

MICROBIAL ANTIMICROBIAL PEPTIDES AS ANTI-CANCER AGENTS WITH SPECIAL REFERENCE TO THE *STREPTOMYCES* SPECIES

Abstract

Despite improvements in tumour diagnosis and treatment, cancer remains one of the major causes of death globally. Conventional cancer therapies are incapable of treating specific cancer types at different stages since they affect solid and tumour cells leading to side effects and undesirable symptoms. Therefore advanced strategies should be developed to overcome cancer. *Streptomyces* species have been studied extensively over the past few decades as a result of their exceptional efficiency in generating antimicrobial peptide compounds that are beneficial to human health. The antimicrobial peptides originated from *Streptomyces* species belongs to different groups including anthracyclines, macrolides, quinones, aminoglycosides and non-ribosomal peptides. These antimicrobial peptides causes DNA cleavage through topoisomerase I and II inhibition, mitochondrial dysfunction, release of cytochrome c molecules, suppression of tumour induced angiogenesis and inhibition of important signal transduction enzymes like proteases or cell metabolism to induce apoptosis. *Streptomyces* Sp. are widely distributed in nature and can be found in various habitats. The members of these organisms have special attention to produce therapeutic peptide compounds which has strong cytotoxic effect against several human cancer cells. In this review, we explored the anticancer impact represented by *Streptomyces* Sp. in search for future chemo preventive and anticancer medications”.

Keywords: Cancer; *Streptomyces* Sp.; Antimicrobial peptides; Angiogenesis; Cytotoxic activity; Apoptosis.

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I. INTRODUCTION

Microorganisms are widely dispersed throughout the biosphere because of their exceptional metabolic ability and ease of growth in various environmental conditions [1]. Soil microbial communities comprise a broad variety of species at various physiological phases [2]. 15% of metabolites are originated from fungi, 25% of them are emerged from bacteria and rest 65 % of the active compound are synthesized from actinomycetes [3, 4]. The generation of secondary metabolites makes extensive use of the microbial genomes and 23, 000, “active biological compounds” are reported from microbial origin [5].

Peptide based antimicrobials such as “Nisin” a widely applied bacteriocin produced by *Lactococcus* Sp. and “Gallidermin” produced by *Streptococcus* Sp. exerts its activity by inhibiting peptidoglycan biosynthesis [6]. Bioactive peptide compounds derived by fungi are bubble protein synthesised by *Penicillium* Sp. “Plectasin” produced by *Pseudoplectania* Sp. [7]. “Copsin” isolated by *Coprinopsis* Sp. “Penicillium” antifungal peptide (PAF) by *Penicillium* Sp. and “Eurocin” produced by *Eurotium* Sp. shows antibacterial efficacy against *Streptococcus* Sp., *Staphylococcus* Sp., *Listeria* Sp., *Corynebacterium* Sp. and *Micrococcus* Sp. [8-10].

Predominantly actinomycetes are investigated for potential source of antimicrobial agents, among actinomycetes *Streptomyces* Sp. are versatile organisms [11]. *Streptomyces* Sp. are Gram positive, spore forming filamentous bacteria and represented as the largest taxonomic units under Actinomycetes. Genetic material of *Streptomyces* Sp. composed of high content of guanine and cytosine [12]. Morphologically *Streptomyces* Sp. exhibit hyphal growth as they are also called as “Ray fungus” and are characterized with extensive branching substrate and aerial mycelia on culture media [13].

Members of these organisms have contributed various antimicrobial peptide compounds [14]. “Streptomycin”, is the first antibiotic compound isolated from *Streptomyces griseus* applied for the treatment of tuberculosis infection [15]. “Neomycin” belongs to aminoglycoside antibiotic isolated from soil dwelling bacterium *Streptomyces fradiae* inhibits the translation process of Gram-negative bacteria namely *E.coli*, *Klebsiella pneumoniae* and *Proteus vulgaris*. Glycopeptide antibiotics known as “Vancomycin” produced by *Streptomyces orientalis*, damages cytoplasmic membrane of methicillin resistant strains *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Mycobacteria* [16-20]. In addition to antibiotics, earlier reports suggest that the anti-cancer compounds including “Bleomycin”, a chemotherapeutic drug derived from *Streptomyces verticillus* applied for the treatment of malignancies, Doxorubicin originated from *Streptomyces peucetius* releases reactive oxygen species for oxidative stress, initiates for DNA fragmentation and causes apoptosis in cancer cells [21].

Streptomyces Sp. derived peptide compounds serve as immune modulators and facilitate a broad spectrum of antimicrobial activity. These peptides are also involved in various signal transduction pathways for therapeutic applications [22].

Cancer is the leading cause of death and growing public health threat globally. It is estimated that 9.5 million people have died from cancer and 1.28 million new cases have been diagnosed [23]. The adoption of “lifestyle” behaviour and causative factors such as

genetics, age, obesity, alcohol consumption, physical inactivity, chemical exposure, preliminary benign diseases, exposure to ionizing radiation and mammographic density has higher risk for cancer [24, 25].

According to projections from the International agency for research on cancer (IARC), 7.6 million cancer deaths and 12.7 million new cases related to cancer are estimated during 2021[26]. Global statistics revealed that the most commonly diagnosed malignancies are lung, breast and colorectal. Over the past several years significant work was implicated to develop new therapies that are patient-safe and selective [27-30]. Despite this, the currently available treatments such as surgery and chemotherapy are generally low in success rates, also there will be possibility of cancer cells reoccurrence. Chemotherapy for metastatic melanoma, prostate, bladder, kidney and pancreatic cancer is ineffective [31].

Changes in the cell membrane have significant implications in the development of cancer. The transformed epithelial cells are immotile, tightly bound to the extracellular matrix of the neighbouring cells to promote cell proliferation, invasion and metastasis [32]. Metastasis is facilitated by cell-cell interactions between tumour cells and endothelium tissues [33]. The malignant tumours secrete “matrix metalloproteases” that splice the proteins which inhibit the movement of migrating cancer cells and access to the lymphatic system [34]. These tumour cells will further develop new blood vessels, a process known as “Angiogenesis” and enters into the blood stream by diffusing through the basement membranes of normal epithelial cells eventually extravasate from the blood circulation into the surrounding tissues [35, 36]

Streptomyces Sp. naturally produces antimicrobial peptide compound which has several cancer therapeutic values. [37, 38]. These peptide molecules adhere to the cancer cell membrane which is involved in mitochondrial damages, reactive oxygen species production and apoptosis [39, 40]. The antimicrobial peptide compound originated from *Streptomyces* Sp. activates the phagocytic cells for the production of pro-inflammatory cytokines to enhance the cytotoxic activity [41, 42].

According to recent investigations, 60% of approved anti-cancer drugs are derived from *Streptomyces* species [43]. Members of these organisms are the producers of effective “anti-tumor” drugs including “Anthracyclines” isolated from *Streptomyces peucetius*, “Dactinomycin” produced from *Streptomyces parvulus*, “Streptozotocin” procured from *Streptomyces achromogenes*, “Duocarmycins’ generated from *Streptomyces zelensis* and “Lyomycin” acquired from *Streptomyces verticillus* [44-47]. The majority of anti-cancer medications obtained from *Streptomyces* strains are cyclic peptide compounds that allow selective destabilization of cancer cell membranes, releases cytochrome c molecules, promotes DNA fragmentation and induces apoptosis [48-50]. These compounds also exert the anti-cancer activity by activating other mechanisms such as autoimmune cell death, DNA polymerase inhibition and “anti-angiogenic” actions [51].

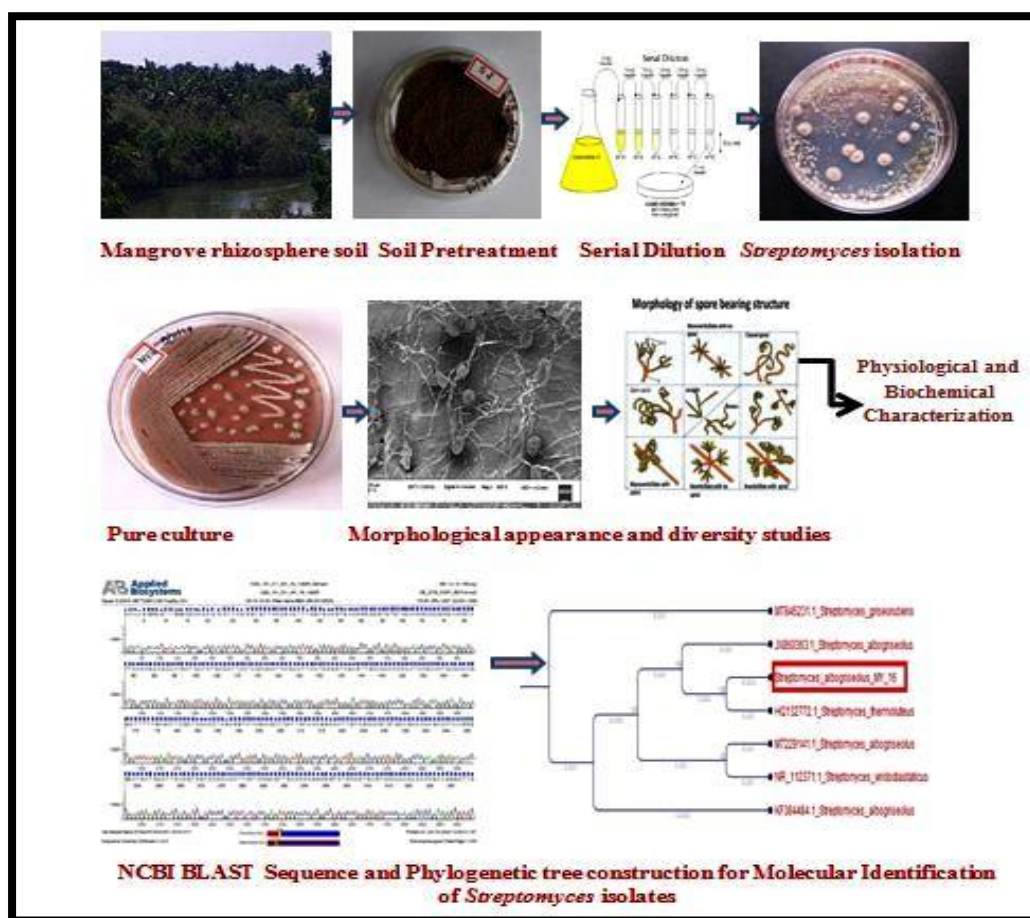


Figure 1: Isolation and Molecular Identification of *Streptomyces* Sp.

II. RECOVERY OF ANTIMICROBIAL PEPTIDES FROM INTRACELLULAR EXTRACTS OF *STREPTOMYCES* SP.

Fermentation optimization is a crucial method to determine the purity and yield of the bioactive product [52]. Various methods have been employed to investigate and analyse putative antimicrobial peptide substances produced by *Streptomyces* Sp. There are two main strategies used in drug discovery, a bottom-up approach focused on identifying compounds or agents that modify the molecules which are crucial to diseases. A top-down approach emphasises on finding substances or molecules that influences cellular process in critical disease [53-55].

“Antimicrobial peptides” are heterocyclic compounds consist of 10-100 amino acid residues having effective biological properties including anti-tumor, antibacterial, anti-biofilm, antioxidant and neuroprotective activities. [56-58].

Complex peptide molecules can be fractionated using general purification techniques which frequently combine ion-exchange chromatography and multi-step reverse phase HPLC methods that are feasible, rapid and efficient process to obtain desired peptide products [59, 60]. Liquid chromatography-mass spectrometry is a reliable method to detect the purity and

total mass of the compound [61]. Cyclic dipeptides such as “Pyrrolo [1,2a] pyrazine-1,4-dione”, “Hexahydro and pyrrolo pyrazine-1-4 dione”, “Hexahydro 3- phenylmethyl” are widely recognized as potent “anti-cancer drugs” [62]. These peptide compounds are involved in the regulation of intracellular signalling mechanisms and function as antioxidants to prevent the cancer cell proliferation [63, 64].

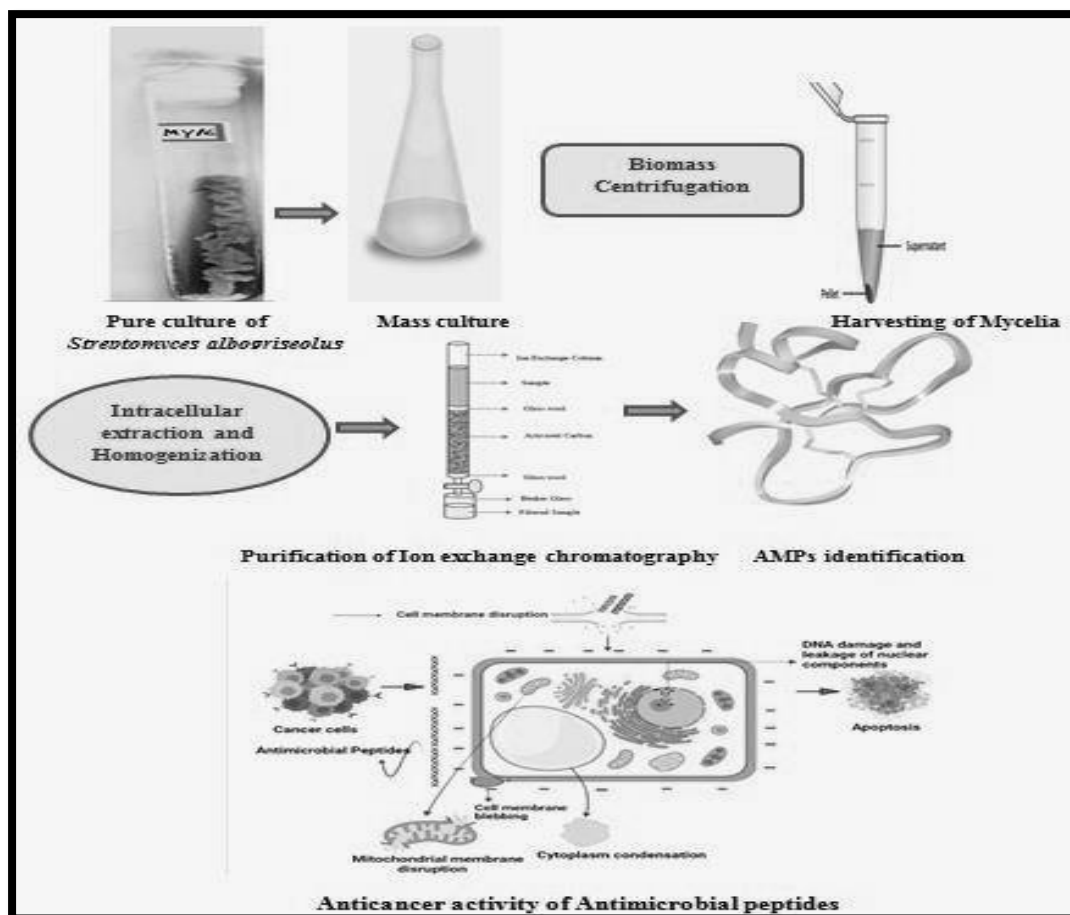


Figure 2: Purification Process and Anti-Cancer Activity of Antimicrobial Peptides Isolated from *Streptomyces* Sp.

III. THE ROLE OF *STREPTOMYCES* DERIVED ANTIMICROBIAL PEPTIDES AS ANTICANCER AGENTS

Normal cells become sensitive to chemical signalling molecules during the development of cancer which causes abnormal cell proliferation by invading surrounding tissues and organs [65]. In general, malignancies are linked to unfavourable environments, genetics and unhealthy lifestyle choices [66, 67].

The current method for treating cancer includes intravenous pharmaceutical administration and local therapeutic approaches like surgery and radiation therapy [68]. Apoptosis is a complicated process in which the affected cells undergo cascade of self-destruction and serves as a key target for cancer prevention measures [69].

In recent years, attention has shifted to the development of novel anti-cancer drugs that serve as adjuvants and genotoxic [70]. Conventional cytotoxic therapies including chemotherapy and radiation therapy are implicated to achieve “cancer management”, but in turn both the treatments are highly toxic with severe side effects [71]. Natural products provide an alternative remedies against the cancer cell proliferation, multi-drug resistance and undesirable side effects (heart failure, diarrhoea and oedema) caused by synthetic drugs [72].

Over the past ten years, an investigation has been conducted to examine the possible anticancer properties of *Streptomyces* Sp. [73]. Many of the anticancer medications from *Streptomyces* species are currently on the market that causes cancer cells to die or induce apoptosis [74].

Streptomyces Sp. derived antimicrobial peptides drugs are the members of anthracyclines. Anthracyclines are the anti-tumour quinone containing antibiotics, currently they are used as chemotherapy medications to treat various types of cancer including leukaemias, lymphomas, neuroblastoma and melanoma [75]. Clinically the most important anthracycline drugs are “Daunorubicin” produced by *Streptomyces peucetius*, “Doxorubicin” isolated from *Streptomyces caesi*us, ‘Epirubicin” produced by *Streptomyces venezuelae*, “Bleomycin” obtained from *Streptomyces verticillus*, “Mitomycin c” isolated from *Streptomyces caespitosus*, and “Dactinomycin” produced by *Streptomyces pratensis* [76]. The anthracyclines drugs are encoded with tetracyclic molecules with anthraquinone group connected to a sugar moiety through glycosidic linkage. They directly act on cancer cells by intercalating with DNA metabolism and mediates in topoisomerase II inhibition. The presence of quinone moiety in the anthracyclines drugs undergo redox reactions to generate reactive oxygen species (ROS) to toxify the cancer cells by causing oxidative stress and induces apoptosis.

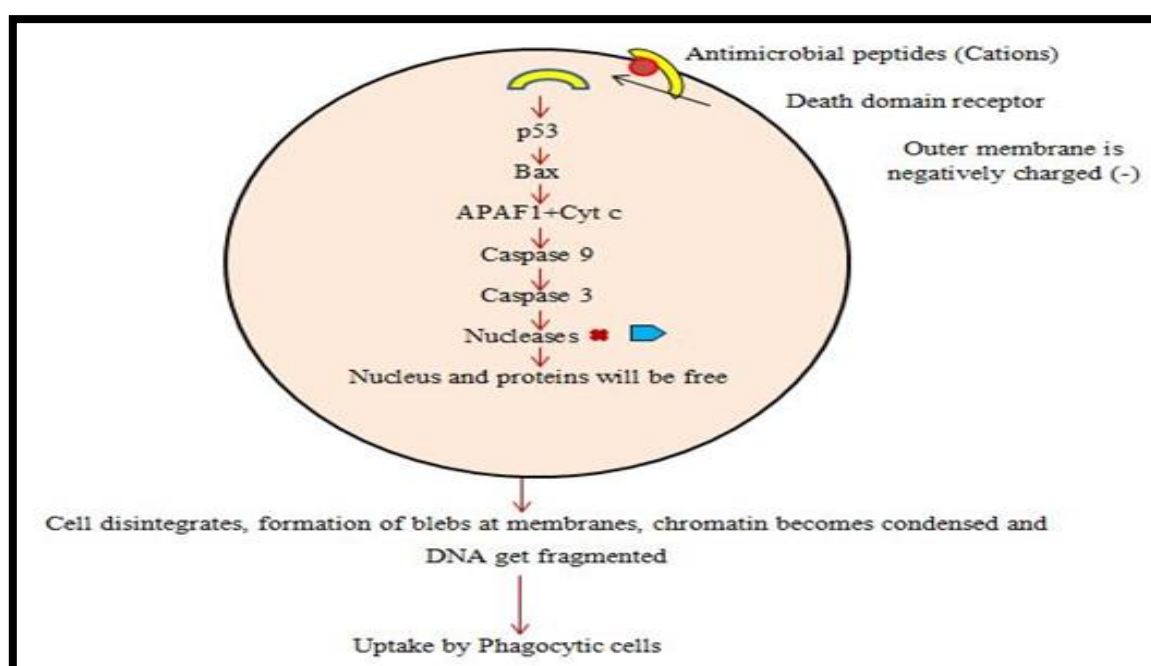


Figure 3: Mechanism of Anti-Cancer Activity from Microbial Antimicrobial Peptides

Table 1: Anticancer activities of *Streptomyces* Derived Antimicrobial Peptide Compounds

Name of the <i>Streptomyces</i> Sp.	Antimicrobial peptide drugs	Anticancer activities on human cancer cells
<i>Streptomyces galilaeus</i>	Cyclic peptide compounds; Aclacinomycin X	Human colon cancer HCT116 ; Cytotoxic action and anti-angiogenesis[81]
<i>Streptomyces chibaensis</i>	Quinone peptide compounds ; Resistoflavine	Gastric adenocarcinoma HMO2, Hepatic carcinoma, HePG2; Cytotoxic activity and apoptosis [81]
<i>Streptomyces scabrisporus</i>	Cyclic peptide compounds; Okilactomycin	Gastrointestinal cancer; Translation inhibition [82]
<i>Streptomyces caespitosus</i>	Heterocyclic peptide compounds; Mitomycin A and B	Human Lung adenocarcinoma cells; DNA damage and apoptosis [83]
<i>Streptomyces coelicolor</i>	Benzoisochromanequinone dimer polyketideantibiotic; Actinorhodin	Human lung carcinoma epithelial cells A549; Oxidative stress and DNA fragmentation [83]
<i>Streptomyces canus</i> FIM0916	Lipopeptide; Amphomycin	Human breast cancer cells MCF-7; Mitochondrial dysfunction, RNA polymerase inhibition and anti-angiogenic action [84]
<i>Streptomyces hygroscopicus</i>	B Amino-glycosidic compound ; Hygromycin ;	Human breast cancer cells MCF-7 and Prostate cancer cells PC-3 and DU145; Cytotoxic activity, release of Cytochrome c molecules and Protein synthesis inhibition [84]
<i>Streptomyces pluricolarescens</i>	Amino-glycoside compound ; Pluramycin	Pleuropulmonary blastoma and cervical cancer cells Hela ; Inhibition of DNA replication and apoptosis [85]
<i>Streptomyces griseus</i>	Amino glycosidic compound; Streptothricin	Human breast cancer cells MCF-7; ROS generation and Cytotoxic activity [85]
<i>Streptomyces monashensis</i>	Amino glycosidic compound Bafilomycin	Human breast cancer cells MCF-7; DNA damage and Transcription inhibition [86]
<i>Streptomyces nogalater</i>	Cyclic peptide compound: Nogalamycin	Human breast cancer MCF 7 and ovarian cancer cells CA125; Inhibition of mitochondrial phosphorylation, caspase enzyme activation and inhibition of translation process [87]
<i>Streptomyces albogriseolus</i>	Antimicrobial peptides pk4 and pk5	Human breast cancer cells MCF 7; cytotoxic activity and DNA damage [88]
<i>Streptomyces minutiscleroticus</i>	Antimicrobial peptides pk5	Human breast cancer cells MCF 7; cytotoxic activity [88]

Other than anthracycline group of antimicrobial peptides, there are efficient anticancer peptides procured from certain *Streptomyces* strains including “Bestatin” is a muramyl dipeptide (MDP) produced by *Streptomyces olivoreticuli* [77]. It is the competitive

inhibitor of aminopeptidase. Aminopeptidase has been implicated in the process of adhesion and invasion of cancer cells. Therefore, inhibiting the aminopeptidase enzyme would result in the death of cancer cells. “Gougerotin” is a peptide nucleoside antibiotic isolated from *Streptomyces graminearus* increase the ROS generation in the cancer cells. “Persipeptide” is an N-methylated cyclopeptides isolated from *Streptomyces coeruleus*. These peptides arrest the cancer cell cycle and increase the level of apoptosis by targeting tumour suppressor proteins [78].

Amino acid residues accumulated in the antimicrobial peptides of *Streptomyces* includes glycine, lysine and leucine that drives cancer cell permeability [79]. These antimicrobial peptides are cationic in nature and can interact selectively by electrostatic force on phosphatidylserine moieties of the cancer cell plasma membrane. After the initial interactions with the target membrane, Antimicrobial peptides inset to the membrane bilayers and aggregate to form pores by developing complex structures. Then antimicrobial peptide lead to the opening of transition pore of the mitochondrial membrane and releases the cytochrome c molecules and apoptogenic factors into the cytosol. As a result mitochondrial electron system gets defected and activates the caspase enzyme to induce apoptosis [80]. Thus the antimicrobial peptides originated from *Streptomyces* Sp. are the efficient cytotoxic compound that could be treated for various cancer disorders through different routes of mechanism.

IV. CONCLUSION

Streptomyces species are truly fascinating microorganisms, produces a novel peptide based therapeutic compounds with diverse structures. In comparison to other conventional medications, *Streptomyces* Sp. derived antimicrobial peptides has potential “anti-cancer” effect because of its desirable cell penetrating properties, strong efficacy and low toxicity to normal cells. Collectively, it is hypothesised that antimicrobial peptides of these organisms has effective chemotherapeutic medications that linked to combat future cancer death rates.

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