Bacillus spp.: Attractive Sources of Anti-cancer and Anti-proliferative Biomolecules

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Abstract

Cancer treatment remains as an expensive process due to the cost of sophisticated infrastructure development as well as its maintenance with skilled personnel. At the same time, the success rate is not very inspiring since non-specific target oriented medication could cause other health complexities leading to death. Research for alternative therapies aimed at minimizing the side effects of treatments and increasing the survival rates of patients includes routine explorations for anticancer agents from numerous sources (e.g. microbes, plants and nanoparticles). Anticancer activities of several bacterial components especially from *Bacillus* spp. were reported in many scientific reports. For economic production of these agents, potential strains from this genus could be feasible and sustainable for their long and successful utilization in industries. The review is therefore, focused on describing the available anticancer and anti-proliferative agents reported worldwide from *Bacillus* spp.

Keywords: *Bacillus* spp., anti-cancer, anti-proliferative, bioactive, cancer therapy.

Abbreviations: EMT, Epithelial-messenchymal transition; MTT-3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; XTT-2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide; B.P. CM- Conditioned medium of *Bacillus polyfermenticus*; ErbB2 and ErbB3 – Receptor Tyrosine protein kinase; E2F-1-transcriptional regulator; cyclin D1- cell cycle regulator; PS- Parasporin; ICR- a strain of albino mice sent from the Institute of Cancer Research in the USA; IC_{50}- the maximal concentration of drug to cause 50% inhibition of biological activity of cancer cells; ED_{50}- the Dose (or Concentration) causing 50% of maximum effect for any measured biological effect of interest; GI_{50}- the concentration for 50% of maximal inhibition of cell proliferation; DHPS- 3,5-Dihydroxy-4-isopropylstilbene; HMA- 14-hydroxy-15-methyl-hexadecanoic acid; ε -PL- ε -Poly-L-lysine; Cry- Crystal; Cyt- Cytolytic; EPS- Exopolysaccharide; FTIR- Fourier-transform infrared spectroscopy; GC-MS- Gas Chromatography Mass Spectrometry; TLC- Thin layer chromatography.

Significance | Potentials of *Bacillus* spp. in anti-cancer drug development.

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Background

Cancer, the second leading cause of deaths worldwide, was responsible for 8.8 million mortalities in 2015 around the globe and approximately 70% of the cases occurred in low- and middle-income countries (WHO media center, 2017). Cancer is characterized by uncontrolled and invasive growth of cells which might spread to other parts of the body if not treated or cured at initial stage. The intrinsic factors influencing cancer development are age, hormonal factors, familial history and genetic predisposition (Devi, 1989; Henderson, Ross, & Bernstein, 1988) whereas the extrinsic factors could be food habit, life style, smoking, alcohol abuse, exposure to toxic chemicals and ionizing radiation, certain infections by virus and bacteria etc. In addition, reactive oxygen species (ROS) and free radicals are considered as few of the most prolific inducers of cancer (Chew, Lim, Omar, & Khoo, 2008; Clayson, Mehta, & Iverson, 1994; Nandakumar, Jayaprakash, Rengarajan, Ramesh, & Balasubramanian, 2011; Parsonnet, 1995).

Cancer is developed through multiple stages including initiation, promotion, malignant conversion and progression (Weston & Harris, 2003). Spontaneous or carcinogen induced mutation in oncogenes oncogenes or tumor suppressor genes or cell cycle regula-

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tor genes or genomic stability associated genes initiates carcinogenesis (Devi, 1989). Cells involved in the initiation stage are subject to subsequent changes in the promotion stage upon prolonged exposures to promoting stimuli (Devi, 1989). Malignant conversion, the third stage, is the transformation of a preneoplastic cell into the neoplastic one i.e. cell that expresses the malignant phenotypes. This could be caused by further genetic changes through exposure of preneoplastic cells to DNA-damaging agents or the activation of proto-oncogenes and inactivation of tumor suppressor genes (Weston & Harris, 2003). In this stage, mutations in the genes of Ras proteins, the biological switches, and p53, the guardian of the genome, could lead to unregulated cell growth (Isoldi, Visconti, Maria, & Castrucci, 2005). Finally, the tumor progression occurs by the expression of the more aggressive malignant phenotypes being accelerated by selection pressures or repeated exposures to carcinogenic stimuli with time. The malignant phenotypes have the tendency for genomic instability and uncontrolled growth (Devi, 1989; Weston & Harris, 2003). Late in tumor progression, the fully malignant cells due to the accumulation of different genetic alterations (Yokota, 2000) lose their adherence capacity, detach from the tumor mass and invade the neighboring tissues leading to metastasis. Metastasis, a multi-stage process, mediates the spread and growth of metastatic tumor at a new metastatic site from the primary tumor involving invasive cancer cells (Sahai, 2007).

In several cases of human cancers, hypoxia-induced epithelial-mesenchymal transition (EMT) has been reported to be associated (Yeo et al., 2017). In hypoxic tumor microenvironment, prolonged hypoxic exposure (oxygen deficiency) of tumor cells might cause a tumor to acquire more aggressive phenotypes (Yeo et al., 2017). Cancer stem cells (CSCs), generated in part as a consequence of epithelial-mesenchymal transition (EMT) are increased in case of hypoxia-induced EMT during tumor progression. Although, EMT causes the conversion of the epithelial cells into mesenchymal cells through loss of cell polarity, the recent observation implies the critical role of EMT in tumor progression and modulation of an early stage tumor into an invasive malignancy (Yeo et al., 2017). This hypoxic microenvironment can also be generated by mitochondrial dysfunction where the mitochondrial metabolites accumulate in the cytoplasm due to the imbalance between glycolysis and oxidative phosphorylation (Roberts & Jean, 2013).

Apoptosis or programmed cell death, a cellular defense mechanism, plays an important role in surveillance of tumors or other malfunctioning cells and it is also highly regulated and non-inflammatory (Steller, 1995). Apoptosis significantly differs from necrosis which is another form of cell death causing inflammation and group of cells death (Payne & Miles, 2008). Apoptotic cells undergo several morphological and biochemical changes, such as chromatin condensation, nuclear segmentation, internucleosomal DNA fragmentation, cytoplasmic vacuolization, cell shrinkage and membrane blebbing with shedding of apoptotic bodies etc. (Häcker, 2000; Wyllie, 1992). Any defect in apoptosis process rendering uncontrolled proliferation of cells could also lead to cancer (Amran, 2017). Beyond self-defense mechanisms, carcinogenesis is prevented by several other modes e.g. the antioxidant effects. Antioxidants such as superoxide dismutase, catalase, glutathione peroxidase, reductase and S- transferases scavenge the ROS before their access into the cell for the target molecules (Halliwell, Gutteridge, & Cross, 1992). Antioxidants like vitamins, α- and β-carotene, curcumin, lycopene, β- Cryptoxanthin, Esculetin, catechin etc., widely distributed in fruits and vegetables, play key roles in cancer inhibition by inducing oxidative stress in cancer cells. Likewise, fatty acids, amino acids and related compounds, flavonoids, resveratrol, different alkaloids and phenolic compounds from natural sources impede carcinogenesis (Reddy, Odhav, & Bhoola, 2003).

The available cancer treatments such as surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy or combination of these therapies are long and expensive processes which require sophisticated infrastructure development and maintenance with skilled personnel. The success of a cancer therapy depends on its preferential wipeout of cancer cells with negligible toxicity to the normal cells (Amran, 2017). Targeted therapy using monoclonal antibodies is, therefore, turning to be useful gradually (Adams & Weiner, 2005). Chemotherapeutic drugs interfere in cancer cell proliferation by cell cycle-specific or cell cycle-nonspecific manner and most common constituents of this are alkylating agents, heavy metals, anti-metabolites, cytotoxic antibiotics, topoisomerase inhibitors to prevent DNA replication or protein synthesis and damage mostly S- phase of cell cycle (Payne & Miles, 2008). Although conventional treatments consisting of surgical resection, radiotherapy and chemotherapy are effective in managing many of the patients (generally prolonged life or permanent cure of cancer), almost 50% of the cases are unmanageable. Also the side effects such as pain, blood clots, fatigue, anemia, thrombocytopenia, constipation, diarrhea, or neurological complications and unpleasant to fatal infections are very often accompanied by these treatments (Aslam et al., 2014).

Research for alternative therapies, aimed at minimizing the side effects and increasing the survival rates, is a continuous process worldwide and in this connection, exploration for anti-cancer agents from numerous sources (e.g. microbes, plants and nanoparticles) are carried out routinely. Anticancer activities of several bacterial components were reported and a safe vaccine was developed by American physician William Coley a hundred years ago from killed bacterial species to treat sarcomas, carcinomas, lymphomas, and melanomas successfully (Hoption Cann, van Netten, & van Netten, 2003; Zacharski & Sukhatme, 2005). After several decades, a variety of natural and genetically modified non-pathogenic bacterial species were explored for their potency against tumor cells either for direct tumoricidal effects or tumoricidal molecules (Patyar et al., 2010).

Microorganisms produce over 50000 metabolites among which more than 40% were reported with biological activities. Microorganism derived anticancer agents are Actinomycin, Bleomycin, Daunomycin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin C, Geldanamycin, Rapamicin and Wortamannin which are used clinically to treat different forms of cancer mainly by blocking signal transduction pathways (Bhanot, Sharma, & Noolvi, 2011). Bacteria produce over 3800 bioactive metabolites and of them, *Bacillus* spp. and *Pseudomonas* spp. are the most prominent sources, producing about 860 and 795 metabolites respectively (Bérdy, 2005). Polyketides, macrolactones, fatty acids, lipoamides, isocoumarin, lipopeptides and polypeptides are most abundant bioactive compounds from terrestrial and marine *Bacillus* spp. (Hamdache, Lamarti, & Collado, 2011; Meena, Sharma, & Kanwar, 2017) which exhibit a wide range of biological activities, such as antibacterial, antifungal, anti-algal, antioxidant, antifouling and most importantly anticancer activity (Baruzzi, Quintieri, Morea, & Caputo, 2011; Hamdache et al., 2011). On the other hand, *Bacillus* spp. are the best characterized Gram-positive bacteria, being utilized industrially for long in producing microbial enzymes and therapeutically important chemicals, due to their feasibility in economic bioprocess (Liu et al., 2013; Papagianni, 2012). Hence, *Bacillus* species could be the appropriate sources of numerous bioactive molecules in developing new drugs for cancer therapy. This review, therefore, focuses on different *Bacillus* species synthesizing metabolites with anticancer activity and reports certain previous clinical trials in assessing their efficacy to cure cancer.

Genus *Bacillus*

A key distinguishing feature of the family *Bacillaceae* is the production of endospores which are round, oval, or cylindrical highly refractile structures formed within bacterial cells. This characteristics attracted the early interest of microbiologists which has continued still (Slepecky & Hemphill, 2006). Certain other special features of the genus *Bacillus* are their aerobic nature (strict or facultative), rod shape and catalase production. *Bacillus* spp. are also renowned for producing antibiotics as secondary metabolites and ca. 169 of them were recorded so far. As for instance, different strains of *B. subtilis* and *B. brevis* produced 68 and 23 antibiotics respectively (Debabov, 1982). Usually, *Bacillus* species were reported to produce at least one extracellular enzyme besides different carbohydrates such as different proteases, penicillinases, nucleases, phosphatases, lipase, phospholipase C, thiaminase, and bacteriolytic enzymes etc (Debabov, 1982). Beside production of large quantities of enzymes for industrial purposes, various biologically active molecules were identified, isolated and checked for their activities from *Bacillus* spp. and these are summarized in the Table 1 and Table 3.

Bacillus amyloliquefaciens

Bacillus amyloliquefaciens is an endophytic bacteria and this type of bacterium is one of the major sources of natural anticancer agents including anthracyclines, glycopeptides, aureolic acids, anthraquinones, enediynes, antimetabolites, carzinophilin and mitomycins (Blunt, Copp, Hu, Munro, & Northcote, 2008).

Bacillus amyloliquefaciens MD-bl

Bacillus amyloliquefaciens MD-bl, isolated from the medicinal plant *Ophiopogon japonicas* was reported for its exopolysaccharides exhibiting dose-dependent inhibitory effects against the gastric carcinoma cell lines, MC-4 and SGC-7901 cells, with an IC_{50} of 19.7 and 26.8 µg/µl, respectively, as revealed in MTT assay (C. Li, 2013). Polysaccharides are a group of water-soluble bioactive compounds associated with immune system modulation, including antitumoral, antiviral and antioxidant activities (Strobel et al., 2004). Upon administration, cancer cells were found to be damaged or dead with evident morphological abnormalities and mitochondrial dysfunction, indicating the apoptosis inducing effect by the polysaccharides. This was the first discovery of such anticancer exopolysaccharides derived from the genus Bacillus (C. Li, 2013).

Bacillus amyloliquefaciens AK-O

Bacillus amyloliquefaciens AK-0, a recently isolated bacterium from the rhizospheric soil of Korean ginseng, exerted anti-proliferative activity against human colorectal cancer cells such as HCT116, SW480, LoVo and HT-29 which effectively decreased cyclin D1 protein level in human colorectal cancer cells (Park et al., 2017).

Bacillus cereus

Bacillus cereus is a Gram-positive, rod shaped, aerobic to facultative, beta hemolytic and soil-dwelling bacterium, one of the causative agents of food poisoning, especially 'Fried rice syndrome' (Bottone, 2010). *Bacillus thuringiensis* (Bt) is closely related to *B. cereus* but Bt produce unique proteinaceous crystalline proteins, only discriminatory fact between these two bacteria. Many strains of Bc can function as probiotics providing health benefits to the host when administered in adequate amounts (Araya et al., 2002). Probiotic bacteria are known to produce bioactive substances that exhibit antibacterial, antiviral and anti-tumor properties (Austin, 1989). Probiotic consumption helps the host to maintain intestinal microbial balance, reduce the number of pathogens, improve bowel regularity, restore normal intestinal microbiota and reduce the level of carcinogens (Reid, Jass, Sebulsky, & McCormick, 2003).

Bacillus cereus (BC1)

Anticancer metabolites were obtained from an Indian *Bacillus cereus* strain after successive solvent extraction with petroleum ether, ethyl acetate or methanol (1:1). One of fractions BC1 showed CTC_{50} (cytotoxicity 50%) values of 225.4 µg/ ml against

Table 1 | **Molecules obtained from Bacillus spp. with anticancer activity.**

Species	Source	Cell lines	Dosage, IC_{50} (µg/ml)*	Bioactive agents	References
***Bacillus amyloliquefaciens* (MD-bl)**	*Ophiopogon japonicas* (medicinal plant)	i. MC-4 ii. SGC-7901	i. 19600 ii. 26800	Exopolysaccharide	(C. Li, 2013)
Bacillus cereus	Soil	i.HepG2 ii. Hep2	i. 225.4 ii. 152.2	ND	(M. L. V. Kumar et al., 2014)
***Bacillus cereus* SVSK2**	Fish	i. MCF7 ii. HeLa	i. 150 ii. 300	Silicic acid, diethyl bis (trimethylsilyl) ester	(Seerangaraj et al., 2017)
***Bacillus subtilis* strain FS05**	Sponge	i. HepG2 ii. HCT iii. MCF	i. 10.42 ii. 4.3 iii. 75.5	ND	(Aboul-Ela, Shreadah, Abdel-Monem, Yakout, & Soest, 2012)
***Bacillus subtilis* SVSK5**	Fish	i. MCF7 ii. HeLa	i. 150 ii. 300	Eicosane, Pentacosane, Phthalic Acid	(Seerangaraj et al., 2017)
***Bacillus subtilis* B1779**	Sea water	HeLa	i. 33.60 µM ii. 4.32 µM	i. Amicoumacin A ii. Bacilosarcin B	(Y. Li et al., 2012)
***Bacillus subtilis* subsp. *subtilis* RG**	Soil	MCF-7	46.64	ND	(Ramasubburayan, Sumathi, Bercy, Immanuel, & Palavesam, 2015)
***Bacillus subtilis* SDNS**	Sea water	i. HelaS3 ii. HepG2	i. 77.2% ii. 56.2%	ε -Poly-L-lysine	(El-sersy, Abdelwahab, & Abouelkhiir, 2012)
***B. subtilis* var. *natto* KMD 1126**	Natto (fermented beans)	EAC	10%	Surfactin	(Kameda, Matsui, Kato, Yamada, & Sagai, 1972)
***B. subtilis* var. KMD 2311**	Straw	EAC	20%	Surfactin	(Kameda et al., 1972; Kameda, Oira, Matsui, Kanatomo, & Hase, 1974)
Bacillus licheniformis	Tunisian thermal source	HepG2	200 mg/ml	Levan	(Dahech, Belghith, Belghith, & Mejdoub, 2012)
***Bacillus licheniformis* 09IDYM23**	Marine sediment	i. NCI-H23 ii. NUGC3	i. 25.18 ii. 17.78	Ieodoglucomide B	(Tareq et al., 2013)
***Bacillus licheniformis* RAM-8**	Soil	i. Jurkat clone E6-1 ii. MCF-7 iii. K-562	i. 0.22 IU ii. 0.78 IU iii. 0.153 IU	L-asparaginase	(Mahajan et al., 2014)
***Bacillus megaterium* SAmt17**	Sea sediments	HepG2	218	EPS	(Abdelnasser et al., 2017)
***Bacillus megaterium* ATCC 13368**		Mel-2	0.1- 0.3	Betulinic acid metabolites	(Chatterjee, Kouzi, Pezzuto, & Hamann, 2000)
Bacillus flexus	Sea sedimennt	HepG2	372	Exopolysaccharide	(Abdelnasser et al., 2017)
***Bacillus* sp. BS3**	solar salt works	mammary epithelial carcinoma	0.25	Biosurfactant	(Makkar, Cameotra, & Banat, 2011)
***Bacillus safensis* strain PDRV**	Sponge	i. HepG2 ii. HCT iii. MCF	i. 46.9 ii. 28.6 iii. 721.3	ND	(Aboul-Ela et al., 2012)
***Bacillus thuringiensis* S13**	Soil	A549	133.27	Exopolymer	(Parthiban, Vignesh, & Thirumurugan, 2014)
Bacillus mojavensis* *B0621A	*Pinctada martensii*	HL-60	100 100 1.6 mM	Mojavensin A iso-C16 fengycin B Andanteiso-C17 fengycin B	(Z. Ma, Wang, Hu, & Wang, 2012)
Bacillus silvestris	Crab	i. BXPC-3 ii. MCF-7 iii. SF-268 iv. NCI-H460 v. KM20L2	10^{-4}– 10^{-5}	Bacillistatins 1 and 2	(Pettit et al., 2010)
***Bacillus vallismortis* BIT-33**	Seawater	i. HT-29, ii. SW480 iii. HCT116	10	PCC	(Jeong, Park, Kim, Kim, & Lee, 2008)
Bacillus polyfermenticus	Probiotic	i. HT-29 ii. DLD-1 iii. Caco-2	i. 56% ii. 33% iii. 95%	ND	(Ma, Elise L., Choi et al., 2015)
***Bacillus* sp. N**	Nematode	HeLa	25	3,5-Dihydroxy-4-isopropylstilbene	(S. N. Kumar et al., 2013)
Marine *Bacillus* sp.	Sea mud	HCT-116	0.68, 1.6, 1.3 mg/ml	Mixirins A, B and C	(ZHang, Hua, & Pei, 2004)
Marine *Bacillus* sp. CND-914	Sea sediment	HCT-116	0.98	Halobacillin	(Trischman, Jensen, & Fenical, 1994)
Marine *Bacillus* sp. BF1-3	Sponge	i. HepG2 ii. HCT iii. MCF-7	i. 13.2 ii. 9.3 iii. 12.2	ND	(Aboul-Ela et al., 2012)

ND: Not defined; *: Unless stated otherwise

Hep-2 (human laryngeal epithelial carcinoma cell lines). From the mass spectroscopic analysis of TLC fractions of BC1, it was revealed that the fraction was devoid of any proteins (Kumar et al, 2014).

Bacillus cereus SVSK2

Bacillus cereus SVSK2, a probiotic bacteria, isolated from *Oreochromis mossambicu* (Seerangaraja et al., 2017) whose cell free extracts exerted significant cytotoxicity on human cervical cancer cell line (HeLa) and breast cancer cell line (MCF-7) with IC_{50} of 150 µg/ml and 300 µg/ml respectively in MTT assay showing reduced growth and disrupted cell wall indicating apoptosis. Gas Chromatography Mass Spectrometry (GC-MS) results revealed that this strain contained Silicic acid, diethyl bis (trimethylsilyl) ester along with other metabolites which had anticancer property (Seerangaraja et al., 2017).

Bacillus subtilis

Bacillus subtilis, an inhabitant of the upper layers of the soil, is a rod-shaped Gram-positive spore forming bacterium and capable of growing in minimal nutritional conditions (Piggot, 2009; van Dijl & Hecker, 2013). In such conditions, *B. subtilis* can undergo a series of responses including synthesis of antibiotics and extracellular enzymes, competence to take up DNA, motility and biofilm formation (Piggot, 2009). Many of the *B. subtilis* strains isolated from different regions with anticancer properties are discussed below.

Bacillus subtilis strain FS05

Crude extracts of *Bacillus subtilis* strain FS05, isolated from Red sea sponge *Amphimedon ochracea*, showed cytotoxicity against three established human cancer cell lines; HepG2 (hepatocellular carcinoma), HCT (colon carcinoma) and MCF-7 (breast carcinoma) with an IC_{50} of 10.42, 4.3 and 5.5 µg/ ml respectively following MTT assay (Aboul-Ela et al., 2012).

Bacillus subtilis SVSK5

Bacillus subtilis strain SVSK5 isolated from the gastro-intestinal tract of fish (*Labeo rohita*) was found to express Eicosane, Pentacosane, Phthalic acid etc. These compounds altogether exhibited cytotoxicity against MCF-7 and HeLa cells at 150 µg/ ml and 300 µg/ ml respectively in MTT assay (Seerangaraja et al., 2017).

Bacillus subtilis B1779

A red sea bacterium, *B. subtilis* strain B1779 expressed 11 amicoumacins, including four novel lipoamicoumacins (type A- D) and a new Bacilosarcin C (Supplementary Fig. 1). Amicoumacin A and bacilosarcin B exhibited cytotoxicity against the HeLa cells with IC_{50} values of 33.60 and 4.32 µM respectively as revealed upon MTT assay. An amide functional group at C-12' might have played a critical role in the mentioned cytotoxicity (Y. Li et al., 2012).

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Bacillus subtilis subsp. subtilis RG

Crude extract of *B. subtilis* subsp. subtilis RG, isolated from the rhizospheric soil of a mangrove plant species, *Excoecaria agallocha* at South east coast of India, exerted significant cytotoxicity against MCF-7 (Human breast adenocarcinoma). The IC_{50} value was 46.64 ± 0.79 µg/ ml as determined through MTT assay. MCF-7 cells, due to the unidentified compound from Bss RG, were subjected to morphological abnormalities i.e. cell shrinkage, membrane blebbing, loss of integrity and cell adhesion properties which indicated the occurrence of apoptosis (Ramasubburayan et al., 2015).

Bacillus subtilis SDNS

The culture supernatant of a marine *Bacillus subtilis* strain SDNS, isolated from Alexandria, Egypt, was investigated against HeLa S3 (human cervix adenocarcinoma cell line), Hep G2 (Human hepatocellular liver carcinoma cell line) and CaCo2 (Human colonic carcinoma cell line) for cytotoxicity. Following MTT assay, highest cytotoxicity was observed against Hela S3 (77.2% inhibition) followed by Hep G2 (56.2% inhibition) and almost no cytotoxicity was observed towards CaCo2. The compound responsible for this toxicity was ε -Poly-L-lysine (ε -PL) (El-sersy et al., 2012) which is basically a homopolymer with antimicrobial and anti-tumor activity (Szende et al., 2002).

B. subtilis var. natto

B. subtilis var. natto (Bn), previously known as *Bacillus natto*, was isolated from Natto, a type of fermented beans and straws. Bn KMD 1126 (Kameda et al., 1972) and KMD 2311 (Kameda et al., 1974) synthesized two types of cytolytic compounds respectively and exhibited mild cytolytic activities (10% and 20% respectively) against Ehrlich ascites carcinoma cells. The Bn KMD 1126 derived surfactin like compound was stable in a wide range of pH and temperature whereas KMD 2311 derived cytolytic compounds were more stable colorless crystalline one with melting point of 247- 249 °C which were identical with surfactin and dimorphic.

Although the surfactin produced by *Bacillus* sp. along with other organisms has mainly antifungal and antibacterial properties, it demonstrated antitumor activity (Gudina, Rangarajan, & Sen, 2013) and cancer cells killing ability through cell cycle arrest and apoptosis (Meena et al., 2017).

Bacillus licheniformis

Bacillus licheniformis, a mesophilic spore-former commonly found in soil and bird feathers (Veith et al., 2004) is part of the subtilis group along with *Bacillus subtilis* and *Bacillus pumilus*. Though *B. licheniformis* possess similar (about 80%) coding sequence to *B. subtilis*, the amount and location of prophages, transposable elements, extracellular enzymes, and secondary metabolic pathway operons make it different from *B. subtilis* (Rey et al., 2004). This bacterium is industrially important because of its ability to produce a range of extracellular enzymes, especially proteases. Due to their activity at high pH and thermostability, proteases from this bacteria became an useful ingredient in laundry detergent which prevents shrinkage and fading of colors (D. Kumar et al., 2008). Apart from this, keratinase produced by *B. licheniformis* is used in leather industry as dehairing agent as well as in feed industry for feather digestion (Hoq et al., 2005; Lin et al., 1992; Tiwary & Gupta, 2010). Protease and keratinase were also expressed in heterologous expression system through recombinant DNA technology in several occasions for easy and feasible downstream processing (Jacobs, Eliasson, Uhlén, & Flock, 1985; Nahar et al., 2016; Radha & Gunasekaran, 2007; Sareen, Bornscheuer, & Mishra, 2005; Tang et al., 2004). *B. licheniformis* produces bacitracin and also used as probiotic (Azarin, Aramli, Imanpour, & Rajabpour, 2014; Haavik, 1979).

Bacillus licheniformis sp. (Levan producing)

B. licheniformis reported by Dahech et al. catalyzes the formation of fructo-oligosaccharides and the synthesis of Levan polymers, a larger group of commercially important polymers which is a source of prebiotic fibre (Dahech et al., 2012; Franken, Brandt, Tai, & Bauer, 2013; GMT, Lima, de Franca, & Lopes, 2000; Kim et al., 2005; Yoo, Yoon, Cha, & Lee, 2004). Levan showed in vitro cytotoxicity against HepG2 cells (highest at 200 mg/ ml) when applied in a dose-dependent manner whereas no effect was observed against WRL68 (Human fetal liver) cells (Dahech et al., 2012).

Bacillus licheniformis 09IDYM23:

Bacillus licheniformis strain 09IDYM23 was isolated from marine sediment sample collected from Ieodo, southern reef of Korea with high salinity and alkaline pH. This bacterium produced two unique glycolipopeptides such as Ieodoglucomides A and B, containing a new fatty acid unit, 14-hydroxy-15-methylhexadecanoic acid (HMA). Ieodoglucomide B (Supplementary Fig. 2) exhibited cytotoxicity against lung cancer NCI-H23 and stomach cancer cell lines (NUGC-3) with GI_{50} (growth inhibition) values of 25.18 and 17.78 µg/ mL respectively in sulforhodamine B (SBR) assay (Tareq et al., 2013).

Bacillus licheniformis RAM-8

B. licheniformis RAM-8 produced an extracellular L- asparaginase enzyme (MW- 134.8 kDa) with low glutaminase activity which is a therapeutic agent to treat the malignancies of lymphoid system, acute lymphoblastic leukemia, non- Hodgkin's lymphoma etc. (Gallagher, Marshall, & Wilson, 1989; Mahajan et al., 2014). L- asparaginase hydrolyses the L-asparagine, obtained from exogenous sources and on which the leukemic cells depend, into L-aspartic acid and ammonia in blood vascular system causing its depletion and inhibiting protein synthesis of leukemic cells leading to their apoptosis (Mashburn & Wriston, 1963; Mccredie, Ho, & EmilJ. Freireich, 1953). L- asparaginase from *B. licheni-*

formis RAM-8 was found to be functionally stable and active over a wide range of pH and temperature and the cytotoxicity was observed against Jurkat clone E6-1, MCF-7 and K-562 cell lines with IC_{50} of 0.22 IU, 0.78 IU and 0.153 IU respectively. The enzyme was reported to be free of any toxic effect on human erythrocytes and CHO cell lines (Mahajan et al., 2014).

Bacillus megaterium

Bacillus megaterium (Bm) is a Gram-positive spore forming bacterium and the key distinguishing feature of this bacterium from other *Bacillus* spp. is its immense size. This bacterium is the largest of all bacilli. Generally, most of the genome sequence of *Bacillus* spp. are closely related to *B. cereus* or *B. subtilis* but Bm is the only distantly related to *B. cereus* or *B. subtilis* (Eppinger et al., 2011; Porwal et al., 2009). Bm is the one of the first bacterial genome that has been fully coded and is frequently used as nonpathogenic host for the biotechnological production of a wide variety of substances like Vitamin B12, penicillin acylase, amylases and many more (Eppinger et al., 2011).

Bm SAmt17, isolated from the Mediterranean sea, produced a low molecular weight exopolysaccharide, EPS-6 (4.296×104 g/ mol) which demonstrated cytotoxicity (IC_{50} of 218 µg/ ml) against HepG2 cells due to the presence of sulfur (46%) and uronic acids (Abdelnasser et al., 2017).

During the biotransformation of betulinic acid by Bm ATCC 13368, it produced four cytotoxic compounds namely 3-oxo-lup-20(29) en-28-oic acid, 3-oxo-11a-hydroxy-lup-20(29)-en-28-oic acid, 1b-hydroxy-3-oxo-lup-20(29)-en-28-oic acid and 3b,7b,15a-trihydroxy-lup-20(29)-en-28-oic acid. The first three compounds showed antimelanoma activity against human melanoma cell lines Mel-2 with an ED_{50} of 0.1, 0.2 and 0.3 (µg/ml) respectively (Chatterjee et al., 2000). Beside the anticancer activity of betulinic acid metabolites, betulinic acid has also anti-tumor activity against different type of cancer cells including human melanoma (Pisha et al., 1995).

Bacillus flexus

Bacillus flexus (SAmt74) produced a low molecular weight exopolysaccharide, EPS-7 (3.756× 104 g/ mol) which showed significant cytotoxicity (IC_{50}- 372 µg/ ml) against HepG2 cells having 24% sulfur content (Abdelnasser et al., 2017).

Bacillus sp. BS3

A halophilic *Bacillus* sp. BS3, isolated from solar salt works, produced biosurfactants such as 3- Docosenamide, Mannosamine, 9- Octadecenamide, 2- Octanol, 2- methyl- 6-methylene, Cylohex- 1, 4, 5- triol- 3- one- 1- carbo and 1, 2-Ethanediamine, N, N, N', N'- tetramethyl-which showed varied cytotoxicities (maximum 24.8%) against mammary epithelial carcinoma cells (Donio et al., 2013). Microorganism derived biosurfactants could be glycolipids, lipopeptides, lipopolysaccharides, polysaccharide- protein complexes, fatty acids and lipids (Makkar et al., 2011) with enormous applications in therapeutic and biomedical fields such as antibacterial, antifungal, antiviral, anticancer, immunomodulator, anti-adhesive, antioxidants, dermal fibroblasts stimulant, vaccines and gene therapy (Bhadoriya & Madoriya, 2013; Gudina et al., 2013).

Bacillus safensis strain PDRV

Crude extracts of *Bacillus safensis* strain PDRV, isolated from Red sea sponge *Amphimedon ochracea*, showed cytotoxicity against three established human cancer cell lines; HepG2 (hepatocellular carcinoma), HCT (colon carcinoma) and MCF-7 (breast carcinoma) with IC_{50} of 46.9, 28.6 and 21.3 µg/ml, respectively following MTT assay (Aboul-Ela et al., 2012).

Bacillus thuringiensis

Bacillus thuringiensis (Bt) synthesizes δ- endotoxins (Cry, Cyt or parasporin proteins) in its parasporal body during sporulation which was reported for antitumor effects and unique activity specifically against cancer cells (Mizuki et al., 1999; Prasad & Shethna, 1974) besides long history and application as biopesticide for larvicidal activity. The toxicity of the parasporins were reported against various cancer cells such as MOLT-4, HeLa, HepG2, JURKAT, HL60, TCS, CACO-2 etc (Table 2) upon their proteolytic activation (Mizuki et al., 1999) with non-toxicity against normal cell lines (S. Okumura et al., 2010). To date, 19 parasporins were discovered and categorized into 6 major classes (PS1- PS6) (S. Okumura et al., 2010) and few other parasporin like proteins are yet to be classified (Poornima et al., 2010; Gonzalez et al., 2011; Ammons et al., 2016). Among these six classes of parasporin, only PS1 kills cancer cells by activating apoptotic signaling pathway causing from attenuation of cellular protein and DNA synthesis, and by increasing influx of calcium ions (Katayama et al.,2007). It was reported that parasporin-1 could bind to the receptor Beclin 1 in the cell membrane (Katayama et al.,2007; Xu, Wang, & Yu, Ziniu and Sun, 2014). In case of parasporin 2, it accumulates in lipid rafts on target cell surfaces through interaction with a putative proteinaceous receptor which gets associated with the glycan core of GPI-anchored proteins for stability. PS2 subsequently forms a membrane embedded oligomer that forms pore and induces permeability of the plasma membrane leading to cell death (Abe et al., 2017). Other PS proteins also kill cells by pore formation.

Bacillus thuringiensis S13

Bacillus thuringiensis S13, found in the coastal soil samples, produced anti-proliferative exopolymer which inhibited lung cancer cell line (A549) with an IC_{50} of 133.27 µg/ ml as detected using XTT assay. FTIR spectra of exopolymer revealed that a brominated compound 1,1,3,1"-Terphenyl,3,3,5,5-tetrabromo-5-(3,5-dibromophenyl) was present in the exopolymer that could be responsible for cytotoxicity (Parthiban et al., 2014).

Bacillus mojavensis B0621A

Bacillus mojavensis B0621A, isolated from *Pinctada martensii*

Table 2 | **Cytotoxicity spectrums of parasporins.** The levels of cytotoxicity, based on EC_{50} as estimated using cell proliferation assays, are denoted as follows: extremely high, ++++; high, +++; moderate, ++; low, + and non- toxic, -; NT, indicates not tested (Ekino et al., 2014; Ito et al., 2004; Katayama et al., 2005; Nagamatsu, Okamura, Saitou, Akao, & Mizuki, 2010; Shiro Okumura, Saitoh, Ishikawa, Inouye, & Mizuki, 2011; Yamashita et al., 2005).

Cell line	Origin	Name	PS1	PS2	PS3	PS4	PS5	PS6
MOLT 4	Human	Leukemic T cell	++	++++	-	-	++++	-
JURKAT		Leukemic T cell	-	++++	-	-	+++	-
HL60		Myeloid Leukemia	+++	++++	++	+++	++	NT
HeLa		Uterus cervix cancer	+++	-	-	-	++++	+
TCS		Uterus cervix cancer	-	-	-	-	++++	NT
Sawano		Uterus cancer	-	++++	-	-	++++	NT
HepG2		Hepatocyte cancer	++	++++	++	++	++++	++++
A549		Lung cancer	-	+++	-	-	+	NT
CACO-2		Colon cancer	-	+	-	-	+++	+
T cell		Normal T cell	-	+++	-	-	-	NT
UtSMC		Normal uterus	-	++	-	-	++	NT
HC		Normal Hepatocyte	-	-	-	-	-	-
MRC-5		Normal Lung	-	+	-	-	++	NT
K562		Myelogenous leukemia	NT	NT	NT	+	+	NT
Vero	Monkey	Monkey Kidney	-	NT	-	-	++++	NT
COS-7		Monkey Kidney	-	-	-	-	++++	NT
PC12	Rodent	Pheochromocytoma	NT	NT	NT	++	NT	NT
CHO		Ovary cell	-	++++	-	+	++	NT
NIH3T3		Embryo cell	-	++++	-	+	++	NT

(Pearl Oyster) in the South China Sea, exerted three iturinic lipopeptides that were isolated by bioactivity-guided fractionation. They were identified as Mojavensin A (Supplementary Fig. 3), iso-C16 fengycin B and anteiso-C17 fengycin B and inhibited the growth of human leukemia cell line HL-60 with IC_{50} of 100, 100 and 1.6mM, respectively as revealed in MTT assay (Z. Ma et al., 2012).

Bacillus silvestris

Bacillus silvestris isolated from a Pacific Ocean (southern Chile) crab, produced bacillistatins 1 (Supplementary Fig. 4) and 2 which strongly inhibited the growth of human cancer cell lines including Human pancreas (BXPC-3), breast (MCF-7), CNS (SF-268), lung (NCI-H460), colon (KM20L2), prostate (DU-145) etc with GI_{50} of 10−4-10−5 µg/ mL (Pettit et al., 2010).

Bacillus vallismortis BIT-33

Bacillus vallismortis BIT-33 produced a secondary metabolite, PCC which exerted cytotoxic effects on HT-29, SW480 and HCT116 cells. It was soluble in methanol (MeOH), ethanol (EtOH), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2) and ethyl acetate (EtOAc) whereas insoluble in hexane and water. PCC demonstrated anticancer cell activity with a concentration of 10 µg/ ml where cell viability was about 40% causing apoptosis of cells in a dose- and time-dependent manner (Jeong et al., 2008).

Bacillus polyfermenticus

Bacillus polyfermenticusis a probiotic bacterium which was first found in the air by Dr. Terakado (1933) and was used in the treatment of intestinal disorders (Lee, Park, Park, & Paik, 2007; E. L. Ma et al., 2010). Probiotic bacteria exert anticancer properties through improvement of normal intestinal microbiota, immune modulation, degradation of potential mutagens and enhancement of local and systemic antioxidant activity (Reid et al., 2003; Yu & Li, 2016).

Bacillus polyfermenticus SCD showed cytotoxicity against colon cancer cells, Caco-2 in a dose dependent manner. After 72 hours of treatment, growth of Caco-2 cells was inhibited 24.6%, 20.3%, 37.1% and 42.2% with *B. polyfermenticus* SCD concentration at 100, 500, 1000 and 2000 µg/ml, respectively (Lee et al., 2007). Conditioned medium for *B. polyfermenticus* (B.P. CM), containing heat stable bacterial protein, inhibited the growth of human colon cancer cells HT-29 (35% - 56%), DLD-1 (69% - 33%), and Caco-2 (99% - 95%) when treated for 7- 14 days respectively (Ma et al. 2015). B.P. CM reduced the mRNA level expression for ErbB2 and ErbB3 receptors, critical players in colon cancer development, followed by reduction of expression of cell cycle regulator cyclin D1 and its transcriptional regulator E2F-1 that significantly block ErbB- dependent tumorigenesis. It was suggested that B.P. CM possess heat stable proteins of molecular weight > 30 kDa, either lipopolysaccharide (LPS) or flagellin, responsible for in vitro suppression of cancer cell growth and *in vivo* suppression of tumor growth due to the anti-proliferative, anti-tumorigenic and anti-angiogenic properties (E. L. Ma et al., 2010).

Bacillus sp. N

Bacillus sp. N, associated with rhabditid entomopathogenic nematode, produced 3,5-Dihydroxy-4-isopropylstilbene (DHPS) which was first identified as bacterial secondary metabolite in spite of being a phytoalexin and DHPS showed cytotoxicity against breast cancer (MDAM B-231), cervical cancer (HeLa), lung cancer (A 549), colon cancer cells but found to be sensitive against HeLa cells line with an IC_{50} of 25 µg/ml using MTT assay. It induced significant morphological changes like chromatin condensation and blebbing and DNA fragmentation with increased Caspase 3 activity indicating apoptosis in HeLa cells (Kumar et al., 2013).

Marine Bacillus sp.

Bacillus sp., isolated from sea mud near the Arctic pole, produced three new cyclopeptides belonging to iturin class named as mixirins A, B and C. Mixirins A, B and C inhibited the growth of human colon cancer cells (HCT-116) with IC50 of 0.68, 1.6, 1.3 mg/ml, respectively (ZHang et al., 2004). Lipopeptides like iturin was reported to be cytotoxic against different cancer cells (Dey et al., 2016).

Bacillus species, isolate CND-914, obtained from a marine sediment core near the Guaymas Basin in Mexico, produced

Table 3 | **Mode of actions of different microbial bioactive agents**

Associated bioactive agents	Mode of action	References
Exopolysaccharide	Cause morphological abnormalities and mitochondrial dysfunction in tumor cells leading to apoptosis	(Chen et al., 2013)
Amicoumacin A	Inhibit mRNA translation	(Prokhorova et al., 2016)
ε -Poly-L-lysine	Cause morphological changes and growth inhibition	(Arnold, Dagan, Gutheil, & Kaplan, 1979)
Surfactin	Inhibit tumor growth, cell cycle arrest, apoptosis and metastasis arrest	(Wu et al., 2017)
Levan	Increase oxidative stress and apoptosis	(Queiroz et al., 2017)
L-asparaginase	Causes nutritional deficiencies and inhibit protein synthesis resulting in apoptosis	(Shrivastava et al., 2016)
Ieodoglucomide B	Inhibit tumor cell growth	(Tareq et al., 2013)
Bacillistatins 1 and 2	Inhibit tumor cell growth	(Pettit, Arce, Chapuis, & Macdonald, 2015)
Mixirins A, B and C	Inhibit tumor cell growth	(Harris & Pierpoint, 2012)
Parasporin 1	Activates apoptotic signaling pathway by binding with Beclin 1 receptor and increase Ca^{2+} influx	(Katayama et al., 2007)
Parasporin 2	Permeabilize plasma membrane through GPI-anchored protein	(Abe et al., 2017)
Parasporin 3	Pore formation	(Ito et al., 2004)
Parasporin 4	Cholesterol independent pore formation	(Yamashita et al., 2005)
Parasporin 6	Swelling of cells and vacuoles formation	(Nagamatsu et al., 2010)

halobacillin which is a novel cyclic acylpeptide of the iturin class, reported to be produced by a marine isolate for the first time. Halobacillin showed moderate human cancer cell cytotoxicity on Human colon cancer cell line HCT116 with an IC_{50} of 0.98 µg/ml. Halobacillin is similar to surfactin but the major difference is the replacement of the glutamic acid of surfactin with a glutamine in halobacillin (Jacqueline et al., 1994).

Bacillus sp BF1-3 was isolated from Red sea sponge *Amphimedon ochracea*. Crude extracts of bacterial culture showed cytotoxicity against HepG2 (hepatocellular carcinoma), HCT (colon carcinoma) and MCF-7 (breast carcinoma) with an IC_{50} of 13.2, 9.3 and 12.2 µg/ml, respectively as estimated using MTT assay (Aboul-Ela et al., 2012).

Clinical trials and animal model experiments

Bacillus oligonitrophilus KU-1

Bacillus oligonitrophilus KU-1, a gram positive and spore forming bacteria, was isolated from soil of Kazan city, Russia. Stationary phase culture of this bacterium at a concentration of $0.5\text{-}1.0 \times 10^9$ cells/ ml was used for cancer treatment after testing toxicity and genotoxicity using Ames test. Culture was administered orally to 13 patients suffering from different types of adenocarcinoma and other forms of carcinoma (tumor in colon, ovary, backbone and maxillary sinus) with varied doses of 2.5- 200 ml (day 1- day 13) at different time intervals. The bacterial treatment showed oncomarker reduction in every patient and life prolongation more than the standard prognosis with minimal side effects. Malkov et al. suggested *Bacillus oligonitrophilus* KU-1 as an effective probiotic and promising anticancer agent which successfully block highly differentiated and mildly differentiated mammary gland adenocarcinoma with metastases into bones and lymph nodes. Presence of silicon was attributed to the death of tumor cells in case of this silicate bacteria (Malkov, Markelov, Polozov, & Sobchuk, 2005).

Bacillus thuringiensis

Parasporin- 4 (PS4), an aerolysin- type β-pore-forming toxin from *Bacillus thuringiensis* strain A1470 produced upon proteolytic activation (Shiro Okumura et al., 2011) was examined in mice model if this promising anticancer protein could be used in cancer therapy (Shiro Okumura, Koga, Inouye, & Mizuki, 2014). In ICR mice (a strain of albino mice sent from the Institute of Cancer Research in the USA), the LD_{50} value was determined as 160 µg/ kg with the reduction of potassium, ammonium, magnesium ion, creatinine and urea nitrogen in urine and increased creatinine and urea nitrogen in mice serum that impaired kidney function. Upon oral administration of Pro- PS4 (10 mg dry wt/200 µL D.W.) in C57BL/6J mice thrice in a week for 40 days, no serious health hazard was observed (Shiro Okumura et al., 2014).

Bacillus polyfermenticus

Probiotic bacterium *Bacillus polyfermenticus* (B.P) produced strong cytotoxic effect against various cancer cell lines including colon, breast, cervical and lung cancers. Anti-cancer effect of B.P. was reported as detected *in vivo* using the mouse xenograft model of human colon cancer which caused the reduction in tumor size and weight by suppressing cell proliferation and angiogenesis. It was suggested that in *Bacillus polyfermenticus* due to the reduction of ErbB2 and ErbB3 expression, the E2F-1 and cyclin D1 expression is down-regulated in tumor cells leading to the inhibition of tumor growth (Ma et al. 2015).

Conclusion

If identified at early stage, cancer is more likely to respond to effective treatments and can result in less morbidity and less expenses. *Bacillus* spp. produce two major lipopeptides i.e. surfactin and iturins besides other unique metabolites like mojavensin, bacillistatins, ε -poly-L-lysine, halobacillin, PCC and EPS etc. which exhibited toxicity against cancer cells. Nevertheless, many of these bioactive agents were not examined *in vivo*, e.g. in rodents, which is a major shortcoming of these metabolites to be used in preliminary cancer therapy (Burger & Fiebig, 2004). Moreover, although the crude extracts or conditioned medium of some *Bacillus* sp. showed cytotoxicity to cancer cells, the specific active compounds are still unidentified. Further investigation in search of those active metabolites as well as *in vivo* study would be helpful in developing new anticancer drug from *Bacillus* species for a sustainable and economic cancer treatment process.

Author contribution

UTF drafted the manuscript. MAS guided the composition and revised it. SNK and MMH did meticulous review and finalized it.

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Competing financial interests

The authors declare no conflict of interest.

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