Brevilaterin B from *Brevibacillus laterosporus* has selective antitumor activity and induces apoptosis in epidermal cancer

Zhou Chen¹ · Lulu Wang¹ · Yangliu Liu¹ · Panpan Han¹ · Dan Hong¹ · Siting Li¹ · Aijin Ma¹ · Yingmin Jia¹,²

Received: 2 October 2021 / Accepted: 28 July 2022 / Published online: 24 August 2022
© The Author(s), under exclusive licence to Springer Nature B.V. 2022

Abstract

Brevilaterins as antimicrobial peptides (AMPs) secreted by a newly discovered species *Brevibacillus laterosporus*, had been demonstrated to display excellent antibacterial and antifungal activities; however, very limited information about their new bioactivity was ever developed. Herein, we discovered Brevilaterin B, an AMP produced by *Br. laterosporus* S62-9, exhibited a new anticancer activity and investigated its anticancer details. Proliferation, membrane permeability and apoptotic rate of cell lines were studied by methods of CCK-8 Assay, LDH Assay and Annexin V-FITC/PI Kits, respectively. ROS levels and mitochondrial membrane potential of tested cells were further detected through the fluorescent probes DCFH-DA and JC-1. Brevilaterin B exhibited broad-spectrum anticancer activity in a dose-dependent manner. It selectively inhibited the proliferation of epidermal cancer cell A431 but had no effect on its control normal cells in a dose of 2.0 µg/mL. In comparison, typical morphological characteristics of apoptosis and an apoptotic ratio of 71.0% in A431 were observed after treatment by 2.0–3.0 µg/mL of Brevilaterin B. The ROS levels increased by 21.3% and mitochondrial membrane potential reduced by 48.8% from A431 were further occurred, indicating Brevilaterin B’s anticancer action was mainly focus on the mitochondrion of cancer cells. In total, Brevilaterin B we reported above maybe believed to be a potential application as an anticancer medicament, increasing its commercial value.

Keywords *Brevibacillus laterosporus* · Antimicrobial peptide · Anticancer · Epidermal cancer cells · Apoptosis

Introduction

Despite unprecedented successes in the field of medicine in the last fifty years, human cancer remains a major cause of high morbidity and mortality worldwide (Deslouches & Di 2017). Chemotherapy drugs are still the principal agents used to treat cancer in the advanced or metastatic stages, but the severe side effects to normal cells and tissues, and the easy formation of multi-drug resistance remain problems (Siegel et al. 2014). In the last few decades, tremendous efforts have been devoted to creating new therapies that are more selective and less harmful for patients. There is increasing evidence that several antimicrobial peptides (AMPs) exhibit potential antitumor activity. AMPs are an untapped resource with a low propensity to elicit the development of resistance and low propensity to cause toxicity to healthy cells undergoing rapid proliferation (Deslouches et al. 2013, 2015; Steckbeck et al. 2014). AMPs, as cationic and amphipathic peptides may bind to the outer membranes of cancer cells, which have been reported to carry more negatively charged molecules, by electrostatic interactions, and hence cause cytotoxicity toward cancer cells with either a necrotic or apoptotic phenotype (Giuliani et al. 2007; Ting et al. 2014). AMPs are therefore potential therapeutic drugs for the prevention and treatment of cancer. AMPs have efficient tissue penetration and uptake by heterogeneous cancer cells, and treatment with AMPs, either alone or acting synergistically with existing therapeutics, is excepted to result in improved anticancer therapies with higher selectivity for neoplastic cells and fewer harmful effects on healthy tissues (Oyston et al. 2009).
Several AMPs from bacteria, filamentous fungi, and actinomycetes have been reported to display anticancer properties (Zhao et al. 2018). In particular, AMPs from Bacillus sp. have been the focus of many studies because of their interesting antitumor properties. For example, Surfactin secreted by Bacillus subtilis has shown good anticancer ability in various cancer cell lines, including the human breast cancer cell lines MCF-7 and MDA-MB-231, the leukemia cell line K562, the cervical cancer cell line HeLa, the rectal cancer cell line LoVo, the histiocytic lymphoma cell line U-937, and another mouse monocyte macrophage leukemia cell line RAW264.7 (Kim et al. 2007; Park et al. 2013). Br. laterosporus, previously classified as Bacillus laterosporus, is a newly discovered species and had been shown to be one of the best candidates for producing multiple short sequence AMPs (Krachkovskii et al. 2002). These peptides contain three structurally unrelated families, a lipopeptide (tauramamide), five linear cationic peptides (bogorols A–E), and four cyclic decapetides (lololatins A–D) (Barsby et al. 2006; Gerard et al. 1999). Originally, the most valuable feature of these AMPs was their broad-spectrum activity against vegetative and nonmultiplying cells of gram-positive/negative bacteria (Singh et al. 2015), drug-resistant bacteria, and pathogenic fungi, such as MRSA, VER and Candida albicans (Barsby et al. 2006; Wang et al. 2017). Later, their potential anticancer activity has ever been explored. For example, Bogorol B-JX strongly inhibited the proliferation of human histiocytic lymphoma U-937 and ConA-activated spleen cells (Jiang et al. 2017). Another AMPs Spargualin also exhibited potential antitumor activity against transplantable leukemias in mice (Nishikawa et al. 1996). However, to the best of our knowledge, these are the only studies of the anticancer activity of such type of AMPs reported to date. Therefore, further systematic research into the selective anticancer activity of these AMPs, including the mode of their anticancer action on specific cancer cells is desirable.

We selected a recently discovered species Br. laterosporus S62-9, which can produce multiple AMPs, and focused on the potential antitumor property of Brevilaterin B, the most valuable component isolated from this new species. Thus, the aim of the present work was to evaluate the activity exerted by Brevilaterin B against various human cancer cell lines and its ability to induce apoptosis in epidermal cancer cell lines in vitro.

Materials and methods

Strains and AMPs. Br. laterosporus S62-9 (CGMCC No. 18,629) used in this research was stored in our Laboratory of Enzyme Engineering. Brevilaterin B, produced by Br. laterosporus S62-9, was obtained according to our previous report (Chen et al. 2022). Its purity was 98.83%, and the yielding titer towards Staphylococcus aureus (ATCC 25,923) was 1888.67 AU/mg.

Cell lines and culture conditions. Different human cancer cell lines (n = 27) and several corresponding normal cell lines were used (Table 1). All cells were cultured at 37 °C in a humidified atmosphere containing 5% CO2 and in media containing 10% FBS and 1% penicillin-streptomycin cocktail. All standard reagents, including FBS, DEME, RPMI 1640, Ham’s F-12, and EGM were obtained from Gibco (Big Cabin, Oklahoma, ME, USA). The cell counting kit 8 (CCK-8), annexin V/propidium iodide (PI) staining kit, lactase dehydrogenase (LDH) and reactive oxygen species (ROS) assay kits were obtained from Biodée (Beijing, China), BD Biosciences (San Jose, CA, USA), and Jiancheng Bioengineering Institute (Nanjing, China), respectively.

Effect of Brevilaterin B on the proliferation of cell lines. The CCK-8 assay was used to determine the proliferation of the cell lines. First, 100 µL of cells (5 × 104 cells/mL) in logarithmic growth phase were seeded on 96-well plates and cultured for 24 h. Cells were then mixed and interacted with Brevilaterin B (0, 1, 2, 4, 8, 16, and 32 µg/mL) for 48 h. Finally, the above mixtures were dyed by CCK-8 solution for 4 h, then examined for absorption at 490 nm using a microplate reader (INFINITE Spark 10 M, TECAN, Switzerland). Afterwards, the IC50 values were calculated for each cell line.

Effect of Brevilaterin B on the membrane permeability of the cell lines. The membrane permeability of the cell lines was evaluated by the release rate of LDH. First, 500 µL of cells (105 cells/mL) in logarithmic growth phase were seeded on 48-well plates and cultured for 24 h. The cells and Brevilaterin B (0, 2, and 3 µg/mL) were mixed and interacted for 24 h. Then, the supernatant was harvested after centrifugation (300 × g) for 5 min. Finally, the LDH assay kit was used to calculate the release rate of LDH.

Ultrastructure observation of the cell lines. Transmission electron microscopy (TEM) was used to observe microscopic changes of cells. Cells (3 × 105 cells/mL) in logarithmic growth phase were cultured for 24 h, then mixed and interacted with Brevilaterin B (0, 2, and 3 µg/mL) for another 24 h. Later, the cells were fixed with 5% glutaraldehyde for 12 h, and treated with osmium tetroxide for 1.5 h. Ethanol was used to dehydrate the fixed cells and embedded in epon812 epoxy resin. Ultrathin sections prepared using an ultrathin slicer was dyed by 0.5% uranyl acetate and lead citrate. Finally, the microscopic changes in cell lines were observed using a JEOL TEM-1400 transmission electron microscope (Hitachi, Tokyo, Japan).

Induction of apoptosis in the cell lines. To evaluate the ability and action of Brevilaterin B to induce apoptosis in
the cell lines, the apoptotic rate, level of ROS, and mitochondrion membrane potential were evaluated.

The annexin V-FITC/PI kit was used for calculation of the apoptotic rate. Cells (10^5 cells/mL) in logarithmic growth phase were seeded on six-well plates and incubated for 24 h. These cells were mixed and interacted with Brevilaterin B (0, 2, and 3 µg/mL) for 24 h. 5 µL of Annexin V-FITC was added to the treated cells (100 µL) followed by 5 µL of PI for staining. Then, 400 µL of binding buffer was added and the mixture was quantitatively measured using a BD C6 flow cytometer from BD Bioscience.

DCFH-DA was the fluorescent probe used for examination of the ROS levels. Cell lines (10^5 cells/well) in logarithmic growth phase were seeded on a six-well plate and incubated for 24 h. These cells were mixed and interacted with Brevilaterin B (0, 2, and 3 µg/mL) for 24 h. 5 µL of Annexin V-FITC was added to the treated cells (100 µL) followed by 5 µL of PI for staining. Then, 400 µL of binding buffer was added and the mixture was quantitatively measured using a BD C6 flow cytometer from BD Bioscience.

Finally, the prepared cell lines were suspended twice in staining solution and evaluated by a BD C6 flow cytometer.

**Statistical Analysis.** Data were expressed as mean ± SD and subjected to one-way analysis of variance (ANOVA, SPSS version 10.0) to determine significant differences. These differences (p<0.05) were reanalyzed by least significant difference multiple-range test.

**Results**

*Effect of Brevilaterin B on the proliferation of cells.* Effect of Brevilaterin B on the proliferation of 27 human cancer cell lines and 12 control normal cell lines was examined (Table 1). IC_{50} values determined in our study indicated that Brevilaterin B could effectively inhibit the proliferation of all tested cancer cells in a dose-dependent manner. However, 8 µg/mL of Brevilaterin B exhibited an obvious cytotoxicity in most of the cancer cell lines. The lowest IC_{50} value observed for Brevilaterin B was 1.40 µg/mL. The IC_{50} values of Brevilaterin B toward the epidermal carcinoma cell line A431 and a gastric cancer cell line were 2.75 and 5.68 µg/mL, while the values toward their control normal cell lines were 12.78 and 10.62 µg/mL, respectively. The results described above indicated that Brevilaterin B could effectively inhibit the proliferation of specific cancer cell lines.

| Table 1 IC_{50} values of Brevilaterin B to cancer and normal cell lines |
|-------------------------|-------------------------|-------------------------|
| Cell lines              | IC_{50}(µg/mL)          | Cell lines              |
| Skin fibroblasts HSF    | 12.78 ± 0.33            | Normal mammary epithelial cells MCF-10 A |
| Epidermal carcinoma cell A431 | 2.75 ± 0.07         | Breast cancer cells MDA-MB-231 |
| Esophageal epithelial cells HEEC | 2.66 ± 0.34         | Breast cancer cells MCF-7 |
| Esophageal cancer cell EC109 | 2.13 ± 0.23         | Normal cervical cells HIBEPIIC |
| Esophageal cancer cell EC9706 | 3.23 ± 0.16         | Cervical cancer cells Hela |
| Pancreatic duct epithelial cells HPDE6-C7 | 3.45 ± 0.20     | Cervical cancer cells HelaS3 |
| Pancreatic cancer cells SW1990 | 13.40 ± 0.08      | Normal ovarian epithelial cells IOSE80 |
| Pancreatic cancer cells PANC-1 | 3.11 ± 0.49         | Ovarian cancer cells A2780 |
| Normal hepatocytes Lo-2 | 2.91 ± 0.07            | Ovarian cancer cells SKOV3 |
| Hepatoma cells SMMC7721 | 13.81 ± 0.31            | Normal prostatic epithelial cells RWPE-1 |
| Hepatoma cells HepG2    | 9.84 ± 0.39             | Ovarian cancer cells DU145 |
| Normal colonic epithelial cells NCM460 | 3.04 ± 0.10     | Prostate cancer cells PC-3 M |
| Colon cancer cells HT-29 | 1.40 ± 0.09           | Human normal gastric epithelial cells GES-1 |
| Colon cancer cells sw480 | 17.15 ± 0.97          | Human gastric cancer cells BGC-823 |
| Colon cancer cells HCT-116 | 7.67 ± 0.57           | Human gastric cancer cells SGC-7901 |
| Rectal cancer cells LoVo | 4.16 ± 0.53            | Squamous cell carcinoma of tongue Tca8113 |
| Human embryonic lung fibroblasts CCD-19 Lu | 4.76 ± 0.03      | Melanoma cells A375 |
| Human non-small lung cancer cells A549 | 5.54 ± 0.55       | Human leukemia cells K-562 |
| Embryonic kidney cell HEK-293 | 4.78 ± 0.32       | Oral cancer cells KB |
| Renal cell carcinoma A-498 | 2.33 ± 0.49            | - |

Based on the findings above, the epidermal carcinoma cell line A431 and normal human skin fibroblasts (HSF)
were selected for further study. We investigated the effect of Brevilatrin B on membrane permeability of A431 and HSF as determined from the LDH release rates (Fig. 1). The results showed that 2 µg/mL of Brevilatrin B could induce LDH release from the cancer cells A431, with a release rate of 107.21%. In comparison, Brevilatrin B did not affect the membrane permeability of HSF cells.

**Effect of Brevilatrin B on cell nuclear morphology and ultrastructure.** Effect of Brevilatrin B on the cell nuclear morphology was observed using Hoechst 33,258 dye solution (Fig. 2). After treatment with 2–3 µg/mL of Brevilatrin B for 24 h, the number of cancer cells was decreased markedly, and the number of irregular cells and the intensity of the blue fluorescence were increased significantly. Later, the typical morphological characteristics of apoptosis appeared, including the occurrence of pyknosis in the nucleus and the fragmentation of some chromatin, while the HSF cells remained in a normal state.

We further observed the ultrastructure changes in the treated cancer cells A431 and the normal cells HSF using TEM (Fig. 3). After treatment with Brevilatrin B, some typical apoptotic characteristics gradually appeared in the A431 cells, including a decrease in the superficial microvilli, the appearance of autophagic vacuoles, “wrinkling” of the nuclear membrane, an increase in nuclear heterochromatin, and the disappearance of the internal structure of the organelles. In comparison, the intracellular organelles and microvilli on the cell surface of the HSF cells were complete and abundant, indicating that Brevilatrin B had no effect on these normal cells.

**Brevilatrin B induced apoptosis in A431 cells.** The apoptotic rate, ROS level, and mitochondrial membrane potential of A431 cells were all affected by treatment with Brevilatrin B in a dose-dependent manner. When the concentration of Brevilatrin B increased from 2 µg/mL to 3 µg/mL, the late apoptotic ratio of A431 was increased from 17.4 to 71.0%, while the live cells decreased from 80.4 to 25.9%, but both of the necrotic cells and early apoptotic cells nearly showed up (Fig. 4). In comparison, none of necrotic cells or apoptotic cells of the corresponding normal cell HSF appeared at the same concentration. Similarly, Brevilatrin B could increase the intracellular ROS level of A431 cells up to 21.3%, when the concentration was increased to 3 µg/mL (Fig. 5). Furthermore, the aggregates of JC-1 were detected to evaluate the ability of Brevilatrin B to induce apoptosis in A431 cells. As shown in Figs. 3 and 6 µg/mL of Brevilatrin B could induce 48.8% reduction in the mitochondrial membrane potential in A431 cells, while a reduction of only 24.0% occurred after treatment with 2 µg/mL of Brevilatrin B.
be developed (Siegel et al. 2014). AMPs have the potential to be developed as anticancer drugs that are more selective and less harmful toward the human body than most of current therapeutics (Deslouches et al. 2013, 2015; Steckbeck et al. 2014). The AMPs from Br. laterosporus are currently of interest because of their new anticancer activity. Such as

**Discussion**

Cancers pose a great threat to human health worldwide. Many functional medicaments have been discovered for the treatment of cancer, but these drugs can have severe side effects on normal cells and multi-drug resistance can easily
Bogorol B-JX from *Br. laterosporus* JX-5 have been shown to inhibit the proliferation of human histiocytic lymphoma cell line U-937 (Jiang et al. 2017). Herein, our reported AMP from *Br. laterosporus* S62-9, Brevilaterin B, could even inhibit the proliferation of 27 cancer cell lines in a dose-dependent manner, showing a broad spectrum of anticancer activity. To the best of our knowledge, very limited reports about bacterial AMPs could inhibit various tumor cells meanwhile, excepting for Laterosporulin10 from *Brevibacillus* sp. and Gageostatins A-C from *Bacillus subtilis* (Baindara et al. 2016; Tareq et al. 2014). In addition, comparing with their anticancer activities (in a dose of 10.5–23.2 µg/mL), Brevilaterin B displayed a stronger activity in a lower dose of 2.33–7.67 µg/mL. Subsequently, we investigated the primary anticancer mechanism of Brevilaterin B against the epidermal carcinoma cell line A431, and further demonstrated that Brevilaterin B could induce apoptosis but was not toxic toward the control normal human cell line.

When cultured cells undergo apoptosis, the cell membrane is the first to be destroyed, and then various enzymes,
appeared in cells, phosphatidylserine in their membrane is exposed, and can be easily stained by annexin V-FITC. Measurement of the amounts of such stained cells can be used to evaluate the apoptotic rate of cancer cell lines, and this property is usually used for the rapid detection of apoptosis. In our results, the addition of Brevilaterin B obviously induced apoptosis and increased the apoptotic rate of human epidermal carcinoma cells A431, in a similar manner to that reported for the AMP ranatuerin-2PLx against the PC-3 M cell lines (Chen et al. 2018). Another AMP temporin-1CEa also had been found to induce apoptosis of the breast cancer cell line Bcap-37 efficiency. The apoptotic rate of Bcap-37 was increased to 80% after treatment with 40 µM of the temporin-1CEa, which was similar to the effect of Brevilaterin B (Wang et al. 2013).

The mitochondrion is the main organelle in cells that plays an important role in cell growth, proliferation, and differentiation. Perturbation of mitochondrial function is a key event in the apoptotic cascade, and the development of a mitochondrial permeability transition state is necessary for cell death to proceed (Gaspar et al. 2013). Additionally, the mitochondrion is the “factory” for ROS release, which is the first important feature for apoptosis evaluation. On stimulation from an external factor like hypoxia, intracellular ROS levels can be increased substantially, which can cause oxidative damage to the cell membrane, proteins, and nucleic acids, until apoptosis occurs (Shahrestanaki et al. 2019). In the present study, a 10-fold increase in the amount of ROS released was observed when the concentration of Brevilaterin B was increased from 2 µg/mL to 3 µg/mL. The same effect of the AMP CM4 on the breast cancer cell lines including LDH, are released and can be rapidly detected in the culture medium (Flores-Guzmán et al. 2019). Accordingly, the rate of released LDH can be used to evaluate the integrity of cell membranes (He et al. 2013). In our study, the levels of LDH detected in the supernatants were obviously increased when epidermal carcinoma cells A431 were treated with Brevilaterin B, which was a similar result to that observed in human promyelocytic leukemia HL-60 cells after treatment with the AMP cecropin A (Cerón et al. 2010). In comparison, normal cells HSF, which were regarded as a control group, were not affected by treatment with Brevilaterin B at the same dose. These results indicated that Brevilaterin B could rupture the cancer cell membrane in a selective way, which was also observed by TEM.

The cell nucleus is an important organelle in active cells. Cell nuclei pyknosis occurs when active cells enter into the apoptotic phase, which can be used as a specific morphological sign to indicate apoptotic cells (Xue et al. 2017). We found that cell nuclei pyknosis occurred in A431 cells, but not appeared in HSF cells, after treatment with Brevilaterin B (2–3 µg/mL), indicating that Brevilaterin B may damage the cell nuclei of cancer cells A431 but not those of HSF cells. Alterations in the cell morphology, including the changes in cell membrane and cell nucleus described above, are usually the first changes to occur when cancer cells undergo apoptosis. More changes in the morphological details appear with the arrival of the apoptotic phase, and these changes can be directly observed by TEM.

Apoptosis is a pivotal homeostatic mechanism that causes programmed cell death to prevent the uncontrolled proliferation of cancer cells (Li et al. 2017). After apoptosis
MX-1, MCF-7, and MDA-MB-231 also had been described by other research. Their results demonstrated that CM4 could cause the release of high levels of ROS, which then induced apoptosis (Li et al. 2018). The mitochondrion is also the “factory” for cell energy generation. Its pathway could be activated when drugs act on cancer cell lines, resulting in changes in the mitochondrial membrane potential, which is the second most important feature for apoptosis evaluation. It had been found that the AMP B11 could infiltrate into cervical cancer cells HeLa, and cause mitochondrial disorder, even cell apoptosis, by effectively decreasing the mitochondrial membrane potential (Xia et al. 2016). In the present study, Brevilatener B caused a decrease in the mitochondrial membrane potential of cancer cells A431, resulting in mitochondrial depolarization, and finally inducing apoptosis of the cancer cells.

In conclusion, we discovered and investigated the potential anticancer activity of Brevilatener B from Br. laterosporus S62-9. Brevilatener B exhibited selective anticancer activity toward the epidermal carcinoma cell line A431 but had no effect on its control normal HSF cells. Our study revealed that 2 µg/mL of Brevilatener B could inhibit the proliferation of A431 and cause damage to the cell morphology, including the cell membrane and cell nucleus. In addition, we have shown that Brevilatener B could induce the apoptosis of cancer cells A431, and the mitochondrion was the main site of action. Overall, these findings indicate that Brevilatener B may have potential application as an anticancer medicament.

Funding This study was supported by Beijing Natural Science Foundation [No. KZ201810011016]; the National Natural Science Foundation of China [No. 31771951, No. 31801510 & No. 32072199].

Declarations

Conflicts of interest There are no conflicts of interest.

References

Baindara P, Singh N, Ranjan M, Nallabeli N, Chaudhry V, Pathania GL, Sharma N, Kumar A, Patil PB, Korpole S (2016) Laterosporulin 10: a novel defense like Class Hld bacteriocin from Brevibacillus sp. strain SKDU10 with inhibitory activity against microbial pathogens. Microbiology 162:1286–1299. DOI: https://doi.org/10.1099/mic.0.000316

Barsby T, Warabi K, Sørensen D, Zimmerman WT, Kelly MT, Andersen RJ (2006) The Bogorol family of antibiotics: template-based structure elucidation and a new approach to positioning enantiomeric pairs of amino acids. J Org Chem 71(16):6031–6037 PMID: 16872185. DOI: https://doi.org/10.1021/jo060667p

Cerón JM, Contreras-Moreno J, Puertollano E, Cienfuegos A, Puertollano MA, Pablo MA (2010) The antimicrobial peptide cecropin A induces caspase-independent cell death in human promyelocytic leukemia cells. Peptides 31(8):1494–1503. DOI: https://doi.org/10.1016/j.peptides.2010.05.008

Chen XL, Zhang LY, Ma CB, Zhang YQ, Xi XP, Wang L, Zhou M, Burrows JF, Chen TB (2018) A novel antimicrobial peptide, Ranaturin-2PLx, showing therapeutic potential in inhibiting proliferation of cancer cells. Biosci Rep 38(6). DOI: https://doi.org/10.1042/BSR20180710

Chen Z, Wang XX, Han PP, Liu YL, Hong D, Li ST, Ma AJ, Jia YM (2022) Discovery of novel antimicrobial peptides, Brevilatener V, from Brevibacillus laterosporus S62-9 after regulated by exoequously-added L-valine. LWT-Food Sci Technol 155:112962. DOI: https://doi.org/10.1016/j.lwt.2021.112962

Deslouches B, Di YP (2017) Antimicrobial peptides with selective antitumor mechanisms: prospect for anticancer applications. Oncotarget 8(28):46635–46651. DOI: https://doi.org/10.18632/oncotarget.16743

Deslouches B, Steckbeck JD, Craigo JK, Doy Y, Burns JL, Montelaro RC (2015) Engineered cationic antimicrobial peptides to overcome multidrug resistance by ESKAPE pathogens. Antimicrob Agents Chemother 59:1329–1333. DOI: https://doi.org/10.1128/AAC.03937-14

Deslouches B, Steckbeck JD, Craigo JK, Doy Y, Mietzner TA, Montelaro RC (2013) Rational design of engineered cationic antimicrobial peptides consisting exclusively of arginine and tryptophan, and their activity against multidrug-resistant pathogens. Antimicrob Agents Chemother 57(6):2511–2521. DOI: https://doi.org/10.1128/AAC.02218-12

Flores-Guzmán F, Alvarado-Sansinena JJ, López-Muñoz H, Escobar ML (2019) Antiproliferative, cytotoxic and apoptotic activity of the bentonite transformation of sesquiterpene lactone glaucolide B to 5β-hydroxy-hirsutinolide on tumor cell lines. Eur J Pharmacol 856:172406. DOI: https://doi.org/10.1016/j.ejphar.2019.172406

Gaspar D, Veiga AS, Castanho MARB (2013) From antimicrobial to anticancer peptides. A review. Front Microbiol 4: 294. PMID: 24101917. DOI: https://doi.org/10.3389/fmicb.2013.00294

Gerard JM, Haden P, Kelly MT, Andersen RJ (1999) Cyclic decapetide antibiotics produced in culture by a tropical marine bacterium. J Nat Prod 62(1):80–85. DOI: https://doi.org/10.1021/np980219f

Giuliani A, Pirri G, Nicoletto SF (2007) Antimicrobial peptides: an overview of a promising class of therapeutics. Cent Eur J Biology 2(1):1–33

He NW, Shi XL, Zhao Y, Tian LM, Wang DY, Yang XB (2013) Inhibitory effects and molecular mechanisms of selenium-containing tea polysaccharides on human breast cancer MCF-7 cells. J Agric Food Chem 61(3):579–588. DOI: https://doi.org/10.1021/jf3036929

Jiang HX, Ji C, Sui JK, Sa RB, Wang XH, Liu XL, Guo TL (2017) Antibacterial and antitumor activity of Bogorol B-JX isolated from Brevibacillus laterosporus JX-5. World J Microbial Biotechnol 33:177. DOI: https://doi.org/10.1007/s11274-017-2337-z

Kim S, Kim JY, Kim S, Bae HJ, Yi H, Yoon SH, Koo BS, Kwon M, Cho JY, Lee C, Hong S (2007) Surfactin from Bacillus subtilis displays anti-proliferative effect via apoptosis induction, cell cycle arrest and survival signaling suppression. FEBS Lett 581(5):865–871. DOI: https://doi.org/10.1016/j.febslet.2007.01.059

Krachkovskii SA, Sobol AG, Ovchinnikova TV, Tagaev AA, Yakimchenko ZA, Azizbekyan RR, Kuznetsova NI, Shamshina TN, Arseniev AS (2002) Isolation, biological properties, and spatial structure of antibiotic loloatins A-D. Russ J Bioorg Chem 28(4):269–273. DOI: https://doi.org/10.1021/bi019531s

Li X, Fan XX, Jiang ZB, Loo WTY, Yao XJ, Leung ELH, Chow WC, Liu L (2017) Shikonin inhibits gefitinib-resistant non-small cell lung cancer by inhibiting TrxR and activating the EGFR pro-survival signaling pathway. Pharmacol Res 115:45–55. DOI: https://doi.org/10.1016/j.phrs.2016.11.011
Li CY, Liu HY, Yang YQ, Xu XX, Lv TT, Zhang HD, Liu KH, Zhang SQ, Chen YQ (2018) N-myristoylation of antimicrobial peptide CM4 enhances its anticancer activity by interacting with cell membrane and targeting mitochondria in breast cancer cells. Front Pharmacol 9:1297 PMID: 30483133. DOI: https://doi.org/10.3389/fphar.2018.01297

Nishikawa K, Shibasaki C, Takahashi K, Nakamura T, Takeuchi T, Umezawa H (1996) Antitumor activity of Spargualin, a novel antitumor antibiotic. J Antibiot 39(10):1461–1466 PMID: 3781914. DOI: https://doi.org/10.7164/antibiotics.39.1461

Oyston PC, Fox MA, Richards SJ, Clark GC (2009) Novel peptide therapeutics for treatment of infections. J Med Microbiol 58(Pt8):977–987. DOI: https://doi.org/10.1099/jmm.0.011122-0

Park SY, Kim J, Lee YJ, Lee SJ (2013) Surfactin suppresses TPA-induced breast cancer cell invasion through the inhibition of MMP-9 expression. Int J Oncol 42(1):287–296. DOI: https://doi.org/10.3892/ijo.2012.1695

Shahrestanaki MK, Bagheri M, Ghanadian M, Aghaei M, Jafari SM (2019) Centaurea cyanus extracted 13-O-acetylsolstitialin A decrease Bax/Bcl-2 ratio and expression of cyclin D1/Cdk-4 to induce apoptosis and cell cycle arrest in MCF-7 and MDA-MB-231 breast cancer cell lines. J Cell Biochem 120(10):18309–18319. DOI: https://doi.org/10.1002/jcb.29141

Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics 2014. CA Cancer J Clin 64:9–29. doi: 10.3322/caac.21208 PMID: 24399786

Singh PK, Solanki V, Sharma S, Thakur KG, Krishnan B (2015) The intramolecular disulfide-stapled structure of laterosporulin, a class IId bacteriocin, conceals a human defensin-like structural module. FEBS J 282(2):203–214. DOI: https://doi.org/10.1111/febs.13129

Steckbeck JD, Deslouches B, Montelaro RC (2014) Antimicrobial peptides: new drugs for bad bugs? Expert Opin Biol Ther 14:11–14

Tareq FS, Lee MA, Lee HS, Lee JS, Lee YJ, Shin HJ (2014) Gageostatins A–C, antimicrobial linear lipopeptides from a marine Bacillus subtilis. Mar Drugs 12:871–885. Doi: https://doi.org/10.3390/md12020871

Ting CH, Huang HN, Huang TC, Wu CJ, Chen JY (2014) The mechanisms by which pardaxin, a natural cationic antimicrobial peptide, targets the endoplasmic reticulum and induces c-FOS. Biomaterials 35(11):3627–3640. doi: https://doi.org/10.1016/j.biomaterials.2014.01.032 PMID: 24477193

Xue ML, Ji XQ, Xue CX, Liang H, Ge YL, He XJ, Zhang L, Bian K, Zhang LH (2017) Caspase-dependent and caspase-independent induction of apoptosis in breast cancer by fucoidan via the PI3K/AKT/GSK3β pathway in vivo and in vitro. Biomed Pharmacother 94:898–908. DOI: https://doi.org/10.1016/j.biopha.2017.08.013

Wang S, Wang QW, Zeng XF, Ye QH, Huang S, Yu HT, Yang TR, Qiao SY (2017) Use of the antimicrobial peptide sublancin with combined antibacterial and immunomodulatory activities to protect against methicillin-resistant Staphylococcus aureus infection in mice. J Agric Food Chem 65(39):8595–8605 PMID: 28906115. DOI: https://doi.org/10.1021/acs.jafc.7b02592

Wang C, Zhou Y, Li S, Li HB, Tian LL, Wang H, Shang DJ (2013) Anti-cancer mechanisms of temporin-1CEa, an amphipathic α-helical antimicrobial peptide, in Bcap-37 human breast cancer cells. Life Sci 92(20–21):1004–1014. DOI: https://doi.org/10.1016/j.lfs.2013.03.016

Xia LJ, Wu YL, Ma J, Yang JH, Zhang FC (2016) The antibacterial peptide from Bombyx mori cecropinXJ induced growth arrest and apoptosis in human hepatocellular carcinoma cells. Oncol Lett 12(1):57–62. DOI: https://doi.org/10.3892/ol.2016.4601

Zhao HB, Yan L, Xu XG, Jiang CM, Shi JL, Zhang YW, Lei SZ, Shao DY, Huang QS (2018) Potential of Bacillus subtilis lipopeptides in anti-cancer I: induction of apoptosis and paraptosis and inhibition of autophagy in K562 cells. Amb Express 8(1):1–16 PMID: 29777449. DOI: https://doi.org/10.1186/s13568-018-0606-3

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.