Novel Marine Secondary Metabolites Worthy

Subjects: Toxicology

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This necessitated the search for potent and efficacious substances from marine sources that will improve or replace existing ones in order to contain multi-drug-resistant neoplasms. This review compiled a total of 731 compounds/derivatives that belong to these classes: glycosides, alkaloids, saponins, lipids, terpenes, ribose, steroids, peptides, xanthones, ethers, lignins, coumarins, carbazoles, azaphilones, nucleosides, polyketides, and quinones (). These compounds/derivatives sourced from soft corals, bacteria, fungi, sponges, algae, sea cucumbers, seaweeds, mollusks, and sea urchins exhibited moderate to high cytotoxic activities against 121 mammalian cancer cell lines as described in 76 articles from January 2019–March 2020.

Keywords: cancer ; marine secondary metabolites ; lead optimization ; cancer cell line ; drug development

1. Introduction

The cell cycle is a normal physiological process that occurs in distinct stages in the cell to enable the proliferation of cell growth, development, and maintenance of the species. Cell proliferation and progression in normal cells are under tight genetic control. For cancer to develop, there must be a change in the genetic machinery that controls cell proliferation and eventual progression of cell cycle stages, which is the hallmark of cancer growth and sustenance [1].

Chemotherapeutic agents, targeted therapy/immunotherapy, radiation, surgery, or a combination of these treatment approaches can all be used to treat cancer, depending on the cancer stage. Chemotherapy is the center of our attention in this review. Cytotoxic agents inhibit or kill cancer cells by diverse mechanisms, some of which are well understood while others are not. Some drugs are designed to target a cancer cell's pathophysiological survival processes, while others function as suicidal agents, altering the proliferation and metabolic activities of the cancer cells.

Anticancer compounds isolated from terrestrial and marine sources have a variety of mode of action for inhibiting cancer cell proliferation and/or by inducing apoptotic cell death. Dolastatin derived from Dolabella auricularia (a shell-less mollusk), for example, prevented cancer cells from entering the metaphase stage and triggered apoptosis in lymphoma cells [2]. By inhibiting Hsp90 in the HL60 cancer cell line, diterpene 5-episinuleptolide acetate, a non-cembranoid derived from Sinularia sp., triggered downstream apoptosis [3]. Flavonoids, tannins, and curcumins are polyphenolic chemicals with anticancer action [4]. Polyphenols also have antioxidant activity and are known for their apoptosis-inducing potential which they initiate by regulating the mobilization of copper ions which are bound to chromatin, causing DNA fragmentation [5]. Curcumin, a polyphenol, suppressed tumor necrosis factor (TNF) when incorporated into cancer cells in various cells lines through interaction with various stimuli [6]. Flavonoid compounds have been shown to cause cancer cell apoptosis via intrinsic and extrinsic signaling pathways, lowering mitochondrial membrane potential and inhibiting the expression of NF-κB needed for cancer cell survival, angiogenesis, and proliferation [7].

The desired goal of anticancer drugs or chemotherapeutic agents is to selectively target the cancerous cells while sparing normal cells. Unfortunately, this ideal situation is far from reality because both normal and cancerous cells share the same metabolic processes, thus, normal cells are damaged. As a result, anticancer agents are not free from toxicity. The normal cells prone to damage by chemotherapy are blood-producing cells, hair follicles, and cells in the oral cavity, alimentary canal, and reproductive system [8]. The toxic effects of these drugs are numerous and include fatigue, peripheral neuropathy, nephrotoxicity, sexual dysfunction, diarrhea, and bone marrow depression, among others [8].

2. Development and Findings

From the Vietnamese marine sediment-derived fungus Aspergillus flocculosus, four new compounds, one aspyrone-related polyketide aspilactonol G (Cpd. 112), one meroterpenoid 12-epi-aspertetranone D (Cpd. 113), two drimane derivatives (Cpds. 114, 115), and five known Cpds. 116, 117, 118, 119, 120 were isolated. These compounds were

screened for anticancer activity against the human prostate cancer cell line 22Rv1, human breast cancer cell line MCF-7, and murine neuroblastoma Neuro-2-A cell line. However, only insulicolide A (Cpd. 114) exhibited cytotoxic activity against 22Rv1 and Neuro-2-A cell lines at IC 50 values of 3.0 and 4.9 μM, respectively, that are below 20.0 μM[9].

Yu et al. isolated three new sesquiterpene quinones/hydroquinones, 20-demethoxy-20-isopentylaminodactyloquinone D (Cpd. 121), 20-demethoxy-20-isobutylaminodactyloquinone D (Cpd. 122), and 19-methoxy-dictyoceratin-A (Cpd. 123), and five known related compounds (Cpds. 124– 128) from the marine sponge Dactylospongia elegans . These compounds belong to the meroterpenoid class of terpenes. The cytotoxicity assay on the compounds against the human cancer cell lines DU145, SW1990, Huh7, and Panc-1 revealed growth inhibitory activity on the cell lines with IC 50 values in the range of 2.33–37.85 μM. Thus, only the compounds with IC 50 below 20.0 μM are in Table S2 [10].

By using chromatographic separation techniques, sixteen known compounds (Cpds. 133– 148), including one new triterpene saponin, aegicoroside A (Cpd. 132), were isolated from Vietnamese mangrove Aegiceras corniculatum leaves. The compounds were tested for cytotoxic activity against MCF-7 (breast), HCT116 (colon), B16F10 (melanoma), and A549 (lung adenocarcinoma) cancer cell lines. Sakurasosaponin (Cpd. 133) inhibited the proliferation of the four cancer cell lines screened, and sakurasosaponin methyl ester (Cpd. 134) inhibited the growth of MCF-7, A549, and HCT116 cell lines with IC 50 values ranging from 2.89 to 9.86 μM [11].

By the use of 1D, 2D NMR, and HR-ESI-MS spectroscopic techniques, the structures of one new compound, named holothurin A5 (Cpd. 657), and eight known triterpene glycosides (Cpds. 658– 665), that were obtained from the methanol extract of the Vietnamese sea cucumber Holothuria edulis , were deduced. Holothurin A5 (Cpd. 657) has a hydroperoxy group at C-25. That was the first report of the isolation of this group of triterpene saponin compounds from sea cucumbers [12]. In addition, the in vitro cytotoxicity of the compounds was screened against five human cancer cell lines (HepG2, KB, LNCaP, MCF7, and SK-Mel-2). The compounds, especially Cpds. 659, 663, and 664, had mild to moderate to strong cytotoxic activity on the cancer cells [13].

3. Conclusions

There has been a growing rate of cancer incidence worldwide due to factors such as an aging population, eating habits, environmental changes, and co-morbidities. Poor treatment outcomes and complications of cancer disease are aggravated by multi-drug resistant malignant tumors, the high cost of treatment, and adverse drug reactions/patient compliance. Therefore, there is high demand for new anticancer agents or for modifying the existing ones. This necessitated the search for potent and efficacious substances from marine sources that will improve or replace existing ones in order to contain multi-drug-resistant neoplasms. This review compiled a total of 731 compounds/derivatives that belong to these classes: glycosides, alkaloids, saponins, lipids, terpenes, ribose, steroids, peptides, xanthones, ethers, lignins, coumarins, carbazoles, azaphilones, nucleosides, polyketides, and quinones. These compounds/derivatives sourced from soft corals, bacteria, fungi, sponges, algae, sea cucumbers, seaweeds, mollusks, and sea urchins exhibited moderate to high cytotoxic activities against 121 mammalian cancer cell lines as described in 76 articles from January 2019–March 2020. The IC 50 (≤20.0 μM) values of both known and novel compounds were shown with structures of the new compounds. Interestingly, some of these compounds exhibited a broad spectrum of anticancer activity and are worth further exploration in terms of mechanism of action, structure–activity relationship, and clinical trials. However, this could serve as a guide for the selection of novel compounds/derivatives for future optimization and drug development.

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