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Anti-cancer agents from medicinal plants

Anti-cancer agents from medicinal plants

Mohammad Shoeb

Department of Chemistry, University of Dhaka, Dhaka 1000, Bangladesh.

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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 anti-cancer 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.

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 anti-cancer activity (Shoeb, 2005). Of the 92 anti-cancer drugs commercially available prior to 1983 in the US and among world wide approved anti-cancer 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).



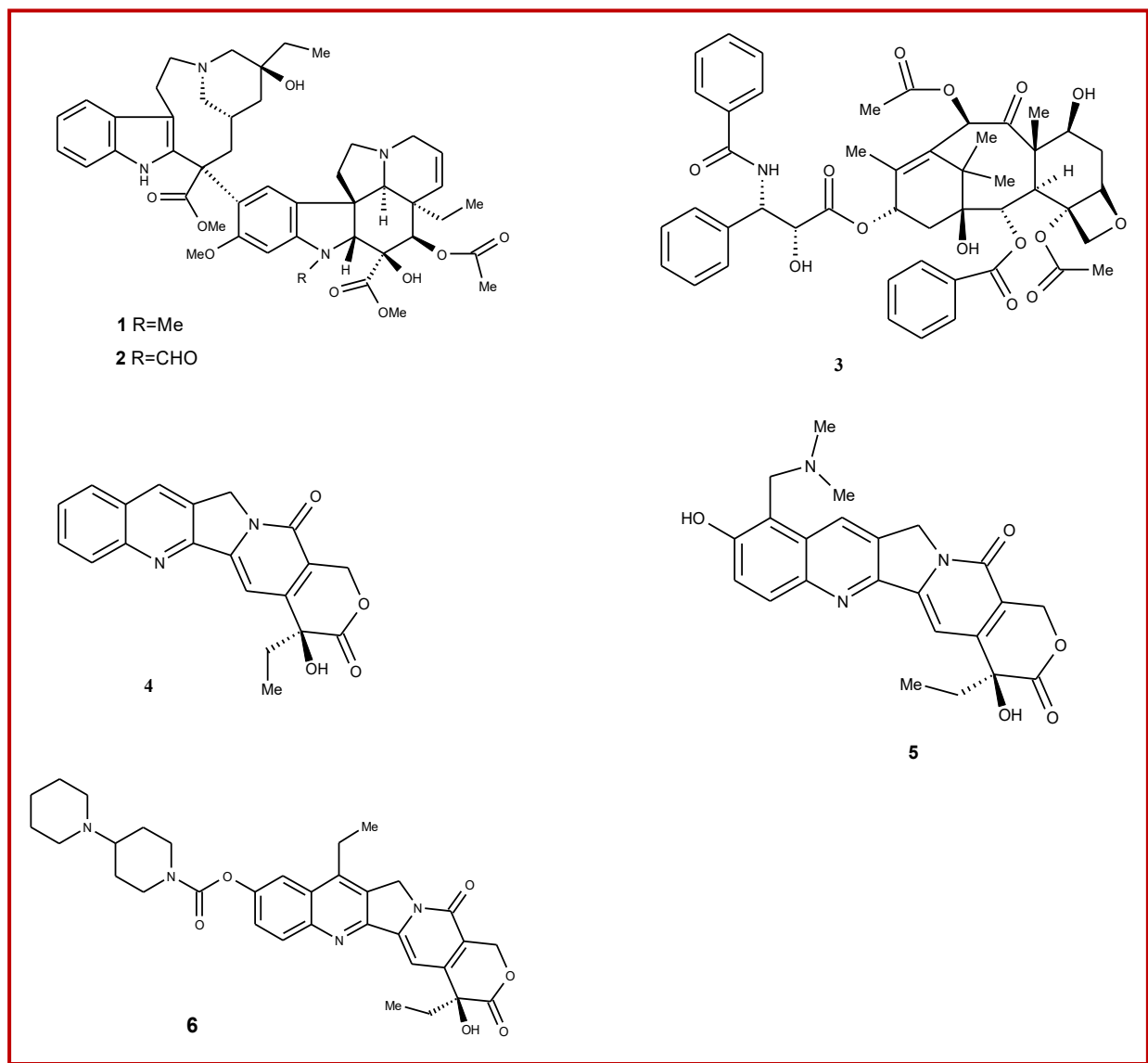


Figure 1: Plant-derived anti-cancer agents in clinical use

Plant-derived anti-cancer 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 anti-cancer 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

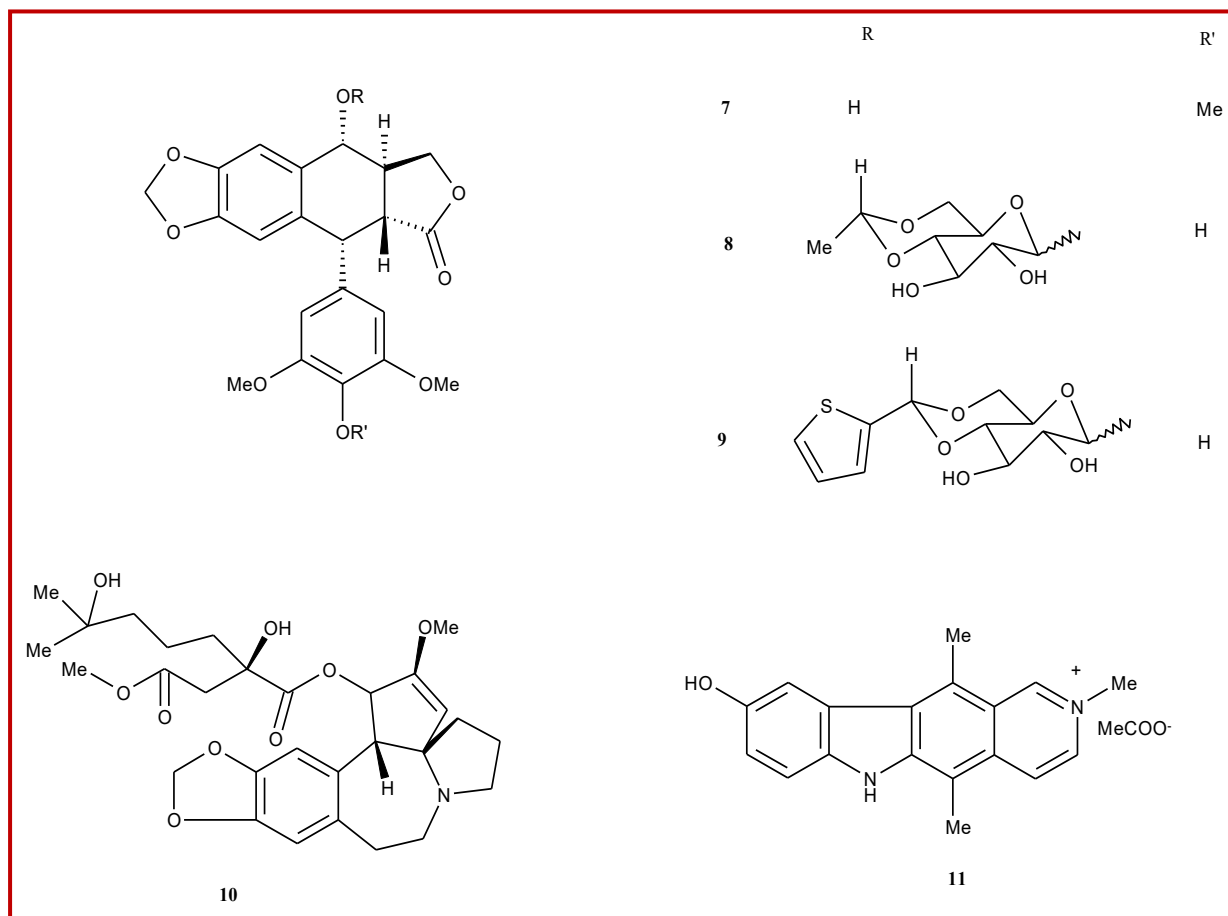


Figure 1: Plant-derived anti-cancer agents in clinical use (Continued)

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).

Plant-derived anti-cancer 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

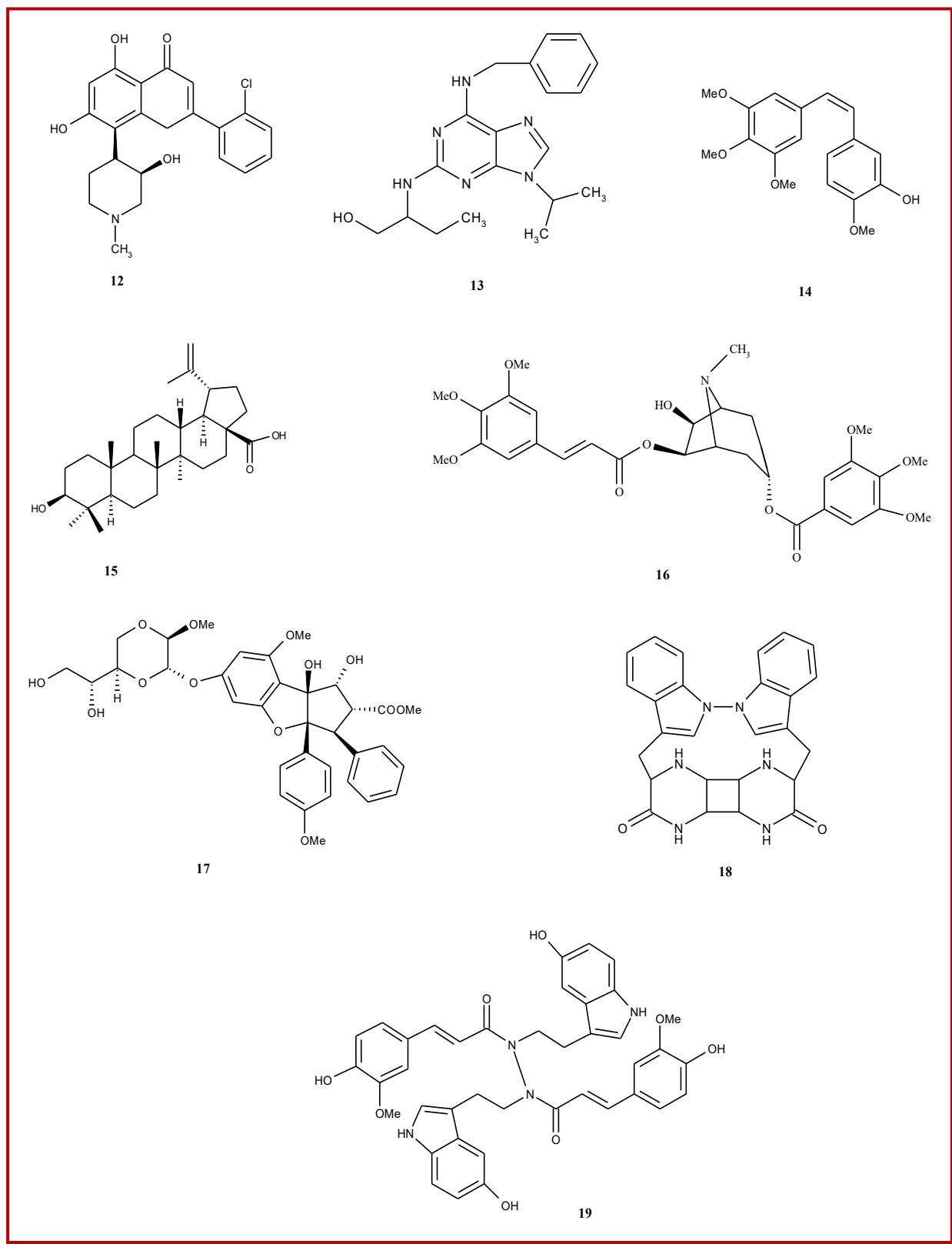


Figure 2: Plant-derived anti-cancer agents for future development

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 phytomolecule isolated so far (Ohsumi et al., 1998; Pettit et al., 1995).

Betulinic acid (**15**), a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from *Betula* species (Betulaceae) (Cichewicz 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 anti-cancer 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 anti-cancer activity. However, further investigations are necessary for their use as anti-cancer agents.

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 anti-cancer 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.

References

- Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. *Life Sci.* 2005; 78: 431-41.
- Bertino JR. Irinotecan for colorectal cancer. *Semin Oncol.* 1997; 24: S18-23.
- Butler MS. The role of natural product chemistry in drug discovery. *J Nat Prod.* 2004; 67: 2141-53.
- Cichewicz RH, Kouzi SA. Chemistry, biological activity, and chemotherapeutic potential of betulinic acid for the prevention and treatment of cancer and HIV infection. *Med Res Rev.* 2004; 24: 90-114.
- Cox PA. Ethnopharmacology and the search for new drugs. In: *Bioactive compounds from plants.* Ciba Foundation Symposium 154. Chichester, England, John Wiley and Sons, 1990, pp 40-55.
- Christian MC, Pluda JM, Ho PT, Arbuck SG, Murgo AJ, Sausville EA. Promising new agents under development by division of cancer treatment, diagnosis, and centers of the National Cancer Institute. *Semin Oncol.* 1997; 24: 219-40.
- Cragg GM, Newman DJ, Snader KM. Natural products in drug discovery and development. *J Nat Prod.* 1997; 60: 52-60.
- Cragg GM, Newman DJ. Plants as source of anti-cancer agents. *J Ethnopharmacol.* 2005; 100: 72-79.
- Creemers GJ, Bolis G, Gore M, Scarfone G, Lacave AJ, Guastalla JP, Despax R, Favalli G, Kreinberg R, VanBelle S, Hudson I, Verweij J, Ten Bokkel Huinink WW. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: Results of a large European phase II study. *J Clin Oncol.* 1996; 14: 3056-61.

- Farnsworth NR, Akerele O, Bingel AS, Soejarto DD, Guo Z. Medicinal plants in therapy. *Bull World Health Organ.* 1985; 63: 965-81.
- Hartwell JL. Plants used against cancer: A survey. Lawrence, MA. Quarterman Publications, 1982, pp 438-39.
- Harvey AL. Medicines from nature: Are natural products still relevant to drug discovery. *Trends Pharmacol Sci.* 1999; 20: 196-98.
- Hoyer DL, Kung HC, Smith BL. Deaths: preliminary data for 2003. *Natl Vital Stat Rep.* 2005; 53: 1-48.
- Hwang BY, Su BN, Chai H, Mi Q, Kardono LB, Afriastini JJ, Riswan S, Santarsiero B D, Mesecar AD, Wild R, Fairchild CR, Vite GD, Rose WC, Farnsworth NR, Cordell GA, Pezzuto JM, Swanson SM, Kinghorn AD. Silvestrol and episilvestrol, potential anti-cancer rocaglate derivatives from *Aglaila silvestris*. *J Org Chem.* 2004; 69: 3350-58 (ibid. 69 (18), 6156).
- Itokawa H, Wang X, Lee KH. Homoharringtonine and related compounds. In: Cragg GM, Kingston, DGI, Newman D, (eds). *Anti-cancer agents from natural products*. Boca Raton, Florida, Brunner-Routledge Psychology Press, Taylor & Francis Group, 2005, pp 47-70.
- Jaspars M, Lawton LA. Cyanobacteria as a novel source of pharmaceuticals. *Curr Opin Drug Discov Devel.* 1998; 1: 77-84.
- Kantarjian HM, O'Brien S, Anderlini P, Talpaz M. Treatment of chronic myelogenous leukemia: Current status and investigational options. *Blood* 1996; 87: 3069-81.
- Kapoor LD. *CRC Handbook of ayurvedic medicinal plants*. Boca Raton, Florida, CRC Press, 1990, pp 416-17.
- Kelland LR. Flavopiridol, the first cyclic-dependent kinase inhibitor to enter the clinic: Current status. *Expert Opin Investig Drugs.* 2000; 9: 2903-11.
- Meijer L, Raymond E. Roscovitine and other purines as kinase inhibitors. From starfish oocytes to clinical trials. *Acc Chem Res.* 2003; 36: 417-25.
- Mi Q, Cui B, Silva GL, Lantvit D, Lim E, Chai H, You M, Hollingshead MG, Mayo JG, Kinghorn AD, Pezzuto JM. Pervilleine A, a novel tropane alkaloid that reverses the multidrug-resistance phenotype. *Cancer Res.* 2001; 61: 430-37.
- Mi Q, Cui B, Lantvit D, Reyes-Lim E, Chai H, Pezzuto JM, Kinghorn AD, Swanson SM. Pervilleine F, a new tropane alkaloid aromatic ester that reverses the multidrug-resistance phenotype. *Anti-cancer Res.* 2003; 23: 3607-15.
- Nahar N, Das RN, Shoeb M, Marma MS, Aziz MA, Mosihuzzaman M. Four triterpenoids from the bark of *Zizyphus rugosa* and *Z. oenoplia*. *J Bangladesh Aca Sci.* 1997; 21: 151-56.
- Oberlines NH, Kroll DJ. Camptothecins and taxol: Historic achievement in natural products research. *J Nat Prod.* 2004; 67: 129-35.
- Ohsumi K, Nakagawa R, Fukuda Y, Hatanaka T, Morinaga Y, Nihei Y, Ohishi K, Suga Y, Akiyama Y, Tsuji T. New combretastatin analogues effective against murine solid tumors: Design and structure-activity relationship. *J Med Chem.* 1998; 41: 3022-32.
- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005; 55: 74-108.
- Pettit GR, Singh SB, Niven ML, Hamel E, Schmidt JM. Isolation, structure, and synthesis of combretastatins A-1 and B-1, potent new inhibitors of microtubule assembly, derived from *Combretum caffrum*. *J Nat Prod.* 1987; 50: 119-31.
- Pettit GR, Singh SB, Boyd MR, Hamel E, Pettit R, Schmidt JM, Hogan F. Antineoplastic agents. 291. Isolation and synthesis of combretastatins A-4, A-5 and A-6. *J Med Chem.* 1995; 38: 1666-72.
- Pisha E, Chai H, Lee IS, Chagwedera TE, Farnsworth NR, Cordell GA, Beecher CW, Fong HH, Kinghorn AD, Brown DM, Wani MC, Wall ME, Hieken TJ, Das Gupta TK, Pezzuto JM. Discovery of betulonic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. *Nat Med.* 1995; 1: 1046-51.
- Potmeisel M, Pinedo H. *Camptothecins: New anti-cancer agents*. Boca Raton, Florida, CRC Press, 1995, pp 149-50.
- Powell RG, Weisleder D, Smith Jr CR, Rohwedder WK. Structures of harringtonine, isoharringtonine, and homoharringtonine. *Tetrahedron Lett.* 1970; 11: 815-18.
- Rowinsky EK, Onetto N, Canetta RM, Arbuck SG. Taxol-the 1st of the taxanes, an important new class of anti-tumor agents. *Semin Oncol.* 1992; 19: 646-62.
- Samuelsson G. *Drugs of natural origin: A textbook of pharmacognosy*. 4th ed., Stockholm, Swedish Pharmaceutical Press, 1999.
- Shoeb M. *Cytotoxic compounds from the Genus Centaurea*. PhD Thesis. Aberdeen, UK, The Robert Gordon University, 2005.
- Shoeb M, Celik S, Jaspars M, Kumarasamy Y, MacManus SM, Nahar L, Thoo-Lin PK, Sarker SD. Isolation, structure elucidation and bioactivity of schischkiniin, a unique indole alkaloid from the seeds of *Centaurea schischkiniii*. *Tetrahedron.* 2005; 61: 9001-06.
- Shoeb M, MacManus SM, Jaspars M, Trevidu J, Nahar L, Thoo-Lin PK, Sarker SD. Montamine, a unique dimeric indole alkaloid, from the seeds of *Centaurea montana* (Asteraceae), and its *in vitro* cytotoxic activity against the CaCo2 colon cancer cells. *Tetrahedron* 2006; 62: 11172-77.
- Silva GL, Cui B, Chavez D, You M, Chai HB, Rasoanaive P, Lynn SM, O'Neill MJ, Lewis JA, Besterman JM, Monks A, Farnsworth NR, Cordell GA, Pezzuto JM, Kinghorn AD. Modulation of the multidrug-resistance phenotype by new

- tropane alkaloids aromatic esters from *Erythroxyllum pervillei*.
J Nat Prod. 2001; 64: 1514-20.
- Stahlin H. Activity of a new glycosidic lignan derivative (VP
16-213) related to podophyllotoxin in experimental tumors.
Eur J Cancer. 1973; 9: 215-21.
- Wall ME, Wani MC. Camptothecin and taxol: Ffrom discovery
to clinic. J Ethnopharmacol. 1996; 51: 239-54.
- Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant
anti-tumor agents. VI. The isolation and structure of taxol, a
novel anti-leukemic and anti-tumor agent from *Taxus
brevifolia*. J Am Chem Soc. 1971; 93: 2325-27.
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Author Info

Mohammad Shoeb (Principal contact)

e-mail: shoeb71@yahoo.com