**Microbial Antimicrobial peptides as Anti-cancer agents with special reference to *Streptomyces* species**

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**Abstract**

Cancer is one of the leading causes of death globally, despite advances in tumour diagnosis and treatment. Conventional cancer therapies are incapable of targeting particular cancer types at different stages since they influence both solid and tumor cells, causing side effects and undesirable symptoms. Therefore, novel strategies should be developed to overcome cancer. For this reason, members of the genus *Streptomyces* have been explored extensively over the past decades, as these filamentous bacteria are highly efficient in producing effective antimicrobial peptide compounds with human health benefits. These antimicrobial peptides belong to several classes such as anthracyclines, macrolides, quinones, aminoglycosides, and other non-ribosomal peptides. They exert anticancer activity by inducing apoptosis through DNA cleavage mediated by topoisomerase I and II inhibition, mitochondrial dysfunction, release of cytochrome c molecules, inhibition of tumour induced angiogenesis and inhibition of key enzymes involved in signal transduction like proteases or cell metabolism . Being ubiquitous in nature, *Streptomyces* species found in various environments and has special attention for their ability to produce therapeutic based peptide compounds which has potent cytotoxic activities against several human cancer cells. In this review we provide the insights and mechanistic anticancer role of *Streptomyces* species in search of lead pharmacological anticancer and chemopreventive drugs for future generation.

Keywords — Cancer; *Streptomyces*; Antimicrobial peptides; DNA cleavage; Angiogenesis; Cytotoxic; Human cancer cells

**I. INTRODUCTION**

Microorganisms are widely dispersed throughout the biosphere due to their remarkable metabolic ability and ease of growth in various environmental conditions [1]. There are wide range of species existed in the soil microbial communities, all of which are in different physiological stages [2]. Microbes including actinomycetes, archaea, bacteria, fungi and yeast, are the auspicious source of vital bioactive compounds [3]. 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 [4]. The generation of secondary metabolites makes extensive use of the microbial genomes and 23,000 acive biological compounds are reported from microbial origin [5].

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

Predominantly actinomycetes are explored for potential sources of antimicrobial agents, among actinomycetes *Streptomyces* species are the versatile organisms [11]. *Streptomyces* is the largest genus of actinobacteria, belongs to Gram-positive bacteria and composed of high guanine and cytosine content in their genetic material [12]. They are spore producing organisms and form branching filaments of cells, which become a network of strands called mycelium [13].

Members of these organisms have contributed various antimicrobial peptide compounds [14]. The lead bioactive peptide compounds yielded by *Streptomyces* sp are streptomycin is the first antibiotic compound isolated by *Streptomyces griseus* applied for the treatment of tuberculosis infection [15]. Neomycin an aminoglycoside antibiotic isolated from soil dwelling bacterium *Streptomyces fradiae* inhibits the translation process of Gram-negative organisms namely *E.coli*, *Klebsiella pneumoniae* and *Proteus vulgaris*. Vancomycin is an glycopeptide antibiotics produced by soil borne *Streptomyces* *orentalis* affects mainly methicillin resistant strains *Staphylococcus aureus*, *Staphylococcus epidermidus* and *Mycobacteria* by damaging its cytoplasmic membrane [16-20]. Other than antibiotics, reports also suggest the extraction of compounds such as bleomycin, a chemotherapeutic drug derived from *Streptomyces verticillus* applicable for the treatment of malignancies, Doxorubicin originated from *Streptomyces* *peucetius* causes oxidative stress by releasing reactive oxygen species also damages the DNA and triggers for apoptosis in cancer cells [21]. These biologically peptide compound are actively derived biological molecules that serve as immune modulators and facilitate a broad spectrum of antimicrobial activity, besides their antimicrobial function they even act as drug delivery vectors and signalling molecules in many signal transduction pathways for various therapeutic applications [22].

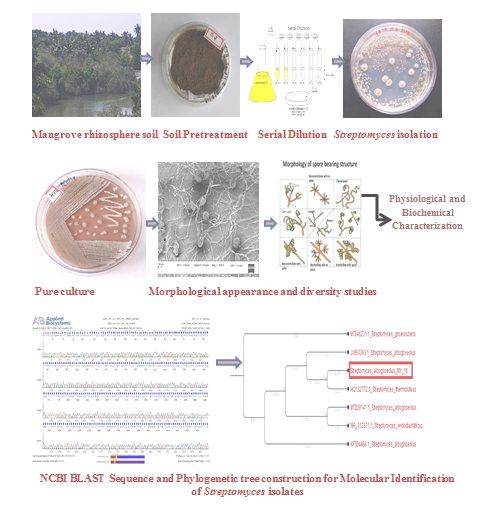
Cancer is the major cause of death and growing public health threat globally. It is estimated that 1.28 million new cancer cases and 9.5 million deaths has accounted in the worldwide [23]. Over past several years cancer incidence rate has declined to 2% in men where as it remains constant in the case of women [24] .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 [25].

Estimates from the International Agency for Research on Cancer (IARC) indicate that 12.7 million of new cancer cases and 7.6 million cancer deaths occurred worldwide during 2021 [26]. Also, the worldwide statistics revealed that the most commonly diagnosed cancers are lung, breast and colorectal. In the last decades many effort has been devoted in creating new therapies that are at the same time more selective and less harmful for the patients [27-30]. Despite this, the methods today available such as surgery and chemotherapy have a relatively low success rate as well as they present a risk of reoccurrence. Indeed, chemotherapy treatment of prostate, bladder, kidney and pancreatic cancer as well as metastatic melanoma is being inefficient [31].

Changes in the membrane of a cell have important implications in the progression of cancer, as they play a key role in the cell's response to its environment [32]. The cell membrane of a malignant tumor cell may influence its ability to grow even without the signals that would normally inspire growth, as well as to attach and respond to neighbouring cells differently [33]. The cell membrane may also affect a cancer cell's motility, aiding in invasion and metastasis. Therefore, it is important to look at the differences between normal cells, non-malignant tumor cells, and malignant tumor cells [34-36].

Antimicrobial peptide molecules derived naturally from *Streptomyces* organisms have provided a number of beneficial cancer chemotherapeutic drugs [37, 38]. These Peptides are able to bind the cancer cells and cause membrane effects through negatively-charged molecules that are exposed on the cells membrane. Cell death also involved mitochondrial damage reactive oxygen species (ROS) production, final interference with necrotic and apoptosis pathways [39-41]. Introducing the active compounds generated from members of these organisms also leads to the activation of various immune mechanisms, which manifests itself in increasing the number and recruitment of congenital immune cells and production of pro-inflammatory cytokines [42].

Recent evidences reported that more than 60% of approved natural anticancer drugs are derived from *Streptomyces* species [43]. Members of these organisms are the producers of effective anti-tumor drugs including anthracycline isolated from *Streptomyces peucetius*, dactinomycin produced from *Streptomyces parvullus*, streptozotocin procured from *Streptomyces achromogenes,* duocarmycins generated from *Streptomyces zelensis* and lyomycin acquired from *Streptomyces phaeverlicillatus* [44-47]. Most of the anticancer drugs originated from *Streptomyces* strains are cyclic peptide compounds that allow selective cancer membrane destabilization, 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 immunogenic cell death, inhibition of DNA polymerase and anti-angiogenic actions [51].

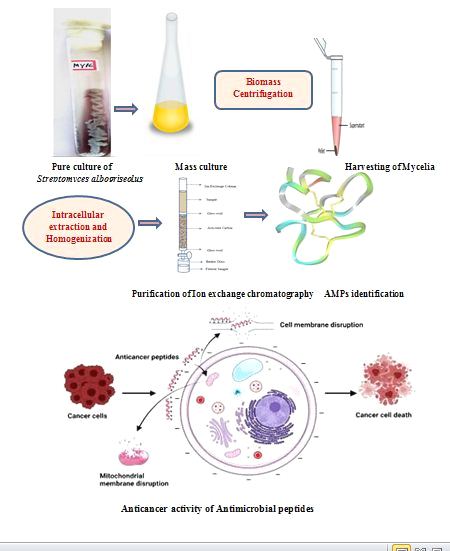


**Figure: 1 Isolation and Molecular identification of *Streptomyces albogriseolus***

**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]. Diverse approaches have been used to examine and explore potential Antimicrobial peptide compounds produced by *Streptomyces* sp. There are typically two primary methods used in drug discovery A bottom-up approach that emphasises finding substances or agents that alter molecules that may be crucial to disease, and a top-down approach that emphasises finding substances or agents that influence cellular processes that may be crucial to disease [53-55].

Depending on the applications, different extraction protocols have been used in the bioactivity studies on *Streptomyces* species. Simple intracellular extractions utilizing solvents (methanol, hexane, ethyl acetate) and buffers (KH2PO4, Na2HPO4, KCl, and NaCl) are enabled to get effective compounds [56-58]. General purification procedures are allowed to fractionate complex samples, often involves the combination of chromatographic methods for peptide separation i.e., Ion exchange chromatography and multistep Reverse phase HPLC methods are feasible, rapid and efficient process to obtain desired peptides. Liquid chromatography-mass spectrometry is a reliable technique to detect the purity and total mass of the compounds [59, 60]. The presence of cyclic dipeptides: pyrrolo[1,2a]pyrazine-1,4-dione, hexahydro- and pyrrolo [1,2a] pyrazine-1,4-dione, hexahydro3- (phenylmethyl) have been widely recognized as potent chemo-preventive agents, acting as antioxidants and modulators of intracellular signalling processes involved in initiation/promotion of cancer [61,62]. Antimicrobial peptides comprises structurally diverse heterocyclic compounds consist of 10-100 amino acid residues with broad range of biological properties including antitumor, antibacterial, antibiofilm, antioxidant and neuroprotective properties [63,64].



**Figure: 2 Anti-cancer activity of *Streptomyces albogriseolus* Antimicrobial peptides (AMPs)**

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

Cancer develops when normal cells are susceptible to chemical signalling molecules and leads to abnormal cell proliferation by invading surrounding tissues and organs [65]. In general, malignancies are linked to unfavourable environments and unhealthy lifestyle choices [66]. The development and spread of cancer are also influenced by genetics [67].

Cancer is currently treated through systematic therapy in which medications are given intravenously or by local therapy that includes surgery and radiation therapy [68]. Programmed cell death is a complex process in which the afflicted cells go through a cascade of self-destruction and serves as a key target for cancer prevention measures [69].

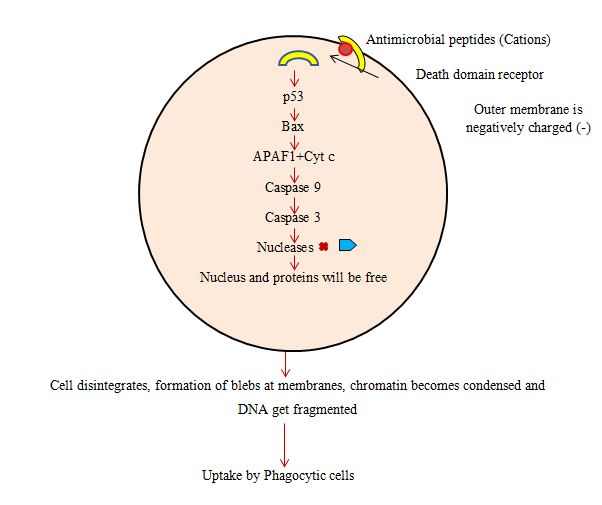
In order to combat the tumour growth, focus has recently switched to the development of novel anticancer drugs, such as peptide-based therapeutics that may serve as adjuvants and genotoxic [70]. Conventional cytotoxic therapies such as radiation therapy and chemotherapy are implicated to achieve cancer management but in turn both the therapies are highly toxic with broad spectrum of severe side effects [71].

Natural products may offer an alternative solution to prevent the growth of cancer and to overcome current chemotherapy issues such as multidrug resistance and undesirable side effects (Heart failure, Diarrhoea and Oedema) [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].

The present review compiled the studies carried out on *Streptomyces sp*.that demonstrated cytotoxic action against human cancer cells (Table: 1) Most of the cytotoxic antimicrobial peptides are derived from *Streptomyces* species. One of the classic drugs derived from *Streptomyces* are anthracyclines family which includes doxorubicin produced from *Streptomyces caesius*, daunorubicin isolated from Streptomyces coeruleorubidus, bleomycin, glycopeptide compound isolated from *Streptomyces verticillus*, mitomycin c obtained from *Streptomyces caespitosus*, dactinomycin non ribosomal peptide group obtained from *Streptomyces pratensis* [75]. These drugs can act at multiple levels to promote apoptosis of cancer cells: (i) inhibiting DNA and RNA synthesis by intercalating between base pairs of DNA/RNA strand or topoisomerase inhibition (ii) Generation of reactive free radicals that damage cellular components. (iii) Chromatin remodelling which may eventually cause DNA double strand breaks [76, 77]. Bestatin is a muramyl dipeptide (MDP) produced by *Streptomyces olivoreticuli* a competitive inhibitor of the protease aminopeptidase which plays an important role in angiogenesis [78]. *Streptomyces graminearus* produces gougerotin, which is a peptidyl nucleoside antibiotic increases ROS generations in cancer cells and persipeptide, N-methylated cyclopeptides isolated from *Streptomyces coerulescens* involved in cell cycle arrest and induction of apoptosis in cancer cells [86].

Amino acid residues accumulated in the antimicrobial peptides of *Streptomyces* includes glycine, lysine and leucine that drives cancer cell permeability [79]. Hydrophobic positively charged lysine- and arginine-rich peptides act as cationic peptides that interact with membranes by destructing cell membrane integrity, disruption of the mitochondrial membrane potential, cytochrome c release and activation of different caspases and serves as a better role in cancer cell toxicity [80]. Thus the Antimicrobial peptides of *Streptomyces* species can be utilized directly as a cytotoxic agent in extent through various mechanisms and it can act as a carrier of cytotoxic agents for various cancer disorders.



**Figure: 3 Mechanism of Anti-cancer activity from Microbial Antimicrobial peptides**

**Table 1: Anticancer activities of *Streptomyces* derived Antimicrobial peptide compounds**

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| --- | --- | --- |
| **Name of the *Streptomyces* species** | **Antimicrobial peptide compounds** | **Mechanism of action/drug target** |
| *Streptomyces galilaeus* | Cyclic peptide compounds; Aclacinomycin  X | Human colon cancer  HCT116  ; Cytotoxic action and antiangiogenesis [81] |
| *Streptomyces chibaensis* AUB(1)/7 | Quninone peptide compounds ; Resistoflavine | Gastric adenocarcinoma HMO2, Hepatic carcinoma, HePG2; Cytotoxic activity and apoptosis [81] |
| *Streptomyces scabrisporus* | Cyclic peptide compound; Okilactomycin | Gastrointestinal cancer; Translation inhibition [82] |
| *Streptomyces caespitosus* | Hetrocyclic peptide compounds; Mitomycin A and B | Human Lung adenocarcinoma cells; DNA damage and apoptosis [83] |
| *Streptomyces coelicolor* | Actinorhodin | Human lung cancer; Oxidative damage, protein damage and DNA damage [83] |
| *Streptomyces canus FIM0916* | Lipopeptide; Amphomycin | Human Breast Cancer cells MCF-7; Mitochondrial dysfunction, blockage of RNA polymerase and antiangiogenic action [84] |
| *Streptomyces chygroscopicus* | Β Amino-glycosidic compound ; Hygromycin ; | Human Breast Cancer cells MCF-7 and Prostate cancer  PC-3 and DU145; Cytotoxic activity, release of Cytochrome c molecules and Protein synthesis inhibition [84] |
| *Streptomyces pluricolorescens* | Amino-glycoside compound ; Pluramycin | Pleuropulmonary blastoma and cervical cancercells Hela ; Inhibition of DNA replication and apoptosis [85] |
| *Streptomyces griseus and Streptomyces sp. strain fd1-xmd* | Amino glycosidic compound; Streptothricin | Human Breast Cancer cells MCF-7; ROS generation and Cyotoxic activity [85] |
| *Streptomyces monashensis* | Amino glycosidic compound Bafilomycin | Human Breast Cancer cells MCF-7; DNA damage and Transcription inhibition [86] |
| *Streptomyces nogalater.* | Cyyclic peptide compound: Nogalamycin | Human Breast cancer MCF 7 and ovarian cancer cells  CA125; Prevention of mitochondrial phosphorylation, activation of caspase and inhibition of protein synthesis [87] |
| *Streptomyces albogriseolus* | Antimicrobial peptides pk4 and pk5 | Human Breast cancer cells MCF 7; Cytotoxic activity and DNA damage [88] |
| *Streptomyces minutiscleroticus* | Antimicrobial peptides pk5 | Human Breast cancer cells MCF 7; Cytotoxic activity [88] |

**CONCLUSION**

*Streptomyces* species are truly fascinating microorganisms, produces a novel peptide based therapeutic compounds with diverse structures. In comparison to other conventional medications, the antimicrobial peptides of *Streptomyces* sp. has promising chemo preventive effect because of its desirable cell penetrating properties, specific cancer cell targets, increased efficacy, low toxicity to normal cells, and decreased side effects. Collectively, it is hypothesised that Antimicrobial peptides of these organisms has effective anticancer medications that linked to combat the future cancer death rates.

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