

## Research Article

# Useful Anti-Cancer Agents of Natural Product Origin

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## Abstract

For over 40 years, natural products have served us well in combating cancer. The main sources of these successful compounds are microbes and plants from the terrestrial and marine environments. The microbes serve as a major source of natural products with anti-tumor activity. A number of these products were first discovered as antibiotics. Another major contribution comes from plant alkaloids, taxoids and podophyllotoxins. A vast array of biological metabolites can be obtained from the marine world, which can be used for effective cancer treatment. The search for novel drugs is still a priority goal for cancer therapy, due to the rapid development of resistance to chemotherapeutic agents. In addition, the high toxicity usually associated with some cancer chemotherapy drugs and their undesirable side-effects increase the demand for novel anti-tumor drugs active against untreatable tumors, with a favorable safety profile and/or with greater therapeutic efficacy. This review points out those technologies needed to produce the anti-tumor compounds of the future.

**Keywords:** *Natural products, anti-cancer, plant, marine, angiogenesis, tumor*

## Introduction

Natural products have offered tremendous benefits to our society as a whole. Not only have these compounds helped reduce pain and suffering but also enabled the transplantation of vital organs. The use of plant and microbial secondary metabolites has aided in doubling of our life span in the 20th century. Since their chemical diversity is based on biological and geographical diversity, the entire globe is explored for bioprospecting by researchers. Researchers have had easy access to terrestrial life from which most of the pharmaceutically successful natural products originate. However, the ocean hosts a vast repertoire of life forms brimming with natural products of potential pharmaceutical importance. New methods are being developed to grow the so-called 'unculturable' microbes from both the soil and the sea. Most biologically active natural products are secondary metabolites with complex structures. In some cases, the natural product itself can be used, but in others, derivatives made chemically or biologically are the molecules used in medicine. Biosynthetic pathways are often genetically manipulated to yield the desired product. With the advent of combinatorial biosynthesis, thousands of new derivatives can now be made by this biological technique, which is complementary to combinatorial chemistry.

The production of specialized compounds via secondary metabolism emerged as a result of the pressures (needs and challenges) from the natural environment. Nature has been continually carrying out its own version of combinatorial chemistry [1] for over the three billion years in which bacteria have inhabited the earth [2]. During that time, there has been an evolutionary process going on in which producers of secondary metabolites evolved according to their local environments. If the metabolites were useful to the producing species,

the biosynthetic genes were retained and genetic modifications further improved the process. Combinatorial chemistry practiced by nature is much more sophisticated than combinatorial chemistry in the laboratory, yielding exotic structures rich in stereochemistry, concatenated rings and reactive functional groups [1]. As a result, an amazing variety and number of products have been found in nature. This natural wealth is tapped for drug discovery using high-throughput screening and fermentation, mining genomes for cryptic pathways, and combinatorial biosynthesis to generate new secondary metabolites related to existing pharmacophores. The success of the pharmaceutical industry depends on the combination of complementary technologies such as natural product discovery, high-throughput screening, genomics, proteomics, metabolomics and combinatorial biosynthesis.

Of the nearly one million natural products currently known, it is estimated that about half (500,000 – 600,000) are produced by plants [3-4]. The structures of 160,000 natural products were already elucidated by the late 1990s, a value growing by 10,000 per year [5]. There are more than 20,000 microbial secondary metabolites [6]. With regard to biological activity, there are about 200,000 to 250,000 biologically active products (active and/or toxic). About 100,000 secondary metabolites of molecular weight less than 2500 Daltons have been characterized. About half are produced by microbes and the other half by plants [3, 7-9].

Many natural products from terrestrial sources have been successful in clinical trials and have greatly benefited the medical field, some for nearly half a century. Over 60% of approved and pre-NDA (New Drug Applications) candidates are either natural products or related to them, not including biologicals such as vaccines

and monoclonal antibodies [10-11]. 6% are natural products, 27% are derivatives of natural products, 5% are synthetic with natural product pharmacophores, and 23% are synthetic mimics of natural products. Almost half of the best-selling pharmaceuticals are natural or are related to natural products. In 2008, there were 225 natural product-based drugs in various testing procedures such as preclinical, clinical phases I to III, and preregistration. [12] Of these, 108 were from plants, 61 were semi-synthetic, 25 were from bacteria, 24 were from animals and 7 were fungal in origin. Of the 18,000 known marine natural products, 22 of these or their chemical derivatives have been in clinical trials.

The approximate number of known isoprenoids (including terpenoids and carotenoids) is 50,000 [13]. Terpenes number 30,500 and as pharmaceuticals, they had a market of \$12 billion in 2002 [14-15]. Other major categories include polyketides, including macrolides, non-ribosomal peptides, etc. About 4,000 of the known natural products are halogenated.

Cancer is a complex group of diseases which is one of the leading causes of morbidity and mortality. In 2016, 1,685,210 new cases of cancer were diagnosed in the USA, of which 595,690 will result in death [16]. Natural products are the most important anti-cancer agents. Three quarters of anti-tumor compounds used in medicine are natural products or related to them. Of the 140 anti-cancer agents approved since 1940 and available for use, over 60% can be traced to a natural product. Of the 126 small molecules among them, 67% are natural in origin [17]. In 2000, 57% of all drugs in clinical trials for cancer were either natural products or their derivatives [18]. From 1981 to 2002, natural products were the basis of 74% of all new chemical entities for cancer. Of the 225 natural product-based drugs in various stages of clinical testing in 2008 mentioned above, [12] the therapeutic categories targeted included 86 for cancer.

A list of compounds which possess anti-neoplastic activity belong to several different structural classes, which include anthracyclines, enediynes, indolocarbazoles, isoprenoids, polyketide macrolides, non-ribosomal peptides (such as glycopeptides), and others. Most of the polyketides are produced by bacteria and fungi [19-20]. They include a number of anti-tumor drugs such as taxol, which is made by both plants and fungi. Halogenated anti-tumor candidates include salinosporamide A and rebeccamycin [21].

The anti-cancer compounds exert their activity through a diverse array of mechanisms. These include inducing apoptosis through DNA cleavage mediated by topoisomerase I or II inhibition, inhibition of critical enzymes involved in signal transduction or cellular metabolism, mitochondrial permeabilization, and inhibition of tumor-induced angiogenesis.

### Anti-cancer compounds from microbes

A significant number of compounds with anti-neoplastic activity are natural products, having been produced by microorganisms. In particular, actinomycetes are the producers of a large number of natural products with anti-tumor properties, many of which also have anti-microbial activity. A broad screening of antibiotically-active molecules for antagonistic activity against organisms other

than microorganisms was proposed in the 1980s in order to yield new and useful lives for 'failed antibiotics'. This resulted in the development of a large number of simple *in vitro* laboratory tests, e.g. enzyme inhibition screens [22-23] to detect, isolate and purify useful compounds. As a result, we entered into a new era in which microbial metabolites were applied to diseases heretofore only treated with synthetic compounds, and much success was achieved. One such area was that of anti-tumor agents.

Newman and Shapiro made the point that microorganisms have been quite useful in the identification of products with therapeutic efficacy against cancer, based on their ability to prescreen anti-tumor compounds [24]. Most of the important compounds used for chemotherapy of tumors are microbially-produced antibiotics or their derivatives. One of the earliest applications of a microbial product was actinomycin D for Wilm's tumor in children. Use of this compound against stage I or stage II Wilm's tumor resulted in a 90% survival rate [25]. Also used for anti-tumor therapy is the enzyme L-asparaginase.

Bleomycin, which is used for the treatment of squamous cell carcinomas, Hodgkin's lymphomas, and testes tumors, is a glycopeptide produced by *Streptoalloteichus hindustanus*. A derivative of the bleomycin family, pingyangmycin, has been used in cancer therapy in China since 1978 [26]. Another bleomycin derivative, Bleomoxane, is used clinically with other compounds against lymphomas, skin carcinomas and tumors of the head, neck and testicles [27].

Derivatives (analogs) can be made chemically or through the alteration of fermentation conditions. For example, addition of KBr to the rebeccamycin producer, *Saccharothrix aerocolonigenes*, yielded a brominated rebeccamycin.[28] Addition of DL-fluorotryptophan yielded two new fluorinated rebeccamycins and addition of DL-fluorotryptophan led to a third.[29] Of interest are the rebeccamycin derivative edotecarin and the geldanomycin derivative 17-allylaminogeldanomycin. Interestingly, a fourth-generation tetracycline known as SF 2575, produced by *Streptomyces* sp., has low antibiotic activity but a high level of activity against P388 leukemia cells *in vitro*, and many other types of cancer cells [30]. It appears to act against DNA topoisomerases I and II, the target of camptothecins and doxorubicin, respectively.

Metastatic testicular cancer represents a compelling example of how natural products can be used to effectively cure this disease. Although this type of cancer was responsible for only 1% of male malignancies in the USA, it did cause 80 000 cases in the year 2000. Indeed, it is the most common carcinoma in men aged 15–35. The cure rate for disseminated testicular cancer was 5% in 1974; later it was 90%, mainly due to the use of a triple combination of the microbial product bleomycin, the plant compound etoposide, and the synthetic agent cisplatin [31].

### Anthracyclines

The anthracyclines are perhaps the most widely-recognized anti-cancer agents, notably daunorubicin (daunomycin), doxorubicin (14-hydroxydaunorubicin), adriamycin, carminemycin, and aclarubicin [32]. By cloning the doxorubicin resistance gene and the akIav1000 11-hydroxylase gene *dnrF* from *Streptomyces peucetius* spp.

*caesius* (doxorubicin producer) into the aclacinomycin A producer, a novel anthracycline, 11-hydroxyaclacinomycin A, was made [33]. The hybrid molecule showed greater activity against leukemia and melanoma than aclacinomycin A. Another hybrid molecule produced was 2'-amino-11-hydroxyaclacinomycin Y, which is highly active against tumors [34]. Additional anthracyclines have been made by introducing DNA from *Streptomyces purpurascens* into *Streptomyces galilaeus*, both of which normally produce known anthracyclines [35]. Other novel anthracyclines were produced by cloning DNA from the nogalomycin producer, *Streptomyces nogalater*, into *Streptomyces lividans* and into an aclacinomycin-negative mutant of *S. galilaeus* [36]. Cloning of the *actI*, *actIV* and *actVII* genes from *Streptomyces coelicolor* into the 2-hydroxyaklavinone producer, *S. galilaeus* 31671, yielded the novel hybrid metabolites, desoxyerythrolaccin and 1-O-methyl-desoxyerythrolaccin [37]. Similar studies yielded the novel metabolite aloesaponarin II [38]. Epirubicin (4 $\epsilon$ -epidoxorubicin) is a semi-synthetic anthracycline with less cardiotoxicity than doxorubicin [39]. Genetic engineering of a blocked *S. peucetius* strain provided a new method to produce it [40]. The gene introduced was *avrE* of the avermectin-producing *Streptomyces avermitilis* or the *eryBIV* genes of the erythromycin producer, *Saccharopolyspora erythraea*. These genes and the blocked gene in the recipient are involved in deoxysugar biosynthesis.

### **Enediynes**

Enediynes are one of the most potent anti-neoplastic compounds produced naturally, but are quite toxic due to their induction of apoptosis in both normal and cancerous cells. They include calicheamicin, dynemicin A, esparamicin, kerdarcidin and neocarzinostatin. Scientists have tried to design non-toxic enediyne-based anti-tumor drugs [41]. Progress towards this goal has proceeded by merging amidines with the natural enediyne, dynemicin A [42].

### **Epothilones**

Myxobacteria, which are somewhat large Gram-negative rods whose primary means of locomotion is by gliding or creeping, provide an unexpected source of secondary metabolites. They form fruiting bodies and have a very diverse morphology. Over 400 compounds had been isolated from these organisms by 2005, but the first in clinical trials were the epothilones, potential anti-tumor agents, which act like taxol (see *Plant anti-tumor agents* below) but are active against taxol-resistant tumors [43]. Epothilones are 16-member ring polyketide macrolide lactones produced by the myxobacterium *Sorangium cellulosum*, which were originally developed as anti-fungal agents against rust fungi [44-45] but have found their use as anti-tumor compounds. They contain a methylthiazole group attached by an olefinic bond. They are active against breast cancer and other forms of cancer [46]. They bind to and stabilize microtubules essential for DNA replication and cell division, even more so than taxol. One epothilone, ixabepilone (Ixempra), produced chemically from epothilone B and which targets microtubules, was approved by FDA. By preventing the disassembly of microtubules, epothilones cause arrest of the tumor cell cycle at the GM2/M phase and induce apoptosis. The

mechanism is similar to that of taxol but epothilones bind to tubulin at different binding sites and induce microtubule polymerization. Production of epothilone B by *S. cellulosum* is accompanied by the undesirable epothilone A. Production of epothilone B over A is favored by adding sodium propionate to the medium. Epothilone polyketides are more water-soluble than taxol. The epothilone gene cluster was cloned, sequenced, characterized and expressed in the faster growing *Streptomyces coelicolor*, resulting in the production of epothilones A and B [47-48].

### **Agents which target angiogenesis**

Tumors rely heavily on angiogenesis, which is the production of new blood vessels, in order to get their oxygen and nutrients. Tumors actively secrete growth factors, which trigger angiogenesis. The concept of angiogenesis was established by Professor Judah Folkman [49]. He proposed that tumor growth depends on angiogenesis and proposed the use of angiogenesis inhibitors as anti-tumor agents, i.e. to target activated endothelial cells. He further proposed that the vascular endothelial growth factor (VEGF) is involved in angiogenesis and that it could be a target for anti-angiogenic drugs. Fumagillin, produced by *Aspergillus fumigatus*, was one of the first agents found to act as an anti-angiogenesis compound. Next to come along were its oxidation product ovalacin and the fumagillin analog TNP470 (= AGM-1470). [50-51] TNP470 binds to and inhibits type 2 methionine aminopeptidase (MetAP2) [52-53]. This interferes with amino-terminal processing of methionine, which may lead to inactivation of enzymes essential for growth and migration of endothelial cells [54-55]. In animal models, TNP470 effectively treated many types of tumors and metastases [56-58].

Avastin (bevacizumab), which is a monoclonal antibody and angiogenesis inhibitor, is a first-line treatment for metastatic colorectal cancer. Anti-angiogenic agents Pegaptanib (Macugen) and ranibizumab (Lucentis) were approved by FDA. Macugen is an aptomer of the VEGF and Lucentis is an anti-VEGF antibody. By the end of 2007, 23 anti-angiogenic drugs were in Phase III clinical trials and more than 30 were in Phase II. By 2008, ten anti-angiogenesis drugs had been approved. Eight are used against cancer and two are employed for treatment of age-related macular degeneration. Anti-angiogenesis therapy is now known as one of the four major types of cancer treatment.

### **Derivatives of Rapamycin (sirolimus)**

Rapamycin is a polyketide anti-fungal agent with a limited spectrum of activity which first gained recognition as an immuno-suppressive agent commonly used for organ transplantation. Rapamycin's mode of action is that of inhibiting the mTOR (mammalian target of rapamycin) phosphatidylinositol lipid kinase. Interestingly, it was also found to have anti-tumor activity [59] by interfering with angiogenesis [60-61] and inducing apoptosis. Rapamycin was the basis of chemical modification and these efforts yielded important products such as temsirolimus (CCI-779; (Torisel), everolimus and deforolimus (A23573) [62] Temsirolimus, an mTOR protein kinase inhibitor, was approved by the FDA for renal cell carcinoma [63].

## Statins

The statins are essential for the reduction of cholesterol levels in humans specifically by targeting and inhibiting blood cholesterol, which is produced in the liver. They are microbially-produced enzyme inhibitors, inhibiting 3-hydroxy-3-methyl-coenzyme A reductase, the regulatory and rate-limiting enzyme of cholesterol biosynthesis in the liver. As a result, they are a leading group of pharmaceuticals. One of the most useful statins is lovastatin (monocolin K, mevinolin) produced by *Monascus ruber* [64] and *Aspergillus terreus* [65]. Statins also have anti-cancer activity, i.e., they inhibit *in vitro* and *in vivo* growth of pancreatic tumors. They also sensitize tumors to cytostatic drugs such as gemcitabine, which is used for pancreatic cancer [66]. It has been shown that there is over a 50% reduction in risk of metastatic or fatal prostate cancer among people taking statins and an 80% reduction in pancreatic cancer among people using statins for 4 years. It has been found that lovastatin has anti-tumor activity against Lewis Lung Carcinoma cells [67].

## The hunt for new and promising agents

Salinomycin was determined to be the most effective agent identified from high-throughput screening of 16,000 compounds for selective inhibition of cancer stem cells [68]. In fact, it was 100 times more active than taxol. Salinomycin is used as a coccidiostat in poultry and in other livestock, and as an agent increasing feed efficiency in ruminant animals. Also active were etoposide, abamectin and nigericin. Both salinomycin and nigericin are structurally-related polyether potassium ionophores.

Modification of an organism's genome offers a promising method to generate unique anti-tumor agents. This is carried out by expressing biosynthetic gene clusters from anti-tumor pathways in other organisms. This has resulted in the formation of some novel hydroxylated and glycosylated anti-tumor agents [69].

Following the discovery of the *S. coelicolor* genome, which contained 22 gene clusters encoding the production of secondary metabolites, the notion of genome mining was established. The technique is useful for identifying genetic units with potential for synthesizing new drugs and has yielded many new antibiotics and anti-tumor agents [70-72]. One anti-cancer compound developed by Thallion Pharmaceuticals is ECO-4601. It inhibits the Ras-mitogen-activated phosphokinase (MAPK) pathway and binds selectively to the PBR (peripheral benzodiazepine receptor), which is over-expressed in many types of tumors. As a result of genome mining with *Micromonospora* sp., a new anti-tumor drug was discovered [73]. The compound, ECO-04601, is a farnesylated dibenzodiazepene, which induces apoptosis.

Within the drainage of an abandoned mine, a co-culture yielded a compound with anti-neoplastic activity. The specific nutrient conditions in the mine likely contributed to an extreme environment [74]. Such an environment results in defensive and offensive microbial interactions for survival of microbes. The two members of the co-culture were the bacterium *Sphingomonas* sp. strain KMK-001, and the fungus *A. fumigatus* strain KMC-901. A diketopiperazine disulfide, glionitrin A, was isolated from the co-culture but was not

detected in monoculture broths of KMK-001 or KMC-901. Glionitrin A is a (3S, 10aS) diketopiperazine disulfide containing a nitro aromatic ring. It displayed significant antibiotic activity against a series of microbes including methicillin-resistant *S. aureus*. An *in vitro* MTT cytotoxicity assay revealed that it has potent sub-micromolar cytotoxic activity against four human cancer cell lines: HCT-116, A549, AGS and DU145.

## Plant anti-tumor agents

Many promising anti-tumor compounds that have been approved are actually plant-derived [75]. Various groups are described below.

### Alkaloids

The Madagascar periwinkle plant (*Catharanthus roseus*) is the source of vinca monoterpene indole alkaloids, such as vinblastine and vincristine. Vinblastine is commonly used to treat cancers such as Hodgkin's lymphoma. Vinblastine and vincristine have important pharmacological activities but are synthetically challenging. Metabolic engineering of alkaloid biosynthesis can provide an efficient and environmentally friendly route to analogs of these pharmaceutically valuable natural products. The enzyme at the entry point of the pathway, strictosidine synthase, has a narrow substrate range and thus limits a pathway engineering approach. However, it was demonstrated by Bernhardt and colleagues [76] that with a different expression system and screening method, it is possible to rapidly identify strictosidine synthase variants that accept tryptamine analogs not utilized by the wild-type enzyme. The variants are used in a stereoselective synthesis of beta-carboline analogs and are assessed for biosynthetic competence within the terpene indole alkaloid pathway. These results presented an opportunity to explore metabolic engineering of 'unnatural' product production in the plant periwinkle.

Serpentines, which are also made by the Madagascar periwinkle plant, have demonstrated encouraging anti-cancer activity. Other plant-produced compounds have shown pharmacological activities including anti-cancer activity, but are too toxic for use in humans. However, researchers have been able to produce a range of halogenated alkaloids [77]. This strategy could help expand the range of available drug candidates for cancer.

Certain seed-producing plants (angiosperms) make camptothecin, a cytotoxic quinoline alkaloid [78]. It also is produced by the endophytic fungus, *Entrophospora infrequens*, from the plant *Nathapodytes foetida*. In view of the low concentration of camptothecin in tree roots and poor yield from chemical synthesis, the fungal fermentation is very promising for industrial production. Camptothecin is used for recurrent colon cancer and has unusual activity against lung, ovarian, and uterine cancers [79]. Colon cancer is the second leading cause of cancer fatalities in the USA and the third most common cancer among US citizens. Camptothecin is known commercially as Camptosar and Campto and achieved sales of \$1 billion in 2003 [80]. Camptothecin's water-soluble derivatives irinotecan and topotecan are also used clinically.

Camptothecin exhibits its anti-cancer activity by inhibiting type 1 DNA topoisomerase. When patients become resistant to irinotecan, its

use can be prolonged by combining it with the monoclonal antibody Erbitux (Cetuximab). Erbitux blocks a protein that stimulates tumor growth and the combination helps metastatic colorectal cancer patients expressing epidermal growth factor receptor (EGFR). This protein is expressed in 80% of advanced metastatic colorectal cancers. The drug combination reduces invasion of normal tissues by tumor cells and the spread of tumors to new areas.

The diterpene alkaloid, Taxol (paclitaxel), has shown great promise as an anti-cancer drug [81]. It was originally discovered in plants but was also found to be a fungal metabolite [82]. Fungi, such as *Taxomyces adreanae*, *Pestalotiopsis microspora*, *Tubercularia* sp. and *Phyllosticta citricarpa*, produce taxol [82-84]. Production by *P. citricarpa* is rather low, i.e. 265  $\mu\text{g l}^{-1}$ . [85] However, it is claimed that another fungus, *Alternaria alternata var monosporus* from the bark of *Taxus yunnanensis*, after ultraviolet and nitrosoguanidine mutagenesis, produces taxol at the high level of 227  $\text{mg l}^{-1}$  [86]. Originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), taxol showed anti-tumor activity but it took six trees of 100 years of age to treat one cancer patient [87]. Later, it was produced by plant cell culture or by semi-synthesis from taxoids made by *Taxus* species. These species make more than 350 known taxoid compounds [88].

Taxadiene (the taxol precursor) was not able to be produced through the genetic engineering of *Saccharomyces cerevisiae* due to the fact that only a small amount of the intermediate, geranylgeranyl diphosphate, was formed. When the *Taxus canadensis* geranylgeranyl diphosphate synthase gene was introduced into *S. cerevisiae*, 1  $\text{mg l}^{-1}$  of taxadiene was obtained [81]. Later, metabolic engineering yielded a *S. cerevisiae* strain producing over 8  $\text{mg l}^{-1}$  taxadiene and 33  $\text{mg l}^{-1}$  of geranyl geraniol.

The technical means by which Taxol is made is dependent on the use of plant cells from *Taxus chinensis*. The addition of methyl jasmonate, a plant signal transducer, increased production from 28 to 110  $\text{mg l}^{-1}$  [89]. The optimum temperature for growth of *T. chinensis* is 24°C and that for taxol synthesis is 29°C. Shifting from 24°C to 29°C at 14 days gave 137  $\text{mg l}^{-1}$  at 21 days [90]. Later a 6-week process yielding 153  $\text{mg l}^{-1}$  with *T. chinensis*, was developed [91]. Mixed cultures of *Taxus* plant cells and taxol-producing endophytic fungi were also examined [92].

Taxol, which inhibits depolymerization of microtubules and is approved for the treatment of breast and ovarian cancer, had sales of \$1.6 billion in 2005. In addition, taxol promotes tubulin polymerization and inhibits rapidly dividing mammalian cancer cells [93]. Taxanes and camptothecins alone accounted for approximately one-third of the global anti-cancer market in 2002, with a market value of over \$2.75 billion. An analog of taxol, docetaxel (Taxotere), had sales of \$3 billion in 2009 [94].

Taxol also possesses anti-fungal activity against oomycetes via the same process of blocking the depolymerization of microtubules [95-96]. Oomycetes are water molds exemplified by plant pathogens, such as Phytophthora, Pythium and Aphanomyces.

#### **Etoposide and teniposide**

Two semi-synthetic derivatives of podophyllotoxin are etoposide and teniposide. Podophyllotoxin is actually an anti-mitotic metabolite

of the plant, *Podophyllum peltatum* [97-98]. The mayapple plant is an old herbal remedy. Etoposide is a topoisomerase II inhibitor. This essential enzyme is involved in eukaryotic cell growth by regulating levels of DNA super-coiling [99]. Etoposide was approved for lung cancer, choriocarcinoma, ovarian and testicular cancer, lymphoma, and acute myeloid leukemia. Teniposide was approved for tumors of the central nervous system, malignant lymphoma and bladder cancer.

#### **Other compounds**

Cell culture of the plant *Lithospermum erythrorhizon* yields the naphthoquinone pigment, shikonin. Shikonin is a herbal medicine used mainly for cosmetic purposes. Unexpectedly, shikonin and two derivatives were found to inhibit tumor growth in mice bearing Lewis Lung Carcinoma [100]. Other plant natural products such as the isoflavone genistein, indole-3-carbinol (I3C), 3,3'-diindolemethane, curcumin (-)-epigallocatechin-3-gallate, resveratrol and lycopene are known to inhibit the growth of cancer cells [101]. These natural compounds appear to act by interference in multiple cellular signaling pathways, activating cell death signals, and inducing apoptosis of cancer cells without negatively affecting normal cells.

#### **Anti-cancer products from the marine environment**

The biological diversity of the ocean represents 34 of 37 phyla of life compared to 17 phyla on land. Because of this, searching marine environments and resources for the purpose of drug discovery is an endeavor of interest. Marine microorganisms encompass a complex and diverse assemblage of microscopic life forms, of which it is estimated that only 1% have been cultured or identified. Coral reefs and other highly diverse ecosystems, such as mangroves and sea grass, have been targeted for bioprospecting, because they host a high level of biodiversity and are often characterized by intense competition for space, leading to chemical warfare among sessile organisms. Marine sponges produce numerous bioactive compounds with promising pharmaceutical properties. Cytarabine (Cytostar), used for non-Hodgkin's lymphoma, was originally derived from a sponge. [102] Sponges have been frequently hypothesized to contain compounds of bacterial origin and the bacterial symbionts have long been suspected to be the true producers of many drug candidates. A number of marine products have anti-tumor activity.

*Paederus fuscipes* beetles are host to an uncultured *Pseudomonas* sp. symbiont, which appears to be the most likely source of the defensive anti-cancer polyketide, pederin. Scientists were able to determine this based on cloning of the presumed biosynthetic genes. Closely related genes have also been isolated from the highly complex metagenome of the marine sponge *Theonella swinhoei*, which is the source of the onnamides and theopederins, a group of polyketides that structurally resemble pederin. Sequence features of the isolated genes clearly indicate that they may belong to a prokaryotic genome and are responsible for the biosynthesis of almost the entire portion of the polyketide structure that is correlated with anti-tumor activity. Besides providing further proof for the role of the related beetle symbiont-derived genes, these findings raise intriguing ecological and evolutionary questions and have important general implications for the sustainable production of otherwise inaccessible marine drugs by using biotechnological strategies [103].

Approximately 32% of the effective marine natural products are used for inflammation, pain, asthma, and Alzheimer's disease, while the remaining 68% are used for cancer treatment. Global sales of marine biotechnology products including anti-cancer compounds exceeded \$3.2 billion in 2007. The marine alkaloid trabectedin (Yondelis) was approved by the FDA [62]. A major problem in this field is that less than 1% of the commensal microbiotic consorta of marine invertebrates are culturable.

Curacin A was isolated from a marine cyanobacterium, *Lyngbya majuscula* in Curacao, and has demonstrated strong anti-cancer activity [104]. Other anti-tumor agents derived from marine sources include eleutherobin, discodermolide, bryostatins, dolastatins and cephalostatins.

Marine invertebrate animals are host to many different symbionts which are the source of compelling natural products [105]. Variants of the toxic dolastin from the sea hare *Dolabella auricularia* seem promising against cancer. These include soblidofin (T2F 1027), against soft tissue sarcoma, and synthadotin (tasidotin, 1LX 651), against melanoma, prostate and non-small cell lung cancers. These are thought to be produced by cyanobacteria sequestered by the marine invertebrates in their diet.

In order to identify new and useful products with anti-cancer activity, there is a need to continue to explore the rich biological diversity of the marine environment [106]. The actinomycete genus *Salinispora* and its two species, *Salinispora tropica* and *Salinispora arenicola*, have been isolated around the world. These require seawater for growth. *S. tropica* makes a novel bicyclic gamma-lactone beta-lactam called salinosporamide A, which is a proteasome inhibitor [107] and has activity against multiple myeloma and mantle cell lymphoma. Also, the genus *Marinophilus* contains species that produce novel polyenes, which have no anti-fungal activity but display potent anti-tumor activity.

## Concluding remarks

To meet the growing demand for new anti-cancer compounds in the future, what is the best and most productive way to go about doing this? Although it was thought that high-throughput screening and combinatorial chemistry would generate a significant number of high-quality leads, unfortunately this has not been the case. Combinatorial chemistry mainly yields minor modifications of present day drugs and absolutely requires new scaffolds, such as natural products, on which to build. Although comparative genomics is capable of disclosing new targets for drugs, the number of targets is so large that it requires tremendous investments of time and money to set up all the screens necessary to exploit this resource. This can only be handled by high-throughput screening methodology which demands libraries of millions of chemical entities. It is clear that future success depends not only on high-throughput screening and combinatorial chemistry, but also on the combining of complementary technologies, such as natural product discovery, genomics, proteomics, metabolomics, metagenomics, structure-function drug design, semi-synthesis, recombinant DNA methodology, genome mining and combinatorial biosynthesis. In addition, 'intelligent screening' methods, such as

robotic separation with structural analysis, metabolic engineering and synthetic biology offer exciting technologies for new natural product drug discovery and the future development of anti-tumor compounds.

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