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MINI-REVIEW

Bacteriocins: perspective for the development of novel anticancer drugs

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Abstract

Antimicrobial peptides (AMPs) from prokaryotic source also known as bacteriocins are ribosomally synthesized by bacteria belonging to different eubacterial taxonomic branches. Most of these AMPs are low molecular weight cationic membrane active peptides that disrupt membrane by forming pores in target cell membranes resulting in cell death. While these peptides known to exhibit broad-spectrum antimicrobial activity, including antibacterial and antifungal, they displayed minimal cytotoxicity to the host cells. Their antimicrobial efficacy has been demonstrated in vivo using diverse animal infection models. Therefore, we have discussed some of the promising peptides for their ability towards potential therapeutic applications. Further, some of these bacteriocins have also been reported to exhibit significant biological activity against various types of cancer cells in different experimental studies. In fact, differential cytotoxicity towards cancer cells as compared to normal cells by certain bacteriocins directs for a much focused research to utilize these compounds as novel therapeutic agents. In this review, bacteriocins that demonstrated antitumor activity against diverse cancer cell lines have been discussed emphasizing their biochemical features, selectivity against extra targets and molecular mechanisms of action.

Keywords Antimicrobial peptides · Bacteriocin · Lantibiotic · Cationic · Cell lines · Anticancer

Introduction

Cancer is the leading cause of death worldwide (http://seer.cancer.gov/statfacts) and death rate is increasing significantly in the last few decades (Siegel et al. 2015; Howlader et al. 2015). Globally, cancer is the second leading cause of mortality and killed about 8.8 million people according to a recent report by the World Health Organization (WHO) (www.who.int/mediacentre/factsheets/fs297/). In addition to mortality, adverse effects of treatment associated with human cancers pose significant global psychological and economic burden to the affected nations. On the other hand, an exponential advance in biotechnology in the recent past is continuously leading to a greater understanding about many human diseases (Jemal et al. 2009). Altered cellular physiology is the characteristic of cancer cells, which leads to abnormal proliferation of cells. Thus, cancerous cells show certain unique characteristics such as initiating growth signals on their own and do not respond to the mechanisms controlling cellular growth. These cells develop the capacity for limitless replication and stimulate new blood vessel development in order to allow tumor growth. The altered cells enable to invade tissues locally and metastasize distantly all across the body (Hanahan and Weinberg 2000). Typically, cancer patients are treated with surgery, radiotherapy, and chemotherapy to remove growing tumor. However, surgical resection of cancer is a limited approach, often mutilating and mostly to be followed up by chemotherapy and radiotherapy. Surgery and radiotherapy are effective against localized cancers but not suitable for disseminated cancers where chemotherapy remains the sole choice. These anticancer therapies including chemotherapy are only reasonably effective along with the serious side effects due to non-selectivity of target cells, recurrence potentials, and emergence of multidrug-resistant cancerous cells (Lao et al. 2014; Klener 1999; Porta et al. 2015). Considering these constraints, few studies have been undertaken in the recent past relating to the action of AMPs having antitumor activity, with the intent of reducing the number of

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cases of tumor growth (Joo et al. 2012; Chu et al. 2015). Therefore, there is an extensive and urgent need of developing novel, more selective, effective, less toxic, and safe biologic therapies such as AMPs against rapidly growing cancer cases.

Bacteriocins as anticancer therapeutics

General perspectives

A multitude of metabolites including antimicrobial peptides (AMPs), such as ribosomally synthesized bacteriocins, are produced by various bacterial strains as a strategy to overcome competitive antagonism by other invading bacteria during habituation of a specific niche (Fons and Tuomo Karjalainen, 2000). Although bacteriocins were previously thought to inhibit the growth of only closely related strains or species, but in the recent past they were reported with broad spectrum of antimicrobial activity. In addition, they exhibit selective activity against distantly related bacteria and inhibited the growth of various cancerous cell lines (Joo et al. 2012; Riley and Wertz 2002; Coburn and Gilmore 2003; Dethlefsen et al. 2006). Most of these bacteriocins with anticancer properties were found to be cationic and amphiphilic in nature, that were often produced by bacteria existing in diverse environments. These cationic peptides are also known to be "membrane active" as they interact with a negative surface charge on the cell in contact (Wang et al. 2013; Johnstone et al. 2000; Zhao et al. 2015; Laverty and Gilmore 2014). Killing of cancer cells is usually reported to mediate via cell membrane lytic effect due to the presence of increased number of negatively charged molecules on their surface (Riedl et al. 2011). While a few cationic AMPs are reported to disrupt the integrity of mitochondrial membrane and cause apoptosis in cancer cells (Cho et al. 2012; Chen et al. 2012), others are known to inhibit blood vessel development (angiogenesis) which is essentially required for cancer progression (Mader and Hoskin 2006).

Historic perspectives

Utilization of microbes or their products against cancer is reported dating back to the nineteenth century. For example, culture supernatants of bacteria like *Streptococcus pyogenes* and *Serratia marcescens* preparation called Coley's toxins were given to patients with unresectable tumors. Evidently, patients with regression of malignant tumors treated with this toxin were cured to good health (Coley 1910; Wiemann and Starnes 1994). Subsequently, induction of enhanced secretion of tumor necrosis factor (TNF-α) in the body of a patient was revealed to be the main factor accountable for therapeutic effect of Coley's toxins. Further, the role of TNF-α factor was also confirmed in animal models (Carswell et al. 1975). On the other hand, it has been reported that the microbial pathogens may proliferate inside the hypoxic cancer lesions, and concurrently, stimulating host immune system against cancer progression during the infection. The vaccine strain BCG (*Mycobacterium bovis* Calmette-Guerin) is an example that was used to treat superficial bladder cancer (Alexandroff et al. 1999; Gandhi et al. 2013; Herr and Morales 2008; Kawai et al. 2013). Members of the genus *Clostridium* like *C. novyi*-NT are also found to be promising in bacteriolytic therapy to treat various tumors (Dang et al. 2001; Maletzki et al. 2010; Agrawal et al. 2004) as they were found to be effective in reducing tumor growth. In the recent past, it has been shown that the selected microbial infections lead to immune activation via macrophages and lymphocytes, resulting in production of anticancer agents like TNF-α (Patyar et al. 2010). Similarly, other microbial metabolites also displayed potential anticancer properties, for example, nisin, the first lantibiotic bacteriocin approved by the Food and Drug Administration, is recently documented as a potential anticancer bacteriocin (Joo et al. 2012; Kamarajan et al. 2015). Currently, several low molecular weight AMPs are emerging as promising novel cancer therapeutics. Therefore, this review aims to provide a detailed insight into the bacteriocins having anticancer properties and their biochemical structures and potential as anticancer therapeutic agents.

Characteristics of bacteriocins relevant to anticancer potential

Most of the bacteriocins are cationic in nature

More than 80% of known bacteriocins are cationic in nature owing to an excess number of lysine or arginine amino acid residues (Hammami et al. 2007, 2010). Usually, they are hydrophobic peptides containing between 20 and 60 amino acids in length (Nes and Holo, 2000; Ennahar et al. 2000), though they were found to be unstructured in aqueous solution, but displayed α-helical structure forming tendency when exposed to trifluoroethanol or anionic phospholipids of biological membranes. Additionally, disulfide or a covalent bond formation in certain peptides helps in acquiring loop structure and its maintenance. In particular, the presence of intramolecular ring structures formed as a result of thioether bonds between amino acids is a characteristic feature of the lantibiotics, which is a predominant bacteriocin group (Moll et al. 1999). It was noted that a number of lantibiotics resemble cationic antimicrobial peptides (cAMPs) by virtue of having long linear structures, a cationic charge, and their ability to form pores in cell membranes (Gunther 1991; Smith and Hillman 2008; Sahl 2000). Other bacteriocins largely produced by Gram-positive bacteria resemble antimicrobial peptides produced by eukaryotes, such as defensins (Papagianni 2003; Singh et al. 2014) with

cationic and amphiphilic nature, and membrane-permeabilizing properties (Breukink et al. 1999).

Bacteriocins are low cytotoxic in nature

Various bacteriocins have been used or consumed naturally in fermented and non-fermented foods (Settanni and Corsetti 2008; Chen and Hoover 2003) from ages, which includes nisin A (Cutter and Siragusa 1998), enterocin 4 (Nuñez et al. 1997), leucocin A (Leisner et al. 1996), lactocin 705 (Vignolo et al. 1996), and enterocin (Aymerich et al. 2000). Interestingly, these are non-toxic as lack of toxicity for these lantibiotics has been demonstrated in several studies that allowed their widespread clinical applications such as probiotics (bacteriocin-producing strains) and antimicrobials in health care and in food industries (Bastos et al. 2010; Pieterse and Todorov 2010; Murinda and Rashid 2003; Jasniewski et al. 2009). Antimicrobial substances from probiotics have been considered to be "Generally regarded as safe molecules" that confer health benefits to host. Contemporary investigations have highlighted the low cytotoxicity of certain bacteriocins, for example, laterosporulin a class IId defensin-like bacteriocin that provided a missing link between prokaryotic and eukaryotic defensins (Singh et al. 2014). It did not show hemolysis even at significantly higher concentrations of MIC values observed for various indicator microbes (Singh et al. 2014). Similarly, carnobacteriocins BM1 and B2 classified under class IIa bacteriocins also did not exhibit cytotoxicity against Caco-2 (human epithelial colorectal adenocarcinoma) cells, even at 100× higher than MIC values against bacterial strains (Jasniewski et al. 2009). Likewise, penisin, a class Ia lantibiotic, was also demonstrated to be non-cytotoxic against RBCs and Raw (mouse macrophages) and RWPE-1 (human prostate epithelial) cells at 20× higher concentration than MIC values against indicator strains (Baindara et al. 2015). However, peptides like MccE492, a class IId bacteriocin, induced biochemical and morphological changes as observed in apoptosis at low or intermediate concentrations leading to a necrotic phenotype at higher concentrations in cancer cells (Hetz et al. 2002). Therefore, such ability of bacteriocins can be exploited to develop novel anticancer peptides naturally or by recombinant technologies and peptide engineering (Lagos et al. 2009). Their low cytotoxic nature in the context of normal host cells makes them particularly an appealing target for novel anticancer agent development.

In vivo efficacy of bacteriocins

In vitro studies demonstrated the prospective role of bacteriocins as alternative to various therapeutic applications due to their minimal cytotoxic nature. Further, in vivo replication efficacy is essential to potentiate these molecules in clinically relevant situations as novel therapeutic candidates. Many bacteriocins have already been extensively examined from this perspective as shown in Table 1. For example, bacteriocins like Pep5 and epidermin have been reported to prevent *Staphylococcus* and/or *Enterococcus* infections in and on catheter tubing (Fontana et al. 2006). In fact, microbisporicin, a novel lantibiotic, demonstrated to have potential inhibitory effect against murine septicemia caused by *S. aureus* upon intravenous and subcutaneous administration (Castiglione et al. 2008). In vivo efficacy of a lantibiotic NAI-107 has been documented against beta-lactam-resistant *S. aureus* in a neutropenic murine thigh infection model that revealed it to be effective in comparison to vancomycin and linezolid (Jabés et al. 2011). Similarly, lacticin 3147 has been shown to prevent the systemic infections of *S. aureus* in a mouse peritonitis model (Piper et al. 2012). Mutacin (B-Ny266), another bacteriocin produced by *Streptococcus mutans*, was found effective against *S. aureus* infection in an intra-peritoneal mouse model and was comparable to vancomycin (Mota-Meira et al. 2005). Importantly, lantibiotic mersacidin has been known to eliminate methicillin-resistant *S. aureus* (MRSA) colonization in a mouse rhinitis model (Kruszewska et al. 2004). Other notable bacteriocins include a novel type B lantibiotic NVB302 effective to manage *Clostridium difficile* infection (CDI) in an in vitro human gut model and this lantibiotic is now under phase I clinical trials (Crowther et al. 2013). Piscicolin 126, produced by *Carnobacterium piscicola*, is an antilisterial bacteriocin retained its antimicrobial activity under in vivo conditions when administered intravenously (Ingham et al. 2003). Penisin, a recently characterized lantibiotic, displayed antimicrobial activity against *S. aureus* in a thigh infection model and thus increased survival rate of mice (Baindara et al. 2015). Nisin, the first lantibiotic used as a food preservative, was extensively studied and results suggested it to be effective against *Streptococcus pneumonia* when compared to vancomycin in an intravenous regimen (Goldstein et al. 1998). Nisin has also been known to have antibacterial and spermicidal activities in in vivo mice model and proved as a potential vaginal contraceptive (Aranha et al. 2004; Reddy et al. 2004). Similarly, nisin F, a natural variant of nisin found to be effective against *S. aureus* in vivo while incorporating into bone cement (van Staden et al. 2012), showed protective ability to the respiratory tract against pathogens when administered intra-nasally (De Kwaadsteniet 2009). Nisin A along with Nisin V and Nisin F also showed protection against *Listeria monocytogenes* in a murine infection model (Campion et al. 2013) and inhibited *S. aureus* in peritoneal cavity of mice model (Brand et al. 2010). Nisin variants are being used as sanitizers against pathogenic *Staphylococcus* and *Streptococcus* species causing mastitis in lactating cows (Cao et al. 2007; Wu et al. 2007; Fernández et al. 2008). Since membrane lytic effects of AMPs are considered as the major mechanism, this mechanism is also attributed for their

Table 1 Selected bacteriocins that have been tested for efficacy in different in vivo models

S.N.	Bacteriocin	Producer organism	Probiotic use			References
1	Nisin A	*Lactococcus lactis*	Skin infections	Human mastitis	In vivo (human model)	Fernández et al. 2008
			Urogenital tract infections	Spermicidal activity	In vivo (rabbit model)	Reddy et al. 2004
2	Nisin F	*Lactococcus lactis*	Systemic infection	Systemic infection	In vivo (murine model)	Brand et al. 2010
			Skin infections	Cutaneous infection	In vivo (murine model)	de Kwaadsteniet et al. 2009
			Hospital-acquired infections	Multidrug-resistant strain	In vivo (murine model)	van Staden et al. 2012, Piper et al. 2011
			Skin infections	Bovine mastitis	In vivo (bovine model)	Cao et al. 2007
3	Ruminococcin C	*Ruminococcus gnavus*	Gastrointestinal tract infections	Stomach and intestine infections	In vivo (rat model)	Wu et al. 2007
4	Mutacin 1140	*Streptococcus mutans*	Gastrointestinal tract infections	Oral cavity	In vivo (animal model/human model)	Hillman et al. 2007
5	Gallidermin	*Staphylococcus gallinarum*	Skin infections	Cutaneous infection	In vivo (rat model)	Manosroi et al. 2010
6	Mutacin B-Ny266	*Streptococcus mutans*	Hospital-acquired infections	Multidrug-resistant strain	In vitro, in vivo (murine model)	Mota-Meira et al. 2005
7	Mersacidin	*Bacillus* sp.	Respiratory tract infections	Rhinitis	In vivo (murine model)	Kruszewska et al., 2004
8	Duramycin	*Streptomyces cinnamomeus*	Respiratory tract infections	Cystic fibrosis	In vivo (human model)	Grasemann et al. 2007; Steiner et al. 2008
9	Salivaricin A	*Streptococcus salivarius*	Gastrointestinal tract infections	Oral cavity	In vivo (animal model/human model)	Burton et al. 2011
10	Lacticin 3147 A1	*Lactococcus lactis*	Skin infections	Bovine mastitis	In vivo (bovine model)	Ryan et al. 1998
11	Lacticin 3147 A2		Hospital-acquired infections	Multidrug-resistant strain	In vivo (murine model)	Piper et al. 2012
12	Lacticin 3147	*Lactococcus lactis*	Urogenital tract infections	Spermicidal activity	In vivo (animal model)	Silkin et al. 2008
13	Pediocin PA-1	*Pediococcus acidilactici*	Gastrointestinal tract infections	Stomach and intestine infections	In vivo (murine model)	Dabour et al. 2009
14	Enterocin CRL35	*Enterococcus mundtii*	Gastrointestinal tract infections	Stomach and intestine infections	In vivo (murine model)	Salvucci et al. 2012
15	Subtilosin A	*Bacillus subtilis*	Urogenital tract infections	Spermicidal activity	In vivo (animal model)	Sutyak et al. 2008
16	Microcin J25	*Escherichia coli*	Gastrointestinal tract infections	Stomach and intestine infections	In vivo (murine model)	Lopez et al. 2007
17	Microcin C7	*Escherichia coli*	Gastrointestinal tract infections	Stomach and intestine infections	In vitro, in vivo (murine model)	Cursino et al. 2006
18	Colicin 1b	*Escherichia coli*	Gastrointestinal tract infections	Stomach and intestine infections	In vitro, in vivo (murine model)	Cursino et al. 2006
19	ESL5	*Enterococcus faecalis*	Gastrointestinal tract infections	Stomach and intestine infections	In vitro, in vivo (murine model)	Kang et al. 2009
20	Lactocin 160	*Lactobacillus rhamnosus*	Urogenital tract infections	Bacterial vaginosis	In vitro, in vivo	Turovskiy et al. 2009
21	OR-7	*Lactobacillus salivarius*	Gastrointestinal tract infections	*Campylobacter* infection	In vivo (chicken model)	Stern et al. 2006

anticancer activity, thus similar mechanisms may remain efficacious in the case of anticancer actions of AMPs. Though few preliminary in vivo investigations with anticancer peptides (ACPs) are available, but they need further extensive investigations.

Bacteriocins are docile to bioengineering

Bacteriocins are small cationic peptides encoded by genes and due to this peptide nature, they are extremely more acquiescent to engineering to increase activity and specificity towards their target when compared with classical antibiotics (Perez et al. 2014). Bacteriocin bioengineering can be done by manipulating the bacteriocin biosynthetic genes through cloning of these genes and in vitro reconstitution of the biosynthesis process required for antimicrobial peptide production (Cotter 2012). However, bacteriocin without posttranslational modifications can be fully or partially synthesized by chemical synthesis process. These engineered peptides have been proven important for further understanding of their activity and structure–function relationships using site-directed mutagenesis to reveal amino acid residues essentially required for activity (Wang et al. 2014; Oppegård et al. 2007; Sun et al. 2015; Haugen et al. 2008). Further, in silico approach of bacterial genome mining and metagenomic DNA analysis provide information about many unexpressed bacteriocin gene clusters, which may be further used for gene synthesis and engineering (Walsh et al. 2015; Mohimani et al. 2014; Letzel et al. 2014). Such technologic advances can further enhance the targeted activity, efficacy, and safety of natural as well as recombinant ACPs.

Bacteriocin interaction with cancer cell membranes

In eukaryotic cells, membrane phospholipids are distributed unevenly between two layers of the lipid bilayer (Op den Kamp 1979; Verkleija et al., 1973; Fadeel and Xue 2009) with phosphatidylserine localized absolutely in the inner leaflet (Rothman and Lenard 1977; Connor et al. 1989) that plays an important role in cell physiology (Bevers et al. 1982; Manno et al. 2002). Interestingly, cancer cell membranes display overexpression of phosphtidylserine (Dobrzyńska et al. 2005; Utsugi et al. 1991) and O-glycosylated mucins (Yoon et al. 1996; Schwartz et al. 1992; Burdick et al. 1997) on the outer membrane leaflet in comparison to non-transformed cells. Thus, they impart a net negative charge on cell membranes, which enables electrostatic interactions between cancerous cell surface and cationic bacteriocins. In contrast, healthy eukaryotic cells contains zwitter-ionic phosphatidylcholine in the outer membrane leaflet that confers an overall neutral charge on these cells resulting in significant reduction of electrostatic interactions. In addition, change of membrane fluidity in cancer cells when compared with their healthy counterparts affects tumor cell adhesion which is related to cancer metastases (Zeisig et al. 2007; Nakazawa and Iwaizumi 1989; Sok et al. 1999; Kozłowska et al., 1999). Plasma membrane fluidity tends to increase metastatic capability and may further assist cancer cell membrane deterioration by membrane interaction of ACPs. Another significant attribute affecting the targeted/selective activity of ACPs is the presence of abundant and irregular microvilli on cancerous cell surface in comparison to their healthy counterpart, a feature adopted for increasing metastatic potential (Chaudhary and Munshi 1995; Domagala 1980; Ren et al. 1990). The net negative charge along with overall increased surface area in cancer cells may enable ACP-mediated cytotoxicity with greater chances of large number of peptide molecules to interact with cellular surface. Collectively, all these properties of cancer cells may assist the ACPs to interact with cell membrane and subsequent killing of cancer cells selectively without affecting healthy eukaryotic cells. Abundance of anionic lipid cardiolipin in mitochondrial membrane of eukaryotic cells result in negatively charged surface of mitochondria (Schenkel and Bakovic 2014; de Kroon et al., 1997; Wriessnegger et al. 2009). Interestingly, mitochondrial membrane is believed to share common ancestry as it originated from endosymbiotic prokaryotes (Gray et al. 2001; Gray 2012). This further may facilitate the ACPs to disrupt the integrity of mitochondrial membrane and resulting in release of several proteins such as cytochrome C and stimulate the apoptotic cell death pathway (Kim et al. 2006; Smolarczyk et al. 2010). Nevertheless, few studies have suggested that many ACPs with cytotoxic properties may cause cancer cell death by necrosis via cell membrane damage (Ye et al. 2004; Vaucher et al. 2010; Maher and McClean 2006).

Contemporary bacteriocins investigated as potential anticancer peptides

Nisin

Nisin (3.49 kDa) secreted by *Lactococcus lactis*, is a lantibiotic class of bacteriocins composed 34 amino acids. Recent reports showed that nisin decreases head and neck squamous cell carcinoma (HNSCC) tumorigenesis by increasing cell apoptosis through activation of CHAC1, increased calcium influxes, and induction of cell cycle arrest (Table 2 and Fig. 1). In fact, nisin is safe for human consumption as approved by Food and Drug Administration and currently used in food preservation and is a potential cancer therapeutic (Joo et al. 2012). Nisin ZP (3.47 kDa, 34 amino acids), a natural variant of nisin, induced a high level of apoptosis in HNSCC cells. Indeed, nisin ZP displayed gradual increase in apoptosis with the increase of concentration. Induction of apoptosis was through a calpain-dependent pathway in HNSCC

Table 2 Bacterial AMPs having anticancer activities against various cancer cell lines

S.N.	Bacteriocin	Source organism	Size (kDa)	Cancer cell lines	
1	Nisin	*Lactococcus lactis*	3.49	MCF7, HepG2, HNSCC	In vitro/in vivo
2	Nisin ZP	*Lactococcus lactis* SIK-83	3.47	HNSCC, HUVEC	In vivo
3	Plantaricin A	*Lactobacillus plantarum* C11	2.98	Jurkat, GH4, Reh, Jurkat, PC12, N2A, GH4	In vitro
4	Azurin	*Pseudomonas aeruginosa*	14	J774, MCF-7, UISO-Mel-2, U2OS, HL60, K562, HUVEC, HCT-116, MDA-MB-231	In vitro/in vivo
5	Colicin E3	*Escherichia coli*	9.8	P388, HeLa, HS913T, V79, BM2	In vitro/in vivo
6	Colicin A	*Escherichia coli*	> 20	HS913T, SKUT-1, BT474, ZR75, SKBR3, MRC5	In vitro
7	Colicin E1	*Escherichia coli*	57	MCF7, HS913T, BM2	In vitro
8	Microcin E492	*Klebsiella pneumoniae* RYC492	7.8	Hela, Jurkat, RJ2.25, KG-1, human colorectal carcinoma cells	In vitro/in vivo
10	Pyocin S2	*Pseudomonas aeruginosa* 42A	74	HepG2, Im9, HeLa, AS-II, mKS-A TU-7, HFFF	In vitro
11	Pediocin PA-1	*Pediococcus acidilactici*	3.5	A-549, DLD-1, HT29, HeLa	In vitro
12	Pediocin CP2	*Pediococcus acidilactici* CP2 MTCC5101		HepG2, HeLa, MCF7	In vitro
13	Pep27 anal2	*Streptococcus pneumoniae*		AML-2, HL-60, Jurkat, SNU-601, MCF-7	In vitro
14	Bovicin	*Staphylococcus bovis* HC5	2.4	MCF7, HepG2	In vitro

cells. Similarly, apoptosis was also induced in human umbilical vein endothelial cells (HUVEC) and reduced intratumoral microvessel density. Long-term treatment with nisin ZP enhanced longevity and maintained the normal histologic structure of the tissue without any evidence of inflammation, fibrosis, or necrosis. It was considered to be a potential novel therapeutic for management of squamous cell carcinoma (Kamarajan et al. 2015). Very recently, the cytotoxic activity of nisin was evaluated against colon cancer SW480 cells where it showed significant antiproliferative impact and raised the apoptotic index (bax/bcl-2 ratio). Further, intrinsic apoptotic pathway was suggested to be responsible for this cytotoxicity induced by nisin (Ahmadi et al. 2017). Moreover, the synergistic effect of nisin with doxorubicin showed significant

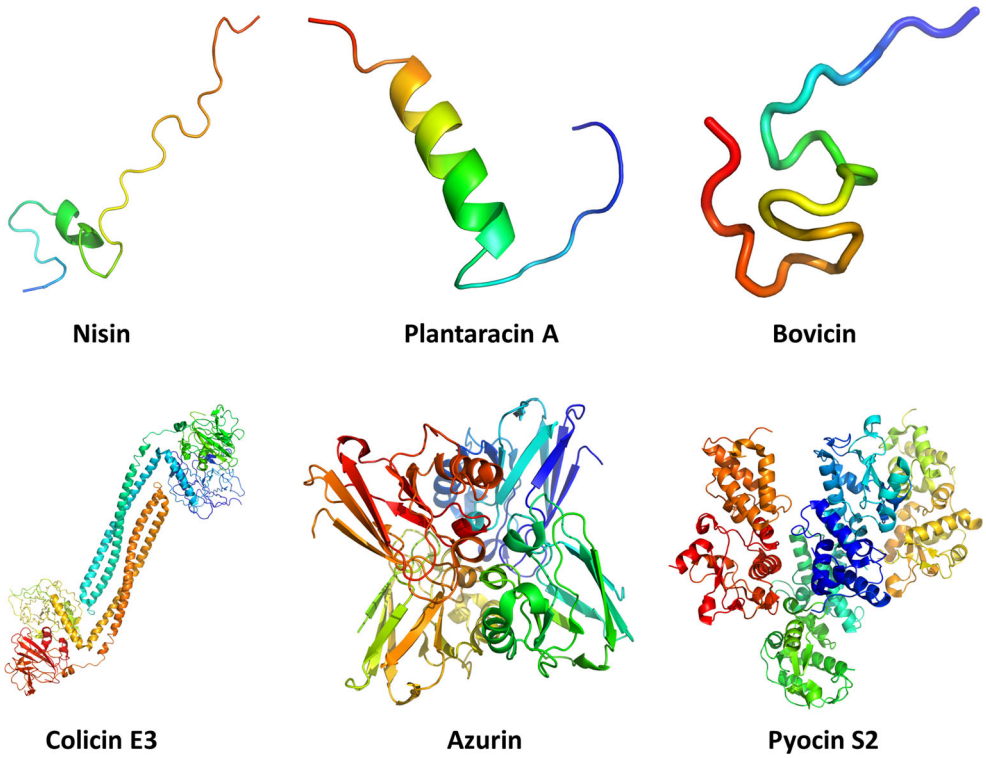

Fig. 1 Structures of different antimicrobial peptides characterized with potential anticancer therapeutics

reduction in tumor volumes when compared to individual treatments of these compounds (Kaur and Kaur 2015). The combined treatment showed apoptosis in tumor tissues as chromatin condensation and marginalization of nuclear material was observed; thus, nisin can be a complement to doxorubicin as chemotherapeutic drug.

Plantaricin A

Plantaricin A (PlnA) is another low molecular weight peptide (2.98 kDa) containing 26 amino acids and secreted by strains of *Lactobacillus plantarum* C11, WCFS1, and V90 (Table 2). It displayed broad-spectrum antibacterial activity with membrane permeabilizing property (Fig. 1). PlnA could permeabilize eukaryotic cells also with a potency that differed between various cell types. It showed electrostatic attraction to negatively charged phospholipids in the membrane as shown by microfluorometric techniques. Interaction with glycosylated membrane proteins is probably being the first and essential first step for PlnA interaction with membrane. Activities against different cell types including cancerous cells is attributed to different glycosylation patterns (Sand et al. 2010, 2013; Andersland et al. 2010). However, others demonstrated similar sensitivity of PlnA towards cancerous lymphocytes, neuronal cells, kidney cortex, and vero cells from green monkey and human Caki-2 cells that were permeabilized by PlnA (Kristiansen et al. 2005; Fialho et al. 2012). In further support, three-dimensional structure PlnA determined by nuclear magnetic resonance spectroscopy revealed effective structure that can be positioned in membrane interface to engage in chiral interaction with receptor (Jeuken et al. 2000).

Azurin

Azurin from *Pseudomonas aeruginosa* is a member of the cupredoxin family of redox proteins with molecular weight of about 14 kDa (Fialho et al. 2012) as shown in Table 2. Though different variants of azurins vary in sequence homology (50 and 90%), their structure is highly conserved. They display a rigid β-sandwich core formed by two main β-sheets in their structure (Jeuken et al. 2000). They are reported to exhibit anticancer properties which can preferentially penetrate cancer cells like breast cancer (MCF-7), melanoma (UISO-Mel-2), and osteosarcoma (U2OS) cells to display apoptotic effects, but did not show any effect against normal cells (Punj et al. 2004; Goto et al. 2003; Zaborina et al. 2000; Yamada et al. 2002; Gupta 2002; Yang et al. 2005). A short variant of azurin p28 peptide with 28 amino acids was identified to act as potential protein transduction domain (PTD) in cancer cells (Yamada et al. 2005). This derivative p28 was also reported to inhibit cancer cell growth and prevention of tumor emergence (Bizzarri et al. 2011; Yamada et al. 2013). Interestingly, similar peptides were detected from *Lactobacillus salivarius* (Shaikh et al. 2012) and other microbes from the human gut (Nguyen 2016) with high binding affinities to cancer targets (Fig. 2).

Induction of apoptosis by these peptides was further confirmed using caspase-mediated mitochondrial pathways as increased p53 intracellular level was observed during the treatment (Yamada et al. 2002). Azurin and peptide p28 displayed selective entry and cytotoxic effects against acute and chronic myeloid leukemia cell line by induction of apoptosis and interfering with angiogenesis of human umbilical vein endothelial cells (Kwan et al., 2009; Mehta et al. 2011). Moreover, they were found to be proficient to interfere in oncogenic transformation as they could halt the formation of

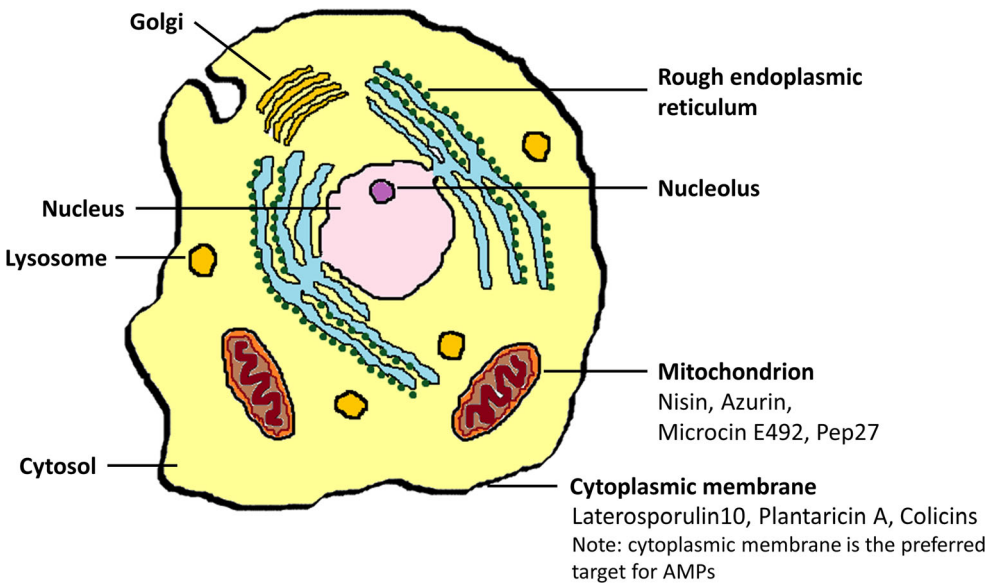

Fig. 2 Cellular targets for described anticancer mechanism of various antimicrobial peptides

precancerous lesions in a dimethyl-1,2-benzanthracene exposed mouse organ culture model (Mehta et al. 2010). Additionally, it was shown to be effective against tumor growth in nude mice that were xenografted with UISO-Mel-2 and MCF-7 cells (Punj et al. 2004; Yang et al. 2005). They also induced apoptosis to inhibit the tumor growth in Dalton's lymphoma-bearing ascites mice model (Ramachandran and Mandal 2011). Interestingly, p28 displayed significant antitumor activities as confirmed using nude mice xenografted with MCF-7 cells (Yamada et al. 2009). Similar results were shown for p28 as it suppressed tumor growth in HCT-116 (colon cancer), UISO-Mel-23 (melanoma), and MDA-MB-231 (breast cancer) cell xenografts in nude mice (Jia et al. 2011). It was also demonstrated that azurin secretion occurred by producing strains in the presence of cancer cells (Mahfoouz et al. 2007). Overall, azurins are antitumor peptides that display induction of apoptosis through p53 stabilization, inhibition of angiogenesis, and binding with ephrin receptor kinases (Mehta et al. 2011; Chaudhari et al. 2007; Riedl and Pasquale, 2015). Most importantly, p28 did not cause any immune reaction and toxicity in mice as well as in non-human primates, highlighting its potential application as a therapeutic agent (Jia et al. 2011). Thus, azurin differentiates itself from other available drugs and brings about an interesting prospect to investigate other bacteriocins, which might have similar or even better anticancer properties.

Pyocins

Pyocins are high molecular weight (> 10 kDa) AMPs (Fig. 1) secreted by strains of *Pseudomonas aeruginosa* (Michel-Briand and Baysse 2002). These peptides are constitutive in chromosomes, but environmental factors such as UV radiation ormitomycin C can initiate the biological activity (Kageyama 1964). Pyocins have been categorized into three types: R-, F-, and S-type. R- and F-type pyocins resemble the tails of bacteriophages with differences in flexibility and contractility of their structure. Specifically, R types are non-flexible and contractile entities, whereas F-type pyocins are just the reverse with flexible and non-contractile rod-like structures. R-type pyocins display nuclease and protease resistance with depolarization activity on membranes that subsequently leads to pore formation in membrane. The killing activity carried by large component may be variable for different varieties of pyocins. While pyocins S1, S2, S3, and AP41 act by DNase activity, pyocin S4 acts through tRNase activity; however, pyocin S5 revealed channel-forming activity. Further, a small component for S-type pyocins acts as immunity protein interacting with large component (Michel-Briand and Baysse 2002). For the first time, a partially purified pyocin from *P. aeruginosa* was shown to inhibit the growth of mouse fibroblast cell line L6OT by Farkas-Himsley and Cheung (1976). Subsequently, anticancer activity of pyocin S2 was observed against diverse cancerous cell lines like HeLa, AS-II, and mKS-A TU-7. However, no such effects were observed against normal mice cells (BALB/3T3), rat kidney cells, and human lung cells. Recently, purified pyocin S2 from *P. aeruginosa* 42A was reported to exhibit cytotoxic effects against tumor cell lines HepG2 (human hepatocellular carcinoma) and Im9 (human immunoglobulin-secreting cell line derived from multiple myelomas) without affecting normal human fetal foreskin fibroblasts (Abdi-Ali et al. 2004).

Colicins

The plasmid-encoded colicins are usually found to be high molecular weight AMPs with molecular weight > 20 kDa (Fig. 1). These were first observed in *Escherichia coli* (Table 2) and named as colicin (Feldgarden and Riley 1999; Cascales et al. 2007; Braun et al. 1994; Gratia 1925). Bacterial strains belonging to the family *Enterobacteriaceae* are known to produce this class of AMPs. Colicin secretion is a result of stress response (Smarda and Smajs 1998). These are three domain proteins and their cellular killing mechanism is accomplished in three distinct steps where the central region acts as a receptor domain, while N-terminal and C-terminals are translocation and cytotoxicity domains, respectively (Helbig and Braun 2011; Arnold et al. 2009). However, unstructured N-terminal was also shown to exhibit antibacterial activity (Johnson et al. 2013). Cytotoxic and cytocidal activities were observed when colicin E3 was used against HeLa cells with specific cleavage of rRNA (Smarda et al., 1978). Studies on colicins E1-E5 and K revealed cellular killing activity against hamster fibroblast V79 cell lines (Smarda 1987). However, selective anticancer activities of colicins such as A, E1, E3, and U were demonstrated to cause cell cycle alterations in human fibroblast cell line (MRC5). Similarly, they were reported against cancerous cell lines like human breast cancer cell lines MCF7 and MDA-MB-231, osteosarcoma cell line HOS, HS913T and MRC5 fibroblasts with predefined p53 gene mutations, but the activity was less towards fibroblasts MRC5 (Chumchalová and Smarda 2003). In another investigation, colicin E3 showed cidal effect against human origin carcinoma cells and HeLa cells (Smarda et al., 1978) with dose-dependent inhibitory response to murine leukemia cells P388 (Fuska et al. 1979). Another evidence was provided in a different study where murine lymphoma cell lines showed decrease in viability with the treatment of colicins A and E2 (Smarda and Oravec 1989). Colicins E1 and E3 destroyed oncogene v-myb transformed chicken monoblasts without affecting the cell cycle events (BM2), indicating the probability of necrosis instead of apoptosis (Smarda et al. 2001). These studies also highlighted the specificity towards anticancer properties of colicins. Several in vivo investigations in mice also supported evidence to the anticancer potential of colicins through intratumor injections that decreased tumor volume

(Cursino et al. 2002; Farkas-Himsley et al. 1995) and enhanced longevity in mice with transplanted LP-2 plasmacytoma (Chumchalová and Smarda 2003).

Microcins

Members of the family *Enterobacteriaceae* are known to produce microcins that are smaller in size (< 10 kDa) in comparison to colicins. So far, there are seven microcins studied in detail and reported (Table 2). The biosynthetic gene clusters of microcins typically contain microcin precursor, ABC transporter for peptide transport and defense, and structural modifications. Genetic machinery such as plasmids and chromosomes harbors most of the secretion factors for the microcin production (Duquesne and Destoumieux-Garzón, 2007). This group includes some low molecular weight molecules with distinct structural modifications, e.g., microcins B17, C7, C51, and J 25 (Agarwal et al. 2011; Metlitskaya et al. 1995; Wilson et al. 2003), others with disulfide bonds. However, microcins like L, V, and 24 did not show any posttranslational modifications (Pons et al. 2004; Jeziorowski and Gordon, 2007; Frana et al. 2004) and microcins E492, M, H47, and I47 have been reported as linear peptides (de Lorenzo 1984; Vassiliadis et al. 2010). Microcin E492 (7.8 kDa) from *Klebsiella pneumoniae* strain RYC492 is reported to inhibit a large number of pathogenic bacteria belonging to genera including *Escherichia*, *Klebsiella*, *Salmonella*, *Citrobacter*, and *Enterobacter* (de Lorenzo 1984). Microcins like E492 were reported to display activity against various human cancer cell lines such as HeLa, Jurkat, RJ2.25, and colorectal carcinoma cells. However, it did not inhibit normal cells such as bone marrow cells, splenocytes, KG-1, human tonsil cells, and nontumor macrophage-derived cells (Hetz et al. 2002). The principal mechanism of action for microcin E492 involved pore formation in the cell membrane and thus disruption of membrane potential (de Lorenzo and Pugsley 1985; Lagos et al. 1993). Studies also emphasized cellular apoptotic features including cell shrinkage, DNA fragmentation, phosphatidylserine release, caspase activity, loss of mitochondrial membrane potential, and release of intracellular calcium ions undermining the significance of apoptosis as the major mechanism of cellular death (Hetz et al. 2002). In fact, microcin E492 was delivered into the host by plasmid-induced bacteriocin production using *E. coli* VSC257pJEM15 as a safer, non-toxic, non-immunogenic method (Hetz et al. 2002). Moreover, systemic administration of the peptide in mice leads to selective colonization of a probiotic *E. coli* strain Nissle191 in cancerous cells (Brader et al. 2008). Additionally, *E. coli* strain Nissle1917 producing both microcin M and microcin H47 is used as a probiotic under the name Mutaflor, that has been extensively used for management of a variety of intestinal diseases (Rembacken et al. 1999; Kruis 2004). These findings suggest *E. coli* Nissle1917 strain is a suitable carrier for the delivery of microcin E492 in preclinical investigations. Antitumor activities of microcin E492 were shown in a preclinical nude mouse model xenografted with human colorectal carcinoma cells (Lagos et al. 2009).

Pediocins

Pediocins are small, cationic, plasmid-encoded AMPs (Table 2) yielded by members of *Pediococcus* and other lactic acid-producing genera (Papgianni and Anastasiadoue 2009). Pediocins are highly stable peptides that are effective over a range of temperature and pH. However, they are sensitive to proteolytic enzymes like papain, pepsin, protease, trypsin, and α-chymotrypsin (Kumar et al. 2011). Different types of pediocins are reported to date including pediocin L50, AcH, AcM, CP-2, F, K1, L, L-50, SJ-1, etc., (Papgianni and Anastasiadoue 2009; Ennahar et al. 1996; Elegado et al. 1997; Cintas et al. 1995; Schved et al. 1993). The N-terminal region of pediocins contains a conserved motif Y-G-N-G-V/L also known as "pediocin box" along with two conserved cysteines that are joined by a disulfide bridge to form a three-stranded antiparallel β-sheet structure. While cationic β-sheet domain at N-terminal mediates binding, the hairpin-like C-terminal region involves penetration of the peptide into hydrophobic region of the target cell membrane (Fimland et al. 2005; Drider et al. 2006). Among various pediocins, pediocin PA-1 from *P. acidilactici* PAC1.0 has been reported to inhibit growth of human lung carcinoma cell line and human colorectal adenocarcinoma cell line (Kaur and Kaur 2015). In a different study, pediocin PA-1 isolated from *P. acidilactici* K2a2-3 revealed cytotoxicity against human colon adenocarcinoma cell line (HT29) and HeLa cell line (Villarante et al. 2011). Other pediocins like CP2 produced by *P. acidilactici* CP2 MTCC 5101 and its recombinant variant displayed cytotoxic effects against human cancer cell lines including HepG2, HeLa, and MCF7 (Kumar et al. 2011).

Pep27anal2

Pep27anal2 is an analogue of Pep27 that is effective against *S. pneumoniae* (Sung et al. 2007). Pep27anal2 contains 27 amino acids with more hydrophobic residues in comparison to Pep27. Pep27anal2 was demonstrated to show cytotoxic effects against leukemic cancer cells such as AML-2, HL-60, Jurkat, gastric cancer cells, SNU-601 and MCF-7 cells. Simultaneously, Pep27 anal2 revealed penetration of cell membrane as a mechanism of action and cell-destroying activity was independent of caspase and cytochrome-C. Results also suggested that the hydrophobic nature of the peptide played an important role in membrane interactions and anticancer activity with potential of being a candidate for

anticancer therapeutic agents (Sung et al. 2007; Lee et al. 2005; Huang et al. 2011).

Bovicin

Bovicin is a low molecular weight (2.4 kDa), broad-spectrum AMP produced by *Streptococcus bovis* HC5 (Table 2). Bovicin resembles nisin in both structure and function with stability towards high temperature and low pH (Fig. 1). Though it was resistant to proteinase K and α-chymotrypsin, enzymes like pronase E and trypsin show effect on bioactivity. The mechanism of activity is mainly by disrupting the integrity of cell membrane through pore formation resulting in ionic imbalance, specifically, affecting potassium efflux in target cells (Mantovani et al. 2002). Bovicin is found to be effective against MCF7 and HepG2 cancer cell lines (Paiva et al. 2012).

Laterosporulins (LS)

Laterosporulin is a defensin-like peptide from *Brevibacillus* spp. strains GI-9 and SKDU10. They have displayed human defensin-like structure and broad-spectrum activity against bacteria (Singh et al. 2014). However, LS10 showed antimycobacterial activity as it inhibited pathogenic strains of *Mycobacterium tuberculosis* Rv strain (Table 2). The amino acid composition analysis of LS10 showed predominance of hydrophobic amino acids (Baindara et al., 2017a, b) and it is capable of killing Mtb H37Rv strain residing inside the phagosomes of murine macrophages. It was found to be non-toxic to macrophage cells even at higher concentrations (Baindara et al. 2016). This was also involved in membrane disruption as demonstrated by alterations in ATP levels and the NAD(P)/NAD(P)H ratios. There was no effect on RBCs as no hemolysis was observed even at increased concentration in comparison to their MIC values. LS10 displayed cytotoxicity against diverse cancer cells like MCF-7, HEK293T, HT1080, HeLa, and H1299 at significantly low concentrations (10 μM), except prostate epithelium cells RWPE-1. Release of lactate dehydrogenase from cancer cell lines at 15 μM concentration indicates the lytic ability of LS10. Furthermore, flow cytometry analysis revealed that LS10 induced apoptosis in cancer cell lines even at 2.5 μM concentration. Nevertheless, RWPE-1 cells remained viable even at 20 μM concentration (Baindara et al., 2017a, b).

Conclusions

Bacteriocins are AMPs with unique biologic properties, which make them quite appealing and promising therapeutic compounds for a variety of disease conditions. Particularly, the anticancer properties of bacteriocins have been studied, but they are applied only to a limited extent yet. Purified bacteriocins including plantaricin, nisin, pyocin, colicin, pediocin, and microcin (Lagos et al. 2009) have shown inhibitory properties against different cancer cell lines as few of them have been examined in xenograft mouse models also (Shaikh et al. 2012; Cornut et al. 2008; Saito and Watanabe 1979). Bacteriocins are membrane active peptides and altered genetic expression of surface charge on cancer cell surface makes them more specific and targeted to interact with bacteriocins (Zhao et al. 2006; Riedl et al. 2011; Martín et al., 2015). Few other salient structural characteristics of bacteriocins are positively charged amino acid residues, hydrophobicity, amphipathic structures and oligomerization that enhance their potential anticancer activities. The anticancer mechanism of bacteriocins largely includes apoptosis, inhibition of cell proliferation, depolarization of cell membrane, blockage of angiogenesis, and inhibition of tumorigenesis as observed in vivo. However, well controlled in vivo investigations must be carried out to gain better insights in mechanism of action against cancerous cell lines. Biophysical studies, structure analysis, dynamics, topology, and molecular mechanisms of membrane disruption and the specific membrane component activities are essentially required to provide new insights to understand the anticancer phenomenon of potential anticancer bacteriocins. However, susceptibility towards the serum components like proteases is one of the major challenges of using bacteriocins in vivo. Chemical syntheses of bacteriocins by incorporating D-amino acids that are less susceptible to proteolytic cleavage in the gut have been tried. For example, synthesis of lactococcin G with replaced D-amino acids in N- and C-terminals for improved stability against peptidases (Oppegård et al., 2010) and site-directed mutations of trypsin recognition sites in salivaricin P (O'Shea et al. 2010) reveal the efforts focused on improving stability of bacteriocins in gut environment. Moreover, the functional vehicles for the controlled focused delivery of bacteriocins could also improve their in vivo stabilities and applicability.

As bacteriocins are amenable to bioengineering, they provide an opportunity to improve the efficacy of naturally occurring bacteriocins by creating the hybrid bacteriocins with desired properties. Molecular screening of three novel bacteriocins Lsl_003, Lsl_0510, and Lsl_0554 from *Lactobacillus salivarius* by Shaikh et al. (2012) revealed binding affinities towards common cancer targets p53, Rb1, and AR. Among these, Lsl_0510 showed the highest binding affinity towards all three receptors (p53, Rb1, and AR) that suggested it as an ideal candidate for future cancer therapeutics (Shaikh et al. 2012). Recent studies provided convincing evidence that oral and gut bacteria may be implicated in carcinogenesis in humans (Ahn et al. 2012; Michaud and Izard 2014; Grover et al. 2016). In these scenarios, it is plausible that bacteriocins having dual activities as antimicrobial as well as anticancer properties like nisin may have greater composite benefits of

reestablishing a healthy microbiome and disrupting the carcinogenesis (Shin et al. 2016). Such agents essentially require a rigorous well-designed quality-focused research to develop them as promising clinical therapeutic agents for human use.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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