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Bacteria as a treasure house of secondary metabolites with anticancer potential

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ABSTRACT

Cancer stands in the frontline among leading killers worldwide and the annual mortality rate is expected to reach 16.4 million by 2040. Humans suffer from about 200 different types of cancers and many of them have a small number of approved therapeutic agents. Moreover, several types of major cancers are diagnosed at advanced stages as a result of which the existing therapies have limited efficacy against them and contribute to a dismal prognosis. Therefore, it is essential to develop novel potent anticancer agents to counteract cancer-driven lethality. Natural sources such as bacteria, plants, fungi, and marine microorganisms have been serving as an inexhaustible source of anticancer agents. Notably, over 13,000 natural compounds endowed with different pharmacological properties have been isolated from different bacterial sources. In the present article, we have discussed about the importance of natural products, with special emphasis on bacterial metabolites for cancer therapy. Subsequently, we have comprehensively discussed the various sources, mechanisms of action, toxicity issues, and off-target effects of clinically used anticancer drugs (such as actinomycin D, bleomycin, carfilzomib, doxorubicin, ixabepilone, mitomycin C, pentostatin, rapalogs, and romidepsin) that have been derived from different bacteria. Furthermore, we have also discussed some of the major secondary metabolites (antimycins, chartreusin, elsamicins, geldanamycin, monensin, plicamycin, prodigiosin, rebeccamycin, salinomycin, and salinosporamide) that are currently in the clinical trials or which have demonstrated potent anticancer activity in preclinical models. Besides, we have elaborated on the application of metagenomics in drug discovery and briefly described about anticancer agents (bryostatin 1 and ET-743) identified through the metagenomics approach.

1. Introduction

Cancer is a major public health concern across the globe and it is one of the leading killers among non-communicable diseases [1]. In 2018, 18.1 million new cancer cases were diagnosed and 9.5 million cancer-related deaths were reported globally. In 2020, 1,806,590 new cancer cases are expected to be diagnosed with an estimated mortality rate of 606,520 in the United States alone [2]. The cancer incidence rate is expected to reach 29.5 million with a death rate of 16.4 million annually by 2040 worldwide [3]. As per World Health Organization, 1 in 6 deaths is contributed by cancer worldwide and about 70 % of cancer-related deaths take place in middle- or low-income countries. The leading type of cancers in 2018 are cancers of lung, breast, colorectal, prostate, skin, and stomach in order of occurrence [4]. The rate of cancer incidence in developing countries is progressing at an alarming pace. Additionally, the rapid development of drug resistance by the cancer cells towards existing therapeutic agents has become a growing concern in their treatment [5]. Many research groups are attempting to design or discover new therapeutic agents against various cancers using different strategies. The discovery of drugs from nature remains as a frontline approach in anticancer therapy. Noteworthy, more than 50 % of approved drugs in the previous three decades for the treatment of

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cancer are natural compounds and their structural analogs/derivatives [6–8]. Natural compounds derived from plants, bacteria, fungi, and other marine organisms are serving as a treasure house of drug-seeds for the development of anticancer agents [9,214–217].

Secondary metabolites are the natural compounds that are produced by an organism as part of its metabolic activities. A few researchers have rightly called them as specialized metabolites or auxiliary compounds [10]. These are not essential for the growth or reproduction of an organism but are synthesized to offer a specific benefit to the organism. Secondary metabolites are essential for an organism to interact with its neighboring organisms, overcome stress, acquire nutrients, and compete with its commensals. It may be interpreted that the microbes have a lion's share in the production of the secondary metabolites compared with other biological sources. Recently, Locey and Lennon estimated microbial biodiversity using the scaling law and lognormal model of biodiversity. They predicted that the Earth is the shelter for 1 trillion microbial species [11]. Among such a large reservoir of microbes, some bacteria may have the potential to produce small molecules endowed with significant therapeutic properties.

The bacterial kingdom has contributed enormously to the medical wellness of human beings and they are truly serving as a treasure house of bioactive secondary metabolites. The use of bacteria for the treatment of cancers was first attempted by Dr. William Colley. He used the combination of culture supernatants of *Streptococcus pyogenes* and *Serratia marcescens* for the treatment of sarcoma patients [12,13]. This method provided the first therapeutic success in inoperable sarcomas. Thereafter, bacteria-mediated cancer therapy and bacteria-derived compounds have gained significant attention in the development of therapeutic agents for various human ailments including cancers. Over 13,000 bioactive natural compounds have been described from the bacterial sources indicating that bacterial source remains as an irreplaceable source of novel compounds for drug discovery. Notably, over 70 % of bioactive compounds have been obtained from actinomycetes (a group of Gram-positive mycelial bacteria) among the bacteria derived compounds [14,15]. Thus, actinomycetes can be regarded as secondary metabolites factory. Moreover, merely 1 % of actinomycetes have been cultured so far, which presents the need for the bioprospecting of actinomycetes as well as other bacterial species from the unexplored habitats for the identification of biologically active metabolites [16]. Despite the isolation of huge number of small molecules from these bacteria, only a few of them have been thoroughly investigated for their pharmacological activities. Secondary metabolites and other components derived from bacteria have been used as antibiotics, anticancer drugs, antifungals, antiparasitics, and immunosuppressant agents for the past several decades. In this review article, we have comprehensively discussed sources, the possible mechanism(s) of action, toxicity issues, and off-target actions of clinically used anticancer drugs that are derived from bacteria. We have also described some of the major secondary metabolites that are in clinical trials or those which have demonstrated potent anticancer activity in preclinical models.

2. Clinically used anticancer drugs derived from the bacteria

For the past several centuries, Mother Nature is serving as a treasure house of chemically diverse and biologically active compounds endowed with many medicinal properties including antineoplastic activities. Traditional medicine systems such as Ayurveda and traditional Chinese medicine have documented the medicinal properties of various

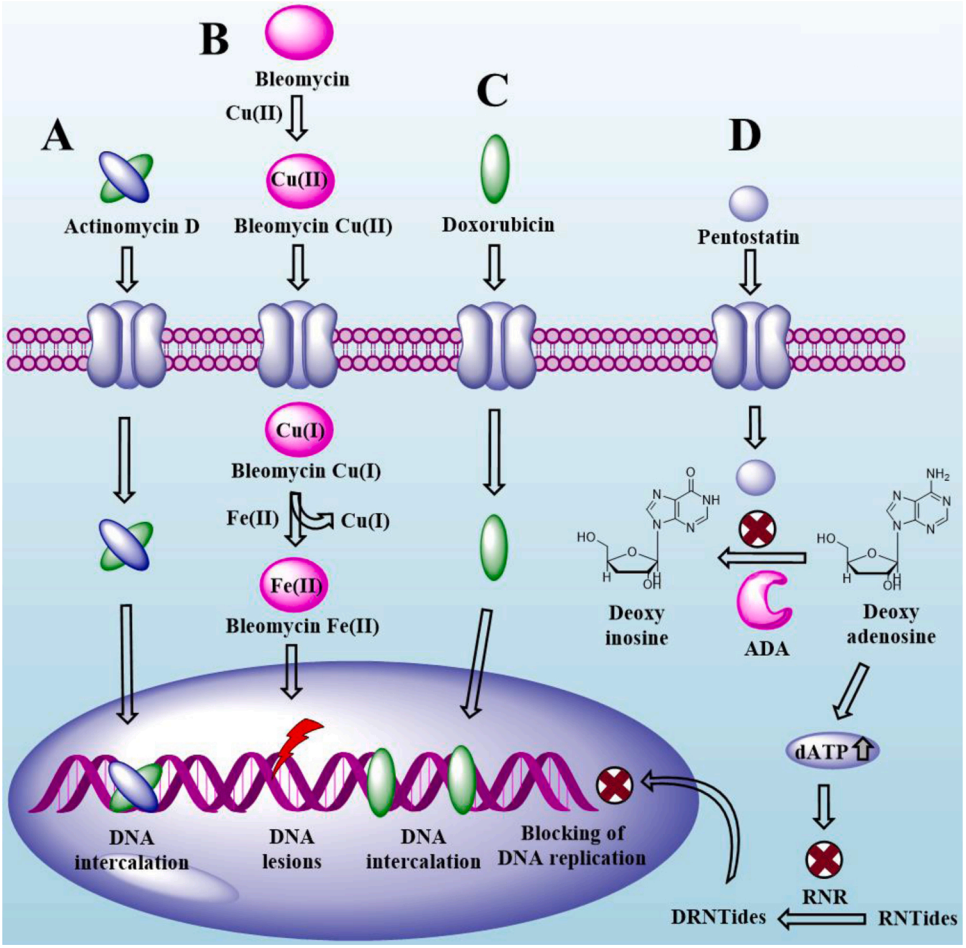

Fig. 1. Diagrammatic representation of the mechanism of action of anticancer drugs targeting DNA. (A and C) Actinomycin D and doxorubicin intercalates into the duplex DNA and thus inhibits replication and transcription which leads to apoptosis of the target cell. (B) Bleomycin binds to Cu(II) and is taken into the cell for reduction to Cu(I) which is subsequently displaced by Fe(II) to obtain the bleomycin-Fe (II) complex which reacts with DNA to generate free radical and thereby creates DNA lesions. (D) Pentostatin inhibits adenosine deaminase (ADA) which blocks the conversion of deoxyadenosine to deoxyinosine in turn results in the accumulation of deoxyadenosine. The deoxyadenosine is converted to deoxyadenosine triphosphate (dATP) and the dATP inhibits ribonucleotide reductase (RNR) which is responsible for the conversion of ribonucleotides (RNTs) to their corresponding deoxynucleotides (DRNTs). During the reduced synthesis of deoxynucleotides, the cell is committed to apoptosis.

herbs. Many drugs available in today's market are natural products or their derivatives. Some blockbuster anticancer drugs such as actinomycin D, bleomycins, carfilzomib, doxorubicin, ixabepilone, mitomycin C, pentostatin, rapamycin, and romidepsin are derived from Mother Nature in general, bacteria in particular. In the following section, we have discussed about the possible sources, mechanism of action, and toxicity issues of bacterial-derived anticancer drugs. The mechanism of cytotoxicity of the selected drugs has been provided diagrammatically in

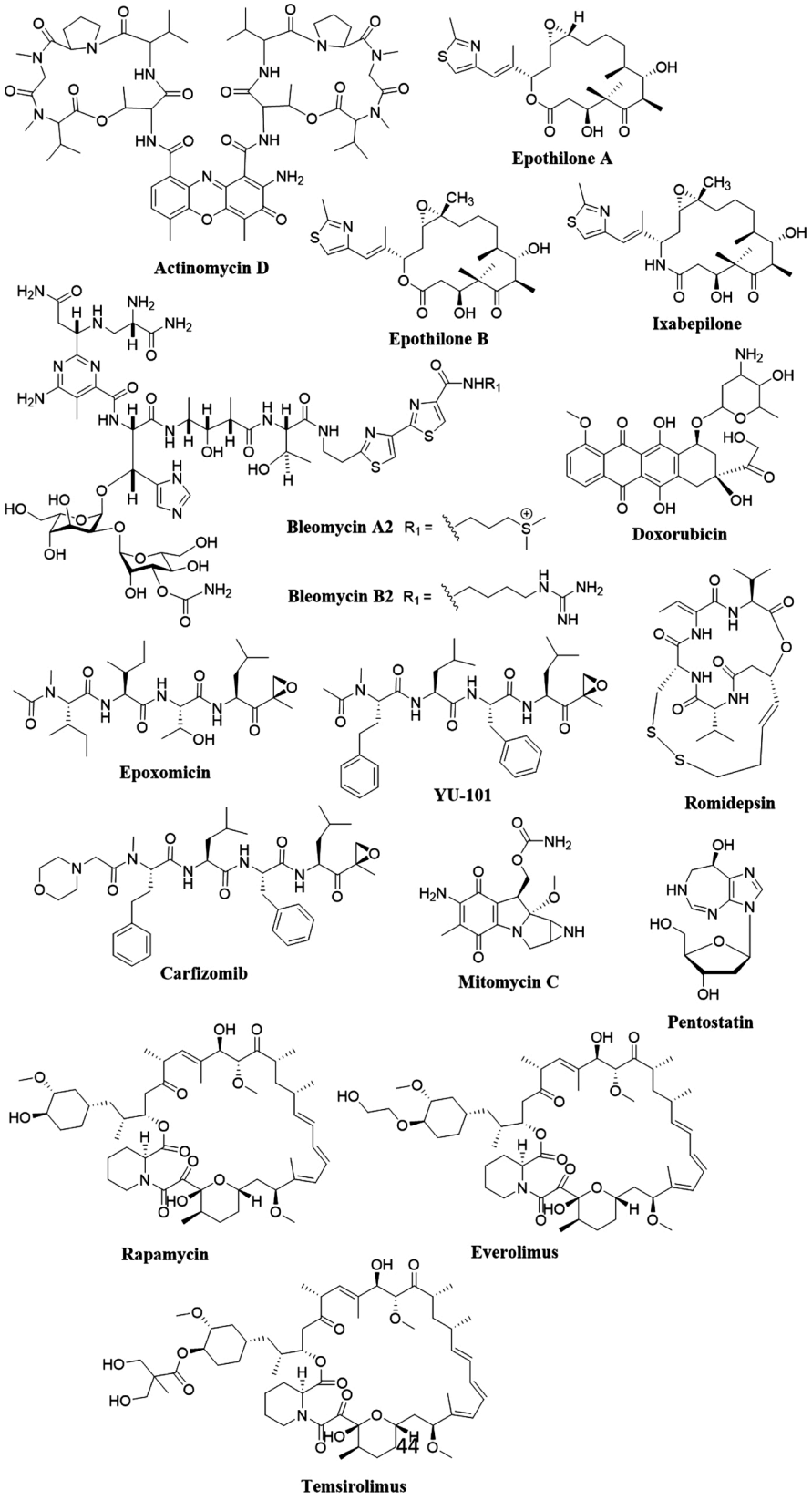

Fig. 2. Structure of clinically used anticancer drugs that are isolated from bacteria or their semi-synthetic derivatives.

Fig. 1 and the chemical structure of all the discussed anticancer drugs derived from the different bacteria have been provided in Fig. 2.

2.1. Actinomycin D

Actinomycin D, otherwise also designated as Dactinomycin, belongs to the family of actinomycins. It is produced by *Streptomyces parvulus* and *Streptomyces antibioticus*. More than 40 actinomycins (including actinomycin C, D, G, F, Y, Z, and N-demethylactinomycins) have been purified from various microbial sources [17]. Structurally, actinomycin D contains a phenoxazine-based chromophore conjugated with two cyclic pentapeptide lactone rings. Actinomycin D has been approved for the treatment of human malignancies such as locally recurrent solid tumors, Wilms tumor, choriocarcinoma, testicular cancer, Ewing sarcoma, and rhabdomyosarcoma as a single agent or in combination with other drugs [18]. Actinomycin D majorly imparts antiproliferative action by DNA intercalation (Fig. 1A). It possesses an uncommon feature among DNA intercalators as it is deficient in net positive charge which may be compensated by its high dipole moment [19]. The other DNA binding antibiotics such as echinomycin and structural mimics were also found to share the same property with actinomycin D [19]. The phenoxazine moiety is a contributing factor for the intercalation of actinomycin D into the duplex DNA and thus inhibition of DNA-directed RNA synthesis. The interaction of actinomycin D is facilitated by the guanine-cytosine base pair. The interaction of DNA-actinomycin D can be stabilized by the formation of hydrogen bonds between the 2-amino group of guanine with the carbonyl oxygen of threonine and also between the nitrogen (3rd position) of guanine and the amino group of the same threonine [20]. It has also been revealed that other amino acids of pentapeptide such as proline, sarcosine (*N*-methylglycine), and methylvaline are involved in establishing hydrophobic interactions with the minor groove of DNA suggesting that actinomycin D can serve as a potential DNA intercalator as well as DNA minor groove binder [21]. The usage of actinomycin D towards a broad range of cancers as an antitumor agent has been limited due to its toxic effects including tissue necrosis, myelosuppression, dermatotoxicity, and gastrointestinal enterotoxicity. Actinomycin D has also been shown to enhance the therapeutic efficacy of some antitumor agents that are in clinical trials or clinics. It showed synergetic cytotoxicity with RG7787 (an immunotoxin which is in clinical trials against refractory pancreatic cancer and mesothelioma) in mesothelin-positive cancer cell lines and has displayed significant tumor regression of pancreatic and stomach cancer xenografts [22].

2.2. Bleomycins

Bleomycins are a group of glycopeptide-based antitumor antibiotics isolated from *Streptomyces verticillus* and which is used for the treatment of squamous cell cancers, melanoma, ovarian cancer, Hodgkin's, and non-Hodgkin's lymphoma [23]. Blenoxane is an anticancer drug majorly comprising of a mixture of bleomycin A_2 and B_2 in the concentration of 60 % and 30 % respectively [24]. Notably, bleomycin produces relatively less bone marrow suppression compared to other drugs and therefore bleomycin is often used in combination with other chemotherapeutic agents or radiotherapy. Bleomycins are extracted as copper complexes from *S. verticillus* and intravenously injected in a metal-free form to reduce irritability at the administration site. It binds to copper [Cu(II)] and is carried into the cell for reduction to Cu(I). The Cu(I) in bleomycin is displaced by Fe(II) to obtain the bleomycin-Fe(II) complex which reacts with DNA to generate free radical at the 4′ carbon atom of the deoxygenated ribose [25]. The free radical produces a break in the phosphodiester skeleton of DNA (Fig. 1B) [25]. Bleomycin produces DNA lesions that are identical to damages (such as single/double-strand breaks *via* liberation of bases resulting in the formation of apurinic/apyrimidinic sites) induced by ionizing radiations [26,27]. Despite their therapeutic efficacy, the clinical uses of bleomycin are limited due to potential adverse effects such as lung fibrosis and toxicity. Additionally, consistent efforts have been made to identify bleomycins that are structurally novel and biologically active with reduced toxicity [28]. The other antitumor antibiotics of the bleomycin family include zorbamycin (from *Streptomyces flavoviridis*), tallysomycins (from *Streptoalloteichus hindustanus*), and phleomycins (from *Streptomyces verticillus*). Recently, Hindra and colleagues used a genome mining approach and identified *Streptomyces mobaraensis* DSM40847 as a producer of bleomycin [29].

2.3. Doxorubicin

Doxorubicin is an anthracycline antibiotic initially isolated from *Streptomyces peucetius*. It has been approved for the treatment of various human malignancies including cancers of breast, endometrium, gastric, liver, ovary, kidney, head and neck, leukemias, lymphomas, multiple myeloma, and childhood cancers [30]. The other important members of the anthracycline family are daunorubicin, epirubicin, and idarubicin which are also produced by *Streptomyces* species. The antiproliferative efficacy of doxorubicin has been demonstrated in a significant number of studies. Despite its efficacy, it suffers from toxic effects towards non-diseased cells, dose-limiting myelosuppression, and fatal cardiotoxicity [31]. Structurally, doxorubicin comprises the tetracyclic ring along with quinine-hydroquinone and one of the rings possesses 3-amino-2,3,4–trideoxy-L-fucosyl moiety [32]. Doxorubicin is known as one of the best chemotherapeutic agents approved by the FDA for the treatment of human malignancies [33]. The anticancer effects of doxorubicin have been attributed through a wide spectrum of mechanisms. It intercalates into the double helix of DNA to abrogate the synthesis of DNA and RNA which results in cell death (Fig. 1C). It has also been categorized as topoisomerase-II poison. Topoisomerases assist replication and transcription by cleaving DNA strands to maintain the topology of duplex DNA without modifying its sequence. Topoisomerase-II targeting agents induce their activity by two mechanisms. They can either block the catalytic activity of topoisomerase-II or elevate DNA-topoisomerase-II covalent complexes (often termed as topoisomerase poisons). Doxorubicin, etoposide, and mitoxantrone are some of the important topoisomerase-II poisons [34]. Besides, doxorubicin can impair the functions of 20S proteasomal subunit, cardiolipin, mitochondrial creatine kinase, and elevate the levels of reactive oxygen species (ROS) to distort the structure of biomolecules [32,33]. The therapeutic efficacy and adverse effects of doxorubicin have prompted the researchers to design nanotechnology-based doxorubicin formulations. Among the nano-systems, liposome-based nano-drug delivery systems (Doxil® and Myocet®) have been approved for the treatment of ovarian cancer, breast cancer, multiple myeloma, and AIDS-related Kaposi's sarcoma.

2.4. Epothilones (Ixabepilone)

Epothilones belong to the class of macrolide compounds with a remarkable cytotoxic activity towards various cancer cells. Epothilone A and B were discovered from the culture of myxobacterium *Sorangium cellulosum* and structurally both variants have similarities with an exception of bearing an extra methyl group at C12 position in epothilone B [35]. In the initial studies, epothilone A and B were reported to induce tubulin polymerization, microtubule bundling, and mitotic arrest which are similar to the effects induced by taxanes. The hyperstable microtubules cease the mitosis at the G2/M phase which could promote cell death [36]. Epothilone A and B compete with paclitaxel for binding to microtubules to repress their dynamics demonstrating that binding sites for paclitaxel and epothilone are the same. Moreover, epothilone B is a relatively more efficacious inducer of tubulin polymerization than variant A. Interestingly, epothilone does not impart G2/M mitotic arrest at low doses, instead, they convert cancer cells into aneuploids which undergo cell death in the G1 phase suggesting that G2/M arrest may not

be essential for epothilone-triggered apoptosis [37]. A significant amount of cancer patients treated with microtubule-stabilizing agents develop resistance to these chemotherapeutic agents due to overexpression of P-glycoproteins. Importantly, epothilones A and B have displayed antiproliferative efficacy towards taxane-resistant cancer cells [38,39]. Unfortunately, epothilones lost their cytotoxic potential upon incubation in mouse plasma suggesting the metabolic instability of these compounds. Administration of esterase inhibitor (bis[4-nitrophenyl]-phosphate) along with epothilones restored cytotoxic activity suggesting the need for the structural modification in the parent compound. Subsequently, BMS-247550 or ixabepilone, an amide analog of epothilone B, was developed using a semi-synthetic approach. Ixabepilone is metabolically stable with potent tubulin polymerization efficacy and active against paclitaxel-resistant cells. Additional studies using ixabepilone as a single agent or in combination with other chemotherapeutic agents (such as paclitaxel, cisplatin) towards a wide range of cancer cell lines and *in vivo* preclinical models (including paclitaxel-insensitive or paclitaxel-refractory) displayed significant growth-inhibitory activity. These results presented ixabepilone as a promising agent with the capability to enter clinics. In 2007, FDA approved the clinical use of ixabepilone (IXEMPRA) against anthracycline/taxane/capecitabine-resistant metastatic or locally advanced breast cancer. The combination of ixabepilone and capecitabine has also been approved for the treatment of patients with anthracycline/taxane-resistant breast cancer. The combination of ixabepilone and capecitabine was found to be more efficacious than capecitabine alone in prolonging progression-free survival and improving objective response rate in advanced triple-negative breast cancer patients who were earlier treated with taxane- and anthracycline-based drugs [40]. The effect of ixabepilone alone or in combination with bevacizumab was also evaluated in phase-II trials for the treatment of advanced renal cell carcinoma [41]. Ixabepilone alone can cause tumor regression in some patients with metastatic renal cell carcinoma and suggested examination in combination regimens with other therapies [42].

2.5. Epoxomicin (Carfilzomib)

Epoxomicin is a linear peptide epoxyketone isolated from *Actinomycetes* strain, No. Q996-17. In the initial studies, this compound showed strong growth-suppression effects against B16 melanoma and moderate activity towards P388 mouse leukemia [43]. The development of epoxomicin as a clinical agent was impeded due to a lack of drug-like properties and unknown mode-of-action. Crews and colleagues tracked the binding partners of epoxomicin by tagging it with biotin. The biotinylated-epoxomicin covalently interacted with LMP7, X, MECL1, and Z catalytic subunits of the proteasome and this demonstrated epoxomicin as a potent and selective inhibitor of the proteasome [44,45]. The epoxomicin was structurally optimized to yield a new derived named YU-101, which was a more efficacious inhibitor of proteasome than epoxomicin and bortezomib. Unfortunately, YU-101 showed poor aqueous solubility which hindered its clinical development. Subsequently, the addition of morpholine ring to the YU-101 resulted in the new derivative named carfilzomib (Kyprolis™) which retained proteasome inhibitory efficacy with increased aqueous solubility. Unlike bortezomib, carfilzomib was devoid of inhibitory activity towards serine proteases. The inhibition of serine proteases by bortezomib is a likely cause of dose-limiting peripheral neuropathy associated with its administration [46]. In phase-II trials, carfilzomib was effective in patients with relapsed and refractory multiple myeloma [47]. In 2012, carfilzomib was approved by the US FDA for the treatment of relapsed and refractory multiple myeloma patients who have previously received at least 2 therapies, including bortezomib and an immunomodulatory agent [48]. A phase-III study suggested that carfilzomib with dexamethasone could be considered in relapsed or refractory multiple myeloma patients in which bortezomib with dexamethasone is an effective therapeutic option [49]. Overall, carfilzomib has now emerged as a new generation proteasome inhibitor with a potent therapeutic efficacy towards multiple myeloma.

2.6. Mitomycin C

Mitomycin C is an antibiotic endowed with antitumor and antifibrotic activity. It is produced by *Streptomyces caespitosus* and approved for the treatment of breast cancer, pancreatic cancer, non-small cell lung carcinoma, and other cancers in combination with another standard chemotherapeutic agent. Although mitomycin C is highly efficacious as an anticancer agent, its clinical application has been significantly hampered due to toxicity towards bone marrow and other tissues. Chemically, mitomycin C possesses quinone and aziridine moieties in its structure and the methylated derivative of mitomycin C named porfiromycin displayed significant activity with radiation therapy in the clinical trials in head and neck cancer [50]. Mitomycin C imparts antitumor activity by crosslinking DNA. Mitomycin C is a prodrug that requires enzymatic bioreduction to induce its pharmacological effects [51]. The enzymatic reduction of the quinone structure in mitomycin C generates an extremely reactive intermediate that can alkylate nucleophiles including DNA. Thus, mitomycin C induces the formation of four monoadducts and two crosslinks [52]. Baird and colleagues demonstrated the Nrf-2-dependent activation of mitomycin C in Nrf-2-positive cancer cells indicating the possibility of bioactivation of mitomycin C by oncogenic proteins in human cancers [53]. Doxorubicin-mitomycin C co-loaded solid polymer–lipid hybrid nanoparticles exhibited synergetic antiproliferative activity in multidrug-resistant breast cancer cells [54]. Recently, Gabizon and coworkers prepared a mitomycin C conjugated distearoyl-glycerol and packed it into PEGylated stealth liposomes to overcome previously reported limitations. This formulation is being tested in clinics under the trademark name of Promitil® [55].

2.7. Pentostatin

Pentostatin (2′-deoxycoformycin) is a purine nucleoside analog isolated from *Streptomyces antibioticus* and used for the treatment of hairy cell leukemia [56]. This is an inhibitor of adenosine deaminase, which catalyzes the conversion of adenosine to inosine in purine metabolism. Although the antitumor mechanism of pentostatin is complex and not precisely understood, three biochemical events are associated with it. Firstly, inhibition of adenosine deaminase leads to the accumulation of deoxyadenosine, which is converted to deoxyadenosine triphosphate (dATP) (Fig. 1D). The dATP inhibits ribonucleotide reductase which is responsible for the conversion of ribonucleotides to their corresponding deoxynucleotides that impairs the concentration of nucleotides and finally this leads to the abrogation of DNA replication [57]. Secondly, increased concentration of adenosine inhibits S-adenosylhomocysteine hydrolase, which leads to the build-up of S-adenosylhomocysteine. In turn, S-adenosylhomocysteine serves as an inhibitor of methyltransferases that are involved in the methylation of DNA. Thirdly, pentostatin is converted to its triphosphorylated form which is aberrantly introduced into DNA [57]. Several studies have demonstrated the anticancer potential of pentostatin in hairy cell leukemia patients. Pentostatin showed a higher response and relapse-free survival rate in comparison with interferon α treatment in a randomized study among 313 hairy cell leukemia patients [58]. Grever and colleagues also conducted the long-term follow-up on overall/relapse-free survival and second malignancies in hairy cell leukemia patients treated with pentostatin [59]. 241 hairy cell leukemia patients treated with pentostatin were monitored for the median period of 9.3 years. The estimated 5- and 10-year survival rates were 90 % and 81 %, respectively [59]. Taken together, the results of many clinical trials have concluded that pentostatin can potentially act as a highly effective regimen for the treatment of hairy cell leukemia patients who had a history of unresponsiveness to therapy.

2.8. Rapamycin and rapalogs

Rapamycin (also known as sirolimus) is a macrolide compound isolated from *Streptomyces hygroscopicus* from the soil of Easter Island [60]. Initially, rapamycin was identified as the inhibitor of p70 S6 protein kinase and subsequently, the precise target of rapamycin was identified [61–63]. Studies have demonstrated that rapamycin forms a complex with its immunophilin named FK506-binding protein (FKBP12). The complex formed between rapamycin and FKBP12 binds to mTORC1 (mammalian/mechanistic target of rapamycin complex 1) which results in its inhibition and subsequent antiproliferative effect [64]. Elevated activity of mTORC1 is seen in many types of human malignancies. The elevated activity is attributed to gain-of-function in the proto-oncogenes or loss-of-function mutations in the tumor suppressor genes of the PI3K/AKT/mTOR signaling pathway. These mutations enhance the proliferative potential of cancer cells over their normal counterpart [65]. In addition, mTORC1 also modulates major metabolic pathways such as glycolysis, hexose monophosphate shunt, lipid metabolism through the regulation of expression of HIF1α, c-Myc, SREBP-1, and SIRT4. Therefore, targeting mTORC1 using rapamycin and other inhibitors serves as an ideal strategy to specifically counteract the proliferation of cancer cells. Despite promising anticancer effects, rapamycin failed to enter clinics due to its poor aqueous solubility which led to the development of its water-soluble analogs termed rapalogs. Everolimus is a water-soluble derivative of rapamycin, which has been approved by the FDA for the treatment of renal cell carcinoma, pancreatic neuroendocrine tumor, and subependymal giant cell astrocytoma. Temsirolimus is another approved rapalog that is used for the treatment of renal cell carcinoma. Besides, these rapalogs in combination with vorinostat are undergoing clinical trials for the treatment of advanced cancer (NCT01087554). Currently, many clinical trials are underway to study the effect of temsirolimus as a single agent or in combination with other therapeutic agents for the treatment of rhabdomyosarcoma and advanced cancers (NCT02567435, NCT02389309, NCT01552434) [66].

2.9. Romidepsin

Romidepsin, also known as Istodax, is a bicyclic depsipeptide anticancer antibiotic isolated from the fermentation broth of *Chromobacterium violaceum*. Structurally, it possesses a 3-hydroxy-7-mercapto-4-heptenoic acid with a pentapeptide comprising of D-valine, D-cysteine, dehydrobutyrine, and L-valine [67]. It promotes apoptosis of cancer cells and induces anticancer function by inhibiting histone deacetylases (HDACs). Romidepsin is a prodrug in which the disulfide bridge undergoes a glutathione-mediated reduction in the cell and the free sulfhydryl group interacts with zinc present in the active site of HDACs to induce catalytic inhibition [68]. Romidepsin has been approved for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma [69]. It was initially named as FR901228 [70] and early studies using romidepsin showed selective cytotoxicity towards a wide range of cancer cell lines without significant cytotoxic effect on normal cells [71–73]. Nakajima and colleagues identified romidepsin as an inhibitor of HDACs [74]. Further studies demonstrated romidepsin as a selective inhibitor of class I HDACs (such as HDAC1, 2, 3, and 8) with a feeble inhibition towards class II HDACs (including HDAC 4, 5, 7, and 9) [75]. Romidepsin is well-tolerated but associated with variable degrees of cardiac toxicity [76]. Since a relatively small number of therapeutic options available for the treatment of cutaneous/peripheral T-cell lymphomas, romidepsin remains as an important therapeutic agent to treat these diseases.

3. Anticancer potential of bacterial metabolites

Consistent efforts have been put forth by researchers to identify new metabolites with good cytotoxic potential from various biological sources. A large number of research papers related to the discovery of novel bioactive compounds from bacterial sources are being published every year in journals such as Journal of Antibiotics and Journal of Natural Products. In this section, we have discussed the possible sources, anticancer efficacy, and mode-of-action of selected bacterial secondary metabolites. The selected metabolites presented in the following section are either being evaluated in clinical trials or displayed good potency in preclinical studies. The chemical structure of the discussed bioactive compounds derived from the different bacteria have been provided in Fig. 3. Some of the selected compounds which have shown good activity in cell-based assays are presented in Table 1.

3.1. Antimycins

Antimycins are a large group of depsipeptide compounds produced by *Actinobacteria* and more than 45 antimycins have been discovered so far [77]. Antimycins exhibit a broad range of biological activities including anticancer, antiviral, antifungal, anti-inflammatory, nematocidal, and insecticidal effects [78]. Moreover, they are also used as piscicidal agents to reduce the population of undesirable fish in pisciculture. In addition to conventional nine-membered ring-bearing antimycins, “ring-expanded” candidates of this family have also been discovered. In the ring expanded category, 12-membered macrocyclic ring (JBIR-06, JBIR-52), 15-membered macrocyclic ring (neoantimycin A/F/G, SW-163A/B), and 18-membered macrocyclic ring (respirantin and other two structurally related compounds) are the major subfamilies reported so far [78]. Many antimycins have displayed promising anticancer activities with different mode-of-action in cancer cells. For instance, antimycin A has been reported to induce anticancer effect *via* inhibiting mitochondrial cytochrome C reductase resulting in blocking of electron transport chain (ETC) and subsequent loss of proton gradient across the membrane [79]. The clinical development of antimycin A has been hindered due to its cytotoxicity towards non-diseased cells probably due to the inhibition of ETC. Besides, antimycin A and other related compounds have been found to inhibit Bcl-2 family antiapoptotic proteins. These proteins are responsible for apoptotic resistance, drug resistance, and prosurvival phenotype of cancer cells. Computational analysis and protein mutagenesis studies showed that antimycins could interact with the BH3-binding groove of Bcl-xL [80,81]. 12- and 15-membered macrocyclic ring bearing antimycins were found to inhibit glucose-regulated protein (GRP78). For instance, prunustatin A (a member of neoantimycins family, isolated from the *Streptomyces violaceoniger* 4521-SVS3) and JBIR-06 (produced by *Streptomyces* sp. ML55) inhibited the 2-deoxyglucose-induced GRP78 expression in human fibrosarcoma (HT1080) cells [82,83]. A similar inhibitory effect was observed towards GRP78 upon treatment with versipelostatin and JBIR-52 [84,85]. GRP78 is a major and well-understood chaperone involved in the maintenance of protein folding and quality control in the endoplasmic reticulum. However, GRP78 is critical for cancer cell survival, cancer progression, and drug resistance [86]. Antimycin A repressed the spheroid-forming potential of side population cells derived from A549 cell lines through interfering with the β-catenin signaling cascade [87]. Maeda and coworkers showed that antimycin suppresses angiogenesis *via* blockade of HIF1α mediated VEGF expression [88]. Several other antimycins such as unantimycin A, neoantimycins, and many more are reported to anticancer activity in cellular models and their mode-of-action has not been precisely deciphered. Taken together, antimycins can impart growth-inhibitory potential in cancer cells by modulating various pharmacologically important targets.

3.2. Chartreusin, elsamicins, and other structural analogs

Chartreusin is an aromatic polyketide glycoside that has a disaccharide (made up of fucose and digitalose) and an uncommon benzonaphthopyranone aglycone designated as chartarin [89]. This compound is isolated from *Streptomyces chartreusis* which displayed significant anticancer activity towards various tumor cells. Despite the

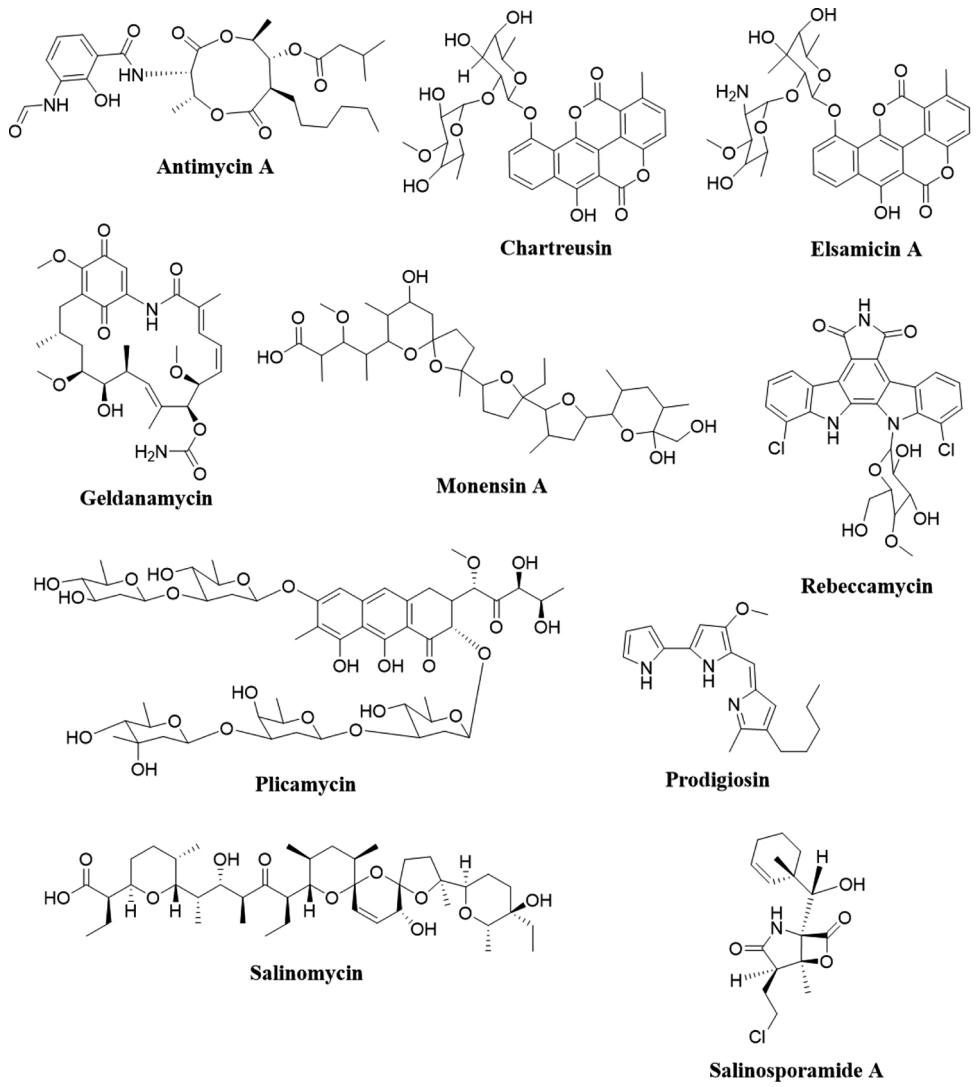

Fig. 3. Structure of bacterial secondary metabolites that are being tested in clinical trials or bacterial metabolites which showed good antiproliferative activity in preclinical studies.

anticancer activity, it was not considered for drug development due to an ineffective pharmacokinetic profile [21]. This led to the development of a semisynthetic derivative of chartreusin named IST-622, which presented marked antitumor activity and advanced to phase-II clinical trials. Studies have demonstrated that chartreusin and its structural analogs could impart cytotoxic effect mainly through interacting with G-C rich region on DNA, topoisomerase-II inhibition, and inducing breakage of single strands of DNA [90]. IST-622 displayed substantial antitumor activity *in vivo* on oral administration possibly because of elevated absorption through the gastrointestinal tract [91].

Elsamicin A and B were obtained from an unidentified actinomycete and these antibiotics are closely related to chartreusin. Elsamicins interact with the G-C rich region on the DNA to induce single-strand breaks [8] and the coumarin-related chromophore (chartarin) of elsamicin A intercalates into the duplex DNA [92]. The binding of these compounds to DNA can inhibit transcription as well. Elsamicin A is one of the most potent inhibitors of topoisomerase-II, without significant activity towards topoisomerase-I. Elsamicin B lacks substantial biological activity. Elsamicin A has shown significant growth inhibitory activities towards cancer cells of various origins [93]. Elsamicin A showed good safety in phase-I studies but failed in phase-II trials as it is not active in metastatic breast cancer, colorectal cancer, non-small cell lung cancer, or ovarian cancers at the administered dose and schedule [94].

3.3. Geldanamycin

It is a benzoquinone ansamycin antibiotic isolated from *Streptomyces hygrocopicus* and *Streptomyces zerumbet* W14 with anticancer activity towards various types of cancer cells. In the initial days, geldanamycin was hypothesized to induce anticancer activity through inhibiting the activity of tyrosine kinases, and later studies demonstrated the blockade of HSP90-pp60v-src heteroprotein complex formation. It was found to exert anticancer activity through abrogating kinase folding by the HSP90 chaperone complex in a broad range of cancer cells [95]. HSP90 is a most abundant cytosolic molecular chaperone that encourages the stabilization of proteins and inhibition of HSP90 promotes the proteasome-mediated degradation of proteins associated with oncogenicity [96]. Geldanamycin induced significant cytotoxicity in most of the cell lines used in NCI anticancer drug screens [97]. Park and team identified that geldanamycin exerts anticancer effects in thyroid cancer cells by reducing c-Raf-1, mutant p53, and epidermal growth factor receptor [98]. Despite its anticancer efficacy, its entry to clinical trials and subsequent translation to clinics has been hampered due to its poor water solubility and toxicity, which may be contributed by the presence of benzoquinone. However, geldanamycin displayed hepatotoxicity and nephrotoxicity at therapeutically relevant doses in experimental animals and thus was found to be unsuitable for use. Many researchers are

Table 1
List of antitumor antibiotics with their mechanism of action.

Sl. No.	Name of the compound	Class	Bacterial source	Mode-of-action	Preclinical models	Reference
1	Androprostamine A and B	Peptide	*Streptomyces* sp. MK932-CF8	Inhibits androgen receptor	Prostate cancer cell lines (LNCaP and VCaP)	[174]
2	Azinomycins A and B	Aziridine	*Streptomyces sahachiroi, Streptomyces griseofuscus*	Interstrand crosslinking of DNA	P388 leukemia, P815 mastocytoma, B16 melanoma, Erlich carcinoma, Lewis lung carcinoma, Meth A fibrosarcoma	[175,176]
3	Brartemicin	Trehalose derivative	*Nonomuraea* sp TP-A0870	ND	26-L5	[177]
4	Bezerramycins A–C	Phenoxazinone	*Streptomyces griseus*	ND	K562, HUVEC, HeLa	
5	Carminomycin I	Anthracycline	*Actinomadura carminata*	Potent suppressor of Von Hippel–Lindau-defective ($VHL^{-/-}$) clear cell renal carcinoma cell proliferation. It Induced the cleavage of Golgi protein p115 and promotes the nuclear localization of the C-terminus of Golgi protein.	786-O, UOK-121, UOK-127	[178]
6	Chandrananimycins	Phenoxazinone	*Actinomadura* sp. M048, *Streptomyces griseus*	ND	CCL HT29, MEXF 514 L, LXFA 526 L, LXFL 529 L, CNCL SF268, LCL H460, MACL MCF-7 PRCL PC3M, RXF 631 L	[179]
7	Elloxazinones A and B	Phenoxazinone	*Streptomyces griseus* Acta 2871	ND	HepG2, MCF-7, HM02, AGS	[180]
8	Gilvocarcins H, M	Polyketide	*Streptomyces* sp. QD01-2	ND	MCF-7, K562, P388 cells	[15]
9	Gilvocarcin V	Polyketide	*Streptomyces griseoflavus* Gö 3592	Intercalate with DNA, Crosslinking of histone H3 and GRP78 to DNA	GM637, GM38, NHDF, and NHLF	[181]
10	IADA-7	2-*N*-methyl-2,4-diazacycloheptanone	*Bacillus* sp. J-89	Adenosine deaminase inhibitor	Jurkat T, J82	[182]
11	Isofuranonaphthoquinone	7,8-dihydroxy-1-methylnaphtho[2,3-c]furan-4,9-dione	*Actinoplanes* sp.	ND	HL-60, HF, 518A2, KB-V1/Vbl, HT-29, MCF-7	[183,184]
12	Kedarcidin	Enediyne	*Actinomycete* sp. L585-6	Induces DNA damage and cleavage	B16, P388	[185]
13	Kigamicin A-E			ND	PANC-1	[186]
14	Kigamicin D	Polycyclic aromatic compounds	*Amycolatopsis* sp. ML630-mF1	ND	Tumor cell-induced angiogenesis in a dorsal air sac model, Xenograft lung cancer mice model	[187]
15	Lemonomycin	Tetrahydro-isoquinoline	*Streptomyces candidus*	ND	HCT116	[188,189]
16	Lidamycin	*Enediyne*	*Streptomyces globisporus* C-1027	Induces DNA strand breakage, arrests cell cycle, and promotes apoptosis. It potentiates the antiproliferative activity of gemcitabine by downregulating NF-κB.	BEL-7402, Panc-1, SW1990	[190,191,192]
17	Lobophorin C and D	Kinjanimicin derivative	*Streptomyces carnosus* AZS17	ND	MDA-MB-235	[193]
18	Lomaiviticin A	Diazotetrahydrobenzo[b] fluorene	*Salinispora pacifica* 37L366	Induces DNA double-strand breaks	K562	[194,195]
19	Nomimicin	Polyketide	*Actinomadura* sp. TP-A0878	ND	HeLa, MCF7	[196]
20	Oxanthromicin	Anthrone	*Actinomodura* sp. BCC47066	ND	KB, MCF-7, NCI-H187	[197]
21	Pitucamycin	Phenoxazinone	*Streptomyces griseus*	ND	K562, HUVEC	[198]
22	Pradimicin-IRD	Aglycone dihydrobenzo naphthoquinone with glycoside substitutions	*Amycolatopsis sp. IRD-009*	Induces DNA damage	HCT116, HT29, SW480, Caco-2	[199]
23	Rhodomycin A	Anthracycline	*Actinomycete*	Targets Src and its related signaling pathways	A549, H1975, PC9	[200]
24	Rubeomycin	Anthracycline	*Actinomadura roseoviolacea*	ND	P388 leukemia in mice	[201]
25	Rubromycins	Naphthazarin and isocoumarin	*Actinomycetes, Streptomyces collinus*	Inhibits telomerase activity	HMO2, Kato III, HepG2, MCF7	[202]
				Inhibits glycogen synthase kinase-3β	TT	[203]
26	Tautomycetin	Polyketide	*Streptomyces griseochromogens*	Inhibits protein phosphatases 1 and 2A	–	[204]
				Induces p21cip/WAF1 *via* ERK pathway	HCT116	[205]
27	Tautomycin	Polyketide with a spiroketal moiety	*Streptomyces spiroverticillatus*	Inhibits glycogen synthase kinase-3β	TT	[203]
					–	[204]

(*continued on next page*)

Table 1 (*continued*)

Sl. No.	Name of the compound	Class	Bacterial source	Mode-of-action	Preclinical models	Reference
28	Telomestatin	Macrocyclic peptide	*Streptomyces anulatus* 3533-SV4	Inhibits protein phosphatases 1 and 2A Telomerase inhibitor	Telomerase, semi-purified enzyme from human B lymphoma Namalwa cells	[206]
29	Thiocoraline	Depsipeptide	*Micromonospora marina*	Interacts with duplex DNA Inhibits DNA polymerase-α Mediates drug resistance through PI3K/Akt/BCRP signaling pathway	L1210 LoVo, SW620 MCF-7	[207] [208] [209]
30	Verucopeptin	*Depsipeptide*	*Actinomadura verrucosospora* Q886-2	Inhibitor of HIF-1α and mTORC1 signaling pathway	B16, HT1080	[210]
31	ZHD-0501	Staurosporine analog	*Actinomadura* sp. 007	ND	A549, BEL-7402, HL60	[211]
32	1-(10-Aminodecyl) pyridinium	Pyridine derivative	*Amycolatopsis alba*	ND	MCF7, HeLa, U87MG	[212]
33	N-(2-hydroxyphenyl)-2-phenazinamine	Phenazinamine	*Nocardia dassonvillei*	ND	HepG2, A549, HCT-116, COC1	[213]

Cell lines:
Acute promyelocytic leukemia: HL-60; Bladder cancer: J82; Breast cancer: CNCL SF268, LCL H460, MACL MCF-7; Cervical cancer: KB-V1/Vbl; Colon cancer: HCT116, LoVo, SW620, CCL HT29; Gastric cancer: AGS, HM02; Glioma: U251MG, U87MG, A172, T98 G, U251 N; Kidney cancer: 786-O, UOK-121, UOK-127; Liver cancer: HepG2, BEL-7402; Lung cancer: A549, H1975, PC9, LXFA 526 L, LXFL 529 L; Prostate cancer: PC-3, Panc-1, MiaPaCa-2; Melanoma: B16, 518A2, MEXF 514 L; Kidney cancer: PRCL PC3M, RXF 631 L; Thyroid cancer: TT; Mouse lymphocytic leukemia: L1210; Murine colon cancer: 26-L5; Normal human diploid fibroblast: GM637, GM38, NHDF, NHLF; Ovarian cancer: COC1; T-cell lymphoma: EL-4; T-cell leukemia: Jurkat T cells.

attempting to overcome the issues of safety, tolerability, and solubility of geldanamycin either by chemically modifying the original structure or synthesizing its structural analogs [99–101]. In one such study, two geldanamycin derivatives with better aqueous solubility and selective cytotoxicity towards cancer cells were synthesized [102]. In another study, a non-benzoquinone geldanamycin analog induced cell death of breast cancer cells through activation of necroptosis [103]. Lee et al. prepared geldanamycin derivatives *via* a semi-synthetic approach using genetically engineered biosynthetic intermediates and the new compounds showed good antiproliferative activity towards breast and ovarian cancer cell lines [104]. The water-soluble derivative of geldanamycin, 17-dimethylaminoethylamino17-demethoxygeldanamycin hydrochloride, displayed a good antitumor effect in *in vitro* and *in vivo* studies posing the scope for the reduction of toxicity and improvement anticancer potential of geldanamycin [105]. In phase-I clinical studies, 17-(allylamino)-17-demethoxygeldanamycin exhibited a tolerable toxicity profile with therapeutic plasma concentrations and target inhibition for 24 h after treatment and some indications of clinical activity in patients with advanced malignancies [106]. In another phase-II clinical study, 17-(allylamino)-17-demethoxygeldanamycin could not achieve objective response in the treatment of clear cell or papillary renal cell carcinoma patients [107].

3.4. Monensin

Monensin is a polyether ionophore antibiotic isolated from *Streptomyces cinnamonensis* and it is endowed with potent anticancer activity. Tumor necrosis factor-related apoptosis-induced ligand (TRAIL) is a cytokine that acts as a death ligand to induce apoptosis preferentially in cancer cells over non-diseased cells. Many cancer cells acquire resistance to TRAIL-induced apoptosis through different mechanisms [108]. Yoon and colleagues demonstrated that monensin potentiates TRAIL-induced apoptosis in glioma cells. Mechanistically, this effect was found to be mediated through the upregulation of death receptor 5 (DR5), endoplasmic reticulum stress, and proteasome-driven cFLIP suppression [109]. Wnt signaling is aberrantly activated in various human cancers and the monensin attenuated Wnt pathway in colon cancer cells and imparted growth-inhibitory activity in multiple intestinal neoplasia mice [110]. Monensin induced apoptosis of prostate cancer cells by promoting ROS generation and thereby disrupting calcium homeostasis [111]. It also activated autophagy to promote cell death in renal cell carcinoma cells with a decline in PRCC-TFE3 fusion transcript. In another recent study, Wang and coworkers showed that monensin suppresses proliferation of the drug-resistant cancer cells and xenograft tumor growth by targeting EGFR signaling cascade [112]. These studies presented the scope for evaluating monensin towards cancer treatment in clinical trials.

3.5. Plicamycin

Plicamycin (also called mithramycin) belongs to the class of aureolic acid antibiotics. It is produced by *Streptomyces plicatus* and *Streptomyces argillaceus* (ATCC 12956). The other members of aureolic acid antibiotics are durhamycin A, UCH9, olivomycin A, and chromomycin A_3 [113]. Although plicamycin possesses a strong antitumor activity, it has not been approved for the treatment of human cancers in the United States due to the concerns of bone marrow, hepatic, and renal toxicities [114]. Because of its efficacy in germ cell and testicular cancers, it is used as an experimental therapeutic agent in resistant and advanced cancers [114]. Historically, it was used as an antihypercalcemic agent in neoplasms. Plicamycin induces substantial anticancer effects by cross-linking of the DNA strands which results in halting of replication and transcription. In another study, plicamycin was found to specifically interact with a guanine-cytosine-rich region of the DNA and thereby preventing the interaction of Sp family transcription factors to DNA regulatory consensus [115]. *c-Src* is a proto-oncogene that is overexpressed in many types of cancers and the expression of the *c-Src* gene is dependent on the interaction of Sp1 proteins. Plicamycin and some of its derivatives generated through combinatorial synthesis have been demonstrated to inhibit the transcription of *c-Src* through the modulation of Sp family proteins [113,116,117]. Plicamycin decreased Sp1 protein by promoting proteasome-mediated degradation and induced antiproliferative function in cervical cancer cells *via* DR5/caspase-8/Bid axis [118]. Plicamycin increased the sensitivity of cancer cells to TNF-driven apoptosis without altering the expression of NF-κB target genes indicating that it may be a good cytotoxic agent towards apoptosis-resistant cancer cells [119]. Plicamycin stabilized p53 and enhanced the expression of its target genes. It displayed synergy with nutlin-3 in gynecologic cancers. Nutlin-3 is a small molecule that interacts with Mdm2 which in turn disrupts the Mdm2–p53 interaction

[120]. In another study, seven new mithramycin analogs were synthesized and among them, demycarosyl-3D-β-D-digitoxosylmithramycin SK displayed significant antitumor activity in cell-based assays and colon and melanoma xenograft models with less toxicity than the parent compound [121,122]. Apart from DNA binding activity, the pleiotropic role of mithramycin has been explored in an interesting study by Banerjee and the team. Plicamycin was found to interact with core histones in chromatin even in the absence of Mg^{2+} and suppresses the acetylation of lysine 18 of H3 *in vitro* and *ex vivo* [123]. This particular acetylation is a hallmark of active chromatin. Plicamycin showed a good antitumor effect and was identified as an inhibitor of EWS-FLI1-driven transcription [124]. A phase I/II trial showed that plicamycin was too toxic at the dose required to inhibit EWS-FLI1 [125,126]. Currently, plicamycin is undergoing clinical trials to find out its pharmacokinetics, toxicities, and maximum tolerated dose upon continuous 24 h infusion in patients with carcinomas, sarcomas, or germ cell tumors with pleuropulmonary metastases (NCT02859415). Several attempts have been made by researchers to prepare semi-synthetic derivatives and nanoparticulate formulations of mithramycin to improve its cytotoxic efficacy and toxicity profile [127,128].

3.6. Prodigiosin

Prodigiosin is a family of red pigments made up of a tripyrrole which is majorly produced by *Serratia* species including a Gram-negative *Serratia marcescens* [129]. The other members of the prodigiosin family are prodigiosin, undecylprodigiosin, and cycloprodigiosin hydrochloride [130]. This pigment has been demonstrated to have various pharmacological effects such as anticancer, antimicrobial, antimalarial, and immunosuppressive effects [131,132]. Prodigiosin imparts antiproliferative function *via* targeting various cellular processes [133]. Pérez-Tomás and colleagues reviewed the anticancer functions of prodigiosin and suggested that they may act by functioning as pH modulators, cell cycle inhibitors, DNA cleavage agents, and MAPK modulators [134]. Soto-Cerrato and coworkers showed the proapoptotic effect of prodigiosin towards multidrug-resistant breast cancer cells which overexpresses breast cancer-resistant protein [135]. Studies have also demonstrated that prodigiosin is not a substrate of multidrug resistance protein [136]. The same group also showed that prodigiosin induces the expression of $p21^{WAF1/CIP1}$ through the mediation of transforming growth factor-β receptor pathway [137]. The gene expression profiling of prodigiosin-treated breast cancer cells using cDNA array technology revealed the significant upregulation of nonsteroidal anti-inflammatory drug-activated gene 1 (NAG-1). Further investigation showed the activation of glycogen synthase kinase-3β on treatment with prodigiosin indicating that the several types of proapoptotic signals are initiated upon its treatment [138]. Prodigiosin also suppresses the expression of survivin to increase the sensitivity of breast cancer cells to paclitaxel [139]. Survivin is an apoptosis inhibitor that is widely expressed in many human cancers. In an interesting study, prodigiosin was found to rescue the deficient p53 signaling in cancer cells by inducing p73 and thus abrogating the interaction of mutant p53 and p73 [140]. Recently, Wang and colleagues showed that prodigiosin exhibits significant growth-inhibitory activity in *in vitro* and *in vivo* breast cancer model by potently abrogating Wnt/β-catenin signaling pathway, which is aberrantly activated in many human cancers [141]. Obatoclax (GX15-070), a structural analog of prodigiosin was tested in phase-I/II trials in acute myeloid leukemia patients, which displayed the maximum tolerated dose of 20 mg/day. The treatment of obatoclax was not associated with an objective response. The investigators suggested the addition of subgroups or combination with other treatment options to increase the efficacy [142].

3.7. Rebeccamycin

Rebeccamycin is an indolocarbazole-based antitumor antibiotic isolated from *Lentzea aerocolonigenes*. In the early days, rebeccamycin was isolated from an actinomycete culture of C-38383 collected from the soil sample of Panama. This was initially grouped under *Streptomyces* sp. and named as *Nocardia aerocolonigenes*, and subsequently, it is renamed as *Saccharothrix aerocolonigenes*, and *Lechevalieria aerocolonigenes* by different research groups [143]. Most recently, it is categorized as *Lentzea aerocolonigenes* [144]. Rebeccamycin imparted a good antiproliferative effect in many types of tumor-derived cells. Mechanistically, rebeccamycin serves as a DNA intercalating chemical that promotes double-strand breakage of DNA and inhibits topoisomerase I [145–147]. The development of this antibiotic as an anticancer drug has been hampered due to its poor solubility in aqueous media. Several semisynthetic derivatives have been generated using rebeccamycin as a template structure to increase hydrophilicity [148]. Becatecarin (NSC655649), a rebeccamycin analog and a dual inhibitor topoisomerase-I/II, entered clinical trials for the treatment of several solid tumors [149–151]. In phase-I/II studies, the new compound was well-tolerated with modest clinical activity in advanced breast and renal cell cancers [152,153]. In another clinical study, rebeccamycin analog as a single agent failed to produce superior effects relative to the existing agents for relapsed small cell lung cancer [154]. The combination of rebeccamycin analog and oxaliplatin showed tolerability and clinical activity, but rebeccamycin analog lacked significant activity as a single agent across a variety of disease sites in refractory solid tumors [155].

3.8. Salinomycin

Salinomycin is a monocarboxylic polyether antibiotic/potassium ionophore isolated from *Streptomyces albus* (ATCC 21838) and is used for the treatment of coccidial (a protozoan parasite) infections of poultry. A large number of studies have demonstrated the antiproliferative effects of salinomycin against various types of cancers. Distinguishingly, salinomycin was demonstrated to have toxicity towards cancer stem cells and decreased the proportion of cancer stem cells by >100-fold in comparison with paclitaxel [156]. Additionally, global gene expression studies indicated that salinomycin eliminates the expression of breast cancer stem cells [156]. It also suppressed the growth of the mammary tumor and other *in vivo* preclinical cancer models [157]. Fuchs and team showed that salinomycin induces apoptosis in cancer cells through a different mechanism independent of p53, caspases, proteasome, and CD95/CD95L system [158]. Remarkably, salinomycin was demonstrated to act as a potent inhibitor of gp170, a multidrug resistance protein that belongs to the family of P-glycoproteins [159]. These proteins are closely associated with conferring resistance against many chemotherapeutic drugs and the poor prognosis of cancer patients. The salinomycin treatment increased the doxorubicin concentration inside the drug-resistant cancer cells. The treatment of vinblastine along with salinomycin displayed strong proapoptotic effects in drug-resistant cancer cells indicating that salinomycin increases drug sensitivity in resistance cells [159]. A similar synergetic effect was observed with dichloroacetate in colorectal cancer cells [160]. Salinomycin also induced autophagy with the generation of ROS in colon and breast cancer cells [161]. Recently, Zhou and others reported that salinomycin counteracts proliferation of uveal melanoma cells, regresses xenograft tumor, eliminates cancer stem-like cells, and reduces hepatic metastasis in the uveal melanoma mouse model [162]. Salinomycin modulates various other cellular networks such as MAP kinases, NF-κB, Akt signaling pathway, Wnt/β-catenin, and Hedgehog, and Notch pathways to impart growth inhibitory activity in various cancers [163]. Overall, salinomycin is a potent candidate that has the ability to enter clinics to treat human malignancies.

3.9. Salinosporamide A

Salinosporamide A (Marizomib) is a γ-lactam-β-lactone produced by *Salinispora tropica* [164]. It showed selective and potent

growth-inhibitory activity towards a panel of 60 cancer cell lines (GI_{50} < 10 nm) at the National Cancer Institute [165]. Salinosporamide A and omuralide share structural similarity, and salinosporamide A is a more potent inhibitor of proteasome than omuralide [164]. Groll and team resolved the crystal structure of salinosporamide A with 20S proteasome core particle and demonstrated their irreversible interaction [166]. The proteasome is cellular machinery entangled with non-lysosomal degradation of intracellular proteins and the proteasome has been proposed as a validated drug target in the treatment of cancers since after the approval of bortezomib. In phase-I clinical trials, salinosporamide was well-tolerated in relapsed or relapsed and refractory multiple myeloma patients [167].

4. Metagenomics approach for the discovery of novel bioactive compounds

The conventional method (bioprospecting) of discovery of novel bioactive compounds from bacteria involves the isolation of bacteria, culturing on selective media, phenotypic screening, isolation and purification of compounds, investigation for their pharmacological effects, and elucidation of mode-of-action in *in vitro* and *in vivo* preclinical models. The use of the conventional method of secondary metabolites extraction cannot be implemented in the case of uncultivable bacteria. Notably, studies have suggested that the members of only 30 phyla out of 61 have cultivable representatives, which poses a challenge for the isolation of pure cultures and propagating them in laboratory conditions [168]. Overall, culturable microorganisms make up a small portion of the total microbial diversity in several environments [169].

The metagenomics approach is a culture-independent strategy that provides a platform to access the genome of the uncultivable bacteria through direct sequencing and cloning methods. Metagenomics has an advantage over traditional culture-dependent methods. The metagenomics technique is more reliable for the study of bacteria from extreme conditions as their propagation is difficult using the conventional methods due to unique growth conditions adapted by these bacteria [170]. The metagenomics approach also offers the upper hand by saving time and decreasing the need for culturing bacteria to explore the biologically active secondary metabolites. Metagenomics employs two major strategies such as random sequencing and targeted metagenomic sequencing to analyze the presence of particular genes or gene clusters/groups in the genome. Many studies have implemented a metagenomics approach for the discovery of new secondary metabolites produced by polyketide synthases and non-ribosomal peptide synthetase. For instance, bryostatin 1 is a polyketide that has been evaluated in many clinical trials for the treatment of cancers. Bryostatin 1 was believed to be produced by bryozoan *Bugula neritina*. Since bryostatin is a polyketide, subsequent metagenomic studies revealed the presence of genes encoding polyketide synthase gene complex in a bacterial symbiont *Candidatus* Endobugula sertula [171]. Also, *E. sertula* remains as an unculturable microbe and heterologous expression of biosynthetic gene cluster may be a viable strategy for the large-scale production of bryostatins.

ET-743 (Trabectedin, Yondelis®) is an anticancer drug approved in Europe for the treatment of relapsed ovarian cancer and soft tissue sarcoma, and this is undergoing phase-III clinical investigation towards other cancers. This was isolated from the sea squirt *Ecteinascidia turbinate* and its chemical structure closely resembles the natural compounds derived from the bacterial origin such as saframycin A, saframycin Mx1, and safracin. The common structural features of ET-743 and saframycins supported the prediction that ET-743 could be from a bacterial origin. Concurrently, several studies have demonstrated that Gammaproteobacterium *Candidatus* Endoecteinascida frumentensis is commonly associated with the host-microbial consortium and the culturing of this organism has not been successful so far. Application of metagenomic analysis of the host-microbial consortium resulted in the assembly of contig bearing non-ribosomal peptide synthetase biosynthetic gene clusters [172,173]. Subsequent extensive sequencing studies demonstrated *Candidatus* Endoecteinascidia frumentensis as the source of ET-743. In similar studies, a metagenomics strategy has been applied by researchers to identify many uncultivable microbes in various environments. Some of these microorganisms were found to produce natural bioactive compounds such as calyculin A, onnamides, patellazoles, polytheonamides, and psymberin. Therefore, it can be concluded that metagenomics can be used as a unique tool for the identification of pharmacologically important unculturable microorganisms from various environments.

5. Conclusion and future perspectives

The world is facing the need for the discovery of novel potent small molecules with significant anticancer potential and favorable toxicity profile. Many anticancer drugs that are in clinical practice today suffer from different degrees of adverse effects. It is the need of the hour to reduce toxicity on non-targeted tissues and improve site targeted approach. Therefore, there is a great demand for the discovery of bioactive cytotoxic natural compounds that are regarded as the best choice over synthetic compounds. In this direction, we have previously reported many natural and synthetic compounds as modulators of various oncogenic proteins in different cancer models. Additionally, several alternative strategies such as the use of nanocarriers have been developed and implemented to reduce the effect of chemotherapeutic agents on non-targeted tissues. The blockbuster anticancer drugs including doxorubicin, paclitaxel, camptothecin, vinblastine, vincristine, topotecan, and many more have been used in nano-based platforms such as polymer-drug conjugates, liposomes, polymeric nanoparticles, dendrimers, and immunoliposomes to increase the targeted tissue delivery and reduce toxicity towards healthy cells. The small molecules derived from Mother Nature and the synthetic origin have contributed substantially to the present-day commercially available drugs. Despite their substantial contribution, natural products take the upper hand over synthetic origin due to their relatively better toxicity profile. It is important to note that, natural compounds-based drugs are not completely devoid of adverse effects. For example, the approval of actinomycin D for the treatment of some cancers has been impeded because of its adverse effects such as tissue necrosis, myelosuppression, dermatotoxicity, and gastrointestinal enterotoxicity. Similarly, doxorubicin imparts dose-limiting myelosuppression, fatal cardiotoxicity, and cytotoxicity towards normal cells. To enhance the aqueous solubility and overcome the adverse effects of chemotherapeutic agents, researchers have developed or have been developing synthetic or semi-synthetic approaches for the preparation of newer derivatives. For an instance, the clinical development of rapamycin as an anticancer drug was withheld due to its poor hydrophilicity. Subsequently, its water-soluble derivatives (Everolimus and Temsirolimus) have turned out to act as potent antineoplastic agents and are approved for the treatment of renal cell carcinoma, pancreatic neuroendocrine tumor, and subependymal giant cell astrocytoma. These examples demonstrate the importance of using natural compounds as a template structure for the preparation of semisynthetic derivatives that are chemically novel, biologically potent, easily soluble, and less toxic in physiological relevance. The discovery of newer natural compounds and chemical derivatization using computational tools provides a huge platform for designing anticancer agents in near future. Considering all these aspects, natural products provide wide scope for the discovery of newer drug-seeds to address the unmet needs in cancer therapeutics.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

There is no conflict of interests to declare.

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