

A Review on the Present and Future Aspects of Various Prokaryotic Pigments and Metabolites Demonstrating Anti-Cancerous Properties

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Abstract— Prokaryotic organisms have always been known to produce a wide variety of metabolites and even various pigments. These pigments and metabolites are known to be associated with a wide range of properties including anti cancerous, anti-bacterial, anti-inflammatory to name a few. The biggest problem that the mankind is facing today is the different types of cancers that have become a threat to humanity. This review mainly focuses on various prokaryotic organisms like Cyanobacteria, Actinomycetes, Staphylococcus gallinarum, Streptomyces peucetius, Serratia mercensens that are widely known to produce several anti-cancerous compounds. These compounds have been observed to demonstrate cytotoxic activity in cancer cell lines. A detailed study will thus help us to understand and design several novel anti-cancerous drugs.

Keywords- Prokaryotic, metabolites, pigments, cancer, cytotoxic

I. A COMPLETE REVIEW

This review aims to provide some understanding related to the varied range of prokaryotes known for producing a large number of various anticancer compounds. According to Newman and Shapiro, microorganisms have always known to produce a number of anti-cancerous compounds which include actinomycin D (dactinomycin), anthracyclines, including daunorubicin, doxorubicin (adriamycin), epirubicin, pirarubicin, idarubicin, valrubicin, various types of glycopeptides (bleomycin, phleomycin), the mitosane mitomycin C, and the anthracenones (mithramycin, streptozotocin, pentostatin) [1,2].

11-hydroxyaclacinomycin A is a modified anthracycline which is produced by cloning. The genes involved for cloning are doxorubicin resistance gene and the aklavinone 11-hydroxylase gene *dnrF* from the doxorubicin producer, *Streptomyces peucetius* subsp. *caesius*, into the aclinomycin A producer. This hybrid compound is found to be highly effective against leukemia and melanoma [1, 2]. 2'-amino-11-hydroxyaclacinomycin Y is another hybrid compound which is reported to be highly effective against tumors. Also some innovative anthracyclines have been prepared by the introduction of DNA from *Streptomyces purpurascens* into *Streptomyces galilaeus* [1]

Myxobacteria are large Gram-negative rods that move by gliding or creeping. More than 400 compounds have been

derived from these organisms and one of the most effective anti tumor compound is epithilone. These are most effective against breast cancers. Epithilones are known to bind and stabilize the microtubules that are most essentially needed for cell division and DNA replication. By the prevention of the disassembly of microtubules, epithilones successfully arrest the tumor cell cycle at the G2/M phase and induce apoptosis [1, 3, 4].

Cyanobacteria are gram-negative photoautotrophic prokaryotes. They are known for carrying out oxygenic photosynthesis and are most commonly known as blue-green bacteria. They are known for producing C-phycoerythrin. Cyanobacterial products have long been known to possess anticancer, antiviral, antibacterial, immune-modulatory and protease-inhibition activities [1]. The anticancer activities are most widely studied. *Lyngbya* produces apratoxin D which is cytotoxic to human lung cancer cells [5]. *Symplocamide A*, isolated from *Symploca* sp. exhibits potent cytotoxicity to not only lung cancer cells but also neuroblastoma cells [6]. The anticancer drugs mainly work as apoptotic modulators [7,8]. Apoptosis is mainly brought out by the implication of intrinsic and extrinsic signals. These can be by reactive oxygen species [8], the UV radiation [9] and also by the flavonoid quercetin [10,11]. A demonstration by Martins and co-workers showed that when HL-60 cells are exposed to aqueous extracts of *Synechocystis* sp. and *Synechococcus* sp. Strains, cell shrinkage and membrane budding are evident which indicates that the cells are developing apoptosis [11,12]. *Lyngbya* sp., produces a macrolide called biselyngbyaside that induces apoptosis in mature osteoclasts [13] and marine benthic *Anabaena* sp. extracts are found to induce apoptosis in acute myeloid leukemia cell line [14].

The marine cyanobacteria brings about cytotoxicity in tumor cell lines mainly by the implication of several apoptotic indicators like cell cycle arrest, mitochondrial dysfunctions and oxidative damage, and by alterations in caspase cascade [11]. Bioactive metabolites like cryptophycin 52, calothrixin A, hectochlorin and lyngbyabellin B obtained from *Nostoc* spp [15], *Calothrix* [16] and *Lyngbya* [17] respectively are found to induce cell cycle arrest in G2/M phase in different human cancer cell lines [11]. Dolastatins [18] also exhibit a similar effect. Cyanobacterial aurilides A and B bring mitochondria fragmentation in HeLa cells and is evident by

MitoTracker Red staining [19]. The activity of caspase -3, the most important caspase related to apoptosis, increases after getting exposed to symplostatin 1 [20] and glicomacrolide biselyngbyaside [13]. Interestingly cryptophycin 1 is found to induce apoptosis in a human ovarian carcinoma cell line [21]. Symplostatin 1 [20] and Dolastatin 10 [22] initiates the phosphorylation of Bcl-2 which inhibits anti-apoptotic properties in human breast cancer cells. Curacin A is also a potential anticancer and antitumor agent obtained from a marine cyanobacterium [23].

Polyether metabolites, halichondrins and caprolactins A, B are also known to possess anticancer properties [24]. Caprolactins A and B exhibit mild cytotoxic activities and are produced by an unidentified Gram-positive bacterium. Another compound γ -Indomycinone, produced by a streptomycete exhibits cytotoxicity against the Chinese hamster ovary (CHO) cell lines [23]. Actinomycetes are also known to produce a large number of compounds with anti-tumour properties [25]. Streptoalloteichus hindustanus is commonly known to produce bleomycin, various glycopeptides, widely used for Hodgkin's lymphomas, squamous cell carcinomas and testis tumours [26]. Bleomycin derivatives like bleomycin, used in combination with other compounds is used to treat lymphomas, skin carcinomas and tumours of the head, neck and testicles [27]. SF 2575, a fourth-generation tetracycline is found to have cytotoxic activity against P388 leukaemia cells and various other cancer cells [28]. One of the most strongest known natural anti cancer agents are enediynes. They include dynemicin A, calicheamicin, kerdarcidin, esparamicin, and neocarzinostatin [29,30]. Enediynes are represented by two classes of antitumor compounds, esperamycins and calicheamicins [30,31,32].

Epothilones are commonly known 16-member ring polyketide macrolide lactones. These are produced by the myxobacterium Sorangium cellulosum [33,34] and are most commonly used as anti-tumour compounds. They generally contain methylthiazole group attached by an olefinic bond and are mostly effective against breast cancer and other forms of cancer. Angiogenesis is an important step for the proliferation of cancer cells. Aspergillus fumigatus produces fumagillin which acts as an anti-angiogenesis compound [36, 37]. Eleutherobin, discodermolide, bryostatins, dolastatins and cephalostatins are other common anti tumor agents obtained from marine sources [25].

The Staphyloxanthin pigment obtained from Staphylococcus gallinarum KX912244 exhibits DNA damage protection activity against reactive oxygen species and anticancer activity which can be easily evaluated by cytotoxicity assay against 4 different cancer cell lines [38]. Bacterial carotenoid pigments are an interesting group of compounds studied in relation to cancer biology. Carotenoid pigments are known to possess antioxidant property that helps fight the reactive oxygen species that are destructive to cellular molecules like DNA, proteins and lipids [39].

An experiment conducted by Avilla et al. to isolate Staphyloxanthin molecule from Staphylococcus gallinarum KX912244, a Gut Microbe of Bombyx mori Delicia proves the cytotoxic effect of the extracted Staphyloxanthin molecule against Dalton's lymphoma ascites (DLA), Ehrlich ascites carcinoma (EAC), Adenocarcinoma human alveolar basal epithelial cells (A549 Lung carcinoma) and Mus mucus skin melanoma (B16F10) and non-cancerous human fibroblast cell line (NIH3T3) cells in vitro using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay [39,40]. Further the demonstration by Clauditz et al. [41] proves that Staphyloxanthin molecule scavenges free radicals with its conjugated double bonds which further boost the anti oxidant capability of staphyloxanthin [42,43,44]. In another set of experiments Liu et al. demonstrated that the pigment Staphyloxanthin is a strong antioxidant that can impart virulence character for the Staphylococci which will help to evade the neutrophil killing [45]. But still there is no confirmation till date that Staphyloxanthin can directly be used as an anticancer agent [38].

Prodigiosin pigment, from Serratia marcescens [46] is widely studied and its role in inducing apoptosis and cell cycle inhibition of cancer cells is no longer a mystery [47]. A study exhibits the cytotoxic and antiproliferative effects of prodigiosin against 60 human tumor cell lines including that of lung, renal, leukaemia, brain cancer, colon and melanoma [48]. Several research on this compound has helped us to obtain several novel compounds like novel prodigiosin analogue 2,20 -[3-methoxy-10 amyl-50 -methyl-4-(100-pyrryl)] dipyrrolylmethene (MAMPDM). This possess potent cytotoxic activity towards cancer cells [49]. The methoxy group plays the most important role [50] in anti-cancer effects that have been observed in several human cancer cell lines in vitro [51,52,53,54,55]. This cytotoxicity is also seen in hepatocellular carcinoma xenografts [56] and in human primary cancer cells [57]. Interestingly it has no marked toxicity toward non-malignant cell lines [58,53,54,55]. A wide variety of bacterial taxa including Gram-negative rods such as Serratia rubidaea, S. marcescens, Vibrio gazogenes, Pseudomonas magnesorubra, Vibrio psychroerythrus, Alteromonas rubra, Rugamonas rubra and Gram-positive actinomycetes such as Streptomyces spectabilis, Streptomyces longisporus and Streptovercillium rubrircetuli are known to produce secondary metabolites related to prodigiosins [59].

Genetically engineered organisms have also proved to be highly beneficial in the production of various anti-cancer and antitumor activities. The attenuated strains of Salmonella enterica serovar Typhimurium have several such properties [60, 61, 62]. Engineered salmonella can demonstrate IL2-expressing properties which can be used as an oncolytic agent in the highly tumorigenic B16F1 melanoma mouse model [62]. Live bacteria has long been used to treat human cancers [63,64,65]. Studies show that a proper and systemic administration of the facultative anaerobic bacteria like Salmonella typhimurium to tumor bearing mice results in a cytotoxic and finally leading to an antitumor effect

[66,67].Salmonella have been engineered in a manner so that it express cytokines or various angiogenesis inhibitors [68,69,70]. Studies by Bashel et al. indicate that employing Salmonella for the treatment of tumor-bearing animals is associated with decreased angiogenesis and increased tissue necrosis within the tumors [62] which establish the possibility that the bacteria most probably accumulate in tumors, and thus they become targets of choice for use as vectors in order to deliver agents with antitumor activity into the tumor tissue [62].A recent study by Loeffler et al.[69] shows that a Salmonella strain expressing LIGHT, a TNF-family cytokine, can be used effectively to target tumor tissue and bring about inhibition of the growth of primary, subcutaneously implanted, colon and breast carcinomas and their dissemination into the lungs. This antitumor activity of LIGHT-expressing Salmonella is found to be associated with the infiltration of inflammatory cells like IL-12 and IFN- γ , two critical antitumor cytokines into the tumor tissue [69,71] The most effective anticancer drugs include bryostatins, discodermolide, eleutherobin and sarcodictyin obtained from bacterial sources [72,73].

Studies done by Carte et al. and Goldin et al. indicate that Lactobacilli and Noctiluca scintillans can demonstrate cytotoxicity and thus can be used as chemopreventive effects which are highly effective against colon and melanoma cancer [74,75] . Additionally Lactobacilli is found to possess the ability to reduce the activities of nitroreductase, β -glucuronidase and azoreductase enzymes in diet of rats which is an indication that Lactobacilli can lessen the incidence of development of colon cancer [75,76, 77]. Experiments and comparative studies done by Bitzer et al. and Sagar et al. indicate that The marine-derived Halomonas spp. strain GWS-BW-H8hM can inhibit the growth of HM02 (gastric adeno-carcinoma), HepG2 (hepatocellular carcinoma) and MCF7 cell lines [78,79].Surprisingly exo-polysaccharides (EPSs) and sulfated EPSs isolated from H. Stenophila obtained from similar environment like Halomonas is reported for their pro-apoptotic effects on T-leukemia cells and most interesting element again is that they affect only only tumor cells and do not show cytotoxicity against the normal cells [80].Halomonas can also produce cytotoxic hydroxyphenylpyrrole dicarboxylic acids, i.e., 3-(4-hydroxyphenyl)-4-phenylpyrrole-2,5-dicarboxylic acid (HPPD-1), 3,4-di-(4-hydroxy-phenyl) pyrrole-2,5-dicarboxylic acid (HPPD-2) and the indole derivatives 3-(hydroxyacetyl)-indole, indole-3-carboxylic acid, indole-3-carboxaldehyde, and indole-3-acetic acid [81].HPPD-1 and HPPD-2 are both antitumor compounds which function by the inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA) induced activation of Epstein-Barr virus early antigen. It is found that the inhibitory effect of HPPD-2 is more potent when compared to HPPD-1 at all tested dose ratios [81]. Marine actinomycetes are nowhere behind. Their cytotoxic activities on various cancer cell lines are proved by many experiment and comparative analysis. They include members of the genera Dietzia, Rhodococcus [82], Streptomyces [83], Salinispora [84,85, 86] and Marinispora [85,86]. Nocardopsis lucentensis (strain CNR-712) produces 3-methyl-4-ethylideneproline-containing peptides. Among them

Lucentamycins A and B is found to exhibit in vitro cytotoxicity against HCT-116 human colon carcinoma [87]. Thicoraline is a depsipeptide isolated from Micromonospora marina. It can successfully display cytotoxic activity against both LOVO and SW620 human colon cancer cell lines[88] .Studies on Streptomyces species by Maskey et al. puts forward the fact that Trioxacarcins A-C obtained from Streptomyces display potent anti-tumor activity against lung cell line [89]. The capacity of Planctomycetes to induce apoptosis and decrease cell growth in human and rat cell lines is evident by a set of experiments conducted by Calistro et al. The study further describes that Planctomycetes strains exhibit active bioactivity against one or both cancer cell lines (MOLM-13 AML cells and PC3 prostate cancer, but not to the normal NRK kidney epithelial cells [90].

II. CONCLUSIONS

This review aims to produce a basic understanding about the different types of prokaryotic metabolites and pigments and their effectiveness in various types of cancer. The capability of prokaryotes to produce antitumor and anti-cancerous activities is not new but the current need is to have an overall understanding so that innovative new drugs and therapeutic agents can be developed to prevent cancer. Engineered Salmonella strains, products obtained from filamentous bacteria [91] ,marine Halomonas [92]and Planctomycetes [90] species provide a lot of hope. The development in molecular biology and the sequencing of microbial genomes promises a greater understanding of the tumor tissue microenvironment .This has resulted in a high boost of interest in using obligate and facultative anaerobic bacterial species, including Salmonella, Bifidobacterium, and Clostridium spp., to control tumor growth [63,65, 93]

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