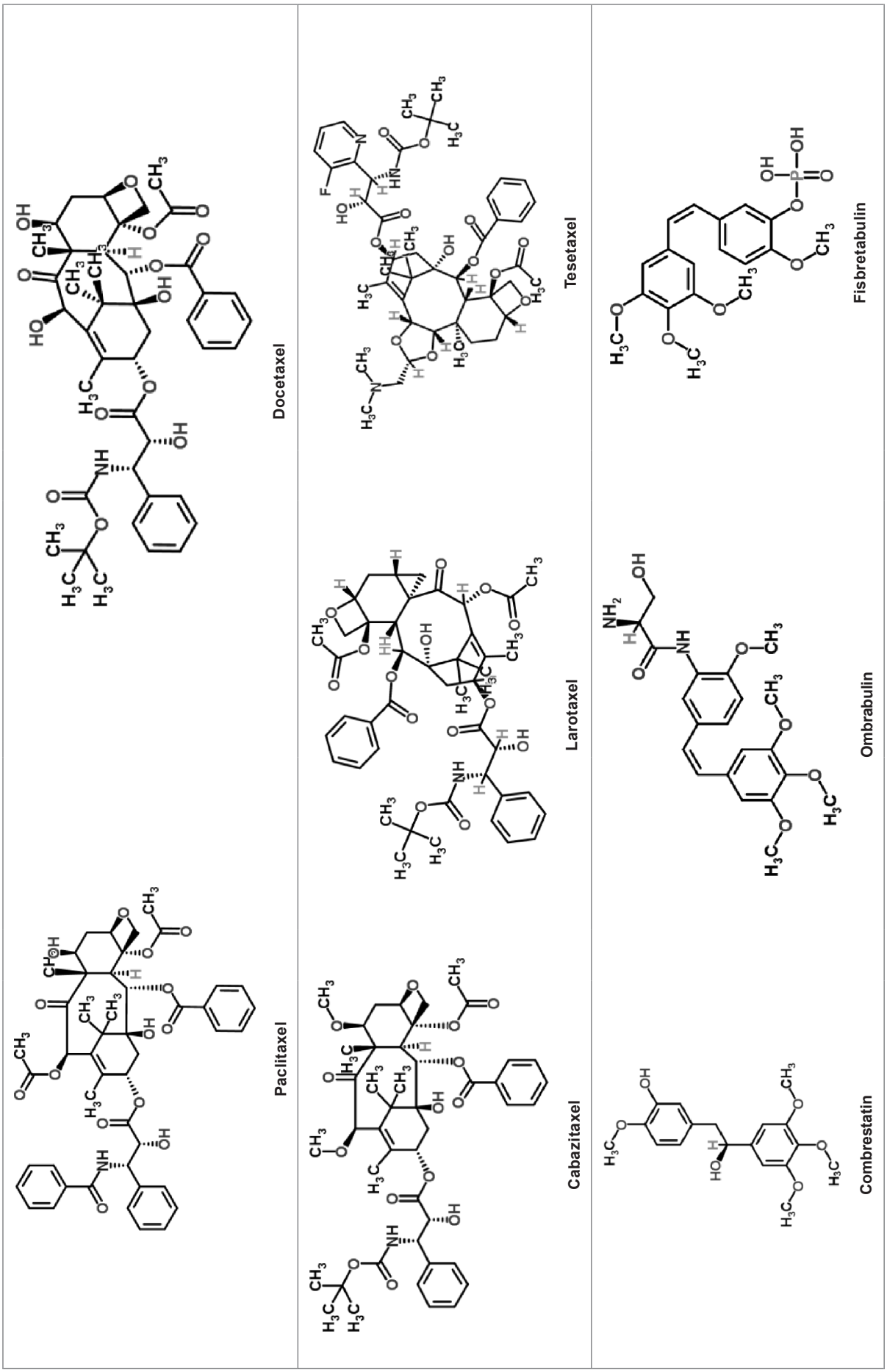


Table 3. Chemical structures of natural microtubule-targeting compounds and their synthetic and semisynthetic derivatives.


Docetaxel
Tesetaxel
Fisbretabulin
Paclitaxel
Larotaxel
Ombrabulin
Cabazitaxel
Combrestatin

(*continued*)

Table 3. (*Continued*)

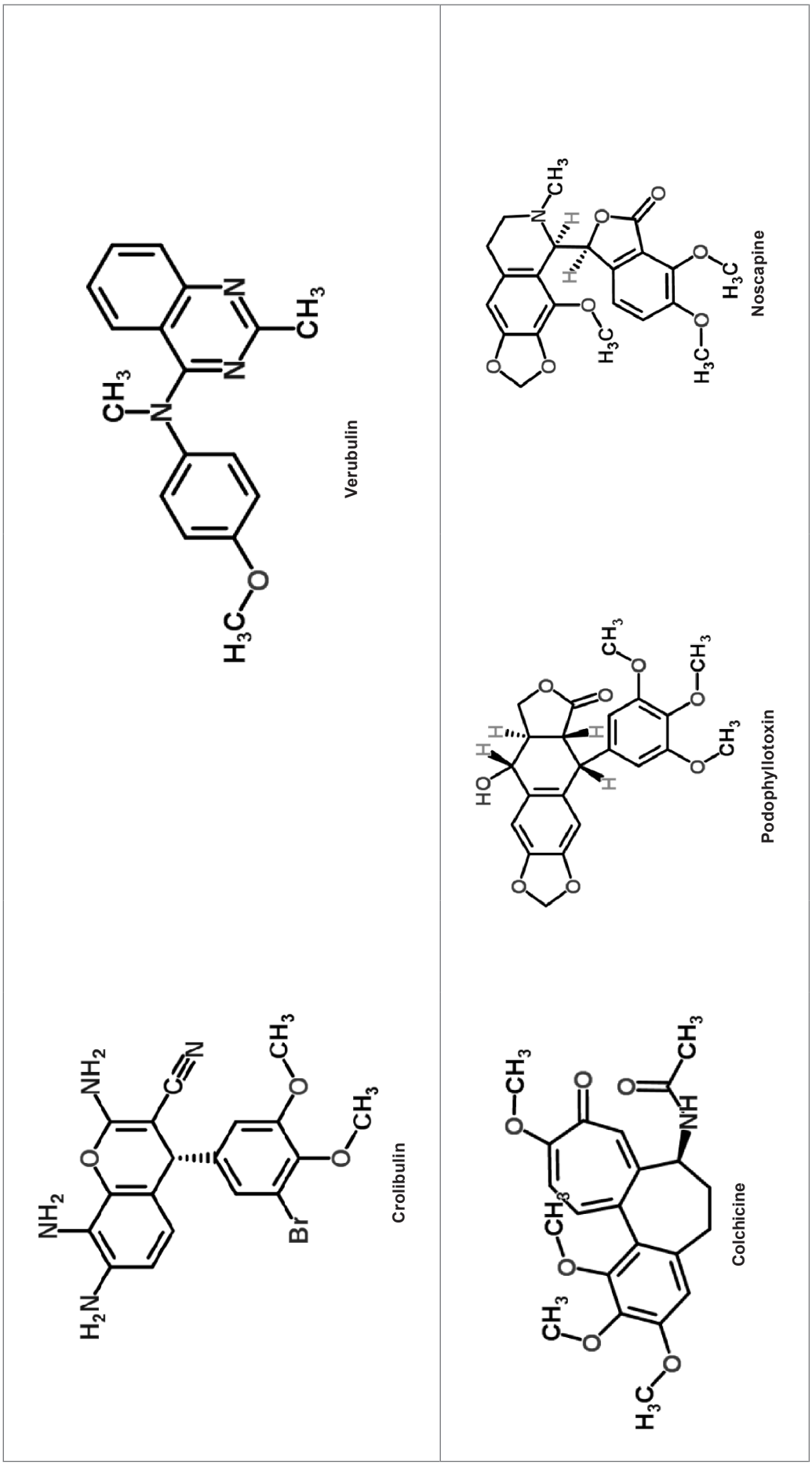


Table 4. Subtypes and isoforms of microtubules.

TUBULIN SUBTYPE	ISOTYPE	GENE	LENGTH (AMINO ACIDS)	TISSUE DISTRIBUTION	PUTATIVE FUNCTION (IF ANY)	ALTERED EXPRESSION IN CANCERS?
α	1A	TUBA1A	451	Ubiquitous	No isoform-specific function identified	No
	1B	TUBA1B	451	Ubiquitous		No
	1C	TUBA1C	449	Ubiquitous		No
	3C	TUBA3C	450	Enriched expression in testis, fallopian tube, soft tissues, central nervous system and other selected tissues		Variable expression
	3D	TUBA3D	450	Enriched expression in testis, fallopian tube, soft tissues, central nervous system and other selected tissues		Decreased
	3E	TUBA3E	448	Enriched expression in testis, fallopian tube, soft tissues, central nervous system and other selected tissues		Decreased
	4A	TUBA4A	446	Ubiquitous		No
	8	TUBA8	449	Ubiquitous, but enriched in heart muscle, skeletal muscle and testis		Decreased
β	1	TUBB1	451	Enriched in haematopoietic cells	May play a role in microtubule stability, as well as interaction with actin	Increased on exposure to microtubule-targeting drugs
	2A	TUBB2A	445	Ubiquitous, enriched in brain	May play a role in neuronal differentation	Increased in microtubule-targeting drug-resistant cancers
	2B	TUBB2B	445	Ubiquitous, enriched in brain	May play a role in neuronal differentation	No
	3	TUBB3	450	Mostly expressed in central and peripheral nervous system	May play a role in neuronal differentiation. May help cells cope with oxidative stress	Overexpressed in aggressive tumours
	4A	TUBB4A	444	Highly expressed in brain, moderate levels in testis, very low levels in other tissues	Occurs in axonemes, may be required for determination of axonemal microtubule structure	Increased on exposure to microtubule-targeting drugs
	4B	TUBB4B	445	Ubiquitous	Occurs in axonemes, may be required for determination of axonemal microtubule structure	No
	5	TUBB	444	Ubiquitously expressed with highest levels in spleen, thymus and immature brain	Unknown	Unknown
	6	TUBB6	446	Ubiquitous, with highest expression in the breast and lung	Unknown	Largely decreased
	8	TUBB8	444	Ubiquitous, enriched in ciliated cells and lymphoid tissue	Unknown	Unknown
γ	1	TUBG1	451	Ubiquitous	Important for nucleation and polarity of microtubules, mostly found in microtubule-organising centres	Unknown
	2	TUBG2	451	Ubiquitous	Important for nucleation and polarity of microtubules, mostly found in microtubule-organising centres	Unknown
δ	–	TUBD1	453	Ubiquitous	Sperm differentiation	Decreased
ε	–	TUBE1	475	Majority of tissues	Centrosome cycle	Decreased

Notes: Data in this table were obtained from Uniprot (http://www.uniprot.org) and ProteinAtlas (http://www.proteinatlas.org).

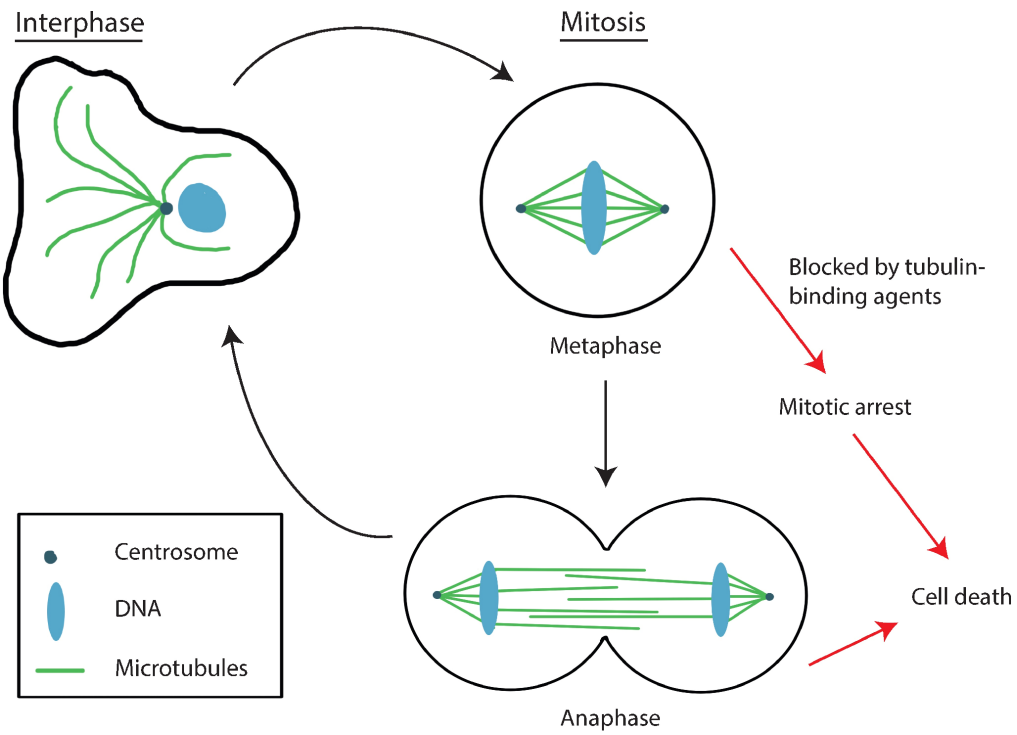


Figure 1. The process of cell division in mammalian cells. This figure illustrates the different microtubule structures present during different stages of the cell cycle. In the interphase stage of the cell cycle, microtubules (green) emanate out from the microtubule-organizing center, the centrosome (dark blue circle), forming an array that extends toward the cell periphery. During the mitotic stage of the cell cycle, the centrosomes are duplicated and separated to form spindle poles, while the microtubule cytoskeleton is reorganized to form a superstructure called the mitotic spindle. The mitotic spindle is responsible for mitotic events such as chromosome congression and chromosome segregation. Two stages of the mitotic stage of the cell cycle are illustrated—metaphase and anaphase. At metaphase, the mitotic spindle holds sister chromatids (blue) together at the cell equator. At anaphase, the cell elongates the spindle poles move further apart and the sister chromatids move toward the opposite poles. Black arrows indicate the path normally followed by a cell in a cell cycle. When the cell cycle is disrupted at mitosis by tubulin-binding agents, the cell is unable to complete mitosis and follows an alternative pathway (red arrows) where it undergoes mitotic arrest and eventually cell death. All stages of mitosis must be regulated for proper development and function of a multicellular organism. Unregulated mitosis may lead to an overgrowth of cells, as in cancer. The ability to carry out an infinite number of cell divisions is one of the hallmarks of cancer. Blockage of any stage of mitosis may not allow the cells to complete mitosis, resulting in cell cycle arrest and ultimately, cell death.

as microtubule dynamicity.[24] Microtubule dynamics are tightly regulated within cells, through the binding of various regulatory proteins, expression of different tubulin isotypes, and posttranslational modifications of tubulin subunits.[25,26] Dynamic microtubules have a very short half-life of a few minutes, or even seconds, whereas stable microtubules have half-lives of minutes to hours.[27]

During mitosis, microtubules are the main components of the mitotic spindle, where microtubule dynamics are increased significantly.[27,28] Dynamic microtubules are required for all stages of mitosis: from capturing and congressing chromosomes to the metaphase plate,[29] pulling chromosomes toward opposite poles and initiating anaphase,[30] and finally cytokinesis to complete mitosis.[31,32] Microtubule-binding compounds may either stabilize microtubules (promoting growth and not supporting shrinkage of the microtubule filament) or destabilize microtubules (promoting shrinkage and not supporting growth of the microtubule filament). Any alterations in microtubule dynamics will affect the different events in mitosis. For example, if microtubule dynamics are suppressed, chromosomes may not be able to congress to the metaphase plate.[33,34] The presence of a single uncongressed chromosome is enough to induce mitotic arrest.[1] Accordingly, altered microtubule dynamics is among the major causes of mitotic arrest. A cell that is arrested in mitosis for a prolonged time may eventually undergo apoptosis, or programed cell death.[35] At present, most of the drugs used to treat cancer target microtubule dynamics in order to arrest cancerous cells in mitosis.

Microtubules—A Potential Target for Cancer Therapy

Unregulated cell division may lead to an overgrowth of cells, as in cancer. The ability to carry out an infinite number of cell divisions is one of the hallmarks of cancer.[36] Blockage of any stage of mitosis may not allow the cells to complete mitosis, resulting in cell cycle arrest and ultimately, cell death. Microtubules represent the best and most successful target thus far

identified in cancer treatment.[37–39] Cancer cells are sensitive to microtubule poisons that arrest cells in mitosis because they undergo mitosis more frequently than normal cells. At high concentrations, anticancer drugs that target microtubules may act in one of the two ways. Each approach has different effects, including affecting the polymerized microtubule mass, destabilization of microtubules (decreases microtubule mass), and stabilization of microtubules (increases microtubule mass), dependent on the site of binding on the microtubule lattice.[40] The effects of each compound on microtubules are indicated in both Tables 1 and 2.

Currently, there are two main classes of microtubule-binding anticancer drugs. These are the microtubule destabilizers, such as the Vinca alkaloids,[41–44] and microtubule stabilizers that prevent microtubule disassembly without affecting their polymerization, such as the taxanes.[6] However, studies have shown that various microtubule-targeting drugs, irrespective of their effects on polymerized microtubule mass at high concentrations, all suppress microtubule dynamics at lower concentrations, ie, prevent the growth or shrinkage of microtubules without changing the microtubule polymer mass[6,8,33,34,42–45] (Fig. 2). In this way, changes in microtubule dynamics can be used as an indicator of the efficacy of the anticancer activities of a naturally derived compound.

Conversely, tumors can acquire resistance to microtubule-targeting drugs. Although a discussion on the resistance mechanisms to these drugs is beyond the scope of this review, the possible methods of resistance include multidrug resistance pumps, altered drug binding, altered microtubule assembly, altered tubulin synthesis, and alterations in microtubule-interacting proteins (refer to Fojo and Menefee[46] for a more extensive review).

As with all drugs, the toxic side effects of microtubule-targeting agents must be taken into account. Owing to the physiological functions of microtubules, treatment with microtubule-targeting agents often exhibits myelosuppression and peripheral neuropathy. The specificity of each compound must therefore be tested. The cancers identified to be susceptible to each drug are illustrated in Tables 1 and 2.

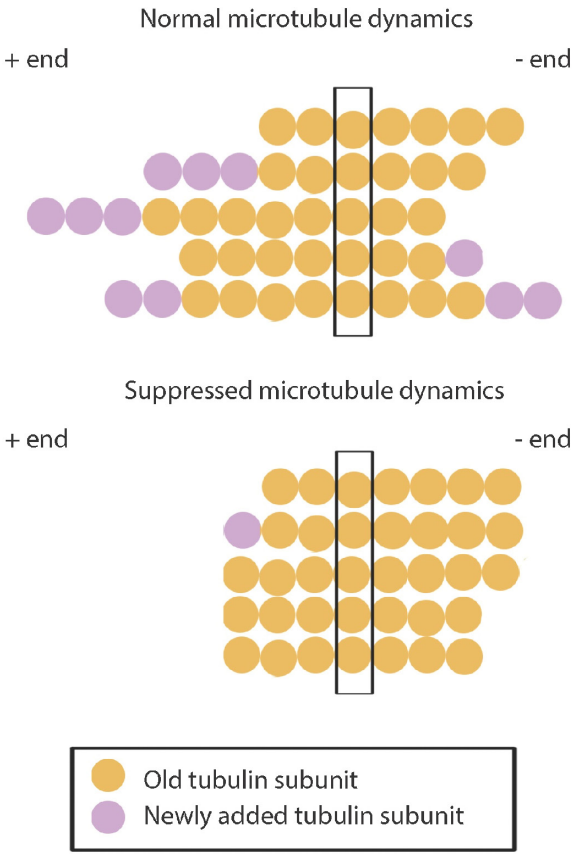


Figure 2. Microtubule dynamic instability. The figure illustrates the growth and shrinkage of a single microtubule, with each row representative of a single time point. Microtubules are composed of stable αβ-tubulin heterodimers that are arranged in a head-to-tail fashion, forming a polar structure. Each heterodimer is illustrated as a single circle. Microtubules therefore consist of two distinct ends: the plus (+) end and the minus (–) end. In vivo, the—ends are anchored at the microtubule-organizing centers. The + ends are more dynamic than the—ends, with the microtubule end constantly switching between growth and shrinkage in what is termed dynamic instability. Microtubules are normally very dynamic (top), with tubulin subunits randomly added or lost from both ends. In vivo, microtubule elongation usually occurs in the plus end. When microtubule dynamics are suppressed (for example, through the action of tubulin-binding agents) (bottom), tubulin subunits are rarely added or lost from the microtubule ends.

Conclusion

Mitosis is an important stage of the cell cycle, which is deregulated in cancer, leading to uncontrolled cancer growth. An important facilitator of mitosis is the microtubule cytoskeleton. Hence, many anticancer drugs target the microtubule skeleton in order to arrest cancer cells in mitosis, which eventually leads to cell death. Most of these microtubule-targeting drugs act by suppressing microtubule dynamics, which is particularly important for the microtubule function in mitosis. Interestingly, many of the microtubule-binding anticancer drugs are derived from natural sources, including Taxol and the vinca alkaloids, two very successful classes of anticancer drugs. Therefore, there is great potential for the isolation of compounds with similar microtubule-targeting activities from medicinal plants. Future aims for the development of novel microtubule-binding agents are the development of compounds specific to cancer cells, thereby reducing potential toxic side effects, as well as the development of compounds that are able to overcome current drug-resistant cancers.

Author Contributions

Prepared the first draft of the manuscript: INZ. Contributed to the writing of the manuscript: SRD, RR, and AI. Jointly developed the structure and arguments for the paper: INZ, SRD, RR, and AI. Made critical revisions and approved the final version: AI. All the authors reviewed and approved the final manuscript.

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