Biochemistry & Physiology: Open Access
ISSN: 2168-9652

Tyagi and Prasad, Biochem Physiol 2015, 4:1
DOI: 10.4172/2168-9652.1000e128

Editorial Open Access

Drug Discovery Inspired by Mother Nature for Cancer Therapy

Amit Kumar Tyagi* and Sahdeo Prasad

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M.D., USA

Cancer is a hyper-proliferative disorder that arises due to dysregulation of multiple cell signaling pathways. It is one of the most common causes of death worldwide. Globally, about 14.1 million new cases of cancer have reported in 2012, and 8.2 million deaths occurred due to cancer (14.6% of all human deaths) (WHO 2014). The most common types of cancer in females are breast, colorectal, lung, and cervical cancer and in males lung, prostate, colorectal and stomach cancer. The rate of cancer incidences is increasing in developing as well as developed countries due to change in lifestyle and increase in average life span of the people [1]. The risk factors associated with cancer are environmental factors such as diet and obesity (30–35%), infections (15–20%), tobacco consumption (25–30%), radiation (10%), stress, lack of physical activity, and environmental pollutants [2]. The remaining 5–10% is due to inherited genetics. Since most common cause of cancer is environmental factors, changing lifestyle can prevent it [3].

Other than lifestyle, several therapeutic measures are available to treat the cancer that includes surgery, chemo, radiation, hormone, targeted, and biological therapy but these therapies are very expensive, unsafe , and have numerous side effects. Because of these, people are always in search for effective and less expensive, nontoxic drugs from Mother Nature. Natural products have been used for the treatment of different diseases since centuries. Since last few decades a number of drugs have been discovered either by serendipity or by rationale against various diseases including cancer. From last few decades, 74.8% drugs approved by United States food and drugs administration (US FDA) are derived from natural sources. Among them, 48.6% are actually being either pure natural products or their derivatives [4]. These US FDA approved drugs are being used for the treatment of different types of cancers including lung, prostate, colorectal and stomach, breast, cervical, lymphoblastic leukemia and brain tumors. Here, we will describe most, if not all, FDA approved drugs derived from natural sources against cancer.

Vincristine, commonly known as leurocristine, is an alkaloid from the *Catharanthus roseus* (*Vincarosea*). It is the combination of indole alkaloids vindoline and catharanthine found in the *C. roseus* and approved by US FDA as a cancer chemotherapy drug in July 1963 as Oncovin. Vincristine binds to GTP-binding site of tubulin dimers, inhibiting assembly of microtubule structures and arresting mitosis at metaphase [5]. Vinblastine, an alkaloid was traditionally obtained from *C. roseus*, a Madagascar periwinkle. Basically, it is the product of joining two alkaloids catharanthine and vindoline in the plants. Vinblastine treatment causes depolymerization of the microtubular network and act as mitotic inhibitor. This agent also interferes with amino acid, cyclic AMP, glutathione metabolism, calmodulin-dependent Ca++ -transport ATPase activity, cellular respiration, and nucleic acid and lipid biosynthesis [6]. Vinblastine received US FDA approval in 1965 to treat various kinds of cancer, including Hodgkin's lymphoma, non-small cell lung cancer, breast cancer, head and neck cancer, and testicular cancer [7].

Vindesine (Eldisine), an alkaloid is a chemotherapy drug traditionally obtained from *C. roseus*. Vindesine stabilizes tubulin by interrupting tubulin polymerization subsequently prevent the formation of mitotic spindle and cell division. It is introduced as a FDA approved drugs in 1965 for the treatment of lung cancer, acute leukemia, melanoma, and breast cancer [7]. Vinorelbine, a ditartrate salt of a semisynthetic vinca alkaloid derived was approved for the treatment of non-small cell lung cancer in 1989. Vinorelbine binds to tubulin, thereby inhibiting tubulin polymerization into microtubules and spindle formation and resulting in apoptosis of susceptible cancer cells. FDA approved it as an anti-mitotic chemotherapy drug in December 1994 for the treatment of breast cancer, mesothelioma and non-small cell lung cancer. Vinorelbine, one of the less toxic outpatient oral drugs is used as a chemotherapeutic agent for breast cancer [8]. Vinflunine (Javlor) is a third-generation bifluorinated semi-synthetic vinca alkaloid obtained from its parent compound, vinorelbine. Vinflunine inhibits the GTP hydrolysis and microtubule assembly formation and shows superior antitumor activity and an excellent safety profile [9].

Etoposide (commonly known as Mayapple) is a semi-synthetic derivative of podophyllotoxin, a substance extracted from the root of *Podophyllum peltatum*. Etoposide was first synthesized in 1966 andapproved by FDA in 1983. Etoposide stabilized a normally transient DNA-topoisomerase II complex, and increased the concentration of double-stranded DNA breaks. Etoposide is an antitumor agent currently in clinical use for the treatment of small cell lung cancer, testicular cancer and lymphomas [10]. Etoposide Phosphate is a water-soluble analogue of etoposide designed to improve the pharmaceutical characteristics of the parent compound and is an anti-neoplastic drug for intravenous use. Etoposide is a phase-specific, particularly late S or early G2 phase, cytotoxic chemotherapeutic agent and it induces a premitotic block in the cell cycle of mammalian cells. Etoposide phosphate was introduced for FDA approval in 1996 for the treatment of small cell lung cancer and testicular cancer. Teniposide was a chemotherapeutic medication, mainly used in the treatment of childhood acute lymphocytic leukemia. FDA approved teniposide in 1965 for the treatment of acute lymphocytic leukemia. The mechanism of action appeared to be related to the inhibition of type II topoisomerase activity, an important enzyme in DNA replication, since teniposide do not intercalate into DNA or bind strongly to DNA.

Irinotecan Hydrochloride is a semisynthetic analogue of the natural quinoline-based alkaloid Camptothecin extracted from the Asian tree *Camptotheca acuminata*. Irinotecan is a prodrug activated by carboxylesterase-converting enzyme to 7-ethyl-10-hydroxy-camptothecin (SN-38), which subsequently inactivated by glucuronidation by uridine diphosphate glucoronosyltransferase 1A1 (UGT1A1). It also inhibits topoisomerase I, an enzyme involved

***Corresponding author:** Amit Kumar Tyagi, Cytokine Research Laboratory, Department of Experimental Therapeutics,The University of Texas M. D., Anderson Cancer Center, Houston TX 77054, USA, Tel: 713-792-6543; Fax: 713-745-6339; E-mail: akumar6@mdanderson.org, amittyagiiitd@gmail.com

Received January 07, 2015; **Accepted** January 07, 2015; **Published** January 14, 2015

Citation: Tyagi AK, Prasad S (2015) Drug Discovery Inspired by Mother Nature for Cancer Therapy. Biochem Physiol 4: e128. doi: 10.4172/2168-9652.1000e128

Drugs	Year	Disease(s)	Target
Vincristine	1963	ALL, NHL, HL	Microtubule
Vinblastine	1965	LC, BC, HL, HTC	Microtubule
Vindesine	1965	MLN, BC, LP, LKA, LC	Microtubule
Teniposide	1965	ALL	DNA (T2T)
Etoposide	1965	EWS, LC, TC, KPS, LKA, GBM	DNA (T2T)
Elliptinium	1983	BC, MBC	DNA (T2T)
Solamargines	1989	LC, CLC	TNFRs, BCl_2
Vinorelbine	1989	MBC, NSCLC, RBDS	Microtubule
Paclitaxel	1992	BLDC, MLN, KPS, PRTC	Tubulin
Masoprocol	1992	SC	LOX
Irinotecan HCl	1994	CLC	DNA (T1T)
Docetaxel	1995	OVC, HDC, GTC, NCC, LC, BC	Microtubule
Etoposide Phosphate	1996	LC, BC, SC	DNA (T2T)
Topotecan HCl	1996	OVC, LC	DNA (T1T)
Arglabin	1999	STC, BC, LC, LVC, RCTC, OVC	FTase
Alitretinoin	1999	KS	RXR
Belotecan HCl	2004	SCLC	DNA (T1T)
Abraxane	2005	BC, LC, mPAC, NSCL	Microtubule
Nanoxel	2007	BC, NCC, HDC, OVC, KS	Microtubule
Cabazitaxel	2010	CRPC	Microtubule
Vinflunine	2010	BLDC	Microtubule

NHL-Non-Hodgkin's lymphoma, **HL-**Hodgkin's lymphoma, **ALL-** Acute lymphoblastic leukemia, **NB** - Nephroblastoma, **PC –** Prostate cancer, **GTC-** Gastric cancer, **HDC-** head cancer **NCC** – Neck cancer. **mPAC-** Metastatic adenocarcinoma of the pancreas, **HTC-** Histiocytosis **KPS** - Kaposi's sarcoma, **EWS** - Ewing's sarcoma, **LC** - Lung cancer, **TC** - Testicular cancer, **LP** - lymphoma, **NLL-** Nonlymphocytic leukemia, **GBM-** Glioblastoma multiforme, **BC-** Breast cancer, **MLN-**Melanoma, **LKA-**Leukaemia, **MBC-** Metastatic breast cancer, **RBDS**- Rhabdomyosarcoma, **NSCLC** - non-small-cell lung cancer, **SCLC** - Small-cell lung cancer, **BLDC -** Bladder cancer, **T2T-** Type II topoisomerases, **T1T**- Type I topoisomerase **SC –** Skin Cancer, **CLC**- colon cancer, **OVC-** Ovarian cancer, **CRPC-** Castration-resistant prostate cancer, TNFRs - Tumor necrosis factor receptors, **LOX**- lipoxygenase , **RCTC-** Rectal cancer, **STC** -Stomach Cancer, **LVC-** Liver cancer, **FTase-** Farnesyl transferase, **RXR**- Retinoid X receptor.

Table 1: FDA approved anti-cancer drugs derived from Mother Nature.

in DNA replication and RNA transcription. Irinotecan received accelerated approval by FDA in 1996 and full approval in 1998. Topotecan hydrochloride (Hycamtin) is a semisynthetic water-soluble derivative of Camptothecin, which is extracted from the bark of the tree *Camptotheca acuminata*. It is a topoisomerase inhibitor. It was approved by FDA in 1996 and used in form of the hydrochloride to treat small cell lung cancer and ovarian cancer. Topotecan is the first FDA approved topoisomerase I inhibitor for oral use. It was evaluated in women with stage IVB recurrent or persistent cervical cancer in one open-label, multicenter, cooperative group trial [11]. Belotecan HCl is semi-synthetic, water soluble, analogue of camptothecin extracted from the Asian tree *Camptotheca acuminate* with potential antitumor activity. Belotecan binds to and inhibits the activity of topoisomerase I, which causes lethal double-stranded DNA breaks, disruption of DNA replication, and apoptosis of tumor cell. It was approved by US FDA in 2004 for the treatment of SCLC.

Paclitaxel was discovered in 1967 from the bark of the Pacific yew, *Taxus brevifolia* [12]. Paclitaxel received FDA approval for the treatment of ovarian cancer and breast cancer in December 1992 and January 2005, respectively. It stabilizes the cellular microtubules as a result normal breakdown of microtubules during cell division is interfered, which causes death of tumor cells. Paclitaxel is used for the treatment of patients with lung, ovarian, breast, and head and neck cancers, and advanced forms of Kaposi's sarcoma [13]. Docetaxel is a semisynthetic product of the '10 deacetyl baccatin III' a non-cytotoxic compound derived from the needles of European yew tree *Taxus baccata* L. In cancer cells, docetaxelis capable of interrupting cell division process by inhibiting M phase of cell cycle through preventing depolymerization of microtubules assembly. Docetaxel is highly bound to plasma proteins, but has a large volume of distribution at steady state. It is primarily metabolised by the cytochrome P450 3A4 isoenzyme and is excreted primarily faecally via the biliary tract. Excretion of the drug is a strong independent predictor of severe haematological toxicity in cancer patients.

Abraxane (Protein-bound paclitaxel) is an injectable albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. It is a mitotic inhibitor drug used in the treatment of breast, ovarian, lung and pancreatic cancer. The US-FDA approved abraxane for the treatment of breast cancer, non-small cell lung cancer and advanced pancreatic cancer in 2005, 2012, and 2013 respectively. Nanoxelis a biodegradable nanoparticle-based paclitaxel delivery system, used in metastatic breast cancer treatment. It is being billed as India's first indigenously developed nanotechnology based chemotherapeutic agent. In March 2009, FDA approved a phase I clinical trial of nanoxel, a polymeric nanoparticle formulation of paclitaxel. Cabazitaxel (Jevtana) is a semi-synthetic derivative of a natural taxoid. In preclinical testing, cabazitaxel demonstrated activity in both docetaxel-sensitive and docetaxel-resistant cancers. US FDA approved it on June 17, 2010 as a second-line treatment in men with metastatic castration-resistant prostate cancer that failed docetaxel-containing regimens [14].

Elliptinium acetate is a derivative of the alkaloid ellipticine isolated from Apocynaceae family members, including *O. Elliptica labill*, *Ochrosia borbonica,* and *Bleekeriavitensis*. Elliptinium stabilizes the cleavable complex of topoisomerase II and induces DNA breakages, thereby inhibiting DNA replication and RNA and protein synthesis. In year 1983, Elliptinium acetate introduced as 'Celiptium' trade name for the treatment metastatic breast cancer [15]. However, its clinical use was hampered by important toxicities such as xerostomia and immune-mediated haemolytic reactions due to development of anti-elliptinium IgM antibodies [16]. Solamargine is a glycoalkaloid derived from solasodine found in plants of the Solanaceae family. Solamargine as a tumor inhibitor was first isolated from *Solanumdu lcamara* in 1965 [17]. FDA approved it against lung and colorectal cancer in 1989. Solamargine interact with cancer cells and leads to marked changes in cell shape and volume including blebs on the membrane, mitochondria swelling, clumping of contents of the nuclei and finally death of cells [18].

Masoprocol (nordihydro guaiaretic acid) is an antioxidant dicatechol originally derived from the plant creosote bush *Larrea tridentata* DC. Initially this plant was used to treat non-insulin-dependent diabetes mellitus. Later, it has shown to antipromoter, anti-inflammatory, and antineoplastic activities. Masoprocol suppress tumor growth by directly inhibiting activation of receptor tyrosine kinases (RTKs), the insulin-like growth factor receptor (IGF-1R), c-erbB2/HER2/neu receptor and stress activated protein kinases (SAPKs). Arglabin is a sesquiterpene gamma-lactone is isolated in the early 1980s from the aerial part of the plant, *Artemisia glabella* Kar. and introduced in 1999 against various cancer including lung, leukemia, prostate, colon cancer. It has been also reported that Arglabin-DMA inhibits the incorporation of farnesylpyrophosphate into human H-ras protein by FTase. Alitretinoin (9-cis-retinoic acid) is an analogue of vitamin A, which is originated from the plant *Daucuscarota Linneus*. It is used in medicine as an antineoplastic agent and gained US FDA approval in February 1999. It has received EMA (11 October 2000) and FDA (2

March 1999) approval for the treatment of cutaneous lesions of AIDS - related Kaposi's sarcoma (KS).

Since cancer is a multifactorial and multi-targeting disease, it cannot be prevented by the mono-targeted therapies. Some of the anticancer drugs have unknown targets even though they exhibit significant efficacy against different cancer. A number of anticancer drugs have been identified with known and unknown targets and approved by FDA, most of them have various side effects and very expensive. Therefore, multi-targeted, cost effective and non-toxic natural compounds are needed to treat the cancer patients (Table 1).

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
2. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, et al. (2008) Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 25: 2097-2116.
3. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB (2014) Curcumin, a component of golden spice: from bedside to bench and back. Biotechnol Adv 32: 1053-1064.
4. Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 75: 311-335.
5. Checchi PM, Nettles JH, Zhou J, Snyder JP, Joshi HC (2003) Microtubule-interacting drugs for cancer treatment. Trends Pharmacol Sci 24: 361-365.
6. Galano G, Caputo M, Tecce MF, Capasso A (2011) Efficacy and tolerability of vinorelbine in the cancer therapy. Curr Drug Saf 6: 185-193.
7. Moudi M, Go R, Yien CY, Nazre M (2013) Vinca alkaloids. Int J Prev Med 4: 1231-1235.
8. Molina-Garrido MJ, Mora-Rufete A, Guillen-Ponce C (2014) Oral chemotherapy in elderly women with metastatic breast cancer. Anticancer Agents Med Chem 14: 665-672.
9. Gerullis H (2011) Vinflunine: a fluorinated vinca alkaloid for bladder cancer therapy. Drugs Today (Barc) 47: 17-25.
10. Zhang J, Qi HW, Zheng H, Chen M, Zhu J, et al. (2014) Etoposide-cisplatin alternating with vinorelbine-cisplatin versus etoposide-cisplatin alone in patients with extensive disease combined with small cell lung cancer. Asian Pac J Cancer Prev 15: 4159-4163.
11. Brave M, Dagher R, Farrell A, Abraham S, Ramchandani R, et al. (2006) Topotecan in combination with cisplatin for the treatment of stage IVB, recurrent, or persistent cervical cancer. Oncology (Williston Park) 20: 1401-1404, 1410.
12. Wall ME, Wani MC (1995) Camptothecin and taxol: discovery to clinic--thirteenth Bruce F. Cain Memorial Award Lecture. Cancer Res 55: 753-760.
13. Mekhail TM, Markman M (2002) Paclitaxel in cancer therapy. Expert Opin Pharmacother 3: 755-766.
14. Galsky MD, Dritselis A, Kirkpatrick P, Oh WK (2010) Cabazitaxel. Nat Rev Drug Discov 9: 677-678.
15. Caillé P, Mondesir JM, Droz JP, Kerbrat P, Goodman A, et al. (1985) Phase II trial of elliptinium in advanced renal cell carcinoma. Cancer Treat Rep 69: 901-902.
16. Rouëssé J, Spielmann M, Turpin F, Le Chevalier T, Azab M, et al. (1993) Phase II study of elliptinium acetate salvage treatment of advanced breast cancer. Eur J Cancer 29A: 856-859.
17. Kupchan SM, Barboutis SJ, Knox JR, Cam CA (1965) Beta-solamarine: tumor inhibitor isolated from Solanum dulcamara. Science 150: 1827-1828.
18. Sun L, Zhao Y, Yuan H, Li X, Cheng A, et al. (2011) Solamargine, a steroidal alkaloid glycoside, induces oncosis in human K562 leukemia and squamous cell carcinoma KB cells. Cancer Chemother Pharmacol 67: 813-821.