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The Medicinal Value of Biodiversity: New Hits to Fight Cancer

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1. Introduction

Natural products are produced by a wide range of different organisms. Microorganisms, plants, marine species, and animals employ such compounds for several purposes such as building blocks, coenzymes and cofactors, host-defense against microbial infection and predators, protection of ecological niches, communication between and within species, pigments, cellular signaling, gene expression, and homeostasis maintenance. Currently, many key therapeutic classes of drugs in use are derived from natural products, such as the antimalarial drug artemisinin, several anticancer agents, the lipid-lowering statins and immunosuppressors used to prevent the rejection of tissue grafts (Harvey, 2010).

Since ancient times, natural products represent the main source of compounds employed in drug discovery and development. Still now, nature provides the mankind with a diversity of small bioactive compounds, opening promising avenues for the treatment of a great variety of diseases. Indeed, through millions of years, natural products have evolved to encompass a broad spectrum of chemical and functional diversity that enables them to target of a nearly limitless number of biological macromolecules in a highly selective manner. In contrast, synthetic molecules generated by combinatorial chemistry show lower chemical diversity and selective action than their natural counterparts. Because of these characteristics, natural products, mostly plant secondary metabolites, have seen great success as therapeutic agents. In fact, about 50% of the drugs introduced in the market during the last 20 years were derived directly or indirectly from bioactive compounds. Interestingly, of the approximately 1,200 new medicines approved by the FDA in the 25-year period up to 2006, only around one-third of the small molecules were completely synthetic in origin, with the remaining being natural products, direct derivatives of natural products or synthetic compounds inspired by a natural product lead (Vuorelaa et al., 2004; Newman & Cragg, 2009; Harvey, 2010).

Besides the known diversity of bioactive compounds, it is certain that a great number of novel nature-based molecular structural models, with novel biological activities, remain to be discovered. It is currently estimated that approximately 420,000 plant species exist in

nature; the majority of which still unknown (Vuorelaa et al., 2004). In addition, less than 1% of microbes known by humans can be cultivable in laboratory conditions. In fact, the therapeutic potential of metabolism-derived microbial products is largely not explored, besides the astonishing number of different microorganisms that inhabit the Earth. Interestingly, despite our reduced knowledge of the microbial diversity, more than 20,000 secondary metabolites derived from microorganisms have already been described, while only a small percentage of these have been carried forward as natural product drugs (Knight et al., 2003). Marine organisms also represent a significant source of bioactive molecules, much of which in phase II, phase III and at the commercialization stage of new drug development (Galeano et al., 2011).

According to the World Health Organization (WHO), cancer is the leading cause of death worldwide and responsible for around 7 million deaths per year, a number estimated to reach 11 million until 2030. However, chemotherapy, the major therapeutic approach for cancer treatment, has to deal with important constraints such as lack of aqueous solubility and selectivity of antineoplastic drugs and the innate or acquired emergence of multidrug resistance by cancer cells. Consequently, there is an overwhelming demand for the discovery of novel chemopreventive compounds and to the development of new, more potent and effective, anticancer drugs. In this scenario, natural products represent the most valuable source of bioactive compounds able to inhibit cancer and serve as leads and scaffolds for the development of more efficacious drugs. Indeed, historically, natural products have been the most significant source of drugs and drug leads. Currently, around 74% of the available anticancer compounds are natural products or natural product-derived (Tan et al., 2006). With this perspective, in this chapter, we outline the historical importance and future perspectives of terrestrial and marine-sourced anticancer agents in oncology, and discuss the impact of novel biodiversity sources, such as venoms and toxins from several animal species, in anticancer drug development. In addition, some general aspects of chemical modifications done in natural products core with the aim to improve their activity and/or effectiveness are described.

2. Plants as a valuable source of anticancer drugs

Natural products with interesting biological activities and complex chemical structures with diverse functional groups result from the phenomenon of biodiversity, which means the richness in variety of organisms in the ecosphere (McChesney et al., 2007). These complex molecules evolve from a natural source of combinatorial chemistry, directed to select specific products with biological advantage. As a consequence of this natural selection, molecules able to interact specifically with biological targets arise, thus providing increased survival to the organisms that generated them. From a historical point of view, natural products have long been used as the mainstay of anticancer pharmacology.

From *Podophyllum peltatum*, which provided the podophyllotoxins in the early 1950s, to the Pacific yew *Taxus brevifolia*, from which emerged the most significant anticancer drug paclitaxel (Taxol®), plants have been a seemingly unimaginable source of effective new drugs. Indeed, since the development of the vinca alkaloids, vinblastine and vincristine, and the isolation of podophyllotoxins, from which derived the semisynthetic derivatives, etoposide and teniposide, plant-derived agents have consolidated their place in the chemotherapy armamentarium of anticancer drugs, remaining largely prescribed today and having decades of success in the clinical set (Cragg & Newman, 2005; Newman & Cragg, 2007; Bailly, 2009).

Drug discovery from medicinal plants is an interdisciplinary and multi-stage process characterized by the collection and identification of plant species with known biological activities or randomly collected for screening purposes, extract preparation and biological screening for pharmacological properties in relevant experimental models, isolation and characterization of active compounds, and screening assays directed toward molecular targets (Balunas & Kinghorn, 2005). Several strategies have been used to identify new compounds for drug discovery, of which natural products, and particularly medicinal plants, are still considered an important source of new drugs. Moreover, compounds with new biological activities can afford important drug leads in the development of new generations of drugs with specific and selective activities against novel molecular targets (Balunas & Kinghorn, 2005; Bailly, 2009). During the glory decades, several classes of plant-derived cytotoxic drugs have entered into clinical trials and some are in clinical use, such as camptothecin, isolated from *Camptotheca acuminata*, the precursor of the topotecan and irinotecan, homoharringtonine, isolated from the Chinese tree *Cephalotaxus harringtonia*, flavopiridol, a synthetic flavonoid structurally based in the natural product rohitukine, isolated from *Dysoxylum binectariferum*, combretastatin from the South African “bush willow” *Combretum caffrum*, vinorelbine, the major semi-synthetic tubulin-binding vinca alkaloid and the taxanes (Cragg & Newman, 2005; Bailly, 2009).

The naphthoquinones, mainly lapachol and β -lapachone, are another class of anticancer agents that has been received most attention. While lapachol failed in clinical trials due to their toxicity, β -lapachone provides significant activity against tumor cell lines from different histological origins, including leukemia, breast, prostate and several multidrug resistant (MDR) cell lines. In addition to these effects, its ability to inhibit the enzyme Cdc25, a dual-specificity phosphatase that promotes cell cycle progression and has been postulated to be an oncogene, renewed interest in this family of compounds (Ravelo et al., 2004; Karlsson-Rosenthal & Millar, 2006).

Sesquiterpene lactones encompass a class of terpenoids derived mainly from Asteraceae, but also found in Umbelliferae and Magnoliaceae, which have the ability to selectively target tumor and cancer stem cells. Artemisinin from *Artemisia annua* L, thapsigargin from *Thapsia* (Apiaceae) and parthenolide from *Tanacetum parthenum* and their synthetic derivatives are the most promising drugs of this family for cancer treatment (Ghantous et al., 2010). Studies indicate that their selectivity against tumor cells is achieved by different mechanisms, including modulation of specific signaling pathways, induction of oxidative stress, and epigenetic, antiangiogenic and antimetastatic activities. For instance, thapsigargin has been shown to inhibit the sarco/endoplasmic reticulum (ER) calcium ATPase (SERCA) pump, thus increasing intracellular Ca^{2+} levels, which ultimately lead to ER stress and cell death (Christensen et al., 2009; Winther et al., 2010). Artemisinin has shown promising antitumor properties *in vitro* and *in vivo*, entering phase I-II clinical trials against metastatic breast and colorectal cancers. As tumor cells express higher levels of transferrin receptors on cell surface and have higher concentrations of intracellular iron than normal or slow-proliferating cells, cleavage of artemisinin endoperoxide bridge upon binding to Fe(II) and subsequent free radical generation in tumor cells have been associated to its toxicity. As simultaneous inactivation of p53 and hyperactivation of nuclear factor κB (NF κB) is a common event in human cancers, drugs able to target both pathways have been considered interesting candidates for anticancer therapy. Both sesquiterpene lactones, parthenolide and artemisinin, are able to inhibit NF κB , rendering cancer cells sensitive to chemotherapy (Ghantous et al., 2010). In particular, parthenolide has been shown to inhibit NF κB and to

activate p53 by promoting the ubiquitination and degradation of its negative regulator MDM2 (Gopal et al., 2009). Furthermore, the elevated NF κ B signaling in leukemia stem cells compared to normal hematopoietic stem cells has been ascribed to parthenolide selectivity against acute myeloid leukemia (Ghantous et al., 2010). A more recent epigenetic role for parthenolide in cancer has been shown, by specifically inhibiting DNA methyltransferase 1 (DNMT1) and histone deacetylase 1 (HDAC1) activities, leading to DNA hypomethylation *in vitro* and *in vivo* (Liu et al., 2009; Ghantous et al., 2010).

Also, the ability of plant secondary metabolites, such as vitamins, isothiocyanates, quercetin, catechins, resveratrol, epigallocatechin-3-gallate (EGCG), genistein and curcumin, to prevent and/or inhibit tumor growth, either alone or in combination with other anticancer drugs and/or other phytochemicals has been documented (de Souza et al., 2005; Justo & Ferreira, 2005; de Souza et al., 2006; Hemalswarya & Doble, 2006; de Souza Queiroz et al., 2007; Newman & Cragg, 2007; de Fátima et al., 2008a; Bailly, 2009; Camargo et al., 2011). In this respect, all-trans-retinoic acid (vitamin A) is now widely used for the treatment of myeloid leukemia (Sanz & Lo-Coco, 2011) and vitamin D is in clinical trial for this disease (Trump et al., 2006). Recently, we provided evidence that photoderivatives of riboflavin, a constituent of the vitamin B complex (vitamin B2), possess strong activity in hematological malignancy as well (de Souza et al., 2006). The molecular mechanism involved the activation of caspase 8 induced by overexpression of Fas and FasL and mitochondrial amplification mechanisms associated with the stimulation of ceramide production by sphingomyelinase and ceramide synthase. In addition, activation of this cascade led to an inhibition of mitogen activated protein kinases c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) kinase (MEK) and ERK and survival mediators [Protein kinase B (PKB/Akt) and inhibitor of apoptosis protein 1 (IAP1)], upregulation of pro-apoptotic Bax and downregulation of cell cycle progression regulators (de Souza et al., 2006). The potential of such vitamin-derived products in solid tumors was also demonstrated in androgen-independent human prostate cancer (PC3) cells (de Souza Queiroz et al., 2007). As reported earlier, riboflavin photoproducts are cytotoxic to these cells in a Fas-FasL-dependent manner. Furthermore, irradiated riboflavin inhibited matrix-degrading proteases, caused downregulation of vascular endothelial growth factor (VEGF) and upregulation of tissue inhibitor of metalloproteinase 1 (TIMP1), suggesting antimetastatic potential (de Souza Queiroz et al., 2007).

The anticancer properties of curcumin, a natural phytochemical obtained from dried root and rhizome of the spice turmeric (*Curcuma longa*), has long been studied, with few analogues showing promising results as future candidates for clinical development (de Fátima et al., 2008a; Ravindran et al., 2009; Agrawal & Mishra, 2010). Decades of research have demonstrated that tumor cell death induced by curcumin occurred by a number of mechanisms, mostly by interfering with multiple cell signaling pathways, including the intrinsic and extrinsic apoptosis pathways, and the NF κ B and phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascades. Furthermore, curcumin can be used for cancer prevention and it also sensitizes cancer cells to radiation and chemotherapeutic drugs (Kunnumakkara et al., 2008; Ravindran et al., 2009).

The flavonoid quercetin, which is abundantly present in fruits, vegetables, wine and tea, has revealed several properties such as antioxidant, antiproliferative and anticancer (Boots et al., 2008; Murakami et al., 2008). Cachexia is a poorly understood syndrome present in already compromised cancer patients, decreasing the quality of life and increasing mortality. Several studies have been performed in an attempt to find an effective way to treat cachexia, but none of the tested therapies has fulfilled expectations. Recently, Camargo and colleagues

(2011), have demonstrated that intraperitoneal injections of quercetin reduced cachexia in rats bearing Walker 256 carcinosarcoma. Moreover, this effect was accompanied by tumor growth inhibition and increased survival. Evaluation of some of the mechanisms involved in quercetin activity showed decreased MMP-2 and VEGF levels in treated animals, suggesting angio-prevention and mitigation of invasion, effects that strongly support the anticancer property of this flavonoid (Camargo et al., 2011).

Even though plants have been an important source of drugs with great chemical diversity, a significant reduction in the number of plant-derived drug candidates occurred since 2000 (Bailly, 2009). Besides the lack of expected efficacy and toxicity, as well as, reduced aqueous solubility and problems with the determination of biological activities of complex extracts, which impair the development process of new drug candidates, issues related to difficulties with sourcing authenticated plant material and the quantity of drug needed for their development are major challenges to be overcome. In addition, the development of effective drugs from naturally occurring agents is time-consuming and requires considerable resources. These limitations, together with the advent of molecular target-based drug discovery programs in the 1990s, significantly impacted the development of the segment of natural product-based pharmacology, leading to a decline in the search for new hits (Schmidt et al., 2007; Bailly, 2009). Interestingly, the percentage of patents involving natural product derivatives remained almost unchanged during this period (Schmidt et al., 2007). Furthermore, despite the introduction of synthetic approaches in the universe of drug discovery, studies demonstrate that natural products and their derivatives continue to play a pivotal role in saving and prolonging the life of millions of patients (Mann, 2002; Newman et al., 2003; Cragg & Newman, 2005; McChesney et al., 2007; Newman & Cragg, 2007; Bailly, 2009). Such incredible better performance of natural products compared to randomly synthesized molecules is the consequence of the common evolutionary roots of plant natural products, enzymes, receptors and proteins, which arise to interact with one another (Schmidt et al., 2007). Thus, the search for drugs from novel biodiversity sources combined with the identification of new targets are still considered as one of the most important strategies to find innovative drug candidates (McChesney et al., 2007; Schmidt et al., 2007; Bailly, 2009), leading to the optimism that novel drugs derived from plants are forthcoming.

3. The microbial world of anticancer drugs

In the world of life organisms the primary metabolism represents the anabolic and catabolic processes that are essential for organism growth and reproduction. In this way, the primary metabolism pathways and the primary metabolites are highly conserved across species, genera, and kingdoms. In contrast, the secondary metabolism works for organism adaptation and secondary metabolites are produced by individual species or genera for specific physiological, social or predatory reasons. These compounds therefore are specie/genera specific and, given the impressive diversity of life organisms on Earth, constitute a valuable source of complex and intricate structures with a wide range of biological activities.

Microbial-derived secondary metabolites are low molecular mass products (<3,000 Daltons) characterized by unusual and complex structures. Indeed, competition for survival and environmental pressures drive the evolution of defense, attack and signaling diversity, which, in turn, determine chemical and biological diversity and potential new drugs. They are represented by peptides, polyketides, carbohydrates, lipids, terpenoids, steroids and alkaloids, most of which used directly or indirectly as scaffolds for antibiotic, antitumor and

cholesterol-lowering drug synthesis. The importance of such compounds in the treatment of a wide range of diseases is demonstrated by the fact that 40% of new drugs discovered since 1980 were derived from natural microbial sources (Koehn & Carter, 2005).

Environmental microbes – mainly actinomycetes, bacilli and filamentous fungi – have an enormous capacity to produce secondary metabolites, which have been exploited for drug discovery. By 2002, microbes were the source for 22,500 bioactive compounds. Of these, 17% were obtained from unicellular bacteria (mainly *Pseudomonas* and *Bacillus*), 45% from filamentous bacteria (*Actinomycetes*) and 38% from fungi (Demain, 2009; Singh & Macdonald, 2010). For over 40 years, natural small organic molecules derived from microbes and plants have played a very important role as established anticancer chemotherapeutics. In particular, microbes have been recognized to contribute significantly to this field. Currently, antibiotics with antitumoral activity have been used in the treatment of cancer patients as the case of anthracyclines (such as doxorubicin), bleomycin, dactinomycin (actinomycin), and mitomycin C (Kingham et al., 2009).

Pericosines A-E are a family of cytotoxic metabolites isolated from *Periconia byssoides* OUPS-N133, a fungus that was collected from the sea hare *Aplysia kurodai*. Among the members of this family of carbasugars, pericosine A is the most important, because it was reported to possess significant inhibitory activity against protein kinase EGFR (epidermal growth factor receptor) and human topoisomerase II, in addition to its antitumor activity against P388 lymphocytic leukemia cell line *in vitro* and *in vivo* (Numata et al., 1997; Yamada et al., 2007). Various reports in literature have shown the efforts of researchers to characterize the structure of pericosine molecules and develop new routes for their synthesis (Usami et al., 2009).

Since 1941, when penicillin was introduced in the market, secondary metabolites of bacteria have been studied as promising drug candidates for the treatment of diverse pathologies, including cancer. Many bacterial products such as proteins, enzymes, immunotoxins, secondary metabolites or even naked DNA can be used or adapted in a proper manner to specifically target cancer cells, causing tumor regression through growth inhibition, cell cycle arrest or apoptosis induction. Interestingly, many bacterial compounds also inhibit cancer metastasis.

Some bacterial enzymes are potential candidate therapeutic agents for cancer treatment. The enzyme arginine deiminase (ADI), found in *Mycoplasma arginine* and *P. aeruginosa* among others, is an example of bacterial product that combat cancer cells through its ability to cause arginine depletion and consequent nutritional stress in cancer cells. Curiously, while arginine is a nonessential amino acid in humans, some cancers, such as hepatocellular carcinoma, melanoma and renal cell carcinomas, do not synthesize arginine, making ADI a promising enzyme for the selective elimination of such cancer cells through arginine deprivation. Furthermore, the crystal structure of ADI demonstrated that this enzyme harbor a putative CARD-like domain (caspase activation domain) with no significant amino acid sequence homology. In this way, it seems that ADI could be a selective inductor of cancer nutritional stress through its enzyme activity, while in the absence of catalytic activity the enzyme could act as a selective inductor of caspase activity and programmed cell death in cancer cells (Barile & Leventhal, 1968; Das et al., 2004). Another bacterial product that exploit cancer metabolism to induce cell death is L-methioninase, a ubiquitous enzyme expressed in all organisms including bacteria, fungi, protozoa, and plants, except in mammals. L-Methioninase is a pyridoxal 5'-phosphate dependent enzyme that catalyzes the direct γ -conversion of L-methionine to methanethiol, α -ketobutyrate, and ammonia. L-Methionine is an essential amino acid with several critical functions, including biosynthesis

of protein, glutathione, and polyamines, in addition to the methylation of DNA, thus regulating gene expression. As in the case of arginine, cancer cells are not able to synthesize methionine and need an external supply of this amino acid to keep alive. Thus inhibiting the use of methionine by cancer cells through L-methioninase has been pointed as a relevant strategy to improve conventional anticancer therapies. However, studies have shown that the therapeutic response of the bacterial enzyme is usually associated with high immunogenicity, low substrate specificity, and hazardous effects to the kidney and liver. In contrast, L-methioninase from eukaryotes may be characterized by their lower immunogenicity reinforcing the need for extensive biochemical and pharmacokinetic characterization of this enzyme from organisms like fungi, which are able to produce it efficiently (El-Sayed, 2010).

Bacterial products can also combat cancer through inhibition of the HDAC enzyme. Romidepsin (FK228), a naturally occurring depsipeptide isolated from *Chromobacterium violaceum*, is a potent HDAC inhibitor with anticancer activity against leukemia, colon cancer and neuroblastoma cell lines, human tumor xenografts and murine tumors, and is therefore expected to be a novel and promising anticancer drug, currently under clinical evaluation in the USA (Ueda et al., 1994; Schrump et al., 2008; Piekarczyk et al., 2009; Mizutani et al., 2010; Panicker et al., 2010). The mechanism of FK228 induction of cancer demise is incompletely known but it seems associated with the ability of this compound to induce hydrogen peroxide synthesis, activation of caspases and programmed cell death (Mizutani et al., 2010). Inhibitors of HDAC are also found in extracts of *Pseudomonas*. Spiruchostatin A (also known as YM753) and B closely resemble FK228, exhibiting greater potency as HDAC inhibitors than several other compounds including FK228, making them promising anticancer agents (Crabb et al., 2008; Shindoh et al., 2008). In addition to FK228, another major product of *C. violaceum* metabolism, named violacein, has been extensively studied for its several biological activities (Durán et al., 2007). Of note, this purple-colored pigment has gained attention for its antitumor properties, which has been demonstrated *in vitro* against a number of cancer cell lines from several histological origins, as well as *in vivo* (Melo et al., 2003; Ferreira et al., 2004; Kodach et al., 2006; Durán et al., 2007; Bromberg et al., 2010). Moreover, studies have shown the ability of violacein to induce apoptosis by mechanisms that include modulation of a number of signaling pathways and the generation of oxidative stress (Melo et al., 2003; Ferreira et al., 2004; Kodach et al., 2006; Durán et al., 2007; Bromberg et al., 2010). Importantly, treatment of Ehrlich ascites tumor (EAT)-bearing mice with micromolar doses of violacein inhibited the tumor volume, the number of viable tumor cells and increased survival, differing from other works with natural products in the literature which spend high doses of the compounds. In addition to present a lower toxicity to normal cells *in vitro*, hematology, biochemistry and histopathological analyses of liver and kidney of mice receiving daily intraperitoneal doses of violacein up to 1 mg/kg indicated that treatment with violacein is well tolerated and does not cause hematotoxicity nor renal or hepatotoxicity (Durán et al., 2007; Bromberg et al., 2005; Bromberg et al., 2010). At this point, it is important to mention that the Amazonian strain of *C. violaceum* (from Rio Negro, Brazil) produces violacein at a higher rate compared to other strains, including the ATCC 553 strain, as well as other bacteria, such as *Janthinobacterium lividum* and *Alteromonas luteoviolacea*. Also, using the Brazilian strain, the biotechnological process of violacein production was optimized by our group, resulting in higher yields of the compound (Durán et al., 2007).

Immunotoxins constitute another source of bacterial compounds with potential use in the antitumoral therapies. Exotoxin A-immunotoxins, such as that produced by *P. aeruginosa*,

kill cancer cells by binding specifically to overexpressed cell surface receptors, which carries them into the cell, where they catalyze the ADP-ribosylation of the eukaryotic elongation factor 2 (eEF-2) in host cells, ultimately affecting protein synthesis and inducing programmed cell death. Clinical trials with different exotoxin A-immunotoxins have demonstrated that such bacterial products present better results in eliminating cells derived from hematological malignancies over those originated from solid tumors (Wolf & Elsasser-Beile, 2009; Bernardes et al., 2010). *P. aeruginosa* has also been demonstrated to produce another immunoglobulin-like product named azurin, a water soluble enzyme involved in the electron transport chain. Azurin has its secretion enhanced from *P. aeruginosa* in response to the presence of human cancer cells. Furthermore, azurin is known to enter preferentially into cancer cells and has multiple antitumor activities (Mahfouz et al., 2007). Azurin binds and stabilizes the tumor suppressor protein p53 besides its ability to bind and inhibit the activity of several Ephrin (Eph) receptor tyrosine kinases, a family of extracellular receptor proteins known to be upregulated in many tumors. Azurin-induced stabilization of p53 results in the increased expression of proapoptotic proteins, thus contributing for the triggering of programmed cell death in cancer cells (Xu et al., 2010). Binding and inhibition of Eph receptors by azurin avoid the activation of cellular signaling pathways that stimulate proliferation, migration, invasion and angiogenesis of many types of human tumors (Chaudhari et al., 2007). Interestingly, *P. aeruginosa* not only secretes azurin, but simultaneously releases in the growth medium an extrachromosomal DNA element rich in stretches of unmethylated CpG dinucleotides. This molecule demonstrates antitumor activity through TLR9 activation and cytokine/chemokine production and allows cancer cell death. In addition to *P. aeruginosa* other bacteria, such as *Mycobacterium bovis*, also secrete unmethylated CpG dinucleotides with antitumor activities (Mahfouz et al., 2007). Recently, preclinical studies were done with the azurin-p28 (NSC 745104), an amphipathic, 28 amino acid fragment (aa 50-77) of the azurin. The results demonstrated that p28 does not exhibit preclinical immunogenicity or toxicity, has a similar metabolic profile among species, and is therapeutic in xenograft models (Xu et al., 2010).

The Ras GTPases (HRAS, NRAS and KRAS) are the founding members of a large superfamily of monomeric small (20-25 kDa) GTPases that regulate diverse cellular processes, including those associated with cancer progression, such as proliferation, differentiation, cell survival and migration. Mutational activation of Ras is found in about 33% of human cancers, making these proteins important targets for reaching successful cancer treatments (Vigil et al., 2010). Activation of the Ras oncogene requires the linkage of a farnesyl group, allowing the protein anchorage to the cell membrane and the subsequent interaction with guanosine exchange factors located in receptor-associated complexes. Some Ras family proteins such as KRAS can be alternatively activated through the addition of a geranylgeranyl moiety. Farnesyltransferase inhibitors (FTI) are metabolites capable of blocking this step, thus impairing Ras activation, even in the presence of a mutant Ras. Several FTIs of microbial origin have been discovered in the past few years specially among fungi (Vilella et al., 2000; Iwasaki & Omura, 2007). Fungi, like *Aspergillus terreus*, *Monascus ruber* and *Pleurotus ostreatus*, produce lovastatin, a member of the drug class of statins, which blocks Ras activation through inhibition of farnesylation and induces apoptosis (Laezza et al., 2008). Manumycin A, a competitive farnesyltransferase inhibitor, is an antibiotic detected in the culture media of a *Streptomyces* strain that has shown both *in vitro* cytotoxic activity against several cell lines (human pancreatic tumor, breast and colon cancers, thyroid carcinoma, leukemias, myeloma and hepatocellular carcinoma) and *in vivo* against human

cancer xenograft models (Bernardes et al., 2010). Gliotoxin is a member of the epipolythiodioxopiperazine class of toxins and is both the major and the most potent toxin produced by *Aspergillus fumigatus*. Gliotoxin and KT7595, a gliotoxin derivative, inhibited DNA synthesis, cellular proliferation and Ras farnesylation in human colon carcinoma, hepatoma and gastric carcinoma (Nagase et al., 1997).

Many secondary metabolites from bacterial origin have entered clinical trials as antitumor drugs. Prodiginines and its derivatives, like prodigiosin and obatoclax, demonstrate powerful and selective anticancer activity against several cancer-derived cell lines, while little or no activity has been documented against normal cells. Importantly, these bacterial metabolites seem to be resistant to multidrug pumps that are often responsible for inducing resistance to other anticancer agents (Nguyen et al., 2007). The epothilones were initially isolated from the slime mold *Sorangium cellulosum* as antifungal compounds. Today, this class of compounds is recognized by its valuable action as microtubule-stabilizing agents that have demonstrated antitumor activity in taxane-resistant models and in cancer cells displaying MDR disease. Natural epothilones B and D and many derivatives are under investigation in several pre-clinical, and phase I and II clinical trials. At this time, ixabepilone (BMS) is the sole drug to reach the market, although sagopilone (Bayer) is currently in phase II clinical trials (Beutler, 2011; Nobili et al., 2011).

Cancer metastasis occurs during tumor progression and causes 90% of human cancer deaths. Many bacteria, like *Staphylococcus aureus*, naturally produce several chemokine/adhesion receptor inhibitors, which actions avoid cancer cell migration. Staphylococcal superantigens-like (SSL) molecules, such as SSL10 and SSL5, showed to bind specific receptors displayed by cervical and leukemia cells, inhibiting their ability to spread through other tissues in the body (Walenkamp et al., 2009; Walenkamp et al., 2010).

Finally, cancer treatment can also be done using live, attenuated or engineered bacteria. *Clostridium*, *Bifidobacterium*, *Salmonella*, *Mycobacterium*, *Bacillus* and *Listeria* have the ability to selectively target cancer cells and act as anticancer agents. They grow in the hypoxic core region of solid tumors, where most of the time radiation or chemotherapy is unsuccessful. In addition, thanks to their selectivity for the tumor microenvironment, these bacteria are also promising vectors for delivering therapeutic genes for anticancer therapies (Bernardes et al., 2010).

As discussed here, microbes constitute a great source of anticancer therapeutic compounds. Indeed microbes are the most diverse (both structurally and metabolically) and abundant group of organisms and account for 60% of the Earth's biomass. However, genomic studies indicate that certain groups of bacteria and fungi have dozens of secondary metabolite pathways that are not expressed under standard laboratory growth conditions. In fact, >99% of environmental microbes are uncultivable, limiting the discovery of new products (Singh & Macdonald, 2010). In this way, understanding community and functional diversity is essential for exploiting the potential of microbes as a source of new drugs. Recently, with the advent of new technologies and genomic data, the discovery of novel drugs from uncultivable microbes has become a reality that brings new opportunities for the development of new anticancer drugs. In particular, metagenomics has been highlighted as a promising strategy for this goal. Metagenomics allows the extraction of total genetic materials from environmental samples followed by its transferring into new host cells, mainly *Escherichia coli*, to generate metagenomic libraries. Using these libraries it is possible to study structural and functional diversity by DNA sequencing or to search for new products based on sequence mining or functional expression without the need for culturing

microbes. In addition, whole genome sequencing have contributed for the discovery of new secondary metabolites with therapeutic effects, as the case of the anticancer drugs diazepinomicin and Eco-7942, discovered from the genome mining of *Micromonospora* and *Streptomyces spp* (Singh & Macdonald, 2010). Furthermore, secondary metabolite pathways, which are not expressed under standard laboratory growth conditions, can be synthesized in the presence of neighboring microbes; a strategy named mixed fermentation. Research to date indicates that mixed fermentation can result in increased antibiotic activity in crude extracts, increased yield of previously described metabolites as well as previously undetected metabolites, analogues of known metabolites resulting from combined pathways and, importantly, induction of previously unexpressed pathways for bioactive constituents (Pettit, 2009). In conclusion, microorganisms constitute a rich source of potential antitumor compounds. Exploring this diverse group of living organisms is a challenge, but a promising strategy. In addition, it is certain that the use of genetic approaches and mixed fermentation will open new opportunities for the discovery of novel therapeutic compounds “hidden” in the genetic information load by such organisms.

4. Venoms and toxins as potential anticancer drugs

Anticancer therapy is one of the main areas for the use of proteins and peptides originating from animals. Some of these proteins or peptides, when isolated, may bind specifically to cancer cell membranes, affecting the migration and proliferation of these cells. Venoms and toxins from snakes, scorpions, frogs, spiders, bee, wasps, ants, centipedes and caterpillars may hold the promises for treating many types of malignancies, especially with the demonstration of complete remission of cancer cells after treatment with molecules derived from animal venom. However, studies focusing on the mechanisms by which these venoms act are still very recent, and much has yet to be found out about these molecules.

4.1 Snake venom and toxins

The presence of anticancer enzymes in snake venom has been reported and phospholipase activity, found in cobra venom, was ascribed to be the enzyme with anticancer potential (Braganca & Khandeparker, 1966). Phospholipase B in the venom of the Australian elapid snake was cytotoxic to cultured rhabdomyosarcoma cells (Bernheimer et al., 1987). Phospholipase A2 (PLA2), isolated from *Bothrops newweidii* venom, has cytotoxic activity in B16F10 melanoma cells (Daniele et. al., 1997), and two toxic PLA2 have been purified from the Indian cobra (*Naja naja naja*) venom, which are neurotoxins presenting cytotoxicity against EAT cells (Basavarajappa & Gowda, 1992).

The Arg-Gly-Asp (RGD)-containing disintegrins are non-enzymatic proteins that inhibit cell-cell interactions, cell-matrix interactions, and signal transduction. Disintegrins also have the ability to inhibit several aspects of tumor cell behavior, both *in vitro* and *in vivo*, including adhesion, migration, invasion, metastasis and angiogenesis (Swenson et al., 2007). A disintegrin named Salmosin was isolated from Korean snake venom and effectively suppressed growth of metastatic tumor, as well as solid tumor in mice (Kang et al., 1999). Contortrostatin, a dimeric disintegrin isolated from Southern copperhead snake venom, prevented invasion of human breast cancer cells through an artificial matrigel basement membrane. Phospholipases, disintegrins and other enzymes of snake venom could progress as a therapeutic tool in the treatment of various cancers and thrombotic diseases in the near future (Gomes et al., 2010).

4.2 Scorpion venom and toxins

The repertoire of scorpion venoms presents a complex mixture of a large variety of molecules that play an important role in the defense and capture of prey. They contain mucopolysaccharides, phospholipases, hyaluronidases, protease inhibitors, low molecular weight molecules such as serotonin and histamine, histamine releasing peptides, inorganic salts, mucus, and many basic small proteins known as neurotoxic peptides (Martin-Eauclaire & Couraud, 1995). The neurotoxic peptides have specific interaction with ion channels, making scorpion venom capable of binding specifically to certain types of cells, such as cancer cells. Therefore, this type of venom holds molecules that are of interest to the pharmaceutical industry in terms of drug design and development. Scorpion toxins are important molecules to fight cancer, since they have shown both *in vitro* and *in vivo* effects in cancer cells, as well as in phase I and phase II clinical trials. The most studied peptides are the long chain toxins composed of 60–70 amino acid residues cross-linked by four disulfide bridges. These peptides activate mainly Na⁺ channels. They are divided in two major classes: a-toxins and b-toxins (Possani et al., 2001). Short chain toxins with 30–40 amino acid residues cross-linked by three disulfide bridges form another polypeptide family, acting mainly upon K⁺ or Cl⁻ channels. The venom also contains peptides without disulfide bridges that act in other targets besides ion channels (Goudet et al., 2002).

Chlorotoxin (Cltx) is a peptide from the species *Leiurus quinquestriatus* that inhibits chloride influx in the membrane of glioma cells. This peptide binds only to glioma cells, displaying little or no activity at all in normal cells. The toxin appears to bind MMP-2 (Deshane et al., 2003; Veisheh et al., 2007), an extracellular matrix enzyme that exhibits gelatinase activity. MMP-2, a proteinase involved in tumor invasion, is specifically upregulated in gliomas and related cancers, but is not expressed in normal brain cells. Cltx binds effectively to MMP-2 endogenously expressed by glioma cells (Deshane et al., 2003; Veisheh et al., 2007) and its exposure to Cltx results in loss of gelatinase activity, disruption in chloride channel currents, reduction in both MMP-2 and chloride channel expressions, and internalization of chloride channels (Veisheh et al., 2007). Thus, these data indicate that venoms from scorpions represent important candidates for the development of new clinical treatments against tumors. However, further studies are necessary to isolate and characterize their active molecules (Heinen et al., 2011).

4.3 Spider venom and toxins

Spider venoms contain a complex mixture of proteins, polypeptides, neurotoxins, nucleic acids, free amino acids, inorganic salts and monoamines that cause diverse effects in vertebrates and invertebrates (Ori & Ikeda, 1998). Regarding the pharmacology and biochemistry of spider venoms, they present a variety of ion channel toxins, novel non-neurotoxins, enzymes and low molecular weight compounds (Rash & Hodgson, 2002). The enzyme phospholipase D has been isolated and purified from the venom of brown spider that displays high hemolytic activity (Silva et al., 2004), which could present anticancer action. Also, hyaluronidases found in the venom of some spiders could be used to increase tissue permeability, thus facilitating the penetration of some drugs, or even being employed directly as antitumor agents (Girisk & Kemparaju, 2007). Other toxins that have been isolated are the oxyopinins from the wolf spider *Oxyopes kitabensis*, which form pores in lipid membranes (Corzo et al., 2002) and could also be considered as candidates for anticancer therapy (Shaposhnikova et al., 1997).

Psalmotoxin 1 isolated from a West Indies tarantula, is a 40-amino acid peptide that inhibits cation currents mediated by acid-sensing ion channels (ASIC) (Escoubas et al., 2000). Bubien and colleagues (2004), using this molecule, inhibited Na^+ currents in high-grade human astrocytoma cells (glioblastoma multiforme, or GBM) (Bubien et al., 2004). The antitumor activity of a potent antimicrobial peptide isolated from hemocytes of the spider *Acanthoscurria gomesiana*, named gomesin, was tested *in vitro* and *in vivo* (Rodrigues et al., 2008). Gomesin showed cytotoxic and antitumor activities in cell lines, such as melanoma, breast cancer and colon carcinoma.

4.4 Toad and frog venoms and toxins

The experiments with the skin extract (TSE) of common Indian toad (*Bufo melanostictus*, Schneider) exhibited significant antineoplastic activity against EAT cells and human leukemia cell lines U937 and K562 (Giri & Gomes, 2004). Leukemia growth inhibition due to TSE was mediated by cell cycle arrest in G1 phase. A large number of early and late apoptotic cells were found in TSE-treated leukemia cells as compared to the untreated cells (Giri et al., 2006). Bufadienolides are molecules present in the skin of toad of the genus *Bufo*. The cytotoxic activity of toad bufadienolides was described in primary liver carcinoma PLC/PRF/5 cells (Kamano et al., 1998). Cinobufagin was isolated from *Bufo siccus* and showed *in vitro* inhibitory effect in five types of human cancer cells (Chen et al., 1998). The cytotoxic activity of bufalin and cinobufagin in prostate cancer cells was associated with constant increase in Ca^{2+} , leading to apoptosis (Yeh et al., 2003). Brevinin-2R, a non-hemolytic defensin has been isolated from the skin of the frog *Rana ridibunda*. It showed pronounced cytotoxicity towards malignant cells, including Jurkat (T-cell leukemia), B-cell lymphoma, colon carcinoma, fibrosarcoma, breast adenocarcinoma and lung carcinoma (Ghavami et al., 2008).

4.5 Bee and wasp venoms and toxins

The melittin and PLA2 are two substances that have been isolated and characterized from bee venoms. Several studies have been published showing their antitumoral effects (Ownby et al., 1997). The melittin enzyme exhibits antimicrobial activities and proinflammatory effects (Sumikura et al., 2003), besides inducing perturbations in the cell membrane and damage to enzyme systems (Wade et al., 1990). Several cancer cells, including leukemia, renal, lung, liver, prostate, bladder, and mammary cancer cells, can be targets of melittin (Son et al., 2007). Melittin has also been reported as a PLA2 activator, increasing the calpain activity and cell necrosis in the hepatocellular carcinoma (Arora et al., 1996).

Research involving wasps shows a complex gland responsible for the production and injection of venom, which exhibits physiological, pharmacological and biochemical activities, playing a role in a variety of survival mechanisms such as defense against predators and prey capture, among others (Yu et al., 2007). Mastoparan, a peptide obtained from wasp venom has been reported to induce the formation of the mitochondrial permeability transition pore (Pfeiffer et al., 1995), and based on its capacity to induce mitochondrial permeability and the lack of specificity for tumor cells, Yamada and colleagues (2005) encapsulated this molecule with a transferrin-modified liposome with a pH sensitive fusogenic peptide (GALA), for selective delivery to mitochondria of K562 cells. This liposome targeted cells having high expression of transferrin receptors, which mediate its internalization by endocytosis. Results have shown that the encapsulated mastoparan was able to release cytochrome *c*, indicating its potential as an anticancer agent (Yamada et

al., 2005). Fujiwara and colleagues (2008) determined the structure of an anticancer molecule from *Vespa simillima*. This molecule is a biologically active quinone, 7,8-seco-*p*-ferruginone (SPF), which exhibited growth inhibitory effect in rat liver cancer cells. The analyses suggest that its cytotoxic activity is related to the morphological changes that induce apoptosis of cells exposed to this molecule (Fujiwara et al., 2008).

4.6 Ant, centipede and caterpillar venoms and toxins

The solenopsin A is a primary alkaloid from the fire ant *Solenopsis invicta*, having antiangiogenic activity. In order to analyze the antiangiogenic activity, studies were conducted to investigate the ability of this toxin to inhibit a series of kinases involved in this process (Bai et al., 2003).

An important study reporting centipede venom antitumor action has shown that a synthetic compound, Man β (1-4)[Fuc α (1-3)]Glc β 1-Cer, (glycosphingolipid 7), from *Parafontaria laminate armigera*, exhibits antiproliferative effects in melanoma cells. This compound suppressed the activation of the focal adhesion kinase (FAK) and ERK pathways, which are both involved in melanoma cell proliferation (Sonoda et al., 2008).

The cecropins are a group of peptides isolated from the hemolymph *Hyalophora cecropia* that display antimicrobial activity (Andreu et al., 1985), and have been used as potent anticancer agents against a variety of tumor cell lines (Suttmann et al., 2008). The mechanism of action of cecropins against tumor cells appears to involve the formation of pores in the membrane of cells (Chen et al., 1997).

Lonomia obliqua induces a hemorrhagic syndrome in humans that accidentally get in touch with its urticating spines. Many molecules from the venom of *L. obliqua* have been isolated and characterized, including fibrinogenases (Pinto et al., 2006; Veiga et al., 2003), hyaluronidases (Gouveia et al., 2005) and an antiapoptotic protein (Souza et al., 2005). The PLA2 hydrolyzes the sn-2 bond in phospholipids, generating fatty acids and lysophospholipids. The so formed lysophospholipids affect the lipid bilayer of cell membranes, leading to cell lysis, while the generated arachidonic acid promotes the activation of caspases and release of cytochrome *c*, culminating in apoptosis in some cell types (Zhao et al., 2002).

It is clear from these data that venoms and toxins from animals can present important pharmacological activities in human physiology. The substances found in the venom of these animals present great potential as antitumor agents. The understanding of the molecular basis of the envenomation processes caused by venoms from snakes, spiders, scorpions, frog, toad, caterpillars and bees are important for the diagnosis and treatment of the clinical profile, but research in the near future with venoms and toxins will definitely add information in the area of cancer biology.

5. Anticancer drugs from marine life

The biological diversity of the marine environment is an untapped source of compounds with several bioactivities and, therefore, is an extraordinary resource for the discovery of new anticancer drugs. The marine environment corresponds to 95% of the biosphere, and all except one of the 33 animal phyla are represented in aquatic environments. In addition, there are several organisms that are found in marine environment like seaweed, jellyfishes, and anemones. The majority of marine species are found near the coast, where there is a high number of species, being one of the most productive environments, with an impressive biodiversity. The large number of organisms living in this habitat is constantly fighting. One of the weapons used in these battles are molecules that are synthesized by marine species.

Many of these molecules have important activities for humans, including medicinal properties, such as antitumor. Invertebrates and seaweeds are sources of anticancer drugs from marine resources (Lin et al., 2010). In this section, we highlight the past and current status of several marine anticancer compounds from different marine groups.

5.1 Anticancer secondary metabolites

The past decade witnessed a dramatic increase in the number of preclinical anticancer lead compounds from diverse marine life entering human clinical trials and several mechanisms of action were suggested. An example is agosterol A, which reversed the resistance to colchicine in KB-C2 cells (P-glycoprotein (P-gp)-mediated multidrug resistant cells) and also the resistance to vincristine in KB-CV60 cells (multidrug resistance-associated protein (MRP1)-mediated multidrug resistant cells), because it directly inhibited drug efflux through P-gp and/or MRP1 pumps (Aoki et al., 2001).

Cephalostatin, a bis-steroidal isolated from the tube worm *Cephalodiscus gilchristi*, induces selectively second mitochondria-derived activator of caspase (Smac)/direct IAP binding protein with Low pI (DIABLO), but no cytochrome *c* release from mitochondria. Nevertheless, caspase 9 is required for apoptosis induction. Interestingly, caspase 9 is activated without the participation of the apoptosome (Rudy et al., 2008). Recently, its enantioselective synthesis was described (Fortner et al., 2010).

Bisramine A is a polyketide derivative isolated from ascidian such as *Lissoclinum bistratum*, but it is also found in a tunicate *Trididemnum cyclops* (Murphy et al., 2009). This compound disrupted the actin cytoskeleton, depolymerized F-actin *in vitro* and bound directly to monomeric G-actin (Rizvi et al., 2010).

Laulimalide was isolated in 1999 from the marine sponge *Cacospongia mycofijiensis*. This molecule stabilizes microtubules in a similar manner to paclitaxel, but it does not bind to the taxoid site on tubulin. It also kills cells resistant to epothilones and paclitaxel (Pryor et al., 2002; Khrapunovich-Baine et al., 2011). Other pharmacological information of several marine intermediate metabolites, with previously determined or undetermined mechanisms of action, is summarized in Table 1.

5.2 Anticancer sulfated polysaccharides

Marine sulfated polysaccharides are found mainly in seaweeds (green, red and brown seaweeds). The well known antitumor polysaccharides from red seaweed are homogalactans, and from brown algae are α -L-fucose-containing sulfated homo and heteropolysaccharides, called fucan and fucoidan, respectively. There is a greater incidence of anticoagulant activity in extracts of the brown algae compared to red and green algae. Few studies describe the presence of anticancer sulfated polysaccharides in green algae, which are mainly heteropolysaccharides (Jiao et al., 2011).

The λ -carragennan (sulfated galactan) from the red seaweed *Chondrus ocellatus* did not inhibit sarcoma S180 and H22 hepatocarcinoma cells in culture. However, when these cells were implanted subcutaneously in mice, the λ -carragennan inhibits the growth of the tumors, supporting a role for the immune system in the antitumor activity of these compounds (Zhou et al., 2004). A sulfated galactan, porphyran, extracted from *Porphyra yezoensis*, induces caspase 3 activation and apoptosis in AGS gastric cancer cells without affecting the growth of normal cells (Kwon & Nam, 2006). A sulfated heteropolysaccharide obtained from the green seaweed *Capsosiphon fulvescens* inhibits AGS gastric cancer cell

Source		
Sponges	Compound	Mechanism of action
<i>Halichondria okadai</i>	Halichondrin B	Inhibits tubulin polymerization
<i>Discodermia dissolute</i>	Discodermolide	Induces a senescent phenotype
<i>Pseudoceratina purpurea</i>	Psammaplins	Activates PPR γ ; inhibits DNMT and HDAC
<i>Hemiassterella minor</i>	Hemiassterlin	Antitubulin activity
<i>Agelas mauritianus</i>	Agelasphin	Immunostimulant compound
<i>Jaspis digonoxea</i>	Bengamide B derivative	Methionine aminopeptidase
<i>Xestospongia sp.</i>	Aaptamine	G2/M cell cycle arrest; affects p21 activity
<i>Reniera sarai</i>	Alkylpyridinium salts	Cholinesterase inhibitor
<i>Mycale adhaerens</i>	13-Deoxytedanoli	Binds to the 60S large ribosomal subunit and inhibits polypeptide elongation
<i>Petrosia sp.</i>	Dideoxypetrosynol	Caspases 3 and 9 activation; degradation of poly(ADP-ribose) polymerase (PARP)
<i>Cliona varians</i>	CvL lectin	Caspase-independent cell death; Lysosomal cathepsin B-mediated cell death
Tunicates	Compound	Mechanism of action
<i>Ecteinascidia turbinata</i>	Ecteinascidin 743	Tubulin inhibition
<i>Aplidium albicans</i>	Dehydrodidemnin B	Ornithine decarboxylase; interruption of tumor cell cycle at G1 and G2.
<i>Trididemnum solidum</i>	Didemnin B	Protein synthesis inhibitor
<i>Didemnum cuculiferum and Polysyncraton lithostrotum</i>	Vitilevuamide	Inhibits tubulin polymerization
<i>Cystodytes dellechiaiei</i>	Ascididemin	Telomerase inhibitor; activation of caspase 2 and JNK
Molluscs	Compound	Mechanism of action
<i>Dolabella auricularia</i>	Dolastatin 10; Synthadotin	Binds to tubulin
<i>Elysia rufescens</i>	Kahalalide F	Induces cell death via oncosis, preferentially in tumor cells
<i>Lamellaria sp.</i>	Lamellarin D	Inhibitor of DNA topoisomerase I
<i>Mactromeris polynyma</i>	Spisulosine	Promotes intracellular ceramide accumulation and Protein kinase C ζ (PKC ζ) activation
<i>Ecteinascidia turbinata</i>	Trabectedin	Production of superoxide near the DNA strand, resulting in DNA backbone cleavage
<i>Aplysia kurodai</i>	Aplyronine A	Binds to hydrophobic cleft in actin molecule

Bacterium	Compound	Mechanism of action
<i>Lyngbya majuscula</i>	Laxaphycins A & B	Increases polyploidy
<i>Salinispora tropica</i>	Salinosporamide A	Proteasome inhibitor
Several species	Cryptophycin	Antimicrotubule agent
<i>Symploca sp.</i>	Belamide A	Antimitotic
<i>Lyngbya majuscula</i>	Curacin	Cytotoxic activity in H-460 human lung carcinoma cells
<i>Micromonospora marina</i>	Thiocoraline	DNA-polymerase inhibitor
Other	Compound	Mechanism of action
<i>Clavularia viridis</i> (soft coral)	Bromovulone	Activation of caspase 12
<i>Clavularia viridis</i>	Clavulone II	Induces the disruption of mitochondrial membrane potential and activates caspases 8, 9 and 3; downregulates cyclin D1 expression and promotes cell cycle arrest in G1 phase
<i>Squalus acanthias</i> (shark)	Squalamine	Induces phospholipid bilayer disruption
<i>Bugula neritina</i> (bryozoans)	Bryostatin	Modulator of several protein kinases
<i>Pentacta quadrangulari</i> (sea cucumber)	Phillinopside A	Cytotoxic and antiangiogenic
Several fungus	Verrucarin A	Protein synthesis inhibitor

Table 1. Marine anticancer compounds from several sources and their suggested mechanisms of action (Amador et al., 2003; Simmons et al., 2005; Paleari et al., 2006; Mayer & Gustafson, 2008; Sánchez et al., 2008; Queiroz et al., 2009; García et al., 2010; Taniguchi et al., 2010).

proliferation and induces apoptosis by inhibiting the insulin-like growth factor 1 receptor signaling and the PI3K/Akt pathway (Know & Nan, 2007). Sulfated polysaccharides from *Caulerpa cupressoides*, *Caulerpa prolifera*, *Caulerpa sertularioides* and *Codium isthmocladum* have also been demonstrated to inhibit HeLa cell proliferation (Costa et al., 2010). Sulfated polysaccharides from *L. saccharina*, *L. digitata*, *F. serratus*, *F. distichus* and *F. vesiculosus* strongly blocked MDA-MB-231 breast carcinoma cell adhesion to platelets, an effect that might have critical implications in tumor metastasis (Cumanshi et al., 2007). In addition, a fucan from *Spatoglossum schröederi* shows anti-adhesive activity by binding directly to fibronectin (FN), and blocking FN sites that are recognized by cell surface ligands, possibly the integrin family of proteins (Rocha et al., 2005).

The heterofucan from *Undaria pinnatifida* induces apoptosis in A549 human lung carcinoma cells through downregulation of the antiapoptotic protein Bcl-2 and activation of caspases. This heterofucan also downregulated p38 mitogen-activated potein kinase (p38 MAPK) and PI3K/Akt, while the ERK1/2 pathway was activated (Boo et al., 2011). Additionally, literature reports that fucans are able to induce cell death by mechanisms independent of caspases. For instance, Aisa and colleagues (2005) showed human lymphoma HS-Sultan cell death induced by a fucan from *Fucus vesiculosus* through activation of the ERK signaling pathway (Aisa et al.,

2005). Hyun and colleagues (2009) also provide evidence that the proapoptotic effect of this fucan is mediated by ERK and p38 MAPK activation, and PI3K/Akt inhibition in HCT-15 colon carcinoma cells (Hyun et al., 2009). Moreover, *F. vesiculosus*-derived fucan also affected the NF κ B pathway (Nakamura et al., 2006). Recently, a heterofucan from *Sargassum filipendula* induces apoptosis in HeLa cells mainly by the mitochondrial release of apoptosis-inducing factor (AIF) into cytosol. Additionally, in SF-1.5v cells, the expression of Bcl-2 is decreased, in contrast to the increased expression of the apoptogenic protein Bax (Costa et al., 2010).

The marine environment is a major source of anticancer molecules. In recent years, more than 2,000 molecules were found. Here we describe a few with known mechanisms of action. They represent potential candidates for the treatment of malignant disease, either to be used as single agents, or as part of a combination regimen. In addition, they provide a very good tool to discover novel targets, which might be important in the understanding and treatment of chemoresistant cancer. However, there are marine environments that are very poorly studied, as regions below 100 m depth. Besides this, many marine microorganisms cannot yet be cultivated. These indicate that there are still several marine anticancer agents to be discovered.

6. Drug design based on natural products

As highlighted in the above sections, natural products are still major sources of innovative therapeutic agents for cancer, as well as for infectious diseases, lipid disorders and immunomodulation (Cragg et al., 1997; Newman et al., 2003; Butler, 2004; Lee, 2004; Butler, 2005; Newman & Cragg, 2007). However, the complexity of many natural products as well as the fact that they are present in the nature can limit the scope for making chemical modifications to optimize their therapeutic use. Moreover, obtaining a renewable supply of active compounds from biological sources may be problematic. Despite these barriers, total synthesis of the potent anticancer natural product discodermolide, recently performed in multigram scale (Mickel et al., 2004a; Mickel et al., 2004b; Mickel et al., 2004c; Mickel et al., 2004d; Mickel et al., 2004e), demonstrates that synthetic organic chemistry is a powerful tool for increasing efficiency of natural products of limited supply, those with very complex structures or those that present no biological desired properties (Nicolaou & Sorensen, 1996; Nicolaou & Snyder, 2003). In this chapter section, we describe two examples of chemical modifications done in natural products core to improve their activity and/or effectiveness. The molecules in focus are podophyllotoxin and goniothalamin, natural products that exhibit anticancer properties. The former substance was the lead compound for the development of etoposide, teniposide and etopophos, three widely used anticancer drugs, while goniothalamin still have work to do on it to get good clinical effects *in vivo*. Both molecules exemplify how important is the biodiversity as a source of chemical weapons to fight cancer.

6.1 Podophyllotoxin: from natural sources to drugs

Podophyllin, a resin produced by species of the genus *Podophyllum* (Berberidaceae), is traditionally known to have biological properties such as purgatives, antihelminthic, vesicant, antiproliferative, anti-venereal warts, and anti-cough agents (For excellent reviews of the historical aspects of the podophyllotoxins see: Imbert, 1998; Canel et al., 2000; Gordaliza et al., 2004). The major component of podophyllin, podophyllotoxin (Fig. 1), was isolated from this resin in 1881 by Podwysotszki (Podwysotszki, 1881 and 1882). Among all biological properties of podophyllotoxin, its antitumor activity is the most explored.

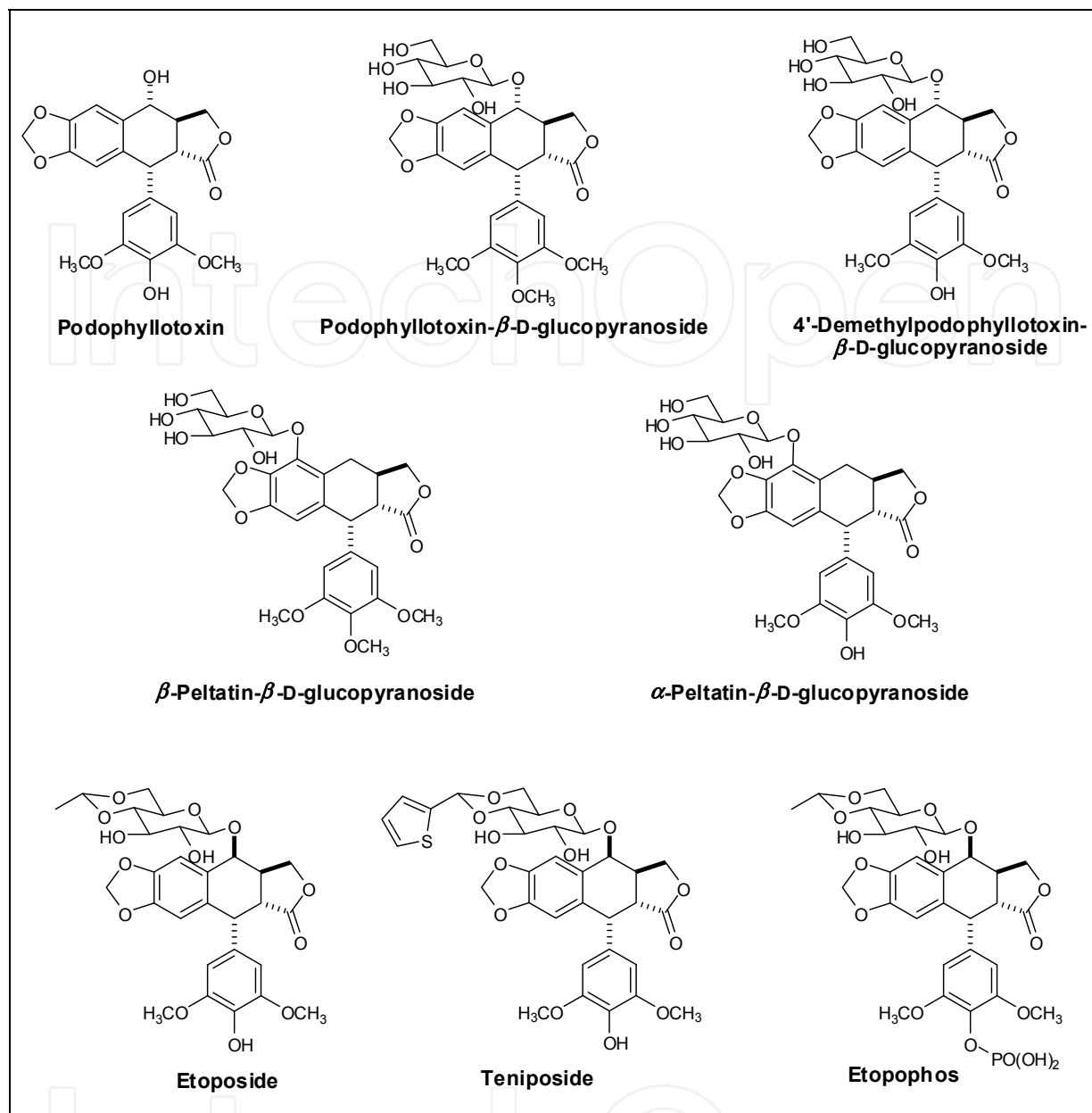


Fig. 1. Structure of podophyllotoxin, glycosides and synthetic derivatives.

Podophyllotoxin is effective in the treatment of Wilms' tumor, genital tumors, non-Hodgkin and other lymphomas, and lung cancer (Utsugi et al., 1996; Subrahmanyam et al., 1998; Liu et al., 2007). However, the gastrointestinal toxicity of this compound was unacceptable (Greenspan et al., 1950; Leiter et al., 1950). Inspired by the potential antitumor activity of podophyllotoxin, the chemists Hartmann F. Stähelin and Albert von Wartburg, working at the Sandoz Company in the mid-1950s, synthesized a large number of podophyllotoxin-derivatives aiming to obtain analogues more active, more water soluble and exhibiting less gastrointestinal toxicity (Stähelin & von Wartburg, 1991; Canel et al., 2000). Their first thought was that glycoside derivatives may be present in the plant and that such derivatives may be less toxic and certainly less hydrophobic than the corresponding aglycones. Indeed, by modifying the procedures of extraction of podophyllin, these chemists were able to isolate four novel glycosides: podophyllotoxin- β -D-glucopyranoside, 4'-

demethylpodophyllotoxin- β -D-glucopyranoside, β -peltatin- β -D-glucopyranoside, α -peltatin- β -D-glucopyranoside (Fig. 1) (Stähelin & von Wartburg, 1991) and these glycosides were more soluble and less toxic. However, the antitumor activities of glycosides were also reduced. Efforts were then directed to chemically modify the glycosides to enhance their cytotoxic activities against cancer cells and from this task force, a range of nearly 600 podophyllotoxin-derivatives were synthesized (Canel et al., 2000).

Two semisynthetic podophyllotoxin-derivatives etoposide and teniposide (Fig. 1), products of condensation of 4'-demethylpodophyllotoxin- β -D-glucopyranoside with acetaldehyde and 2-thiophenecarboxaldehyde, respectively, showed to have good clinical effects against cancer cells (Stähelin & von Wartburg, 1991 and cited references). Additionally, etoposide and teniposide, have potent cytotoxicity in several cancer cell lines, including testicular and small cell lung cancer, lung cancer, lymphoma, leukemia and Kaposi's sarcoma; however, they were still less soluble than the corresponding glycoside (Gordaliza et al., 2004). To overcome solubility problems, the Bristol-Myers Squibb Co., Princeton, New Jersey, USA, developed the etoposide phosphate derivative (etopophos®), which was better suited for intravenous administration. In 1996 the US Food and Drug Administration approved this prodrug for having similar pharmacological and pharmacokinetic profiles of the parent compound, but different solubilities. In fact, the bioavailability *in vivo* was 1,250-fold increased using this prodrug, which is an important improvement of etoposide formulation (Schacter et al., 1994; Budman, 1996; Greco & Hainsworth, 1996).

It is noteworthy to mention that the traditional sources of podophyllotoxin as raw material will not attend the increasing demand of this substance to produce their derivatives etoposide, teniposide and etopophos®. Currently, approximately 298 clinical trials are under way to test these derivatives for new indications and/or new formulations. Each year more podophyllotoxin-derivatives are synthesized and evaluated as new chemical entities for cancer treatment (Liu et al., 2007). This scenario requires an urgent effort to develop short synthetic routes and/or the use of genetic engineering to manipulate the biosynthetic pathways of podophyllotoxin in order to increase the synthetic and natural sources of an important molecule for human health. In summary, podophyllotoxin is a classical example of the importance of biodiversity in furnishing new chemical entities and how powerful is the organic chemistry to increase the efficiency of natural products to get useful drugs to fight cancer.

6.2 Goniiothalamine: a lead compound for drug design?

Phytochemical studies of the genus *Goniiothalamus* have resulted in the isolation and characterization of many compounds with a variety of biological activities (Blázquez et al., 1999; de Fátima et al., 2006a). The styryl lactones and acetogenins of Annonaceae are a group of secondary metabolites mainly isolated from this genus (Bermejo et al., 2005; de Fátima et al., 2006a). The natural form of goniiothalamine [(R)-goniiothalamine; Fig. 2] is the styryl lactone most extensively studied and its promising antiproliferative activity have prompted scientists to investigate with more details its potential as antitumor agent (Zhou et al., 2005; de Fátima et al., 2006a and cited references; Dumitrescu et al., 2010; Wach et al., 2010; Vendramini-Costa et al., 2010; Kasaplar et al., 2010). This natural compound displayed *in vitro* cytotoxic effect especially by inducing apoptosis in different cancer cell lines (Ali et al., 1997; Pihie et al., 1998; Inayat-Hussain et al., 1999; Inayat-Hussain et al., 2003; Chen et al., 2005; de Fátima et al., 2005; Chan et al., 2006; de Fátima et al., 2008b; Inayat-Hussain et al., 2010). This effect was shown to be selective for cancer cell lines with no significant

cytotoxicity toward non-malignant cells (Pihie et al., 1998; de Fátima et al., 2005 and cited references). In *in vivo* models, (*R*)-goniothalamine was reported to have tumoricidal and tumorigenic activities in Sprague-Dawley rats with 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors and in Ehrlich solid tumor in mice (Meenakshii *et al.*, 2000; Vendramini-Costa et al., 2010). Although the biological activities exhibited by the natural form of goniothalamine (6*R* absolute configuration) have been widely investigated, no studies about the biological activities of (*S*)-goniothalamine (Fig. 2) were reported up to 2005 (de Fátima et al., 2006b; Kasaplar et al., 2009). Recently, we have described not only the synthesis, but also the antiproliferative activities of both (*R*)- and (*S*)-goniothalamine. Interestingly, we found that (*S*)-goniothalamine ($IC_{50} = 6.4 \mu M$) was 1,600-fold more potent than (*R*)-goniothalamine ($IC_{50} = 4.0 \text{ nM}$) in renal 786-0 cancer cells (de Fátima et al., 2006b). As reported for (*R*)-goniothalamine (Pihie et al., 1998; de Fátima et al., 2005 and cited references), we demonstrated that (*S*)-goniothalamine exhibited pronounced selectivity for cancer cells, while presenting minor cytotoxicity against non-tumor cells (de Fátima et al., unpublished results). The extremely high antiproliferative activity and selectivity presented by (*S*)-goniothalamine for 786-0 cell line ($IC_{50} = 4.0 \text{ nM}$) prompted us to synthesize eight analogues (compounds **1-8**; Fig. 2) to identify the pharmacophoric groups responsible for this antiproliferative activity.

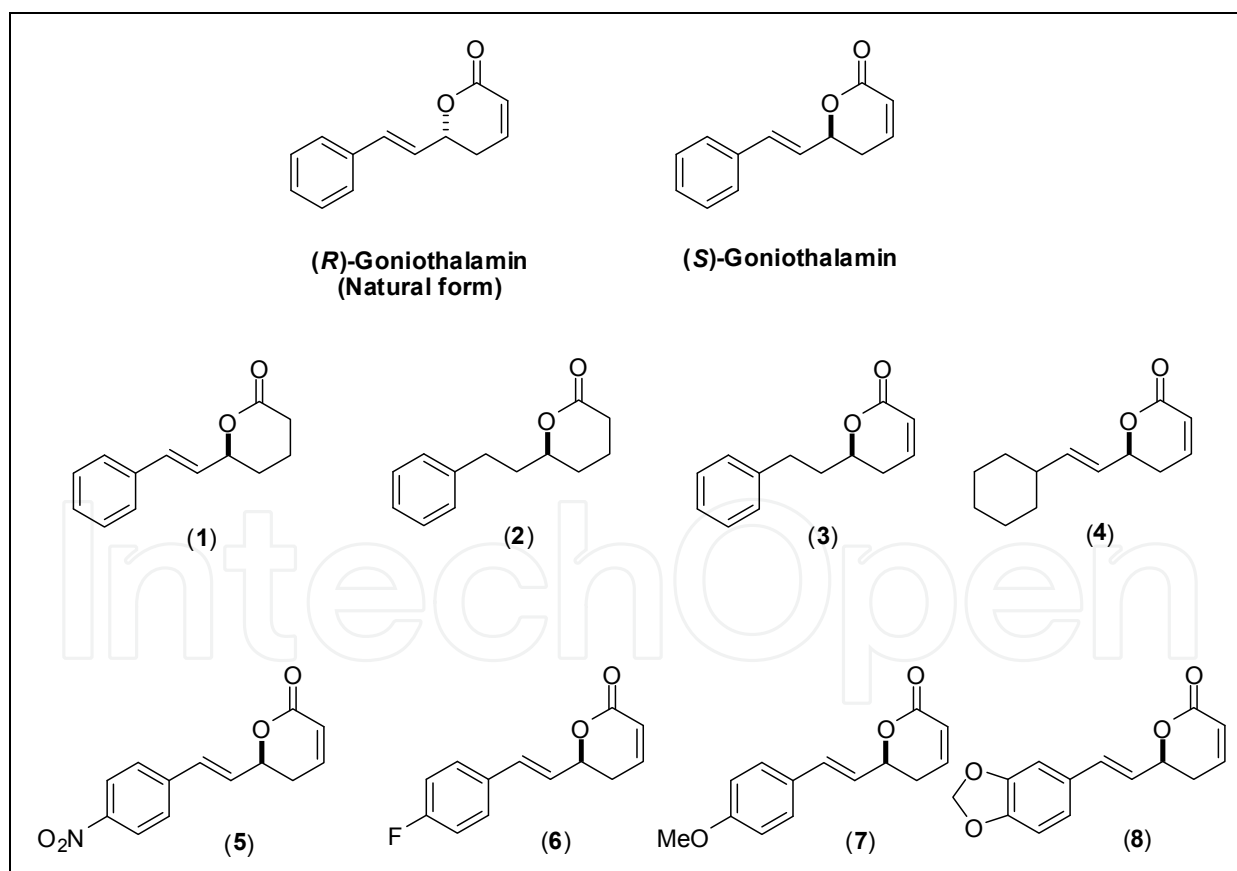


Fig. 2. Structure of natural goniothalamine and its synthetic analogues.

We found that (*S*)-goniothalamine was 4,750- and 5,200-fold more potent in inhibiting proliferation of kidney cancer cells (786-0) than analogues **1** and **3**, respectively (de Fátima et al., 2006b). Remarkably, analogue **4** with a cyclohexyl substituent conserved the same

cytotoxic activity as (*S*)-goniothalamin against renal 786-0 cancer cells, being active at the nanomolar level ($IC_{50} = 5$ nM). No antiproliferative activity was found for analogue **2** under our experimental conditions. These results demonstrate that the *endo* and *exo* double bonds in the pyranone ring are essential for the activity of (*S*)-goniothalamin against 786-0 cells. It is noteworthy that analogues **1**, **2**, and **3** lacking either one or both double bonds had much lower activity than (*S*)-goniothalamin (de Fátima et al., 2006b). Recently, the importance of the *E*-configuration of the styryl moiety in (*R*)-goniothalamin for its antiproliferative activity was shown (de Fátima et al., 2005) and the α,β -unsaturated lactone group has already been implicated in the biological activity of other natural lactones such as cytostatin (Bialy & Waldmann, 2003) and fostriecin (Buck et al., 2003). This behavior is most probably due to its role as a Michael acceptor for nucleophilic amino acid residues (cysteine, lysine, serine or threonine) present in the natural receptors that interact with these compounds (de Fátima et al., 2006b).

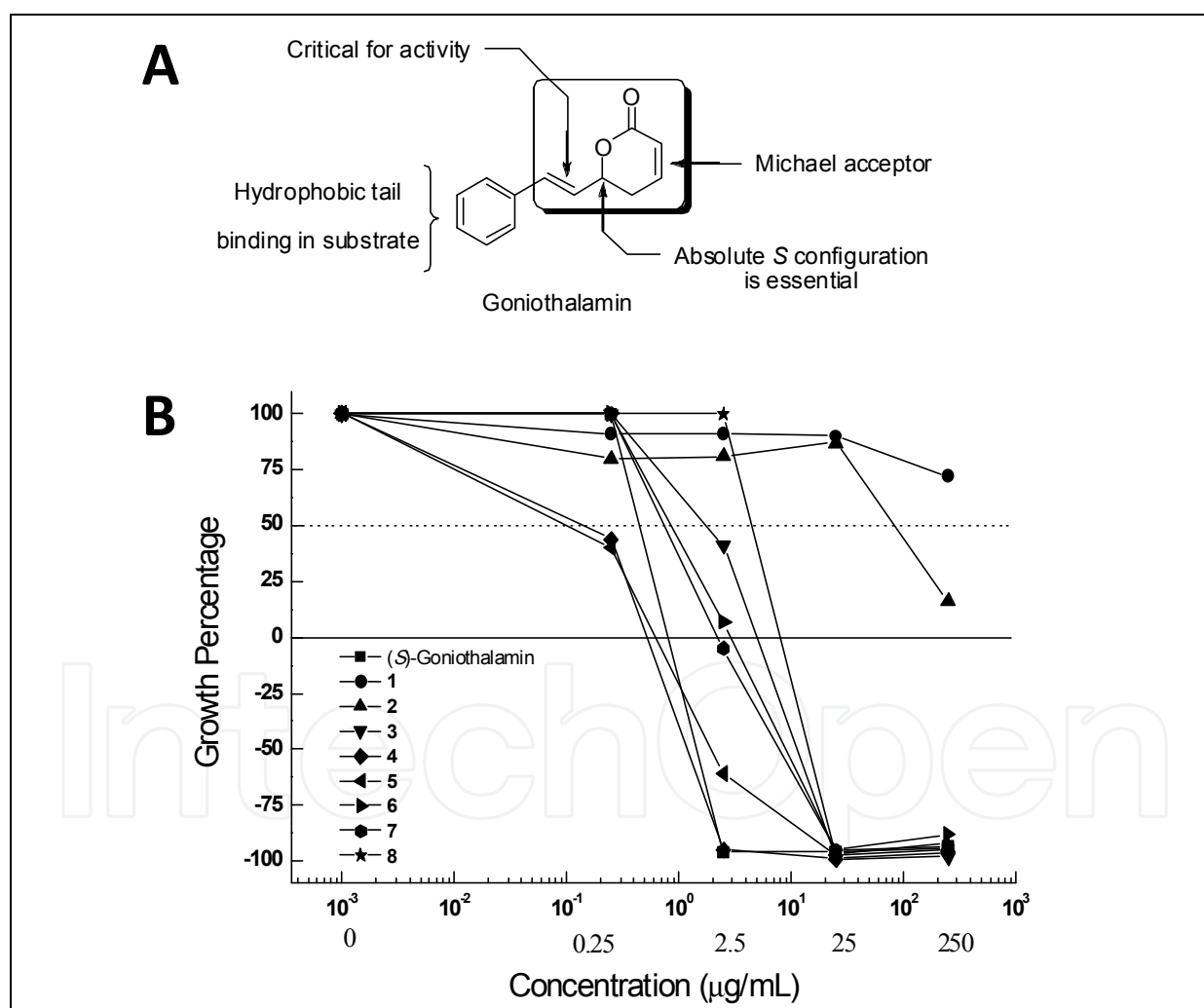


Fig. 3. **A**: Pharmacophoric groups of goniothalamin identified by the cytotoxicity in renal cancer cell line (786-0); **B**: Percentage growth of 786-0 cells after 48 h of treatment with different concentrations (0.25, 2.5, 25 and 250 µg/mL) of (*S*)-goniothalamin and its analogues **1** to **8**. Positive values in relation to y axis correspond to cytostatic activity, while the others refer to the cytotoxic activity of the compound analyzed.

Interestingly, (*R*)-analogue of **1** and **2** were shown to be the main metabolites detected and identified in urine and blood samples of (*R*)-goniothalamine-treated Sprague–Dawley rats, thus signaling the double bond reduction in (*R*)-goniothalamine as a potential detoxification route in this species (El-Sharkaway et al., 1996). Moreover, the results obtained from the treatment of renal cancer cells with pyranones **5** to **8** demonstrated that electron-donating or electron-withdrawing groups in the aromatic ring decreased their potency when compared to (*S*)-goniothalamine. Overall, the findings for renal 786-0 cancer cells suggest that aromatic ring or cyclohexyl in (*S*)-goniothalamine and **4**, respectively, likely interacts with a hydrophobic domain of a biomolecule present in the cancer cell since these compounds were shown to be the most active in inhibiting cell proliferation at nanomolar concentrations (de Fátima et al., 2006b). From all these results, we have identified the pharmacophoric groups of goniothalamine as presented in Figure 3.

Goniothalamine represents an interesting example of the different sensitivity of cell lines to enantiomers compounds. Indeed, not only a distinct cytotoxicity profile was described for (*R*)- and (*S*)-goniothalamine but also different mechanisms of action were described (de Fátima et al., 2006b; de Fátima et al., 2008). (*R*)-Goniothalamine caused renal cell death primarily by apoptosis, whereas autophagy was involved in (*S*)-goniothalamine-induced cell death (de Fátima et al., 2008). Again, it is important to point out the importance of both, biodiversity and organic chemistry to increase and modulate the efficiency of natural products to get useful drugs to fight cancer; however, in this particular case, much more information is necessary to have a goniothalamine-derivative as a useful drug in cancer chemotherapy. Finally, the studies performed until now clearly demonstrate that goniothalamine is indeed a lead compound for drug discovery from natural sources.

Besides the molecules cited here, many other interesting natural products are suitable as lead compounds for the design of new drugs (Koehn & Carter, 2005; Gullo et al., 2006; Gordaliza, 2007; Lam, 2007; Molinski et al., 2009), such as curcumin, riboflavin, resveratrol, and caffeic acid (Aggarwal et al., 2003; Kaminaga et al., 2003; Aggarwal et al., 2004; de Souza et al., 2005).

7. Conclusion

The potential of nature as a primary source for anticancer drug discovery is astonishing, since it offers an unlimited structural diversity of molecular models for bioprospection unmatched by any synthetic chemical collection or combinatorial chemistry approach. Furthermore, natural products are invaluable as tools for identification of exploitable molecular targets and as templates for exploring novel molecular diversity by structural modification or by the synthesis of new designed compounds. This not only provides a plenty and renewable supply of starting materials for screening, but also contributes to improve current libraries with new lead generations. Furthermore, expansions in the fields of chemistry and biology have guided new drug discovery strategies to maximize the identification of pharmacologically relevant natural product structures. In this context, the recent approval of ixabepilone, trabectedin and temsirolimus for cancer treatment (Bailly, 2009) illustrates the important contribution of natural products, mainly from microbial sources, in oncology, even with the increasing use of molecular target-based therapy. Therefore, a cooperative interdisciplinary action on modern drug discovery approaches, driven by biodiversity, genomic and chemical rationales is emerging with the optimism that examining new natural products will continue to turn up useful drugs to treat cancer. In this

scenario, Brazilian biodiversity made this country a unique source of leads and structural templates from which new therapeutic agents may be developed. Indeed, with so much terrestrial and marine diversity awaiting exploration, the Brazilian territory constitutes a true treasure for the discovery of new anticancer drugs, providing a further stimulus to the preservation of the precious ecosystem where these “golden molecules” can be found.

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