

Minireview

Anticancer agents from medicinal plants

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[Received 29 November 2006]

Abstract

Cancer is a major public health burden in both developed and developing countries. Plant derived agents are being used for the treatment of cancer. Several anticancer agents including taxol, vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, and etoposide derived from epipodophyllotoxin are in clinical use all over the world. A number of promising agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol are in clinical or preclinical development.

Key words: anticancer, cytotoxicity, medicinal plants, natural products, taxol

Introduction

Natural Products, especially plants, have been used for the treatment of various diseases for thousands of years. Terrestrial plants have been used as medicines in Egypt, China, India and Greece from ancient time and an impressive number of modern drugs have been developed from them. The first written records on the medicinal uses of plants appeared in about 2600 BC from the Sumerians and Akkaidians (Samuelsson, 1999). The "Ebers Papyrus", the best known Egyptian pharmaceutical record, which documented over 700 drugs, represents the history of Egyptian medicine dated from 1500 BC. The Chinese *Materia Medica*, which describes more than 600 medicinal plants, has been

well documented with the first record dating from about 1100 BC (Cragg et al., 1997). Documentation of the Ayurvedic system recorded in Susruta and Charaka dates from about 1000 BC (Kappor, 1990). The Greeks also contributed substantially to the rational development of the herbal drugs. Dioscorides, the Greek physician (100 A.D.), described in his work "De Materia Medica" more than 600 medicinal plants (Samuelsson, 1999). The World Health Organization estimates that approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care (Farnsworth et al., 1985). Cancer is a major public health burden in both developed and developing countries. It was estimated that there were 10.9 millions new cases, 6.7 million deaths, and 24.6 million persons living with cancer around the world in 2002 (Parkin et al., 2005). Cancer is the second

leading cause of death in the United States (Hoyert et al., 2005), where one in four deaths is due to cancer. Plants have long been used in the treatment of cancer (Hartwell, 1982). The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity (Shoeb, 2005). Of the 92 anticancer drugs commercially available prior to 1983 in the US and among world wide approved anticancer drugs between 1983 and 1994, 60% are of natural origin (Cragg et al., 1997). In this instance, natural origin is defined as natural products, derivatives of natural products or synthetic pharmaceuticals based on natural product models (Jaspars and Lawton, 1998).

Plant derived Anticancer agents in clinical use

The isolation of the vinca alkaloids, vinblastine (**1**) and vincristine (**2**) from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae) introduced a new era of the use of plant material as anticancer agents. They were the first agents to advance into clinical use for the treatment of cancer (Cragg and Newman, 2005). Vinblastine and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma (Cragg and Newman, 2005).

The discovery of paclitaxel (Taxol®, **3**) from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae), is another evidence of the success in natural product drug discovery. Various parts of *Taxus brevifolia* and other *Taxus* species (e.g., *Taxus Canadensis* Marshall, *Taxus baccata* L.) have been used by several Native American Tribes for the treatment of some non-cancerous cases (Cragg and Newman, 2005) while *Taxus baccata* was reported to use in the Indian

Ayurvedic medicine for the treatment of cancer. The structure of paclitaxel was elucidated in 1971 and was clinically introduced to the US market in the early 1990s (Wani et al., 1971; Rowinsky et al., 1992). Paclitaxel is significantly active against ovarian cancer, advanced breast cancer, small and non-small cell lung cancer (Rowinsky et al., 1992). Camptothecin (**4**), isolated from the Chinese ornamental tree *Camptotheca acuminata* Decne (Nyssaceae), was advanced to clinical trials by NCI in the 1970s but was dropped because of severe bladder toxicity (Potmeisel, 1995). Topotecan (**5**) and irinotecan (**6**) are semi-synthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers, and colorectal cancers, respectively (Creemers et al., 1996; Bertino, 1997). Epipodophyllotoxin is an isomer of podophyllotoxin (**7**) which was isolated as the active anti-tumor agent from the roots of *Podophyllum* species, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich (Berberidaceae) (Stahelin, 1973). Etoposide (**8**) and teniposide (**9**) are two semi-synthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas and bronchial and testicular cancers (Cragg and Newman, 2005; Harvey, 1997).

Homoharringtonine (**10**), isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.) (Cephalotaxaceae), is another plant-derived agent in clinical use (Itokawa et al., 2005; Powell et al, 1970). A racemic mixture of harringtonine and homoharringtonine has been used successfully in China for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia (Cragg and Newman, 2005; Kantarjian et al., 1996). Elliptinium (**11**), a derivative of ellipticine, isolated from a Fijian medicinal plant *Bleekeria vitensis* A.C. Sm., is marketed in France for the treatment of breast cancer (Cragg and Newman, 2005).

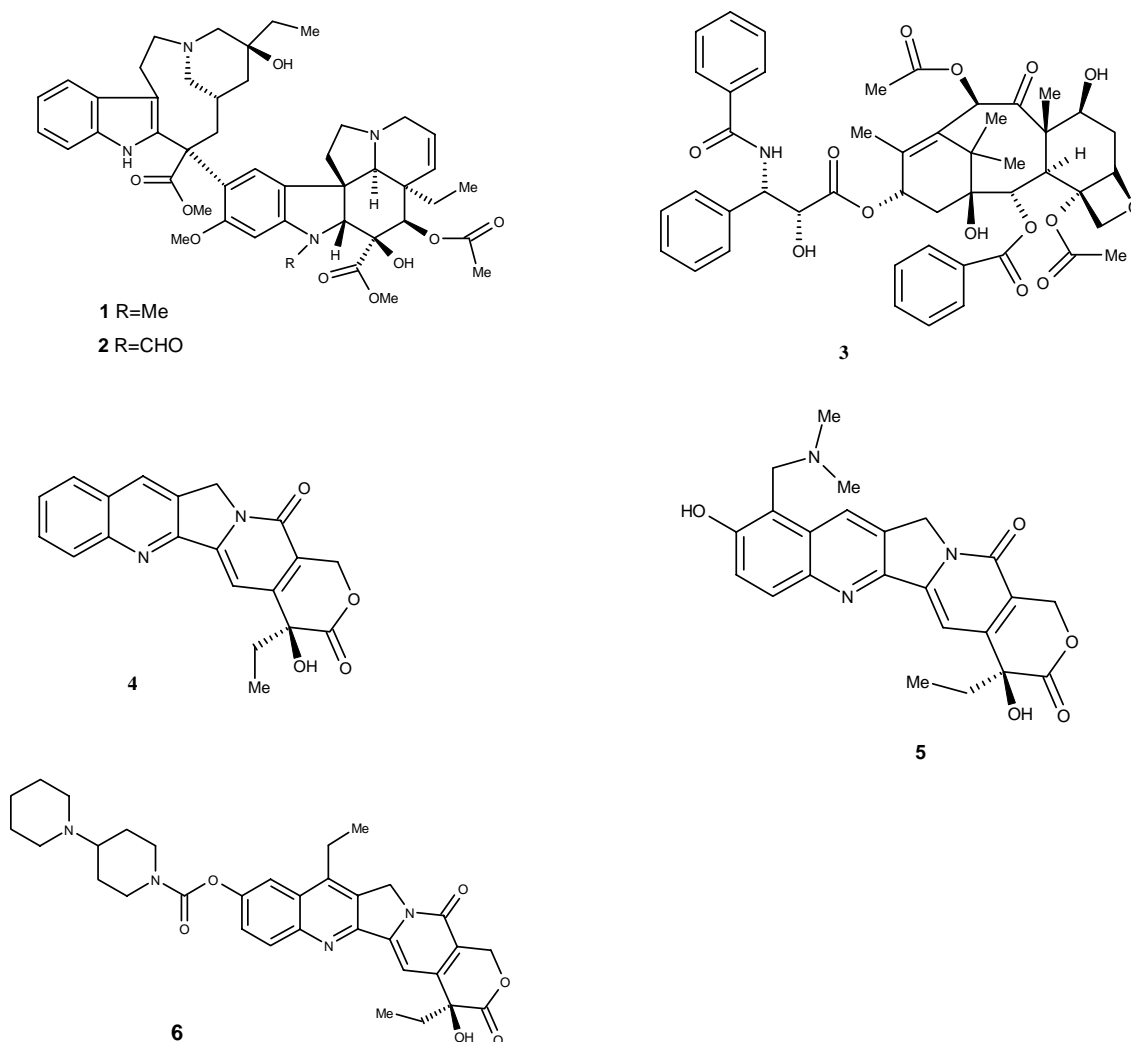


Figure 1: Plant-derived anticancer agents in clinical use

Plant-derived anticancer agents for future development

Numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation. Flavopiridol (**12**) is a synthetic flavone, derived from the plant alkaloid rohitukine, which was isolated from *Dysoxylum binectariferum* Hook. f. (Meliaceae) (Kellard et al., 2000). It is currently in phase I and phase II clinical trials against a broad range of tumors, including leukemia, lymphomas and solid tumors (Christian et al., 1997). Synthetic

agent roscovitine (**13**) which is derived from natural product olomucine, originally isolated from *Raphanus sativus* L. (Brassicaceae), is in Phase II clinical trials in Europe (Cragg and Newman, 2005; Meijer et al., 2003). Combretastatins were isolated from the bark of the South African tree *Combretum caffrum* (Eckl. & Zeyh.) Kuntze (Combretaceae) (Pettit et al., 1987). Combretastatin A-4 (**14**) is active against colon, lung and leukemia cancers and it is expected that this molecule is the most cytotoxic phyto-molecule isolated so far (Ohsumi et al., 1998; Pettit et al., 1995).

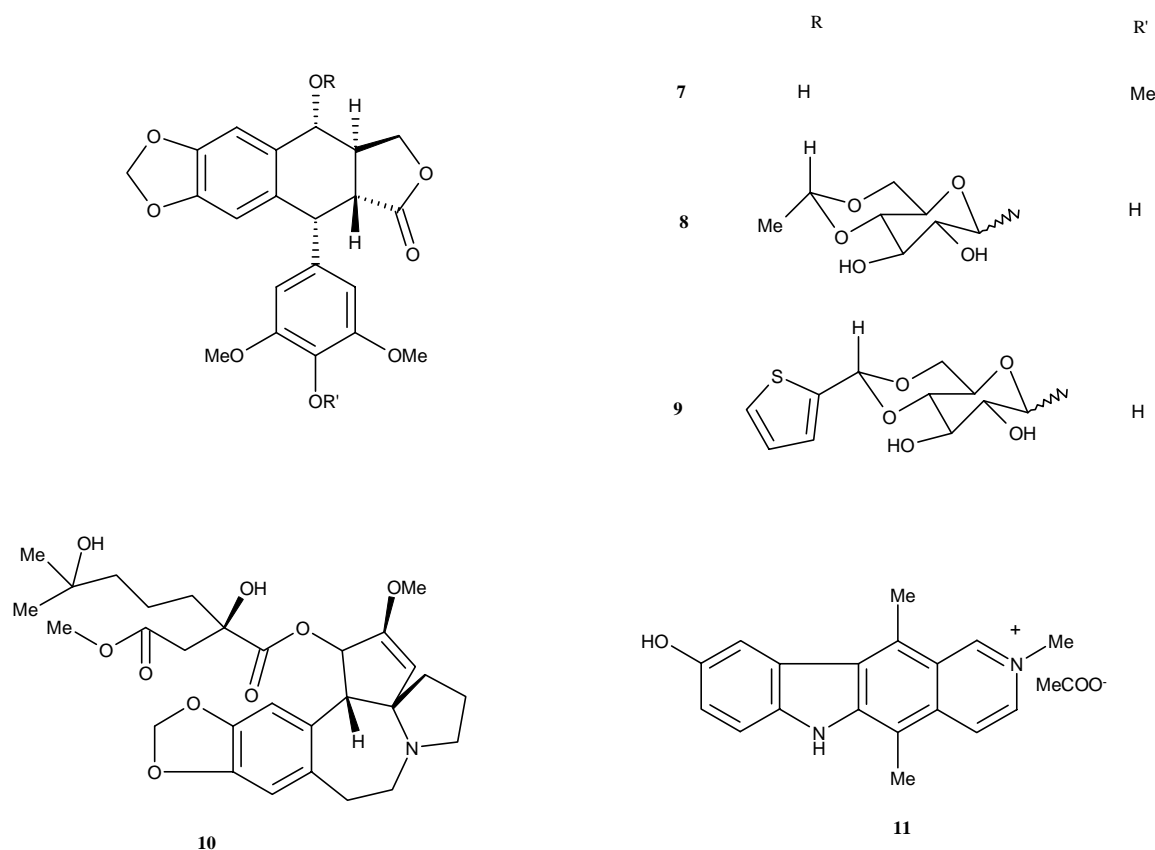


Figure 1 (Cont.): Plant-derived anticancer agents in clinical use

Betulinic acid (**15**), a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from *Betula* species (Betulaceae) (Cichewitz et al., 2004). Betulinic acid was isolated from *Zizyphus* species, e.g. *mauritaniana*, *rugosa* and *oenoplia* (Pisha et al., 1995; Nahar et al., 1997) and displayed selective cytotoxicity against human melanoma cell lines (Balunas et al., 2005). The development of systemic and topical formulations of the agent for potential clinical trials by the NCI is ongoing (Cragg and Newman, 2005). Pervilleine A (**16**) was isolated from the roots of *Erythroxylum pervillei* Baill. (Erythroxylaceae) (Silva et al., 2001). Pervilleine A was selectively cytotoxic against a multidrug resistant (MDR) oral epidermoid cancer cell line (KB-V1) in the presence of the anticancer agent vinblastine (Mi et al., 2001). Pervilleine A is currently in preclinical development (Mi et al.,

2003). Silvestrol (**17**) was first isolated from the fruits of *Aglaila sylvestre* (M. Roemer) Merrill (Meliaceae) (Hwang et al., 2004). Silvestrol exhibited cytotoxicity against lung and breast cancer cell lines (Cragg and Newman, 2005). Biological studies are ongoing to determine the mechanism(s) of action for silvestrol.

Two novel alkaloids, schischkinnin (**18**) and montamine (**19**) have been isolated from the seeds of *Centaurea schischkinii* and *Centaurea montana* (Shoeb et al., 2005; 2006). Both of the alkaloids exhibited significant cytotoxicity against human colon cancer cell lines. The unique structural features of **18** and **19** can be exploited as a template for generating compounds with enhanced anticancer activity. However, further investigations are necessary for their use as anticancer agents.

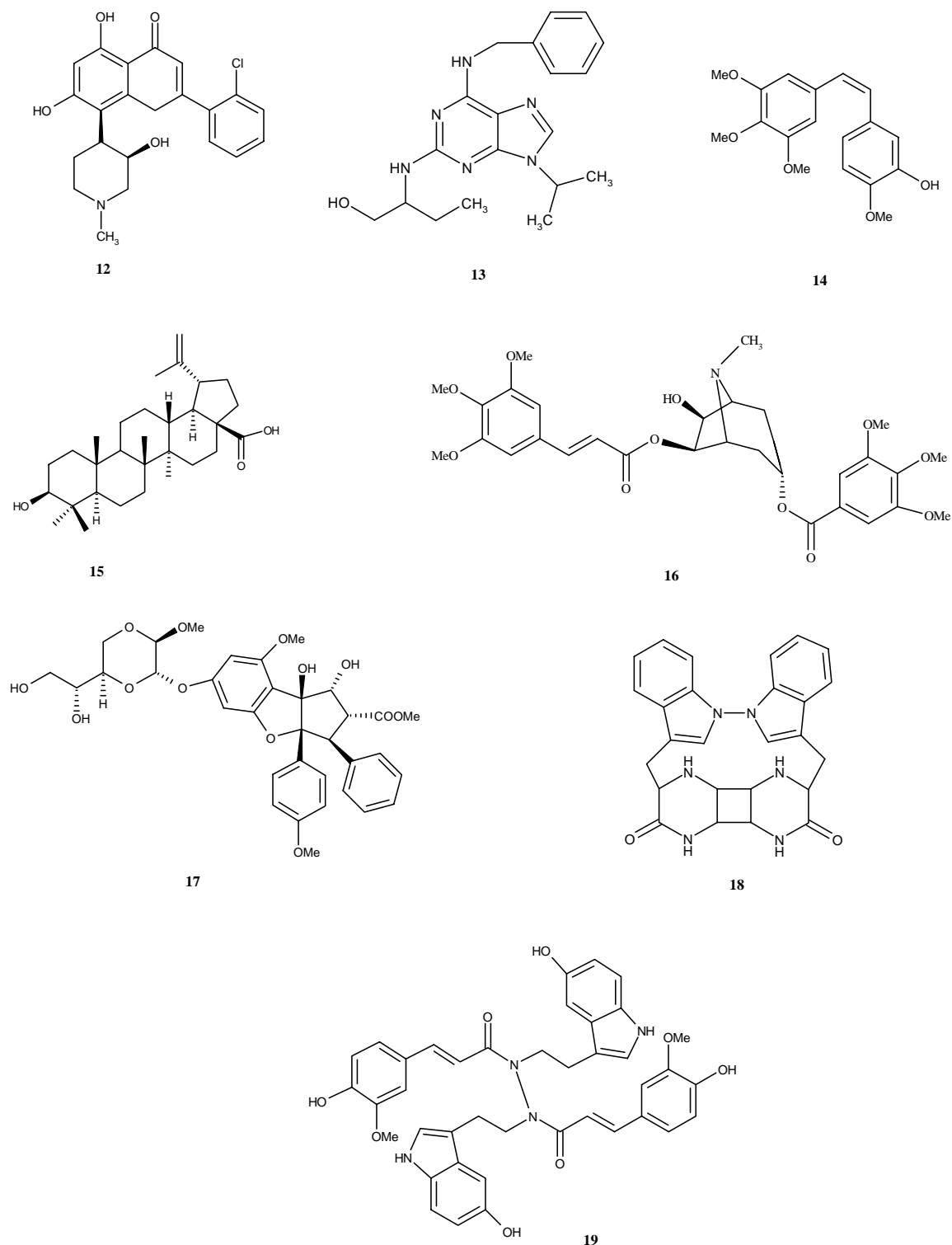


Figure 2. Plant-derived anticancer agents for future development

Conclusion

Natural products discovered from medicinal plants have played an important role in the treatment of cancer. Natural products or natural

product derivatives comprised 14 of the top 35 drugs in 2000 based on worldwide sales (Butlet, 2004). Two plant derived natural products, paclitaxel and camptothecin were estimated to

account for nearly one-third of the global anticancer market or about \$3 billion of \$9 billion in total annually in 2002 (Oberlines and Kroll, 2004). There are more than 270,000 higher plants existing on this planet. But only a small portion has been explored phytochemically. So, it is anticipated that plants can provide potential bioactive compounds for the development of new 'leads' to combat cancer diseases.

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