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.

Authors

Akshatha S. J
Department of Microbiology
Jnana Kaveri campus
PG centre Mangalore University
Kodagu, Karnataka, India
akshathasj7@gmail.com

Dr. Manjula Ishwara Kalyani
Department of Microbiology
Jnana Kaveri campus
PG centre Mangalore University
Kodagu, Karnataka, India
manjuganesh7176@gmail.com

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., *Cornybacterium* 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].

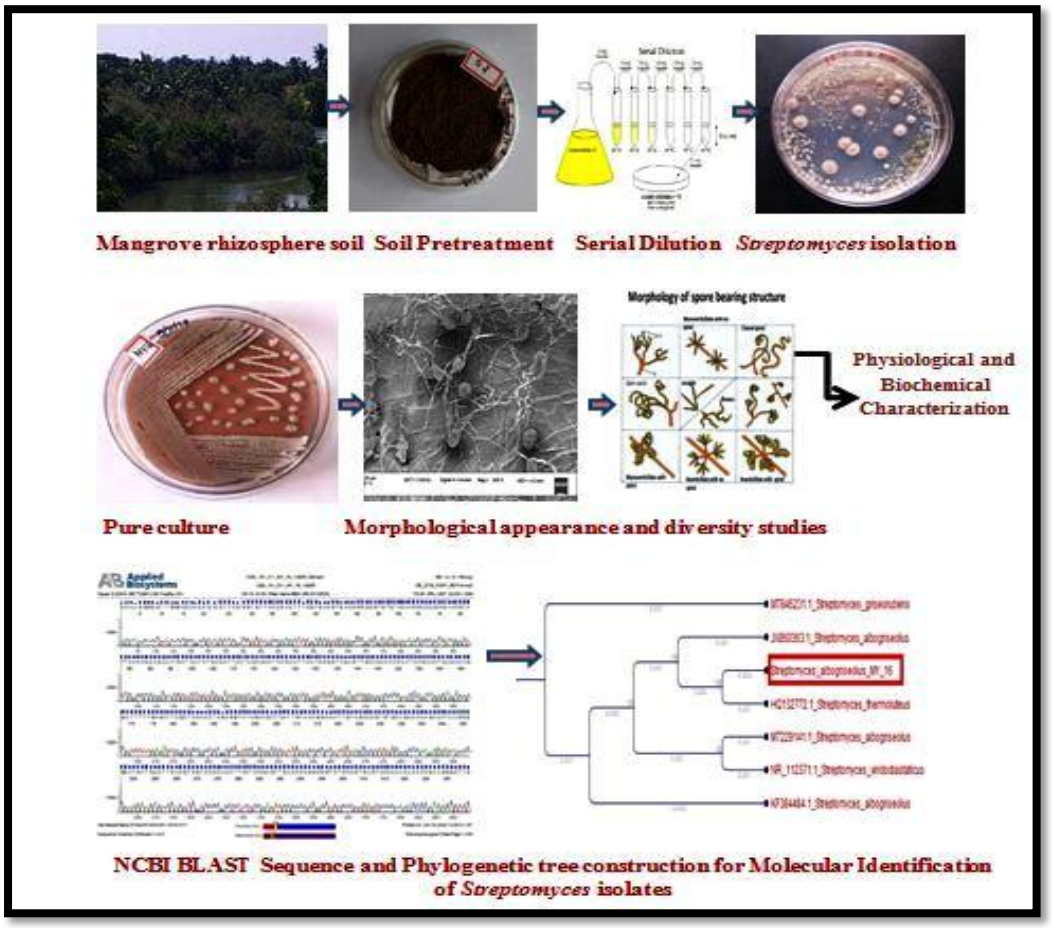

Figure 1: Isolation and Molecular Identification of *Streptomyces* Sp.

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].

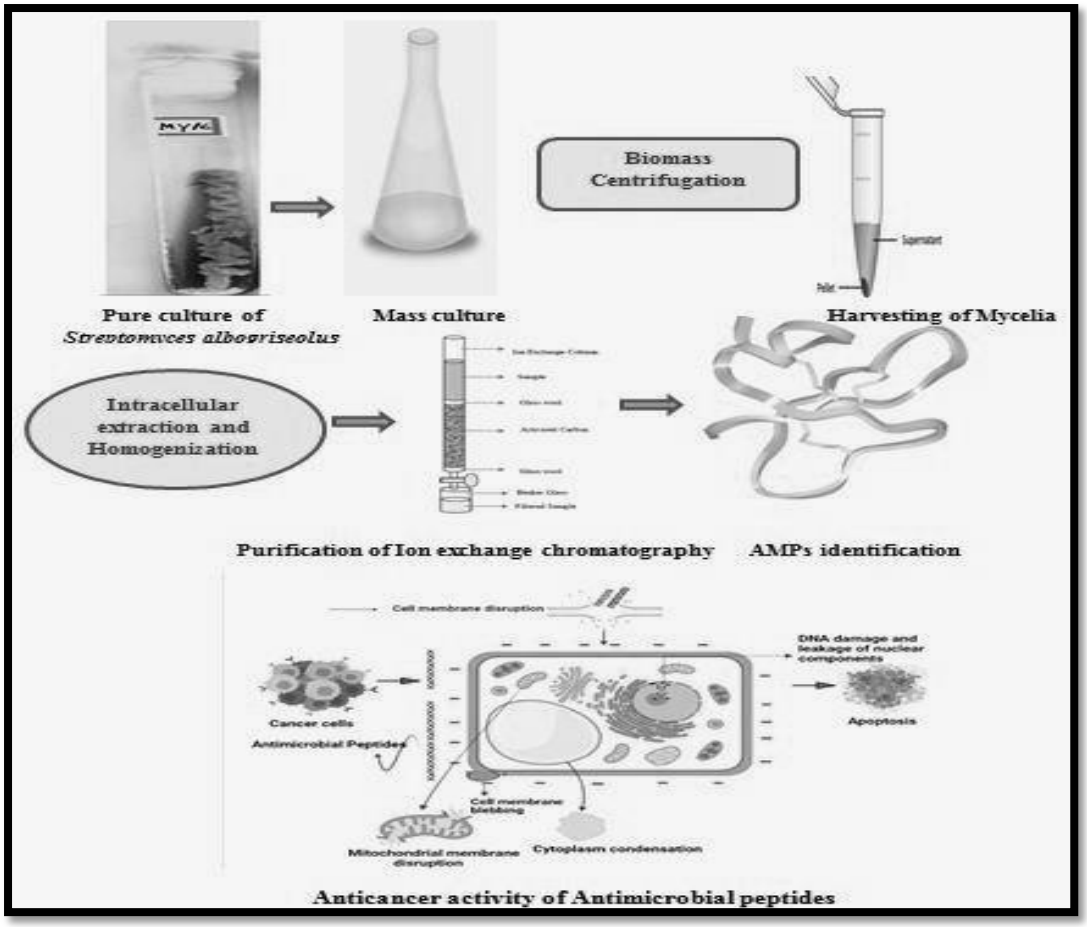

Figure 2: Purification Process and Anti-Cancer Activity of Antimicrobial Peptides Isolated from *Streptomyces* Sp.

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 caesius*, 'Epirubicin" produced by *Streptomyces venezuelae*, "Bleomycion" 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.

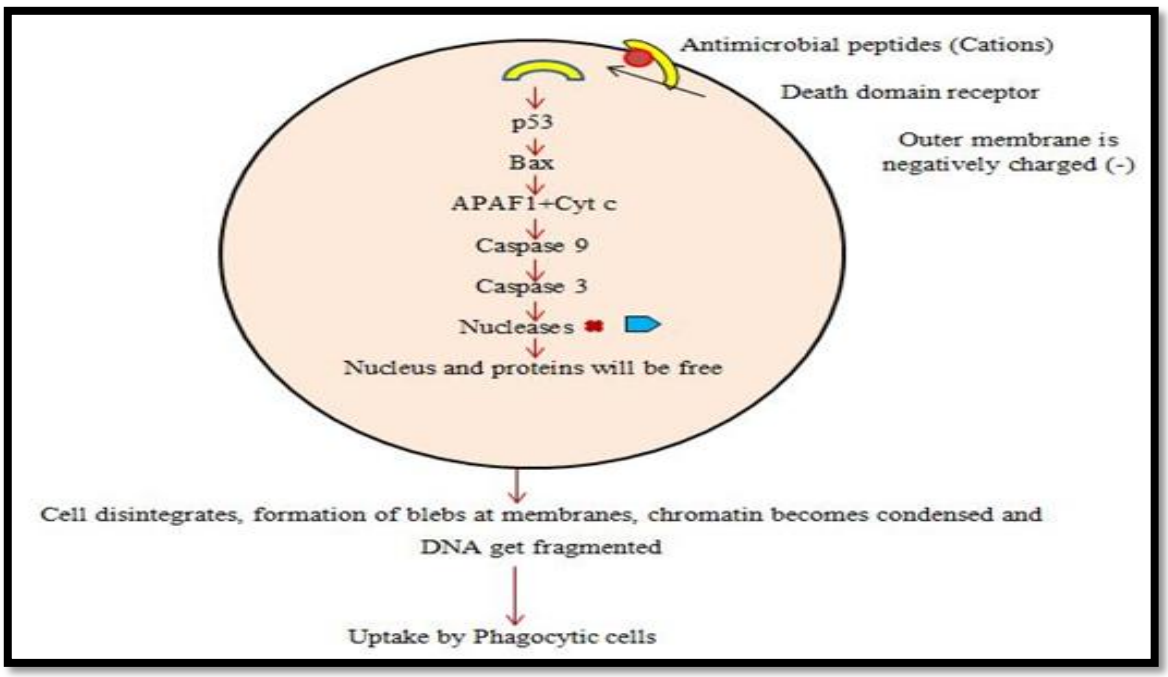

Figure 3: Mechanism of Anti-Cancer Activity from Microbial Antimicrobial Peptides

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

Name of the *Streptomyces* Sp.	Antimicrobial peptide drugs	Anticancer activities on human cancer cells
Streptomyces galilaeus	Cyclic peptide compounds; Aclacinomycin X	Human colon cancer HCT116 ; Cytotoxic action and anti-angiogenesis[81]
Streptomyces chibaensis	Quninone peptide compounds ; Resistoflavine	Gastric adenocarcinoma HMO2, Hepatic carcinoma, HePG2; Cytotoxic activity and apoptosis [81]
Streptomyces scabrisporus	Cyclic peptide compounds; 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	Benzoisochromanequinone dimer polyketideantibiotic; Actinorhodin	Human lung carcinoma epithelial cells A549; Oxidative stress and DNA fragmentation [83]
***Streptomyces canus* FIM0916**	Lipopeptide; Amphomycin	Human breast cancer cells MCF-7; Mitochondrial dysfunction, RNA polymerase inhibition and anti-angiogenic action [84]
Streptomyces hygroscopicus	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]
Streptomyces pluricolorescens	Amino-glycoside compound ; Pluramycin	Pleuropulmonary blastoma and cervical cancer cells Hela ; Inhibition of DNA replication and apoptosis [85]
Streptomyces griseus	Amino glycosidic compound; Streptothricin	Human breast cancer cells MCF-7; ROS generation and Cytotoxic activity [85]
Streptomyces monashensis	Amino glycosidic compound Bafilomycin	Human breast cancer cells MCF-7; DNA damage and Transcription inhibition [86]
Streptomyces nogalater	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]
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]

Other than anthracycline group of antimicrobial peptides, there are efficient anticancer peptides procured from certain *Streptomyces* strains including “Bestatin” is a muramyldipeptide (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 coerulescens*. 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.

REFERENCES

[1] E. Peterson , P. Kaur, ''Antibiotic Resistance Mechanisms in Bacteria: Relationships between resistance determinants of antibiotic producers, environmental bacteria and clinical pathogens'', Front. Microbial, 9, 2018, pp. 1-21.
[2] Z.A. Abidin, N.A. Malek, Z. Zainuddin, AJ. Chowdhury, ''Selective isolation and antagonistic activity of actinomycetes from mangrove forest of pahang, Malaysia'', Front Life Sci, 9, 2016, pp. 24-31.
[3] O. Messaoudi, M. Bendahou, I. Benmar, "Abdelwouhid. Identification and preliminary characterization of non-polyene antibiotics secreted by new strain of actinomycetes isolated from sebkha of Kenadsa, Algeria", Asian Pac J Trop Biomed, 5, 2015, pp. 438-445.
[4] M.E. Buyukkiraz and Z. Kesmen, "Antimicrobial peptides (AMPs): "A promising class of antimicrobial compounds", J Appl Microbiol, 132, 2022, pp. 573–1596.
[5] F. Xie, and W. P. Aree, Actinobacteria from desert: Diversity and Biotechnological applications. *Front. Microbiol*. 2021; 12(765531): 1-27.
[6] O. Messaoudi, M. Bendahou, I. Benmar, et al, "Identification and Preliminary characterization of non-polyene antibiotics secreted by new strain of actinomycetes isolated from sebkha of Kenadsa, Algeria". Asian Pac J Trop Biomed 5, 2015, pp. 438-445

[7] I. Panina I. Taldaev, R. Efremov, et al, "Molecular dynamics insight into the Lipid II recognition by Type A Lantibiotics: Nisin, Epidermin, and Gallidermin". Micromachines, 12 2021, 1-10
[8] R.M. Epand, C. Walker, R.F. Epand, N.A, et al, "Molecular mechanisms of membrane targeting antibiotics", Biochimica et Biophysica Acta, 1858, 2015, 980–987.
[9] Y.M. Burgo, J.S. Aberturas , A.R. García, et al, "Activation of Secondary Metabolite Gene Clusters in *Streptomyces clavuligerus* by the PimM Regulator of *Streptomyces natalensis*". Front. Microbiol 10, 2021, 1-14
[10] S. Hwang, Y. Lee, J.H. Kim, et al, "*Streptomyces* as Microbial Chassis for Heterologous Protein Expression". Front. Bioeng. Biotechnol, 9, 2021, pp. 1-23.
[11] A. Vasilchenko, W. Julian, O. Lapchinskaya, et al, "A Novel Peptide antibiotic produced by *Streptomyces roseoflavus* strain INA-Ac-5812 with directed activity against gram-positive bacteria". Front. Microbiol, 11, 2020, pp. 1-13.
[12] S.J. Akshatha and M.I Kalyani "Mangrove-soil *Streptomyces sps* exhibiting culture and biochemical variation for determining antibacterial activity", Journal of pure and applied Microbiology., in press.
[13] Y. Karthik and M.I Kalyani, "Occurrence of *Streptomyces tauricus* in mangrove soil of Mangalore region in Dakshina Kannada as a source for antimicrobial peptide", Journal of basic Microbiology, 62, 2022, pp. 1-15
[14] Y. Karthik and M.I Kalyani,"Cytotoxic and antimicrobial activities of microbial proteins from Mangrove soil actinomycetes of Mangalore, Dakshina Kannada", Biomedicine, 40, 2020, pp. 59-67.
[15] S. Nakamura, N. Tsuda, T. Miyata, et al, "Antimicrobial effect and mechanism of bovine lactoferrin against the potato common scab pathogen *Streptomyces scabiei*". PLoS ONE, 17, 2022, pp. 1-16.
[16] G. Kaur, S. Kapoor, S. Kaunda, et al,"Structure-Guided Designing and Evaluation of Peptides Targeting Bacterial Transcription". Front. Bioeng. Biotechnol, 8, 2020, pp. 1-10.
[17] M. Lilic , J. Chen, H. Boyaci, et al, "The antibiotic Sorangicin A inhibits promoter DNA unwinding in a *Mycobacterium tuberculosis* Rifampicin-resistant RNA polymerase". PNAS 117, 2020, pp. 30423–30432.
[18] D. Degen, Y. Feng , Y. Zhang Y, et al, Transcription inhibition by the depsipeptide antibiotic Salinamide A. eLife 3, 2014, pp. 1-29.
[19] B. Candiroglu ans N.D. Gungor, "The Biotechnological potentials of Bacteria isolated from Parsik Cave, Turkey". Johnson Matthey Technol. Rev, 64, 2020, pp. 466–479.

[20] S. Singh, S. Kaithal, B. Navya, et al, "Fascinating diversity and Potent Biological activities of *Streptomyces* metabolites". Journal of Pharmacy, 3, 2017, pp. 250-56
[21] I.C. Juarez, B.E. Luciano,R.G. Contreras et al, "Antimicrobial peptides properties beyond growth inhibition and bacterial killing". Peer J 10, 2022, pp. 1-25.
[22] Seo, Oliver, Stackebrandt, "Purification and characterization of antimicrobial peptides from *Streptomycetes* KCTC3594". J. Appl. Biochem. Biotechnol, 162, 2010, pp. 146-154
[23] S.H. Hassanpour and M. Dehghani, "Review of cancer from perspective of molecular". Journal of cancer research and practice 4, 2017, pp. 127-129.
[24] O. Ginsburg , F. Bray, M. Coleman, et al "The global burden of women's cancers: an unmet grand challenge in global health". Lancet, 16, 2017, pp. 847-860.
[25] M. Obeidat, "Cytotoxicity of n-Butanol extracts of *Streptomyces* against human breast cancer cells". International Journal of Pharmacology, 13, 2017, pp. 969-979
[26] S. Reddy,S. Ramesh, R. R Anupalli, "A mini-review on breast cancer-risk factors, treatment and prevention". JETIR, 6, 2019, pp. 1-13
[27] S. Sharma, R. Dave, Sanadya, et al, Various types and management of breast cancer: an overview. J. Adv. Pharm. Tech. Res, 2, 2010, pp. 1-18.

[28] S. Eslami, K. Majidzadeh, S . Halvaei, et al, "Micro biome and breast cancer: new role for an ancient population". Front. Oncol 10, 2020, pp. 1-18
[29] N.Stjepanovic, J. Lubinski, P.Moller, et al, "Breasst Cancer risk after age 60 among BRCA1 and BRCA 2 mutation carriers". Breast cancer res treat, 187,2021, pp. 515-523.
[30] G.M. Cragg, P.G. Grothaus, D.J. Newman, "Impact of Natural products on developing new Anti-cancer agents" Ind.J.Pharm, 109, 2009, pp. 3012-3043.
[31] M. Manimaran, K. Kannabiran , "Marine *Streptomyces* sp. VITMK1 Derived Pyrrolo [1, 2-A] pyrazine-1, 4-dione, hexahydro-3- (2-methylpropyl) and its free radical scavenging activity", Open Bioactive compounds journal, 5, 2017,pp. 23-30.
[32] H. L. Ser, L.T. Tan, U. Palanisamy, et al, "*Streptomyces antioxidans* sp. nov., a novel Mangrove Soil Actinobacterium with antioxidative and neuroprotective potentials". Front. Microbiol, 7, 2016, pp. 1-14.
[33] C. Yao, S and Narumiya S,"Prostaglandin-cytokine crosstalk in chronic inflammation". British Journal of Pharmacology 176, 2019, pp. 337–354.
[34] J. Zhong, G. Shi, "Editorial: Regulation of inflammation in chronic disease". Front. Immunol 10, 2019, pp. 1-12.
[35] M. Gao, S. B. Lee, J. E Lee, et al, "Anti-Inflammatory Butenolides from a marine-derived *Streptomyces* sp. 13G036". Applied Sciences,12, 2022, pp. 1-11.
[36] N.M. Fahmy, and A.M. Tawab et al, "Isolation and characterization of marinesponge–associated *Streptomyces* sp. NMF6 strain producing secondary metabolite(s) possessing antimicrobial, antioxidant, anticancer, and antiviral activities. Journal of Genetic Engineering and Biotechnology''19, 2021, pp. 1-14.
[37] B. Shao, Y. Feng, H. Zang, "The 3p14.2 tumour suppressor ADAMTS9 is inactivated by promoter CpG methylation and inhibits tumour cell growth in breast cancer", J. Cell. Mol. Med, 10, 2019, pp.1-15.
[38] S. Choyam, P. M. Jain , R. Kammara, "Characterization of a potent new generation antimicrobial peptide from marine *Streptomyces akiyoshiensis* GRG 6 effective on anticancer activity". *Front Microbiol*, 12, 2021, pp. 1-13.
[39] T. Roncevic, L. Krce, l M. Gerdo, et al, "Membrane active antimicrobial peptide identified in *Rana arvalis* by targeted DNA sequencing". Biomembranes, 1861, 2019 pp. 651-659.
[40] H. Ma, X. Zhao, L. Yang, et al,"Antimicrobial peptide AMP-17 affects *Candida albicans* by disrupting lts cell wall and cell membrane integrity". Infection and Drug Resistance, 13, 2020, pp. 2509-2520.
[41] Z. Xue, A. Yokota, J.F. Peberdy et al, "Indole3-acetic acid production by *Streptomyces sp*. isolated from some Thai medicinal plant rhizosphere soils". EurAsia J BioSci, 4, 2020, 23-32.
[42] M. I. Kalyani, S. M. Lingaraju, B. P. Salimath, "A pro-apoptotic 15-kDa protein from *Bacopa monnieri* activates caspase-3 and down regulates Bcl-2 gene expression in mouse mammary carcinoma cells", J Nat Med, **67**, 2013, pp. 123-136.

[43] K. Krishnan, A. Mani, S. Jasmine, ''Cytotoxic activity of bioactive compound 1, 2- benzene dicarboxylic acid, mono 2- ethylhexyl ester extracted from a marine derived *Streptomyces* sp. VITSJK8''. IJMCM,3, 2014, pp, 1-9.
[44] L.H. Hurley ans S. Rokem,"Biosynthesis of the antitumor antibiotic cc-1065 by *Streptomyces zelensis*". Journal of Antibiotics 4, 1982, pp. 383-390.
[45] L. Janardan, O. T. Jin, L. H. Chan , et al, Mediation of Rubradirin Resistance by ABC Transporters (RubT1) from *Streptomyces achromogenes* var. rubradiris NRRL3061. Journal of Microbiology and Biotechnology 16, 2006, pp. 1928-1934
[46] M. Barreca, V. Spano, A. Montalbano et al, "Marine Anticancer Agents: An Overview with a Particular Focus on Their Chemical Classes. Marine drug'', 18, 2020, 1-28.
[47] M. Eskandani, S. Vandghanoon, J. Barar et al, "Cell physiology regulation by hypoxia inducible factor-1: Targeting oxygen-related nanomachineries of hypoxic cells". Int. J. Boil. Mol, 99, 2017, pp. 46-62.

[48] P. M. Manickan and B. P. Venkataesan, "Crude protein extract of actinobacteria exhibits antibacterial activity against *Salmonella typhi*", Int J Curr Microbiol Appl Sci,3, 2014, pp. 319-326.
[49] M. Sharma and R. K. Manhas, "Purification and characterization of actinomycins from *Streptomyces* strain M7 active against methicillin resistant *Staphylococcus aureus* and vanomycin Enterococcus'', BMC Microbiol, 19, 2019, pp. 5-14.
[50] M. G. Chevrette, C. M. Carlson, H. E. Ortega, et al, "The antimicrobial potential of *Streptomyces* from insect microbiomes", Nat Commun, 10, 2019, pp. 1-11.
[51] R. Banu, A. Raj, R. Janardhan, "Isolation, characterization and anticancer activity of marine halophilic *Streptomyces* species from the west coast of India". Curr. Sci, 86, 2021. pp, 593-597
[52] A. J. Mc carthy and S. Williams, "Actinomycetes as agents of biodegradation in the environment - A review", Gene, 115, 1992, pp. 189-92.
[53] P. A Jose and B. Jha, "New dimensions of research on Actinomycetes: Quest for next generation antibiotics", Front Microbiol,7, 2016, pp.1295-1299
[54] O. Genilloud, "Actinomycetes: still a source of novel antibiotics", Nat Prod Rep, 34, 2017, pp. 1203-1232.
[55] S.D. Bentley, K.F. Chater , N. R. Thomson, e t al, "Complete genome sequence of the model acinomycete *Streptomyces coelicolor* A3", *Nature*, 417, 2002,pp. 141–147.
[56] B. Deslouches and Y. P. Di, "Antimicrobial peptides with selective antitumor mechanisms: Prospect for anticancer applications", Oncotarget, 8, 2017, pp. 46635-46651
[57] L. Soblosky, A. Ramamoorthy, Z.Chen, "Membrane interaction of antimicrobial peptides using *E. coli* lipid extract as model bacterial cell membranes and SFG spectroscopy", Chem Phys Lipids, 187, 2015, pp. 20–33.
[58] Xin Y, Sun Z, Chen Q, Wang J, et al. Purification and characterization of a novel extracellular thermostable alkaline protease from *Streptomyces sp* M 30. *J. Microbiol Biotechnol*. 2015; 25: 1944-1953. doi: 10.4014/jmb.1507.07017
[59] J. Nachtigall A. Kulik, S, et al, "Atacamycins A-C, 22-membered antitumor macrolactones produced by *Streptomyces* sp. C38". J. Antibiot, 64, 2011, pp. 775–780.
[60] S. Siddarth and R. R. Vittal, "Evaluation of Antimicrobial, enzyme inhibitory, antioxidant and cytotoxic activities of partially purified volatile metabolites of marine *Streptomyces* sp.S2A", 6, 2018, pp. 1-13.
[61] L. T. Tan, K. G. Chan, P. Pusparajah, Mangrove derived *Streptomyces* sp. MUM265 as a potential source of antioxidant and anticolon-cancer agents. BMC Microbiology 19, 2019, pp. 1-16.
[62] S. Um, T. J. Choi, H. Kim, et al, "Ohmyungsamycins A and B: cytotoxic and antimicrobial cyclic peptides produced by *Streptomyces sp*. from a volcanic island''. Journal of organic chemistry,78, 2013, pp. 12321−12329.
[63] N. Zaburannyi, M. Rabyk, B. Ostash, et al,"Insights into naturally minimised *Streptomyces albus* J1074 genome". BMC genomics, 15, 2014, pp. 1-11
[64] R. Polapally, M. Mansani, K. Rajkumar, et al, "Melanin pigment of *Streptomyces puniceus* RHPR9 exhibits antibacterial, antioxidant and anticancer activities". PLoS ONE,17, 2022, pp. 1-14.
[65] H. Shao, M. Chen, X. Fei, et al. "Complete genome sequence and characterization of a Polythene biodegradation strain *Streptomyces albogriseolus* LBX-2". Microorganisms,7, 2019,pp. 1-13.
[66] D. E. Waturangi, B. S. Rahayu, K.Y. Lalu, et al, "Characterization of bioactive compound from actinomycetes for antibiofilm activity against Gram-negative and Gram-positive bacteria", Malaysian Journal of Microbiology, 12, 2020, pp. 291-299.
[67] N. R. Rajivgandhi, G. J. Ramachandran, L. Li , et al, "Molecular identification and structural detection of anti-cancer compound from marine *Streptomyces akiyoshiensis* GRG (KY457710) against MCF-7 breast cancer cells'', Journal of King Saud University, 32, 2020, pp. 3463–3469.

[68] G. T. Dow, J.B. Thoden, H.M. Holden, "The three-dimensional structure of NeoB: An aminotransferase involved in the biosynthesis of neomycin *Protein science*". 2018; 27: 945-956. doi: 10.1002/pro.3400
[69] P. A Jose, I. A. Maharsh, B. Jha, "Actinobacteria in natural products research: progress and prospects". Microbiol. Res, 246, 2021, pp. 1-14.
[70] M. Dhaneesa, B.C. Naman, K.P. Krishnan, et al, "*Streptomyces artemisiae* MCCB 248 isolated from Arctic fjord sediments has unique PKS and NRPS biosynthetic genes and produces potential new anticancer natural products". 3 Biotech,7, 2017, pp. 1-10.
[71] A.L Bultimea, C.R. Cardenas, J.A. Cervantes, et al, "The demand for new antibiotics: Antimicrobial peptides, Nanoparticles, and Combinatorial therapies as future strategies in antibacterial agent design". Front. Microbiol, 11, 2020, pp. 1-11.
[72] J. Claesen and M.J, "Biosynthesis and regulation of grisemycin, a new member of the linaridin family of ribosomally synthesized peptides produced by *Streptomyces griseus* IFO" 13350, J Bacteriol, 193, 2011, pp. 2510–2516.
[73] U. Aftab, D. Zechel and I. Sajid, "Antitumor compounds from *Streptomyces* sp. KML- 2, isolated from Khewra salt mines, Pakistan", Biol Res, 5, 2015, pp.48-58.
[74] N. Osama, W. Bakeer, M. Raslan, et al, "Anti-cancer and antimicrobial potential of five soil *Streptomycetes*: a metabolomics-based study", R. Soc. Open Sci, 9, 2021, pp. 1-17.
[75] J.W. Law, L.N. Law, V. Letchumanan , et al, "Anticancer drug discovery from microbial sources: The unique mangrove *Streptomycetes*". Molecules, 25, 1, pp.1-18.
[76] S. Narendhran, R.P. Vanathi, R. Sivaraj. "Spectroscopic analysis of bioactive compounds from *streptomyces cavouresis* KUV39: Evaluation of antioxidant and cytotoxicity activity". Int J Pharm Pharm Sci, 6, 2014, 319-322.
[77] S.P. Wasser , F. Fares, "The shaggy ink cap medicinal mushroom *Coprinus comatus* (Higher Basidiomycetes) extract induces apoptosis in ovarian cancer cells via extrinsic and intrinsic apoptotic pathways", International journal of medicinal mushrooms, 17, pp.1127-1136
[78] T. Rhen and J.A. Cidlowski,"Anti-inflammatory action of glucocorticoids –New mechanisms for old drugs". New England Journal of Medicine, 353, pp. 1711–1723.
[79] A. Mukherjee, S. Basu, N. Sarkar , et al, "Advances in cancer therapy with plant based natural products''. Current Medicinal Chemistry, 8, 2001, pp. 1467–1486.
[80] C. Feng, X. Li, C .Dong, et al, "RGD-modified liposomes enhance efficiency of aclacinomycin a delivery: evaluation of their effect in lung cancer". Drug Design, Development and Therapy, 9,2015, pp.4613-4620.
[81] A. Banerjee, K.T. Johnson, A.Ipsita,"Nano formulation enhances anti-angiogenic efficacy of tunicamycin", Transl Cancer Res, 2, 2013, pp. 240–255.
[82] A. Gorajana, M. Venkatesan, S.Vinjamuri, et al, "Resistoflavine, cytotoxic compound from a marine actinomycete, *Streptomyces chibaensis* AUBN1/7", Microbiological Research, 2007, pp. 322-327.
[83] T.W. Martin, Z.Dauter, Y. Devedjiev, "Molecular Basis of Mitomycin C Resistance in *Streptomyces*: Structure and Function of the MRD Protein", Elsivier science, 10, 2002, pp. 933-942.
[84] S. Torkkell, K.Y.lihonko, J.Hakala, et al, "Characterization of *Streptomyces nogalater* genes encoding enzymes involved in glycosylation steps in nogalamycin biosynthesis", Mol Gen Genet, 256, 1997, pp.203-209.
[85] N.Tanaka, H. Yamazhaki, K. Okabe, et al, "Raromycin, a new tumor-inhibitory antibiotic produced by a *Streptomyces*", Journal of Antibiotics, 5, 1957, pp.1-6
[86] C. Zhang, J.G. Ondeyka, D.L. Zink, et al, "Discovery of Okilactomycin and congeners from *Streptomyces scabrisporus* by antisense differential sensitivity assay targeting ribosomal protein S4", The Journal of Antibiotics, 2009, pp. 55-61.

[87] S.J. Akshatha and M.I Kalyani,"Isolation and extraction of antimicrobial peptides from *Streptomyces minutiscleroticus* and *Streptomyces albogriseolus* from Mangrove soil of Mangalore Coast, Karnataka", Indian. J.nat .prod resour, 13, pp.1-12.

