Drug Discovery Inspired by Mother Nature for Cancer Therapy

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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 (Vincusrosea). 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 (Javelor) 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 and approved 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 premiotic 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 glucuronosyltransferase 1A1 (UGT1A1). It also inhibits topoisomerase I, an enzyme involved in DNA replication.

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in DNA replication and RNA transcription. Irinotecan received accelerated approval by FDA in 1996 and full approval in 1998. Topotecan hydrochloride (Hyacintin) 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 anti-cancer drugs derived from Mother Nature.

Abrazxane (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 abrazxane 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, Ochna borbonica*, and *Bleekeriaventii*. 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 *Solanum lycamara* 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].

Masprocol (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. Masprocol 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 plant *O. Elliptica labill*. The sesquiterpene has been studied for its potential antitumor activity. It was reported that Arglabin inhibits the HER2/neu receptor and stress activated protein kinases (SAPKs). Arglabin and its analogues have been shown to inhibit the growth of various cancer cell lines.

In conclusion, the study revealed that the use of these natural products as anti-cancer agents is promising. Further research is needed to investigate their mechanism of action and their potential use in clinical trials.

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