A Marine Natural Products as Modulators of Multidrug Resistance

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Abstract: Multidrug resistance (MDR) which enable the tumor cells to possess intrinsic or acquired cross resistance to multiple chemotherapeutic agents simultaneously is considered to be a major challenge in cancer chemotherapy during the 21st century. numerous efflux pumps and transport proteins have been found to play important roles in MDR either the phenomenon of lowering the total intracellular retention of chemotherapeutic drugs or the redistribution of intracellular accumulation of drugs away from target organelles are two of the basic mechanisms involved in this process of MDR by transmembrane proteins which are expressed in varying concentrations in different neoplasms. Multiple compounds that have the potential to inhibit these pumps or proteins can be a future prospective for adjuvant treatment of neoplastic conditions. In this regard, compounds derived from natural products bear the advantages of low-cost and relative nontoxicity thus providing a great pool of lead structures for chemical derivatizations. This review gives an overview on chemical substances isolated from natural products of marine origin which possess the MDR modulating properties

Keywords: Multidrug resistance, Chemotherapy, ABC transporters, P-glycoprotein, MDR modulators, Cytoprotective activity, Quantitative structure-activity relationship (QASR).

INTRODUCTION

Chemotherapy is the most effective treatment for patients with cancer. However, the success of chemotherapy is seriously limited by the phenomenon of multidrug resistance (MDR) [1,2]. Anticancer drugs fail to kill cancer cells for various reasons including variations in the absorption, metabolism and delivery of the drug molecule to target tissues and tumor location in parts of the body into which the drugs do not easily penetrate [3,4,5]. Despite more than three decades of research on the subject, multidrug resistance remains one of the major obstacles to successful cancer chemotherapy [6]. This phenomenon occurs when cancer cells spontaneously become insensitive to drugs that are structurally unrelated [7]. A leading cause of MDR in cancer is the overexpression of ATP-Binding Cassette (ABC) transporters that utilize energy derived from ATP hydrolysis to actively transport anticancer drugs across biological membranes, preventing drugs from reaching their targets within a cancer cell [8,9]. Substantial efforts have been carried out to develop potent modulators of ABC drug transporters for the past two decades [10-12]. Unfortunately, these efforts have not provided successful results. The difficulty in finding an ideal inhibitor is often associated with specificity, potency and intrinsic toxicity. Adverse interactions of modulators with drugs administered in parallel or nonspecific side effects are also extremely problematic [13]. According to previous research data, modulators targeting P-glycoprotein (P-gp)-induced MDR belong to a number of chemical classes and have been classified as the first, second and third generation of MDR reversal agents on the basis of their affinity for the transporter proteins and relative toxicity towards normal cells as marker of their side effects [11, 14, 15]. First generation modulators included drugs that were coincidentally found to be effective in sensitizing the drug resistant tumors towards chemotherapy. These include verapamil, quinine, cyclosporine A, tamoxifen and erythromycin [16,17]. The second generation modulators constituted drugs that were designed by modification of the first generation modulators and such modifications were aimed at reducing their adverse effects by eliminating their non-MDR pharmacological activities. In this group of drugs are valspodar and R-verapamil [15,18,19]. The third generation inhibitors are designed specifically for high transport affinity and low pharmacokinetic interaction [20]. These include tariquidar, biricodar, annamycin, mitotane, zosuquidar, and laniquidar. These compounds exhibit effective and potent MDR modulating activity, high affinity and selectivity for target MDR transporter(s) at low nanomolar range [21, 22]. Nevertheless, most of the agents from the first, second or third generation of MDR modulators suffer clinically from their intrinsic toxicity or from undesired effects on the pharmacokinetics of the accompanying anticancer drugs [13,23].

MDR Modulators from Natural Products

Inhibitors or modulators originating from natural sources are sometimes referred to as “Fourth

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Generation Inhibitors". In fact, bioactive compounds from natural products provide one of the most diverse and novel chemical scaffolds suitable for the development of new inhibitors [4,24].

There is a great chemical diversity that can be utilized, as bioactive components are now extracted from plants, fungi and marine organisms, then purified and characterized [25-34]. Most importantly, natural extracts are usually low in toxicity and are well tolerated in the human body [35,36]. Accordingly, there have been significant efforts, but the progress in discovering natural MDR inhibitors is still in the early stages of exploring various extracts/active components. The main natural products that have been recognized as modulators of MDR in cancer include: flavonoids, curcumin, lignans; a variety of marine compounds including agosterol A and derivatives, sipholenol A, kendarimid A, bryostatin-1, lamellarins, ecteinascidin-743 [36-38 and references therein]. These substances belong to very different families of chemical compounds. Some of them have very complex structures and their bioactive and anticancer activities effect different levels of tumor cell growth including blocking metabolic/enzymatic reactions, interrupting cell cycle, and direct cell killing. At least a dozen of them are in various phases of clinical trials for the treatment of cancer [39-41].

MDR Modulating Compounds Originating from Marine Organisms

Marine organisms represent a plentiful source of new bioactive compounds with promising cancer therapeutic potential, including MDR modulation properties [42-45]. A large number of distinctive secondary metabolites isolated from a wide variety of marine microorganisms, plants and invertebrates have been shown to exert anticancer effects. The most significant groups of marine compounds with anticancer properties are alkaloids, anthraquinones, benzothiazoles, macrolides, peptides, sphingolipids,

Table 1: Gives a Brief Overview of the Compounds Isolated Form the Marine Organisms that have been Undergone the Clinical Trials and Found Useful in the Treatment of Cancer in Humans

Compound name	Origin	Brand name& Manufacturer	Indication	Reference
Cytarabine	Caribbean sponge,*Cryptothecacrypta*	Cytosar-U, Ara-C (*Phizer*), DepoCyt (*Pacira Pharmaceuticals*)	Treatment of cancer and various types of leukemia	[46]
Ecteinascidin-743 (trabescedine)	Marine tunicates, *Ecteinascidia turbinate*	Yondelis® (*PharmaMar*)	Treatment of soft tissue sarcomas	[47]
Erbulinmesylate (synthetic form of the natural molecule halichondrin B)	Halichondrin B was isolated from marine sponge *Halichondria sp.*	Halaven® (*Eisai Inc.*)	Treatment of: - advanced or metastatic breast cancer; - unresectableliposarcoma	[48]
Brentuximabvedotin (	Monoclonal antibody brentuximab with the monomethyl- auristatin E (MMAE), which is a synthetic analog of dolastatin-10) Dolastatin 10 was found in the sea hare *Dolabellaauricularia*	Adcetris® (*Seattle Genetics)*	Treatment of anaplastic large T-cell systemic malignant lymphomas and Hodgkin's lymphomas	[49]
Enfortumabvedotin	Antibody, specific to nectin-4, as conjugate with MMAE	PADCEVTM® (*Astellas Pharma* and *Seattle Genetics*)	Treatment of metastatic urothelial cancer	[50]
Belantamabmafodotin	Andtibody-drug conjugate with MMAE, bound to an antibody targeting B-cell maturation antigen	Blenrep® (*GlaxoSmithKline*)	Treatment of relapsed and refractory multiple myeloma	[51]
Plitidepsin (dehydrodidemnin B)	Marine tunicate *Aplidiumalbicans*	Aplidin® (*PharmMar*)	Treatment of leukemia, lymphoma, and multiple myeloma	[52]
Lurbinectedin	Synthetic derivative of trabectedin	Zepzelca® (*PharmMar*)	Treatment of metastatic small cell lung cancer	[53]

steroids, tannins, terpenes and terpenoids. Literature data point out the most significant marine sources of novel anticancer agents: sponges, coelenterates, microorganisms, algae, echinoderms, tunicates, mollusks and bryozoans [42 and references cited therein].

Among secondary metabolites of sea sponges a number of P-gp inhibitors were discovered [45]. It has been reported that a sipholane triterpene, sipholenol A, isolated from the sponge *Callyspongia siphonella* efficiently reversed P-gp caused-MDR in malignant cell lines. Sipholenol A increased cytotoxic effect of paclitaxel, vinblastine and colchicines in resistant malignant cell lines [52,54]. One more efficient P-gp inhibitor is polyhydroxylated sterol acetate, agosterol A, found in marine *Spongia* sp. [55-57]. Furthermore, kendarimide A isolated from the sponge *Haliclona* sp. has been shown to reverse resistance to colchicine in P-gp overexpressing KB-C2 malignant cell line [58]. Significant class of marine compounds with diverse biological and pharmacological activities including notable potential for overcoming MDR in cancer are lamellarins, polyaromatic alkaloids, which were found in *Lamellaria* sp., in ascidian, *D. chartaceum*, then in sponge, *Dendrillacactos* and in species of unidentified ascidians [45]. Interestingly, lamellarin I exert remarkably stronger activity than verapamil in human adenocarcinoma LoVo cells resistant to doxorubicin mediated by direct inhibition of the function of P-gp pump [59]. In addition, it was reported that tetrahydroisoquinoline ecteinascidin-743, also known as trabectedin produced by chemical synthesis, originally isolated from the marine tunicate *Ecteinascidia turbinate* reversed resistance to doxorubicin and vincristine in MDR epidermal carcinoma P-gp/MDR1 overexpressing cancer cell lines [60]. Trabectedin is the marine-derived orphan drug approved for the treatment of advanced, recurrent soft tissue carcinoma in USA and Switzerland and advanced, recurrent ovarian cancer inUSA and Switzerland [61]. Another effective modulator of P-gp mediated-MDR in cancer cells is bryostatin-1, a macrocyclic lactone, isolated from the marine Bryozoan *Bugula neritina*, probably a product of symbiont bacteria [62]. Moreover, marine bacteria, cyanobacteria and alga represent notable source of bioactive compounds which MDR modulation properties, such as alkaloids welwitindolinones [63] found in cyanobacteria *Hapalosiphon welwitschii*, thenbrominated diterpenes, parguerenes I and II derived from the Australian marine red alga *Laurencia filiformis* [64] and prenylated diketopiperazines no cardio azine A and nocardioazine B isolated from bacterium *Nocardiopsis*sp. [65].

N-Methylwelwitindolinone-cis-othiocyanate, alcaloid isolated from the blue-green alga *Hapalosiphon welwitschii* were reported to reverse p-glycoprotein MDR. N-Methylwelwitindolinone C isothiocyanate had MDR efficacy similar to verapamil in two tested cell lines. Also it was shown that N-methylwelwitindolinone C increased the cytotoxicity of actinomycin D and daunomycin [66]. Cyclic peptide, patellamide d, isolated from ascidian *Lissoclinum patella,* has shown cytotoxic activity and resistance in the MDR human leukemic cell line against vinblastine, adriamycin and colchicine [67]. In the marine sponge, *Discodermia dissoluta* was identified discodermolide, a polyketide, that expressed immunosuppressive and anti-tumor activities [68]. Fordiscodermolide is known that posses the same mechanism of anti-tumor activity as taxol, and its ability to drasticly decrease the MDR to taxol in ovarian carcinoma and pataxel-resistant colon carcinoma cell lines [69,70]. Polyoxygenated steroids, first identified in octocoral *Isis hippuris*are identified in various forms as: gorgosterol, hippuristerone, hippuristanol and hippuristerol types [71].

Many investigators tried to find the potential of well-known polysaccharide fucoidan, identified in brown algae, as the novel anticancer drug. Unfortunately, despite the cytoprotective activity of fucoidan in uveal melanoma cells and its pro-angiogenic properties, this polysacharide showed no potential to be used as the novel medicine [72]

The extracts derived from marine bacteria family, seaweeds family andmarine invertebrate superfamily, for example *Padinapavonia, Halimeda tuna, Codium bursa, Dysideaavara, Axinella cannabina, Achantella acuta, Haliclona mediteranea* extracts have shown very strong activity against human malignant cells *in vitro* [28,29,73-79]. These samples could be promising candidates for testing the ability to overcome MDR in cancer by bioactive compounds such as flavonoids, triterpenoids, quinones, lactones and sesquiterpenes.

CONCLUSION

The mentioned literature data as well as many others evidence-based data about fourth generation MDR inhibitors indicate that many of these natural products have a synergistic growth inhibitory effect with cancer drugs that are P-gp substrates including actinomycin D, puromycin, paclitaxel, vinblastine and doxorubicin [3,80,81]. Also, at the same toxicity levels the natural extracts were found to be more effective than verapamil, a standard MDR modulator, in enhancing cellular doxorubicin accumulation [82,83].

Finally, natural products represent a starting point for discovery and development of potent and effective MDR modulators, not only for their potential to be used in combination with chemotherapy treatment, but also to rationally design the semi-synthetic QSAR study analogues, with higher potency and fewer pharmacokinetic interactions.

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