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Natural products as anticancer drug: A review

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Abstract
Cancer is one of the leading causes of death of mankind. WHO predicted that this cancer, if no immediate action is taken, would be the most threatening to human by 2030. By the classical treatment therapy, the people with cancer are suffering from so many toxic side effects. So the scientists are in search of new and safer drugs. Natural products, being less toxic and safe, are of much interest of the medicinal chemists to find new therapeutics for the treatment of cancer. Natural products are playing an important role in drug discovery process, particularly in the area of cancer. Plant based drug discovery has resulted the development of many anticancer drug currently in use. So, natural products give a platform for the search of new drugs for the treatment of cancer. Attempts have been made to develop new naturally occurring plant based lead molecules for anticancer drug formation. A good number of drugs originated directly from natural products or derived from natural products are approved as anticancer drugs and commercially available for cancer treatment. Anticancer drugs derived directly from natural products or a semi-synthetic analog of natural products approved from 2000 to 2017 are discussed in this review. Their source, chemical structure and their mechanism of action are discussed in this resume. The review cites 141 references.

Keywords: Cancer, natural product, anticancer, natural product derived drug

1. Introduction
Chemical products are central to the global economy and enhance people's lives the world over. We look to chemistry to meet our most fundamental needs for food, shelter, and clothing. We use it to develop materials vital to advances in biotechnology, communications, and medicine. Society has benefited enormously from advances in chemistry. One of the most dramatic examples is the increase in life expectancy from 47 years in 1900 to 75 years in the 1900s [1-2]. Much of this increase can be attributed to improved health care, including the development of pharmaceuticals that cure what ails us and ease our pain and sufferings. To maintain our current standard of living and improve our quality of life, society has come to depend on the products of the chemical industry [3-7]. However, with the advent of the 21stcentury, the public is equally aware of the hazardous substances used and generated by the chemical processes. Our environment, which is endowed by nature, needs to be protected from ever increasing chemical pollution associated with contemporary lifestyles and emerging technologies. Addressing these concerns is a key aspect of achieving sustainability. Answer to all these problems is nature. We should surrender to the nature [8-9].
Nature stands as an infinite source of novel pharmacologically active agents and as a source of medicinal agents for thousands of years. Thus, a good number of modern drugs find their origin in natural products [10-11].
Natural products chemistry has lately undergone enormous growth due to advances in easier isolation techniques, synthetic methods, chemical measurements as well as more new concepts. It is needless to say that in recent years there has been an overgrowing interest in studying natural products from different angles around the Globe. Both the developed and developing countries including our India have been giving much attention on conservation of medicinal plants and also on emplaning multi-purpose uses of safe and eco-friendly natural products.
Interest in herbal medicines and natural products is very high from the very past of our civilisation. This phenomenon has been established by an increasing attention to phytochemicals as form of Alterative therapy by the health professions. Man has been using plant products as traditional medicines and other purposes for thousands of years [10, 12-14].

A multidirectional therapeutic uses of vast number of plant products in traditional way are known in India from *Vedic* times as *Ayurvedic* and *Unani* system of medicine. So, Natural products continue to be a significant source of biologically active substances that may serve as commercially important lead structures for the development of drugs. Thus, natural products still constitute a major source of novel lead compounds or pharmacophores for medicinal chemistry. It has been estimated that over 40% of medicines have their origin in these natural products [15, 16].

Plants are the key source of natural products and plants had already yielded a vast number of phytochemicals and still continue to a major source of biologically active molecules. Numerous plants have been already known as a source of naturally occurring insecticides, pesticides, fungicides and agro-chemicals as an alternative to toxic and hazardous synthetic chemicals. Owing to ever-increasing awareness to the hazardous side effects of synthetic chemicals, more and more emphasis is being given on the use of products obtained from natural sources so that environment is well-maintained. To minimise the hazardous effects and to control environmental pollution, attempts are now being made to develop naturally occurring plant-based lead molecules for drug formulation [17-18]. A good number of commercially approved drugs are being originated now from natural products. Beside these, a huge number of natural product-derived compounds in various stages of clinical development indicate that the use of natural product is still a significant source for new drug for the treatment of various diseases including cancer.

Cancer is a multifaceted disease that represents one of the leading causes of mortality in developed countries. Worldwide, one in eight deaths is due to cancer and it is the second most common cause of death in the US, accounting for nearly one of every four deaths [19]. The World Health Organization (WHO) projects that without immediate action, the global number of deaths from cancer will increase by nearly 80% by 2030. External factors (such as tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) are mostly responsible for cancer. These causal factors may act together or in sequence to initiate or promote the development of cancer [19]. While tremendous efforts have been made over the past decades to improve the available therapeutic options, and a large number of potent chemotherapeutic anticancer agents have been identified and successfully used in clinical practice, cancer still remains a major threat in most countries. New therapeutic options to treat cancer are a high priority for most of the pharmaceutical companies and independent research organizations worldwide. Considerable research activity is devoted to the discovery of more potent treatments, while minimizing their toxic side effects. However, most anticancer agents display a narrow therapeutic window due to their lack of selectivity against cancer cells [20-21]. The main objective of cancer therapy is the development of selective drugs that can kill malignant cancer cells without affecting normal cells. Thus, there is an over-whelming need to develop new chemo-preventative agents that are both effective and safe [22]. One practical approach to this problem is the use of Natural products as a platform for drug development. Anticancer agents from natural products are, thus, hot point of study because more people suffer and lack effective and safe drugs. Plants products have a long history of use in the treatment of cancer. More than 3000 plant species are recorded as the source of anticancer agents [23]. Natural product based drug discovery has resulted in the development of many anticancer drugs currently in clinical use. Besides this, it also provides a platform for design of novel and safe drugs through proper understanding of the complex synergistic interaction of various constituents of anticancer herbs [24-26].

Thus, it is felt pertinent to focus on anticancer drugs derived from natural products. Anticancer drugs derived directly from natural products or a semi-synthetic analog of natural products approved from 2000 to 2017 are discussed in this review. There source, chemical structure and their mechanism of action are discussed in this resume. The review cites 141 references.

2. Natural Products as drug already in use

Present scientific scenario in the field of natural products chemistry provides one to conceive an idea about the multidirectional ways on which a huge number of scientists make themselves engaged in finding important and new natural molecules. Narcotic morphine is generally considered as the first pure natural product used commercially for therapeutic drug which was marketed by Merck in 1826 [27]. In the last of 19th century Aspirine, first semi synthetic drug from natural products, was introduced in the clinical system [28]. A huge number of phytochemicals are found to possess potential therapeutic efficacies against various ailments ranging from simple cough and cold to parasitic infection. As for examples, antibacterial drug Ertapenem, derived from thienamycin [29], cefditoren [30], the tranquilliser reserpine from the genus *Rauwolfia* [31], the antimalarial quinine from *Cinchona* species [32], the antidysentric drug emitine from *Ipecae* roots [33], the anti-tumoric compounds of the Pedophyllotoxin group [34] and the anticoagulant dicoumarol from the family *Rutaceae* [35] are a few to cite with. Two other drugs, which were found to be highly potent against a very complex and non-curable disease – the AIDS, having tremendous socio-economic impact should be mentioned here. These two drugs are (+)-calanolide-A and (−)-calanolide-B, isolated from the leaves of *Calophyllum lanigerum* [36]. In the 1970s for example, the discovery of cholesterol biosynthesis-inhibiting drugs compactin [37] and mevinolin, isolated from cultures of *Aspergillus terreus* [38], led to the development of the hugely successful statin therapeutics, which even today represent successes in medical treatment [39-40]. So, natural product or natural product-derived drugs are the cornerstones of modern clinical therapy.

3. Natural products as anticancer drugs

Natural products are continuing to play invaluable role in the drug discovery process, particularly in the areas of cancer and infectious diseases. For example, the antileukemic drugs, vinblastine [41], vincristine [42], vincaleukoblastine [43] from *Vinca* (Apocynaceae), are in use for cancer treatment. The isolation of two alkaloids Vinblastine (1) and Vincristine (2) from the Madagascar periwinkle, *Catharanthus roseus* G. Don (Apocynaceae) started a new era of natural products as anticancer agents [44]. These two drugs have been used in clinical therapy for cancer for almost 50 years. These two alkaloids work by blocking the polymerization of tubulin molecules into micro-tubules, preventing the formation of the mitotic spindle which result in metaphase arrest and apoptosis [45]. Vinorelbine (Navelbine), is another semisynthetic derivative of vinblastine was approved in France in 1989

under the brand name Navelbine for the treatment of cancer and It gained approval to treat metastatic breast cancer in 1991 [46].

Today, Taxol® (paclitaxel) (3) [47] is being used as a very important anticancer agent on the forefront of cancer chemotherapy. Paclitaxel was approved for treatment of drug-resistant refractory ovarian cancer by the Food and Drug Administration (FDA) in 1992 and for breast cancer followed in 1994. Paclitaxel was the first compound discovered to promote microtubule formation and has been used in the treatment of several types of cancers particularly ovarian and breast cancers [48]. A number of its semisynthetic derivatives have been developed. The first to reach clinical use was Docetaxel (4) which have shown significant clinical activity in a wide range of tumours and a different toxicity pattern than the parent compound [49-50]. The semi-synthetic taxol analog from 10-deacetylbaccatin III, an abundant taxane with taxol score from the needle of *Taxus baccata*, docetaxel (Taxotere®) was approved to treat breast cancer by FDA in 1996. Clinical use of taxol has increased steadily since then and today it is also used routinely to treat lung, head and neck, prostate, cervical cancers and AIDS-related Kaposi's sarcoma [51]. Despite increasing competition from combinatorial and classical compound libraries, there has been a steady introduction of natural product-derived drugs in the clinical system. Substances like taxol, are the bases of modern anticancer therapy with natural origin [52].

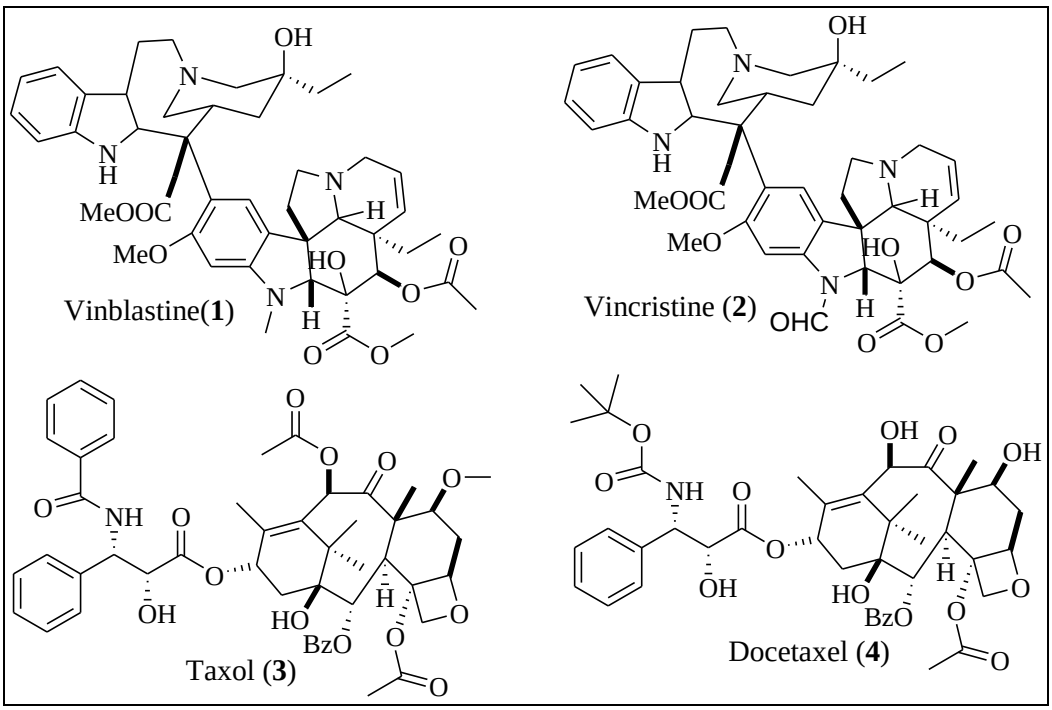

Fig 1: Chemical structure of anticancer drug already in use

4. Natural Products Based Anticancer drugs during 2000 to 2017

Natural products play an important role in the discovery of lead molecules for the development of drugs to treat human diseases including cancer. Such natural agents have traditionally played a major role in drug discovery and still constitute an indigenous source of novel chemotherapeutic agents for medicinal chemistry. Natural product-based compounds find key importance in drug discovery. The impact of natural products on the development drug molecules of the pharmaceutical industry is very high. So many natural product-derived drugs in the past years were introduced in the clinical system. Substances like taxol, cyclosporines and the "statins" are cornerstones of modern anticancer protocols.

There are four major structural classifications of plant-derived anticancerous compounds, namely vinca alkaloids, epipodophyl-lotoxin lignans, taxane diterpenoids and camptothecin quinoline alkaloid derivatives. These substances embrace some of the most exciting new chemotherapeutic agents currently available for use in a clinical setting. Natural products based anticancer drugs approved during 2000 to 2017 were discussed here. All the approved anticancer drugs were summarized in Table 1.

4.1 Gemtuzumab ozogamicin

Enediynes are organic compounds that possess two triple bonds and one double bond, and it is known for their limited use as antitumor antibiotics [53-54]. These are efficient at inducing nonspecific apoptosis in both normal and cancer cells. Calicheamicin (6), which was isolated from *Micromonospora echinospora* in 1980s is an example of antitumor agent of this class [55-56].

Gemtuzumab ozogamicin (5; Mylotarg®; Wyeth, 2000, Fig.2), was co-developed by Wyeth and UCB Pharma and launched in 2000 for the treatment of refractory acute myeloid leukaemia. It is the first and approved antibody–anticancer conjugate [57-60]. Gemtuzumab ozogamicin (5) consists of *N*-acetyl-calicheamicin dimethyl hydrazide (CalichDMH), a derivative of the enediyne natural product calicheamicin (6), linked through a pH-labile hydrazone moiety to a recombinant humanized IgG4 k antibody. This is a prodrug of calicheamicin bound to the anti-CD33 monoclonal antibody and cleaved by lysosomes in the cells to release calicheamicin. Calicheamicin is a hydrophobic member of the enediyne family of DNA-cleaving antibiotics and is effective in the treatment of patients with acute myeloid lymphoma [61-63]. Calicheamicin (6) is an extremely potent cytotoxin that binds in the minor groove of DNA causing double strand

DNA breakage. In 2001, the drug was approved by the FDA for use in patients with relapsed acute myelogenous leukemia (AML), or those who are not considered candidates for standard chemotherapy [58].

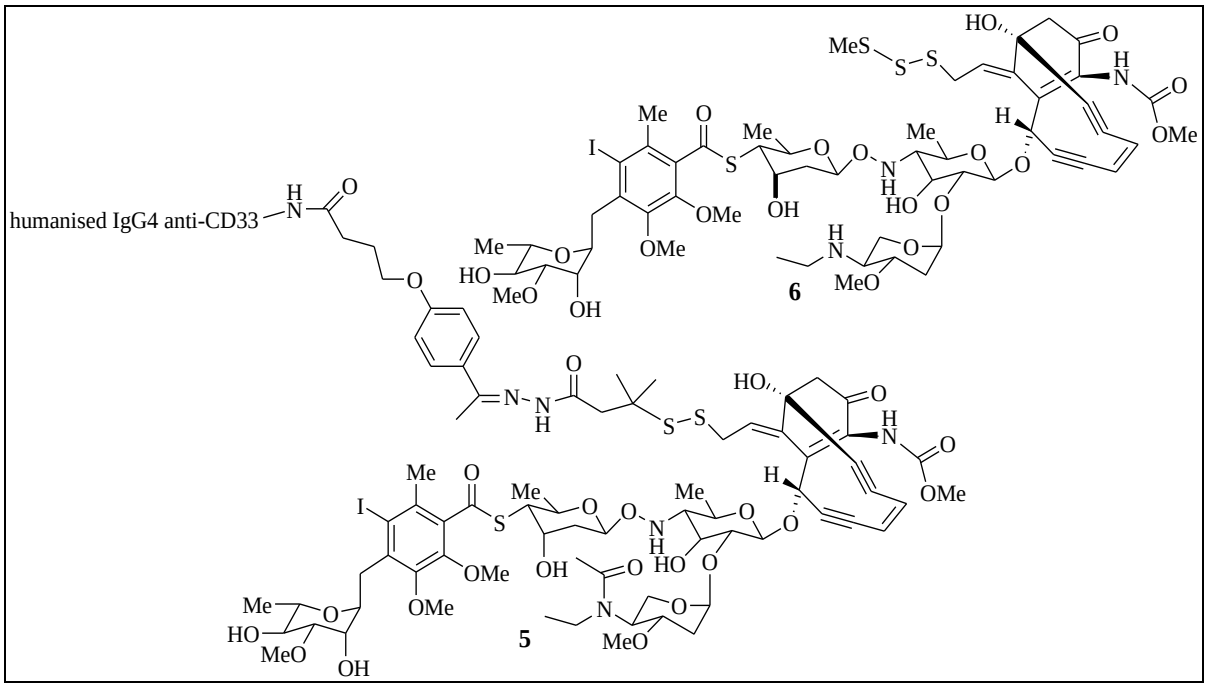

Fig 2: Chemical structure of compounds 5-6

This has been in use for the treatment of non-solid tumor cancer acute myeloid leukemia. In 2017, a calicheamicin-linked monoclonal antibody, marketed as Besponsa, was approved by the FDA for use in the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia [63].

4.2 Amrubicin hydrochloride

Amrubicin hydrochloride (7 Calsed®, Sumitomo Pharmaceuticals Co, 2002, Japan, Fig.3), was isolated from *Streptomyces peucetius* var *caesius*. It is a derivative of doxorubicin (8). It is reported to show anticancer activity like doxorubicin on P388 leukemia, sarcoma 180, and Lewis lung carcinoma. Again, it is reported to exhibit more potent antitumor activity against human tumor xenografts of breast, lung, and gastric cancer [64-65]. The drug converting to its active form in the body, acts as an inhibitor of topoisomerase II, thereby finding an application in the treatment of lung cancer [66-68]. It has been marketed in the brand name of Calsed® in Japan since 2002 by Sumitomo Pharmaceuticals.

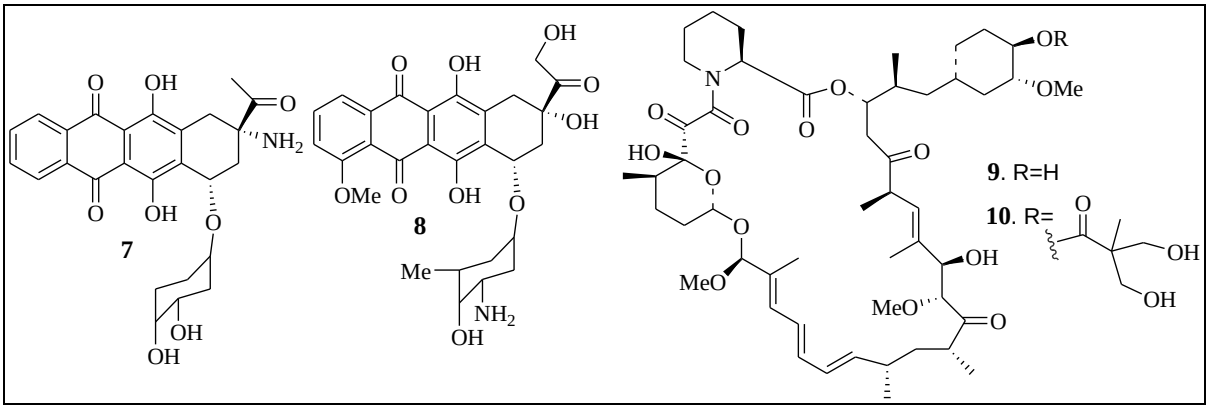

Fig 3: Chemical structure of compounds 7-10

4.3 Temsirolimus

Temsirolimus (9; Torisel™, Wyeth, 2007, Fig. 3) is a semi-synthetic derivative of sirolimus (10). It is an intravenous drug for the treatment of renal cell carcinoma (RCC) [69-71] developed by Wyeth Pharmaceuticals. Temsirolimus (9; Torisel™,) is approved by the US Food and Drug Administration (FDA) in May 2007, and later by the European Medicines Agency (EMEA) in November 2007 for anticancer drug. Sirolimus (10), a macrolide antibiotic, was first traced as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Easter Island [72-73]. Temsirolimus (9) has been found to act as a specific inhibitor of mTOR (mammalian target of rapamycin) and also regulates the synthesis of proteins responsible for proliferation, growth, and survival of tumor cells [74-75]. Treatment with temsirolimus leads to cell cycle arrest in the G1 phase, and also inhibits tumor angiogenesis by reducing synthesis of vascular endothelial growth factor (VEGF) [76-77].

4.4 Trabectedin

Trabectedin (11, Yondelis™, ecteinascidin-743, ET-743; Zeltia and Johnson and Johnson, 2007, Fig. 4) is a tetrahydroisoquinoline alkaloid. It is isolated from ascidian *Ecteinascidia turbinate* [78-80]. It is approved as anticancer drug for its sale in Europe, Russia and South Korea by Zeltia and Johnson and Johnson under the brand name Yondelis™ for the treatment of advanced soft tissue sarcoma (STS) [81]. Trabectedin (11) binds to the minor groove of DNA and inhibits cell proliferation by arresting the cell cycle. It is also believed to cleave the DNA backbone resulting apoptosis of cell by production of superoxides near the DNA strand. There is also some speculation the compound becomes "activated" into its reactive oxazolidine form. In September 2007, the EMEA approved the use of trabectidin against ovarian cancer (OC) and STS. In November 2009, Yondelis™ received its second marketing approval from the European Commission for its administration in combination with pegylated liposomal doxorubicin (Doxil, Caelyx) for the treatment of women with relapsed ovarian cancer. Now trabectedin (11) is under Phase II trials for the treatment of paediatric sarcomas as well as breast and prostate cancers. The European Commission and the FDA have granted orphan drug status to trabectedin for soft tissue sarcomas and ovarian cancer. Trabectedin (11) is produced commercially semi-synthetically from the eubacterium-derived cyanosafracin B (12) [82-83].

4.5 Ixabepilone: Ixabepilone (13, Ixempra™, BMS-247550; Bristol-Myers Squibb, 2007, Fig.4), a semi-synthetic derivative of epothilone B (14) produced by *Sorangium cellulosum*, was developed by Bristol-Myers Squibb (BMS) as an anticancer drug, as injection, which binds directly to □-tubulin subunits on microtubules. This causes suppression of microtubule dynamics which ultimately leads to cell death [84-86]. In October 2007, the FDA approved ixabepilone, for the treatment of aggressive metastatic breast cancers that no longer respond to currently available chemotherapies. It is also suggested to be use this as a monotherapy and as combination therapy with Xeloda against breast cancer patients, resistant to normal therapy [86-88].

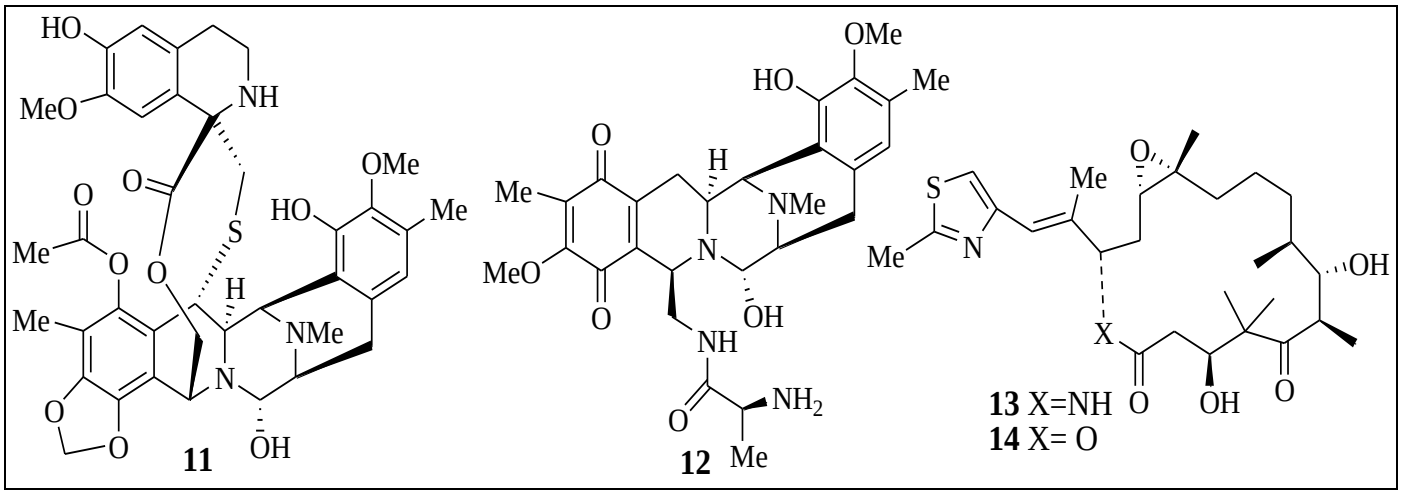

Fig 4: Chemical structure of compounds 11-14

4.6 Everolimus

Everolimus (15, Afinitor®; Novartis, 2009, Fig. 5), a rapamycin analog, is the 42- *O*-(2-hydroxyethyl) derivative of sirolimus (10). This is marketed by Novartis under the tradename Afinitor® for use in advanced renal cell carcinoma [89-90]. In March 2009, the FDA approved everolimus (15) for use against advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib [91-92]. The drug works similarly to sirolimus as an inhibitor of mTOR and downstream of the PI3K/AKT pathway. Everolimus (15) attaches itself to an intracellular protein, FKBP-12, forming an inhibitory complex which can inhibit of mTOR kinase activity. Everolimus also reduces the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP) all of which are involved in protein synthesis. In addition, everolimus (15) inhibited the expression of hypoxia-inducible factor (e.g. HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). It is also reported that the mechanism of anticancer activity of the drug is different from that of Pfizer's Sutent (sunitinib malate) or Onyx Pharmaceuticals' Nexavar (sorafenib), used for standard anticancer treatment. The FDA has approved everolimus for organ rejection prophylaxis on April 22, 2010 [93]. A Phase II trial reports it is effective in the treatment of subependymal giant cell astrocytomas (SEGA). In Oct 2010, the FDA approved its use in SEGA unsuitable for surgery. As of Oct 2010 Phase III trials are under way in breast cancer, gastric cancer, hepatocellular carcinoma, pancreatic neuroendocrine tumors (NET) and lymphoma [92].

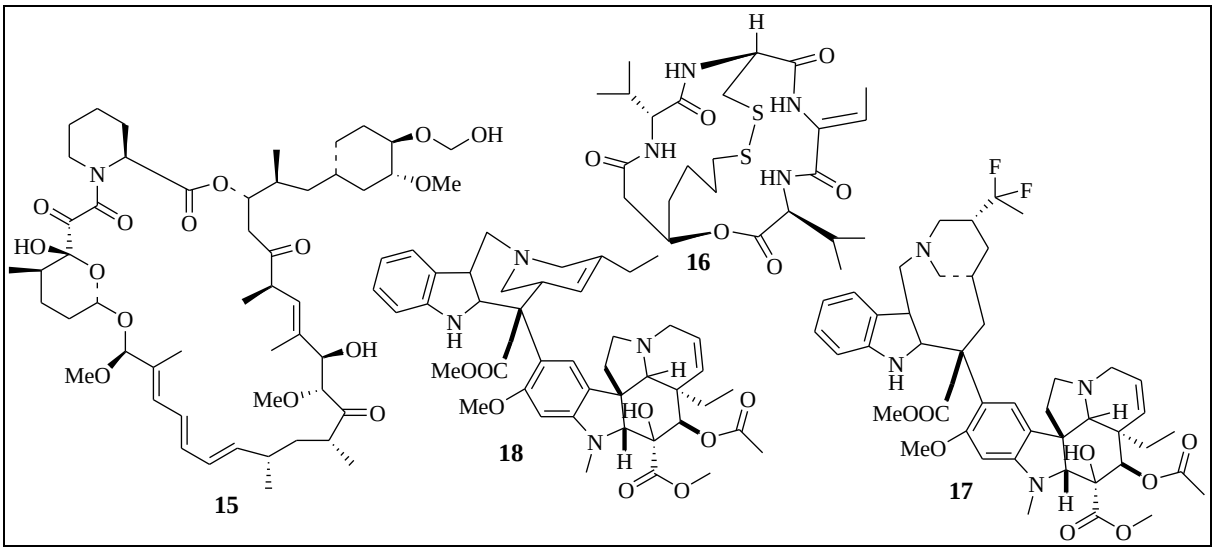

Fig 5: Chemical structure of compounds 15-18

4.7 Romidepsin

Romidepsin (16, Istodax®; Gloucester Pharmaceuticals, 2009, Fig.5) is a natural compound isolated from the bacteria *Chromo bacterium violaceum*. It was developed and evaluated by Gloucester Pharmaceuticals in various Phase I/II trials sponsored by the National Cancer Institute (NCI) to use against cutaneous and peripheral T-cell lymphoma (TCL) [94-96]. In November 2009, romidepsin (16) was approved by the FDA under the trade name Istodax® against selective cutaneous TCL patients. Romidepsin acts as a histone deacetylase (HDAC) inhibitor. Romidepsin causes *in vitro* accumulation of acetylated histones and induces arrest of cell cycle causing apoptosis of some cancer cell lines with IC_{50} values in the nanomolar range. The mechanism of the anticancer effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized [97-98].

4.8 Vinflunine

Vinflunine (17, Javlor, Pierre Fabre, 2009, Fig.5) is a dihydro-fluoro derivative of vinorelbine (18). Vinorelbine is actually a derivative of Vinblastine which is isolated from Madagascar periwinkle, *Catharanthus roseus* G. Don (Apocynaceae) [44]. Vinflunine (17) was approved by the European medical agency (EMEA) in 2009 as second line chemotherapy in metastatic urothelial cancer [99-100]. Similar to other members in the vinca alkaloid class, vinflunine binds to the tubulin molecules, inhibiting microtubule polymerization and the formation of tubulin paracrystals [101-103]. This interaction causes G2/M phase arrest resulting apoptosis in the cells [104-105]. It has *in vitro* and *in vivo* activities against many different malignant cell lines. Vinflunine is actively being studied in patients with advanced stage diseases especially MBC, and NSCLC in phase II/III clinical trials. More phase I/II trials are also being organized to evaluate its efficacy in other advanced solid tumours [106].

In August 2012, the FDA approved vincristine sulphate liposome injection (Marqibo, Talon Therapeutics, Inc.) for the treatment of adult patients with Philadelphia chromosome-negative (Ph_) (ALL) in second or greater relapse or whose disease had progressed following two or more antileukaemia therapies. It is a new, targeted, nanoparticle-encapsulated, cancer therapeutic agent specifically designed to improve patient condition [19].

4.9 Cabazitaxel

Cabazitaxel (19) (Jevtana ®, Natco Pharma Ltd., 2010, Fig.6) is a semi-synthetic derivative of naturally occurring taxane and it was approved by FDA and launched in 2010 for use in combination with prednisone for the treatment of prostate cancers [107]. Cabazitaxel binds to and stabilizes tubulin, resulting in the inhibition of microtubule depolymerization and cell division. It causes cell cycle arrest in the G2/M phase and the inhibition of tumour cell proliferation [107]. Unlike other taxane compounds, this agent is a poor substrate for the membrane-associated, multidrug resistance (PGP) efflux pump and may be useful for treating MDR tumours. In addition, cabazitaxel, in combination with prednisone, significantly extends overall survival in men with hormone-refractory prostate cancer improving disease control [108].

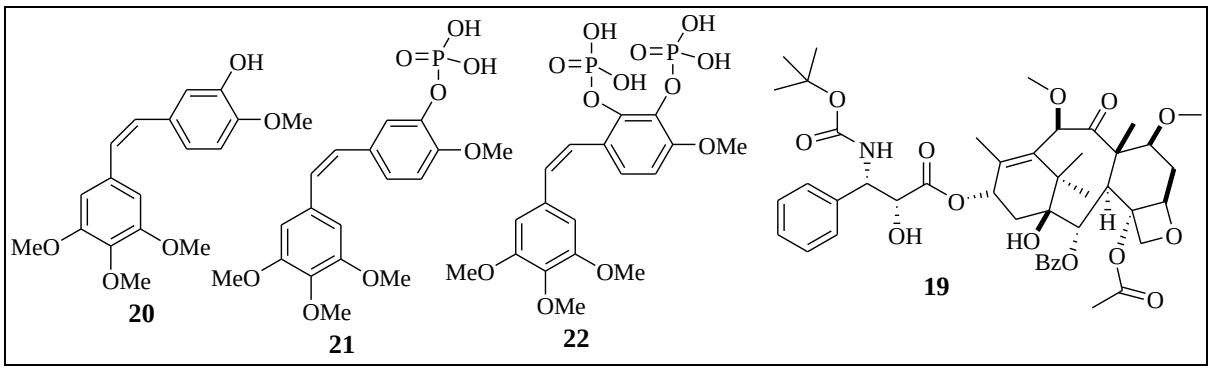

Fig 6: Chemical structure of compounds 19-22

4.10 Combretastatins

Combretastatins (OXi-4503) was isolated from the bark of the South African tree *Combretum caffrum* Kuntze (Combretaceae). Combretastatin A4 (20) is active against colon, lung and leukaemia cancers *in vitro* cytotoxicity against human cancer cell lines. CA-4P (21) and CA-1P (22) which binds at the colchicine site of β-tubulin are among the most active prodrugs of the natural products isolated from *C. caffrum* [109]. Combretastatin A4 phosphate (CA4P, 21, fosbretabulin; Zybrestat, OXiGENE, 2012, Fig. 6) is a phosphate prodrug of CA4 (20, fig. 2). In 2003, CA4P (21) was granted orphan drug designation by the FDA for the treatment of anaplastic thyroid cancer. In 2006, CA4P (21) was granted orphan drug designation by the FDA for the treatment of ovarian cancer [19]. A number of phase I/II trials have been studied with these natural products. The phosphate prodrug of combretastatin A-1 (CA-1P, OXi4503) has been reported to show excellent activity in preclinical studies and has entered in seven clinical trials. Two clinical studies are currently underway using OXi-4503– One is in phase I study evaluating the safety and tolerability in patients (NCT01085656). The second one is in phase IIb to study its safety and efficacy against solid tumour in liver [110]. OXiGENE announced that OXi-4503 has been granted orphan designation by the US FDA in 2012 for the treatment of acute myelogenous leukemia (AML) [111-112]. It being a tubulin-binding and vascular disrupting agent (VDA), causes morphological changes in endothelial cells. This leads vascular collapse in solid tumors resulting shutdown of the nutrient supply for malignant cells [113].

4.11 Omacetaxine mepesuccinate

Omacetaxine mepesuccinate (Homoharringtonine 23, Synribo, Teva Pharmaceutical Industries Ltd., 2012, Fig 7) is an alkaloid, isolated from *Cephalotaxus harringtonia*. On October 26, 2012, the FDA granted accelerated approval to omacetaxine mepesuccinate as for the treatment of adult patients with chronic- or accelerated-phase CML, with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs). Harringtonine has been used in China for the treatment of AML and chronic myelogenous leukemia (CML) and purified HHT has shown efficacy against various leukemias. Omacetaxine is a protein translation inhibitor which inhibits protein translation process in protein synthesis [114]. The drug interacts with the ribosomal A-site disturbing the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs [114].

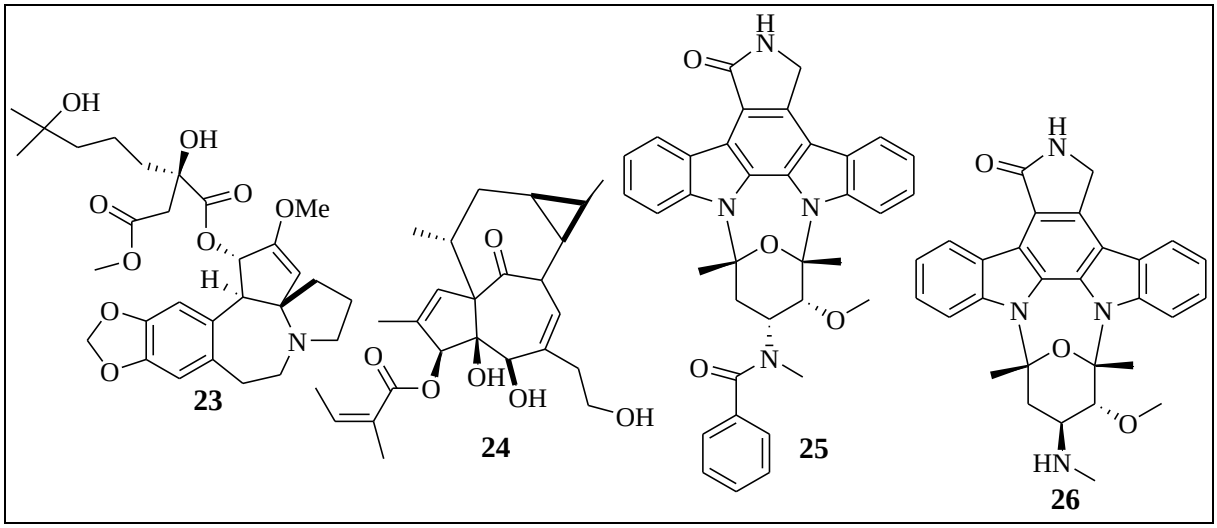

Fig 7: Chemical structure of compounds 23-26

4.12 Ingenol mebutate

Ingenol mebutate (Ingenol-3-angelate **24**, Picato, LEO pharma, 2012, Fig.7) is found in the sap of the plant *Euphorbia peplus* [115]. The drug has been introduced for the treatment of actinic keratosis on the face of scalp, usually caused by excessive exposure to the sun or UV radiations. In higher concentrations ingenol mebutate has been shown to induce cellular necrosis and in lower concentrations it has been shown to potently affect PKC isoforms and thereby intracellular signaling [116]. A gel form of the compound was approved for use by the US FDA and EMA in January 2012 for the treatment of acid keratosis [117-118]. The drug is an ester of diterpene and angelic acid and is marketed by LEO pharma. This anticancer drug was developed and approved in Australia in 2013 [119-120].

4.13 Midostaurin

Midostaurin (25, PKC-412, Rydapt, Novartis, 2017, Fig. 7) is a semisynthetic derivative of staurosporine (26) which is an naturally occurring indolocarbazole alkaloid isolated from *Streptomyces staurosporeus* [121]. Midostaurin is a PKC and Flt3 (FLK2/STK1) inhibitor and it has completed a phase IIB clinical trial in patients with AML [122] and is in phase III clinical development for the oral treatment of AML. Again, clinical trials of midostaurin either as single drug or in combination with agents such as azacitidine, bortezomib, cytarabine, daunorubicin for the treatment of patients with AML are now ongoing. Orphan drug designation for the treatment of AML was approved by the EMA in 2004 and later in 2009 by the FDA. It is also approved for the treatment of mastocytosis by the EMA and FDA in 2010. In 2017, Novartis has announced that FDA approved Midostaurin for the treatment of acute leukemia. It is also being marketed by LEO pharma [122].

4.14 Maytansinoids

Maytansine (27, Fig. 8), a novel macrocyclic compound, was isolated in extremely low yield in the early 1960s from the Ethiopian plant, *Maytenus serrata* (Hochst. ex A. Rich.) Wilczek [123]. It was reported to exhibit very potent *in vitro*

antitumor activity. Thus the compound demanded further research. But, surprisingly, the compound was reported to exhibit very weak activity on human preclinical trials, inspite of promising activity on preclinical animal testing. So, chemists were in the search of structurally similar molecule of natural origin. 'Ansa' antibiotics, such as the rifamycins, were one of the answers. The isolation of the closely related ansamitocins from the bacterium *Actinosynnema pretiosum* [123] in 1977 inspires the scientists and a very closely related *Actinosynnema* sp. in the microbial root system of plants producing maytansine, provided further bacterial source of the maytansinoids [124]. The ansamitocins provided a ready and sustainable source of maytansinoids, and the derivatives DM1 (28, Fig. 8) and DM4 (29, Fig. 8) have been prepared from appropriate ansamitocins.

DM1 (28) and DM4 (29), conjugated through either thioether or disulfide linkages with various monoclonal antibodies, have been used for treatment of a variety of cancers [123, 125]. Linkage of DM1 to the approved antibody, trastuzumab, gives T-DM1 or ado-trastuzumab emtansine (Kadcyla ®, Genetech, 2013) and this shows significant activity in the treatment of patients with advanced or metastatic HER2- positive breast cancer [126- 128]. This non-reducible linker is stable in both the circulation and the tumor microenvironment. So, release of active DM1 occurs only as a result of proteolytic degradation of the antibody part of T-DM1 in the lysosome. Following release from the lysosome, DM1-containing metabolites inhibit microtubule assembly, eventually causing cell death [129]. Based on these results, Kadcyla ® was approved by the FDA in 2013 as a new therapy for patients with HER2-positive, metastatic breast cancer [130].

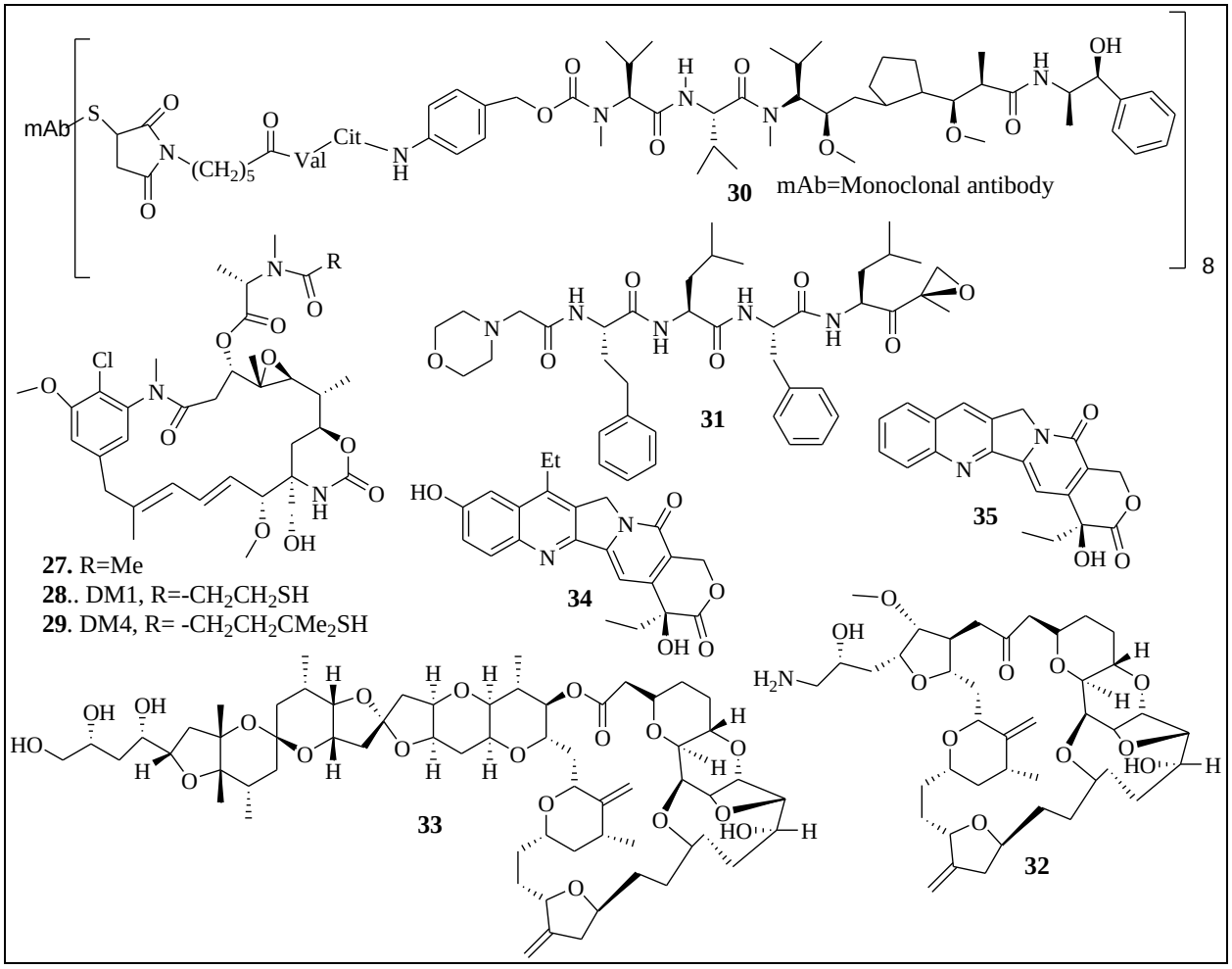

Fig 8: Chemical structure of compounds 27-35

4.15 Brentuximab Vedotin

Brentuximab vedotin (30, Adcetris ®, Seagen and Takeda Pharmaceuticals, 2012, Fig. 8) is formed by conjugation of monomethyl auristatin E (vedotin), a derivative of dolastatin 10. Dolastatin 10 is a secondary metabolite isolated from the marine mollusk, *Dolabella auricularia.* It is also later isolated from a *Symploca* species of cyanophyte which was shown to be in the diet of the mollusk [131]. It inhibits microtubule assembly and this eventually causes metaphase arrest in the cell cycle. It was approved as drug for treatment of Hodgkin's lymphoma by the FDA and the EMA in 2011 and 2012, respectively [131-132].

4.16 Carfilzomib

Carfilzomib (**31,** Kyprolis TM, Onyx Pharms Amgen, 2012, Fig. 8), a synthetic analogue of epoxomicin. Epoxomicin is a peptide α ′,β ′-epoxyketone isolated from an *actinomycete* strain [133]. This binds through a stereospecific linkage to the chymotryptic subunit (20S) of the proteasome and acts as a proteasome inhibitor [130]. It was approved by the FDA in 2012 for the treatment of patients with relapsed and refractory multiple myeloma after prior treatment with thalidomide or lenalidomide. Its 30Mg doses is approved in 2016 [134- 136]. Phase II trials are ongoing for the treatment of a variety of other cancers.

4.17 Eribulin

Halichondrin B analogue, now known as eribulin (32, Halaven ®, E7389, Eisai Pharmaceuticals India Pvt Ltd.,2010, Fig. 8), with structural similarities to halichondrin B (33; fig. 8) showed significantly more potent activity in the *in vivo* studies. This compound was chosen for advanced preclinical and then clinical studies. It was shown to act through a tubulin-destabilizing agent. After thorough clinical trials, eribulin (Halaven ®) was approved for the treatment of breast cancer by the FDA in 2010 and commercialized as Halaven® for metastatic breast cancer chemotherapy. Halichondrin B (Fig. 8) was isolated from several species of marine sponges, *Axinella spp*. (Fam: Axinellidae), *Halichondria okadai* (fam: Halichondriidae) and *Phakellia* spp. (fam: Axinellidae). It is now used as a model for the synthesis and development of the anticancer drug, eribulin mesylate (E7389) [137-140].

4.18 SN-38

The recent advances with SN-38 (7-Ethyl-10-hydroxy-Camptothecin: 34, Camptosar, Pfizer INC, Fig. 8) have been summarized in a recent review. SN-38 is a derivative of naturally occurring Camptothecins. Camptothecin (CPT, 35, fig. 8) was isolated from the Chinese ornamental tree *Camptotheca acuminata* Decne (Nyssaceae) [137]. Among the products developed, DTS-108, is very important because in this prodrug, SN-38 is strongly linked to a 20-amino acid and by rupturing this linkage, it releases SN-38. IMMU-130 (labetuzumab-SN-38; hMN14-SN-38) is an antibody-drug conjugate (ADC) and IMMU-132 (hRS7-SN-38) is another ADC in which SN-38 and the humanized monoclonal antibody hRS7 are linked at the C-20 hydroxyl group in the same manner as that of IMMU-130. The mechanism of action of this drug is believed to bind to the topoisomerase I-DNA binary complex resulting in a stable complex and this, thereby, prevents DNA relegation resulting apoptosis. In November 2013, the FDA designated IMMU-132 orphan drug status for the treatment of small cell lung cancer, and in May 2014, orphan drug status was designated for the treatment of pancreatic cancer.

5. List of the anticancer drugs derived from natural products: Drugs with their trade name are listed. The natural compounds from which it is derived, source and mechanism of action are given in the tabular form here for the ready references.

Table 1: All the approved anticancer drugs were summarized

Name og the drug	Mother Compound	Class of compound	classification	source	Mechanism	References
Gemtuzumab ozogamicin (5; Mylotarg®)	Calicheamicin(6)	Enediyne	NP-derived	Microbial	DNA-damaging	57-63
Amrubicin hydrochloride (7; Calsed®)	Doxorubicin (8)	Anthraquinone	NP-derived	Microbial	Inhibition topoisomerase II	64-68
Temsirolimus (9; ToriselTM)	Sirolimus (10)	Macrolide	Semi-synthetic NP	Microbial	Cell cycle arrest in the G1 phase	69-77
Trabectedin (11; YondelisTM)	Trabectedin (11)	alkaloid	NP	Marine animal	Cell cycle arrest	78-83
Ixabepilone (13; Ixempra TM)	Epothilone B (14)	Macrolide	NP-derived	Microbial	Disruption tubulin, ultimately leading to cell death	84-88
Everolimus (15; Afinitor®)	Sirolimus (10)	Macrolide	Semi-synthetic NP	Microbial	Inhibition mTOR kinase activity	89-93
Romidepsin (16; Istodax®;	Romidepsin (16)	Cyclo-depsipeptide	NP	Microbial	Cell cycle arrest causing apoptosis	94-98
Vinflunine (17, Javlor)	Vinorelbine (18)	Alkaloids	NP-derived	Plant	Cell cycle arrest	99-106
Cabazitaxel (19) Jevtana ®	Taxol (3)	Diterpenoid	Semi-synthetic NP	Plant	Cell cycle arrest	107-108
CA-1P (21, OXi4503, Zybrestat)	Combretastatin A4 (20)	Stilbene	NP-derived	Plant	Disrupt the tubulin cytoskeleton	19, 109-112
Omacetaxine mepesuccinate (23, Synribo)	Homoharringtonine	Alkaloid	NP	Plant	Inhibition of protein synthesis and apoptosis	114
Ingenol-3-angelate (24, Picato)	Ingenol-3-angelate (24)	Diterpene	NP	Plant	Acting through activ-ation of protein kinase C	115-120
Midostaurin (25, PKC-412)	Staurosporine (26)	Alkaloid	Semi-synthetic NP	Microbial	A PKC and Flt3 inhibition	121-122
DM1(28) and DM4 (29), (Kadcyla ®)	Maytansine (27)	Macrocyclic compound	NP-derived	Plant	DM1-containing metabolites inhibit microtubule assembly, eventually causing cell death.	123-130
Brentuximab vedotin (30, Adcetris ®	Dolastatin 10	Peptide	NP-derived	Plant	Inhibition of microtubule assembly, then arresting the cell cycle	131-132
Carfilzomib (31, Kyprolis TM)	Epoxomicin	Peptide	Semi-synthetic NP	Microbial	proteasome inhibitor	133-136
Eribulin (32, Halaven)	Halichondrin B (33)	Polyether macrolide	Semi-synthetic NP	Microbial	shown to act as a tubulin-destabilizing agent	137-140
SN-38 (7-ethyl-10-hydr oxy CPT: 34,Camptosar)	Camptothecins (CPTs, 35)	Alkaloid	NP-derived	Plant	Apoptosis by DNA damage	140-141

NP: Natural Product

Here it should be noticed that beside the plant source, microbial source of the drug is also very important. It may also be suggested from the table that alkaloid and macrolide are the major class of natural products for the anticancer drug.

6. Conclusion

The large number of plants demands for thorough investigation that would unearth tremendous potential against cancer at large. The marine kingdom stands as an enormous resource for the discovery of potential chemotherapeutics, and is waiting for its proper exploration. Another vast unexplored area is the microbial world for the leads of cancer treatment. The quality of leads arising from natural product discovery is better and often more biologically friendly, due to their co-evolution with the target sites in biological systems. Natural products, thus, still serve as an excellent source for modern drug discovery and development. The traditional strengths of natural products in cancer are still ahead from the compounds under clinical trials. Through a medicinal chemistry approach, natural products can be modified synthetically to improve their activity against cancer. This resume, thus, can enrich the ongoing research on anticancer natural products.

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