Natural products in anticancer therapy
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Many pharmaceutical agents have been discovered by screening natural products from plants, animals, marine organisms and microorganisms. Vincristine, irinotecan, etoposide and paclitaxel are examples of plant-derived compounds that are being employed in cancer treatment, and daunomycin, bleomycin and doxorubicin are anticancer agents derived from microbial sources. Cytarabine is an example of an anticancer agent originating from a marine source. Other agents originating from marine sources are brevetoxin-1, aplidine, dolastatin 10 and ET-743, which have recently entered phase I and II clinical trials.

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Introduction
The role of natural products as a source for remedies has been recognized since ancient times [1,2]. Despite major scientific and technological progress in combinatorial chemistry, drugs derived from natural product still make an enormous contribution to drug discovery today. Table 1 shows some examples of agents derived from natural sources that are currently used in clinical practice [3–5].

Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, animals, marine organisms and microorganisms. For many living organisms, this chemical diversity reflects the impact of evolution in the selection and conservation of self-defense mechanisms that represent the strategies employed to repel or destroy predators.

The development of novel agents from natural sources presents obstacles that are not usually met when one deals with synthetic compounds. For instance, there may be difficulties in accessing the source of the samples, obtaining appropriate amounts of the sample, identification and isolation of the active compound in the sample, and problems in synthesizing the necessary amounts of the compound of interest. These problems became evident when the tubulin-interacting agent paclitaxel was introduced in clinical use. Initial antitumor activity was observed in various types of cancer, including ovarian and breast adenocarcinoma. Paclitaxel was originally isolated from the bark of the yew tree Taxus brevifolia [6], a finite source of the compound. It took some years to develop a semi-synthetic analog (docetaxel) which is derived from a renewable source, the leaves of Taxus baccata [7]. Currently, total synthesis has been achieved for both agents and drug supply is no longer a problem.

An analysis of the number of chemotherapeutic agents and their sources indicates that over 60% of approved drugs are derived from natural compounds [2]. In recent years, advances in deep-sea collection and aquaculture technology have led to a significant number of compounds derived from marine organisms entering preclinical and early clinical evaluation as anticancer candidates [8,9]. A number of natural product derived anticancer compounds in late preclinical development and in early clinical trials are briefly discussed in this review.

Plant-derived agents
Plant species with a capacity to defend themselves from potential predators and to inhibit other plants competing for space have been selected for (‘natural selection’) [10]. In order to survive, plants have developed sophisticated mechanisms including an elaborate chemical arsenal of toxic substances, such as terpenes and alkaloids, that inhibit the growth of other plants and make them unattractive to predators. An interesting example is tannin production by certain species of trees. When a predator starts eating a tree in a grove, that tree releases ethylene into the air. This signals to other trees in the grove to increase leaf tannin production, making themselves poisonous and unpalatable to the predator animal. Some plants are also able to produce phenol and tannin when attacked by caterpillars, using a similar signaling process.

Several plant-derived compounds are currently successfully employed in cancer treatment (Table 2). One of the most significant examples is the vinca alkaloid family isolated from the periwinkle Catharanthus roseus, which is found in the rain forests of Madagascar [11]. The introduction of the vinca alkaloid vincristine was responsible for an increase in the cure rates for Hodgkin’s disease and some forms of leukemia [12]. Vincristine inhibits microtubule assembly, inducing tubulin self-association into coiled spiral aggregates ([11]; see also the review by K.W. Wood, W.D. Cornwell and J.R. Jackson, this issue, pp 370–377).

Another example of a highly active agent derived from a natural product is etoposide, which has produced high cure rates in testicular cancer when used in combination with bleomycin (also derived from a natural product) and cisplatin [13]. Etoposide is a epipodophyllotoxin, derived from the mandrake plant Podophyllum peltatum and the wild chervil Podophyllum emodi [14]. It has also significant activity against small-cell lung carcinoma [15–17]. Etoposide is a topoisoasemase II inhibitor, stabilizing enzyme–DNA cleavable complexes leading to DNA breaks [18].

The taxanes paclitaxel and docetaxel, mentioned briefly in the introduction, show impressive antitumor activity
against breast, ovarian and other tumor types in the clinic. Paclitaxel stabilizes microtubules, leading to mitotic arrest [6]. In addition, the camptothecin derivatives irinotecan and topotecan, have shown significant antitumor activity against colorectal and ovarian cancer respectively [19,20]. These compounds were initially obtained from the bark and wood of Nyssacea *Camptotheca accuminata* and act by inhibiting topoisomerase I [21]. The taxanes and the camptothecins are presently approved for human use in various countries.

Flavopiridol is one of the most exciting plant-based agents currently in development, representing the first cyclin-dependent kinase inhibitor to enter the clinic [22*]. Flavopiridol is a synthetic flavone derived from the plant alkaloid rohitukine, which was isolated from the leaves and stems of *Amoora rohituka* and later from *Dysoxylum binectariferum* (Maliaceae) [22•,23–26]. The mechanism of action of flavopiridol involves interfering with the phosphorylation of cyclin-dependent kinases, hampering their activation and blocking cell-cycle progression at growth phase 1 (G₁) or G₂ [22*,25]. In phase I clinical trials with flavopiridol [27,28], secretory diarrhea was found to be the dose-limiting toxicity, and encouraging response rates were noted in a variety of solid and hematological malignancies. These results led to the initiation of phase II trials in patients with colorectal, prostate, renal cell and non-small-cell lung carcinoma, as well non-Hodgkin’s lymphoma and chronic lymphocytic leukemia. Based on *in vitro* synergy of flavopiridol with several conventional cytotoxic agents [29], phase I combination studies to evaluate flavopiridol with paclitaxel or cisplatin against advanced solid tumors are also ongoing.

A number of additional plant-derived agents are currently under investigation (Table 2). Homoharringtonine, for instance, is an alkaloid isolated from the Chinese tree *Cephalotaxus harringtonia* (Cephalotaxacea) [30], and has shown efficacy against various leukemias [31]. The principal mechanism of action of homoharringtonine is the inhibition of protein synthesis in the malaria parasite [32]. 4-Ipomeanol is a pneumotoxic furan derivative isolated from the sweet potato *Ipomoeca batatas* (Convolvulaceae) [33] and has been under clinical evaluation as a lung-cancer-specific antineoplastic agent [34]. This compound is converted into DNA-binding metabolites upon metabolic activation by cytochrome P450 enzymes that are present in cells of the lung [33]. Finally, β-lapachone is a DNA topoisomerase I inhibitor that induces cell-cycle delay at G₁ or S (synthesis) phase before inducing either apoptotic or necrotic cell death in a variety of human carcinoma cells, including ovary, colon, lung, prostate and breast [35].

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical use</th>
<th>Mechanism of action</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Analgesic, anti-inflammatory, antipyretic</td>
<td>Inhibition of COX</td>
<td>Plant</td>
</tr>
<tr>
<td>Atropine</td>
<td>Pupil dilator</td>
<td>Antagonist of ACh at muscarinic receptors at post-ganglionic parasympathetic neuroeffector sites</td>
<td>Plant</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Stimulant</td>
<td>Adenosine receptor antagonist</td>
<td>Plant</td>
</tr>
<tr>
<td>Codeine</td>
<td>Analgesic, antitussive</td>
<td>Opioid receptor agonist</td>
<td>Plant</td>
</tr>
<tr>
<td>Digoxin</td>
<td>For atrial fibrillation and CHF</td>
<td>Inhibition of the Na⁺/K⁺ ATPase membrane pump</td>
<td>Plant</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Toothache</td>
<td>Reduces excitability of sensory nerves (increased K⁺ efflux and reduced Ca²⁺ influx)</td>
<td>Plant</td>
</tr>
<tr>
<td>Morphine</td>
<td>Analgesic</td>
<td>Opioid receptor agonist</td>
<td>Plant</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Glaucoma</td>
<td>Muscarinic receptor agonist</td>
<td>Plant</td>
</tr>
<tr>
<td>Quinine</td>
<td>Malaria prophylaxis</td>
<td>Inhibition of protein synthesis in the malaria parasite</td>
<td>Plant</td>
</tr>
<tr>
<td>Taxol</td>
<td>Anticancer agent</td>
<td>Antimitotic agent (binds to and stabilizes microtubules)</td>
<td>Plant</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Antibiotic</td>
<td>Inhibition of synthesis of cell wall peptidoglycan</td>
<td>Microbe</td>
</tr>
<tr>
<td>Tetracyclin</td>
<td>Antibiotic</td>
<td>Inhibition of protein synthesis by binding to the ribosome 30S subunit.</td>
<td>Microbe</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Immunosuppressant</td>
<td>Inhibition of clonal proliferation of T lymphocytes (via inhibition of lymphokine production)</td>
<td>Microbe</td>
</tr>
<tr>
<td>Aurantosides</td>
<td>Antifungal</td>
<td>Inhibition of tubulin polymerization</td>
<td>Marine organism</td>
</tr>
<tr>
<td>Spongistatin 1</td>
<td>Antifungal</td>
<td>Inhibition of tubulin polymerization</td>
<td>Marine organism</td>
</tr>
<tr>
<td>Manoalide</td>
<td>Analgesic, anti-inflammatory</td>
<td>Inhibition of phospholipase A₂</td>
<td>Marine organism</td>
</tr>
</tbody>
</table>

ACh, acetylcholine; CHF, congestive heart failure; COX, cyclooxygenase.
Antitumor antibiotics are among the most important cancer chemotherapeutic agents, and include members of the anthracycline, bleomycin, actinomycin, mitomycin and aureolic acid families [36]. Clinically useful agents from these families are the daunomycin-related agents (daunomycin itself, doxorubicin, idarubicin and epirubicin), the peptolides (exemplified by dactinomycin), the mitosanes (such as mitomycin C) and the glycosylated anthracenone mithramycin. The anthracyclines are among the most used antitumor antibiotics in the clinic and exert antitumor activity mainly by inhibiting topoisomerase II [37].

Many pharmaceutical agents have been discovered by screening natural products from a wide range of microorganisms. For example, cyclosporin A (CyA) and FK506 (Prograf, tacrolimus) were discovered at Sandoz and Fujisawa Pharmaceuticals, respectively, in screens for immunosuppressive agents that would block a mixed lymphocyte response. These two immunosuppressant drugs have had a dramatic impact on clinical medicine and are widely used to prevent and treat graft rejection and graft-versus-host disease following both solid-organ transplants and bone-marrow transplants.

The immunosuppressant rapamycin (sirolimus) was originally discovered at Wyeth-Ayerst Pharmaceuticals in a screen for antifungal agents, and was later found to have potent immunosuppressive activity. In addition rapamycin, wortmannin and geldanamycin (also natural products) have been found to have antiproliferative actions and may therefore find clinical use as novel chemotherapeutic agents (Table 3; [38]). Rapamycin and its analogs are products of Streptomyces hygroscopicus and inhibit signaling pathways required for T-cell activation and proliferation. Rapamycin blocks progression of the cell cycle at middle-to-late G1 phase in T cells and B cells, and osteosarcoma and rhabdomyosarcoma cell lines, among others [39]. Geldanamycin is a benzoquinone ansamycin natural fermentation product that was originally thought to be a direct protein tyrosine kinase inhibitor. However, subsequent studies have revealed that geldanamycin binds to, and inhibits the 90kDa heat-shock protein HSP 90 [40]. Wortmannin is a product of the fungus Talaromyces wortmanni and inhibits signal transduction pathways by forming a covalent complex with an active-site residue of phosphoinositide 3 kinase (PI3K), inhibiting PI3K activity [41].

Thus, toxins that originally evolved to kill competing microorganisms can have a variety of physiological effects in animals. In several cases, the targets of these compounds are components of signal transduction cascades that are conserved in many species, and that have been considered novel targets for anticancer drug discovery [42••].

### Marine-organism-derived agents

Marine organisms are a rich source for natural products and many compounds that are derived from these organisms have generated interest both as challenging problems for structure elucidation and synthesis and for their cytotoxicities (Table 4). The new classes of anticancer drugs that have been isolated from marine organisms have been shown to possess cytotoxic activity against multiple tumor types [8,9]. Most of these compounds were identified during the 1980s following great improvements in deep-sea sample collection and in technologies that allowed the production of drugs on a large scale through aquaculture and synthesis [43]. Overall, more than 3000 new substances have been identified from marine organisms during the

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**Table 2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cancer use</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>Leukemia, lymphoma, breast, lung, pediatric solid cancers and others</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Breast, lymphoma, germ-cell and renal cancer</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Ovary, breast, lung, bladder, and head and neck cancer</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Breast and lung cancer</td>
<td>Phase III</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Ovarian, lung and pediatric cancer</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Colorectal and lung cancer</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Flavopiridol</td>
<td>Experimental</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Acronyciline</td>
<td>Experimental</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Bruceantin</td>
<td>Experimental</td>
<td>Preclinical/phase I</td>
</tr>
<tr>
<td>Thalicarpin</td>
<td>Experimental</td>
<td>Preclinical/phase I</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cancer use</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin</td>
<td>Sarcoma and germ-cell tumors</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Germ-cell, cervix, and head and neck cancer</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>Leukemia</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Lymphoma, breast, ovary, lung and sarcomas</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Breast cancer</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Breast cancer and leukemia</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>Gastric, colorectal, anal and lung cancer</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Streptozocin</td>
<td>Gastro-enteric tumors</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Wortmannin</td>
<td>Experimental</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Rapamicin*</td>
<td>Experimental</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Geldanamycin</td>
<td>Experimental</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

*Rapamicin is also a potent immunosuppressant.*
past three decades, demonstrating the great potential of the sea as a source of novel chemical classes [44,45].

The first anticancer product derived from marine sources to enter clinical trials was didemnin B, a cyclic depsipeptide isolated from the tunicate Trididemnum solidum [45]. Preliminary results from these clinical trials showed a partial activity against non-Hodgkin’s lymphoma [46]; however, the observation of severe neuromuscular and cardiac toxicity led to the discontinuation of clinical trials [47,48]. Didemnin can inhibit protein synthesis and induce G1 cell-cycle arrest [49]. Aplidine is a related depsipeptide that appears to be more active than didemnin B in preclinical models, and so far does not seem to produce similar life-threatening neuromuscular toxicity [49]. Preclinical studies indicate that aplidine is active against several tumor types through blockade of cell-cycle progression at G1 [49].

Numerous ecteinascidins have been isolated from the marine tunicate Ecteinascidia turbinata. Preclinical studies have shown that one of these ecteinascidins (ET-743) is toxic to most tumor cell lines in nanomolar and sub-nanomolar concentrations [45]. This compound was selected for clinical trials, and antitumor effects have been observed in phase I trials with concentrations of less than 2mg/m² body surface [50,51]. ET-743 is a tetrahydroisoquinoline alkaloid that acts by selective alkylation of guanine residues in the DNA minor groove. It therefore differs from the other DNA-alkylating agents so far introduced in the clinic [52,53], and also interacts with nuclear proteins [54]. ET-743 is currently in phase II clinical trials in Europe and the United States [50,51].

The dolastatins are a class of peptides that were originally derived from a mollusk from the Indian Ocean, the sea hare Dolabella auricularia. These peptides have cytotoxic activity and of the various compounds of this class, Dolastatin 10 and Dolastatin 15, have received the greatest clinical interest [55]. Indeed, Dolastatin 10 has entered Phase I and Phase II trials, after showing significant antitumor activity in preclinical models [55]. Its mechanism of action involves inhibition of microtubule assembly, which causes cell-cycle arrest in metaphase [56,57]. The toxicity profile for Dolastatin 10 includes bone marrow toxicity and local reaction at the injection site. Also, a mild peripheral neuropathy was observed in some patients. Despite its remarkable activity in in vitro studies, Dolastatin has failed to show significant antitumor effects in Phase I and II trials conducted for several types of solid tumors [58–61].

The bryostatins comprise a structurally and functionally novel group of 20 macrocyclic lactones originally isolated from Bugula neritina and other marine bryozoa. These macrocyclic compounds have shown significant activity against murine P388 (a lymphocytic leukemia cell line) [62], and have subsequently been identified as important leads in cancer chemotherapy. Bryostatin 1 has recently entered phase II clinical trials for the treatment of melanoma, non-Hodgkin’s lymphoma, renal cancer and colorectal cancer [63–66] and continues to be evaluated in phase I clinical trials, alone and in combination with other drugs, for the treatment of other types of cancer. Bryostatin 1 has been found to promote the normal growth of bone marrow progenitor cells, to provide in vivo protection against normally lethal doses of ionizing radiation, and to serve as an immune stimulant, enhancing the normal production of interleukin 2 and interferons [67].

**Conclusions**

The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. Experimental agents derived from natural products are offering us a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- **of outstanding interest**


domain.

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2000, antineoplastic drug ecteinascidin-743.

Mantovani R:

Cancer pathways.

Foiani M, D'Incalci M:

Eur J 11(Suppl 4)
in adult: A STBSG-EORTC trial

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