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Review Article

Exploring Actinomycetes metabolites in cancer therapy

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ABSTRACT

Cancer poses a serious threat to human health, with its incidence and mortality rates rapidly increasing worldwide. Current therapies often fall short of clinical needs, particularly due to challenges such as tumor resistance to chemotherapy and severe toxic side effects. Therefore, there is an urgent need to develop highly effective anticancer drugs with low toxicity. Natural products derived from microorganisms serve as a vital source of valuable pharmaceuticals and therapeutic agents. Among them, actinomycetes represent a rich reservoir for the discovery of numerous medicinal natural products and play a crucial role in the development of new microbial drugs. In particular, actinomycetes of the genus Streptomyces have attracted significant global attention due to their ability to produce a wide range of bioactive secondary metabolites. The potential of these Gram-positive bacteria to synthesize diverse compounds with potent biological activities makes them ideal candidates for anticancer drug discovery. This review article focuses on the natural products secreted by actinomycetes, their biological functions and their possible roles in anticancer activity.

Keywords: Actinomycetes, Anticancer, Drugs

INTRODUCTION

Actinomycetes are filamentous bacteria that contain a large amount of guanine-plus-cytosine (G+C) in their genomes. These bacteria are known as actinobacteria. These bacteria resemble fungus in appearance and are gram-positive.[1] Their growth occurs through a combination of elongation at the tip and the formation of branches in the hyphae. Historically, actinomycetes were regarded as intermediary organisms, bridging the gap between fungi and bacteria.

In fact, many *Actinobacteria* species make a mycelium, which is similar to filamentous fungi. A large number of these mycelial actinomycetes proliferate by sporulation. Nevertheless, the similarity to fungi is merely surface-level. Similar to other bacteria, actinomycetes possess slender cells with a prokaryotic nucleoid containing a chromosome and a cell wall made of peptidoglycan. Additionally, these cells are vulnerable to antibacterial substances.[2] Actinomycetes, which are a diverse group of microorganisms, are highly valuable due to their practical applications. They are responsible for approximately 70% of the antibiotics produced and also generate a variety of other bioactive compounds, including enzymes, enzyme inhibitors, immunological regulators and anti-oxidation agents.[3] Actinomycetes are very valued prokaryotes in terms of both commercial and biotechnological significance.

They have the responsibility of generating approximately 50% of the recognized bioactive secondary metabolites. It has been demonstrated that the microbes generate over 23,000 advantageous secondary metabolites. More than 10,000 of these substances are produced by actinomycetes, which make up 45% of all known bioactive microbial metabolites. *Streptomyces* species are among the actinomycetes that manufacture the most chemicals,

producing about 7600 compounds. Other actinomycetes, such as Micromonospora, Nocardia and Actinoplanes, also play significant roles in the production of antibiotics, enzymes and other bioactive molecules.[4]

Actinomycetes possess the capacity to yield prospective pharmaceuticals for combating critical ailments, including drug-resistant bacteria, cancer, several viral diseases, malaria, many infections and inflammations.[5] Cancer is a significant global public health issue among the numerous diseases. The adverse reactions and developing drug resistance to conventional chemotherapeutic agents present a formidable obstacle in the field of cancer treatment. Utilizing natural chemicals or their derivatives as antitumor agents presents a possible alternative to existing cancer treatments.

Microbial species called actinomycetes have a big effect on drug development because they can make a lot of different bioactive secondary metabolites with a lot of different chemicals.[6] Actinomycetes are capable of synthesizing a diverse range of medically valuable anticancer medications, including actinomycin D, aclarubicin, azynomycin B, bleomycin, daunomycin, doxorubicin, mithramycin, mitomycins, neocarzinostatin and pentostatin. The potential of unexplored species of actinomycetes in drug discovery for addressing drug resistance issues in cancer therapy is receiving increasing attention. This article provides a comprehensive overview of the biology of this significant bacteria and their possible involvement in anticancer activities.

DIVERSITY OF ACTINOMYCETES (SOIL, MARINE AND PLANTS)

Soil

Actinomycetes, comprising over 500 species, are found in soil. The decomposition of organic matter in soil, which gives soil its unique fragrance and decaying leaf appearance, as well as its general fertility, is largely dependent on a number of species. Certain species are known for their capacity to produce wide-ranging antibiotics; these occur naturally as substances that organisms employ to eradicate or inhibit the proliferation of other microbes.[7]

Actinomycetes are abundant soil microbes, often exceeding one million per gram, with over 20 genera identified. Streptomycetes appear in 95% of samples. Streptomyces, gram-positive aerobic bacteria, form branching mycelia and this mycelium produces chains of spores when it reaches maturity. Their branching filaments have a diameter ranging from 0.5 to 1.0 micrometers. The antibiotic-producing organisms include *S. aureofaciens* (chlortetracycline producer), *S. rimosis* (oxytetracycline producer), S. griseus (streptomycin producer), S. erythraeus (erythromycin producer) and *S. venezuelae* (chloramphenicol producer) They make up 10–70% of soil microbes. Their abundance and diversity, including genera like Micromonospora and Nocardia, decrease with soil depth, reducing ecological and metabolic potential.[8,9]

Hydromarine

Actinoplanes and related actinomycetes are commonly found in marine and freshwater environments, as well as terrestrial soils. They thrive on decaying plant matter and contribute to the breakdown of chitin, lignin and cellulose. Micromonospora is often found in freshwater sediments, while Streptomycetes spores can enter aquatic systems and persist without active growth. Some aquatic streptomycetes grow on chitinous exoskeletons in streams. Actinomycetes produce compounds like geosmin and methyl iso-borneol, causing earthy odors and altering the taste of drinking water. Their presence is often linked to plant and animal waste near water bodies.[1]

There is growing recognition that aquatic actinomycetes may serve as a source of bioactive substances. These are molecules that are very complex and have pharmacological properties. Marine actinomycetes have a high likelihood of containing bioactive chemicals that possess many beneficial properties, such as being effective against malaria, bacteria, fungi, cancer, tumours, inflammation and microbes.[10]

Along with their capacity to synthesize naturally occurring chemicals, marine actinomycetes also facilitate the breakdown and degradation of pollutants and organic matter. The biogeochemical processes occurring in the water are greatly influenced by them and this contributes to the stability and proper operation of a particular marine ecosystem. Because marine actinomycetes account for two-thirds of polyketide medicines, researchers investigating marine-derived pharmaceuticals have mostly focused on examining these organisms.[11]

Marine actinomycetes are economically and biotechnologically significant prokaryotes. Prior reports indicate that documentation of actinomycetes is limited to less than 1%, mostly due to the intricate and dynamic nature of the microbial population.[12,13] Actinomycetes are extensively found throughout the ocean's limits, exhibiting well-developed morphological and cultural traits.

Consequently, a significant portion of these microorganisms remains unexplored or difficult to locate. They are segregated according to the degree of extremity in marine environments, ranging from milder to more severe habitats such as sediment and seawater. Marine actinomycetes constitute 10% of the total population of marine bacteria.[14] The great variety of maritime habitats is thought to be the reason for the great diversity of marine actinomycetes. *Rhodococcus marinonascene* is a newly discovered species of marine actinomycetes that has been thoroughly characterized and other investigations have conclusively demonstrated the existence of marine actinomycetes. However, the general consensus was that marine actinomycetes originated mostly from spores that

dominated terrestrial environments. Numerous studies have shown that in order to survive, certain actinomycetes strains have acquired features associated with marine adaptation.[14]

Plants

Recent research has shown that plant microorganisms can produce important therapeutic compounds. Fungi, bacteria and actinomycetes may occupy plant tissues in symbiotic relationships.[15] Endophytes normally do not harm their host plants during their whole life cycle. Endophytes are widely distributed and develop mutualistic or antagonistic relationships with host plants, but they are not parasites. They produce phytohormones and other growth-promoting substances that help host plants develop. They get nourishment and refuge from the host plant. They also protect the host from diseases, pests and insects and enhance its resilience to biotic and abiotic stressors.

Endophytes are found in most plants, according to research. Dead and hollow hyaline cells, fruits, buds, seeds, weed inflorescences, stems, roots, petioles and leaf segments provide a unique environment for these microorganisms. Endophytes invade plants depending on the host's developmental stage, habitat and microbial diversity. More research is needed to understand how endophytes and hosts affect bioactive chemical synthesis.[16]

BIOLOGY AND TAXONOMY OF ACTINOMYCETES

Morphological traits they produce spores and grow mycelium. In most species, aerial hyphae septate during spore formation. Infiltrating the plasma membrane and disintegrating the internal cell wall while densifying it creates a strong barrier. Upon sporulation, nuclear material divides. New material forms a strong spore wall. Sporioles result from hyphae fragmentation or spore generation. Soil and climate allow spores to survive. The spores germinate and create germ tubes under these conditions. Later, these tubes mature into mycelium. The organism's cell wall contains amino acids, amino sugars and carbohydrates. Diaminopimelic acid furthers the cell's peptidoglycan layer. Heterotrophic creatures depend on other living things. They release cellulases, proteases, keratinases and amylases to break down their surroundings. Amylases break down starch, keratinases break down keratin, cellulases break down carbohydrates and proteases break down protein. Some actinomycete bacteria form symbiotic relationships with leguminous plants in order to survive.[17]

Taxonomy

Kingdom

These creatures belong to the bacterial kingdom, making them unicellular with a basic cellular structure. These organisms can be found in diverse ecosystems worldwide and have the potential to cause minor-to-severe health ailments in humans. Due to their gram-positive nature, these bacteria possess a peptidoglycan layer within their cell walls.

Phylum

Actinomycetes are classified under the phylum Actinobacteria. Their DNA structure has the largest "G + C" content and they are classified as gram-positive microbes.

These organisms can be found in both water and land environments and they possess a wide spectrum of dietary adaptability. They also generate mycelium.

Subclass

They belong to the large and diverse actinobacteria subclass, which is made up of a variety of species that are present in most habitats.

Order

The Actinomycetes are classified under the order Actinomycetales. In their native habitat, which is both aquatic and terrestrial, they display a great deal of diversity. They exhibit distinct growth features as they develop in the shape of filamentous formations. The sub-orders found within it include Actinomycineae, Corynebacterineae, Catenulispora and Micrococcineae.[17]

The members of this phylum display a wide range of variations in their physical structure, functioning and ability to carry out chemical reactions. The classification of Actinomycetes has undergone substantial changes as our understanding of the subject has grown. The classification of Actinomycetes is determined by its position in 16S rRNA gene trees, specifically based on its branching. Nevertheless, rRNA sequences have little discriminatory power when it comes to distinguishing closely related species or even genera, hence leading to potential ambiguity. There has long been disagreement over how to classify the genus Kitasatospora in the family Streptomycetaceae.

However, a recent thorough genomic investigation has shown compelling data that supports its classification as a distinct genus.[2] Micromonospora, Verrucosispora and Salinispora share a comparable intimate association. Consequently, a variety of genetic markers, such as ssgB and, more recently, rpoB, have been employed to differentiate between closely related taxa. These markers are particularly useful for distinguishing between closely related genera.

Furthermore, a better understanding of genome evolution and the discovery of species-specific genes at the genus and family levels have been made possible by the increased availability of genome sequence data in recent

years. Based on 16S rRNA trees, a novel taxonomy for the phylum Actinobacteria has been disclosed by a recent study.[2]

The upgrade removed the taxonomic ranks of suborders and subclasses. It promoted the prior subclasses to the rank of classes and the previous suborders to the status of orders. The six classes that comprise the phylum are Acidimicrobiia, Coriobacteria, Actinobacteria, Rubrobacteria, Nitriliruptoria and Thermoleophilia. Bifidobacteriales and Actinomycetales, the two previously proposed orders, are two of the sixteen orders that make up the class Actinobacteria.[2]

ANTICANCER COMPOUNDS FROM MARINE DERIVED ACTINOMYCETES

Many actinomycetes form filaments and create many natural chemicals. The increased toxicity, side effects and drug resistance of current medicines have increased the demand for new anticancer drugs. The physiologically active secondary metabolites of marine actinomycetes are important. Marine-derived actinomycetes produce 39% of bioactive microbial metabolites, according to statistical analysis.[18]

These compounds, which are important in agriculture, biotechnology and medicine, make up most FDA-approved antibiotics.[19] Endiynes have been used to produce many anticancer drugs, including Besponsa® and Mylotarg®.[20,21] Natural products (NPs) from marine actinobacteria are increasing in diversity. In addition to their medical uses, biocatalysis and the production of biological or microbial pesticides increasingly exploit marine NPs. For years, researchers have discovered more unique chemical and bioactive compounds from marine-derived actinomycetes than from soil-derived ones.

These actinomycetes are often found in aquatic environments, such as the sea shallow microlayer, a thin layer of water that is one millimetre thick on the ocean's surface. These actinomycetes do not grow well in laboratory conditions. Additionally, they can be found in seabed habitats made of marine sediments, which offer an ideal setting for the coexistence of microorganisms with smaller and bigger marine species. Fish surfaces, beaches, coastal waters and even the bottom itself are home to actinobacteria.[22] Micromonosporas and Streptomyces have a lot of potential for finding substances that can fight cancer and stop it from growing.[22]

Marine actinomycetes have produced a large number of chemicals from type I polyketides that can help fight cancer. The marine actinomycete *Salinispora arenicola* strain CNR-005 is one instance of this, producing arenicolides 26-membered polyunsaturated macrolactones. This strain was identified from a marine silt sample collected from the coastal seas of the island of Guam, which was taken 20 meters below the surface. Arenicolide selectively targets the HCT-116 colon cancer cells in humans. With an IC50 of 30 µg/mL, it demonstrated moderate cytotoxicity.[23]

Streptomyces sp. M491, a 16-member macrolide, produces chalcomycin. It was separated from Qingdao's beach. Chalcomycin and chalcomycin B have been extracted from Hawaiian mangrove sediments using Streptomyces strain B7064.[24] Protein synthesis in HeLa cells is chalcomycin-resistant.[25] The marine actinomycete Streptomyces sp. B6007 makes the chemicals (R)-10-methyl-6-undecanolide and (6R, 10S)-10-methyl-6-dodecanolide when it is extracted using ethyl acetate. This species inhabits Papua New Guinea mangroves. The chemical (6R, 10S)-10-methyl-6-dodecanolide works well against HepG2 liver cancer cells, MCF-7 breast cancer cells and HM02 stomach cancer cells.[26]

Chinikomycin A's quinone form was isolated from Jiaozhou Bay silt-found Streptomyces sp. M045. The study identified Chinikomycins A and B. Chinikomycins A and B had moderate anticancer activity. Chinomycin A selectively reduced breast cancer MAXF 401NL cell proliferation with an IC50 value of 2.41 µg/ml. It also suppressed melanoma MEXF 462NL and renal cancer RXF 944L cell proliferation. Chimiciomycin B inhibits the proliferation of breast cancer cells in MAXF 401NL with an IC50 value of 3.04 µg/ml.[27] The monoterpene-alkaloid skeleton of S. sioyaensis SA1758 was isolated from coastal mud in Gamo, Miyagi Prefecture, Japan and produces altemicidin. The chemical significantly reduced the growth of murine lymphoid leukemia L1210 and carcinoma IMC cell lines, with IC50 values of 0.84 and 0.82 µg/ml, respectively. It was acutely poisonous to mice (Table 1).[28]

Sediments gathered in the Bay of Bengal were used to isolate Actinobacterium sp. MS1/7. The chemicals 4a, 8a-dimethyl-6-(2-methyl-propenyloxy)-3, 4, 4a, 4b, 5, 6, 8a and 9-octahydro-1H-phenanthren-2-one are thought to originate from this bacteria. This substance suppressed the human leukemia HL-60 cell line's growth by 54% at 0.05 µg/ml. Merely 2.3% of mouse and 1.6% of human erythrocytes were killed at 35–40 µg/ml, suggesting minimal toxicity to non-tumor cells.[29]

ANTICANCER COMPOUNDS FROM TERRESTRIAL ACTINOMYCETES

One gram of soil contains one billion microbial cells and thousands of bacteria species. Actinomycetes boost biodiversity. The majority of actinobacteria in this ecosystem are actinomycetes (90%). The soil ecosystem can store anti-cancer compounds from terrestrial actinobacteria.[30] Table 2 summarizes some important substances in this review. Different Streptomyces strains have yielded many tumor-fighting compounds. Streptomyces sp. KML-2 generated chromomycin SA and 1-(1H-indol-3-yl)-propane-1, 2, 3-triol. When given to MCF-7 and HeLa cancer cells, these compounds dramatically limit tumor growth. HeLa's IC50 values are

7.8 and 8.9 µg ml−1, while MCF-7's are 0.97 and 12.6.[31] Benzoxazole from Streptomyces sp. soil has been demonstrated to inhibit AGS, MCF-7 and HepG2 cell growth. In order, the IC50 values for these cell lines were 0.06, 0.68 and 0.4 µg/ml.[32] Di-(2-ethylhexyl) phthalate from Streptomyces mirabilis NSQu-25 has been shown to fight cancer in HepG2, HCT 116 and MCF-7 cell lines, which are linked to liver, colon and breast cancer, respectively. Cell line growth was inhibited at IC50 values of 6.941, 9.028 and 3.681 µg ml−1.[33]

One polycyclic molecule generated by the terrestrial actinobacterium *Amycolatopsis sp.* IRD-009 is called pradimicin-IRD. By concentrating on human colon cancer cell lines that frequently had mutations in TP53 and KRAS, the chemical showed anti-cancer properties against colon cancer. All malignant fibroblasts were extremely susceptible to the pradimicin-IRD combination, in contrast to non-cancerous fibroblasts.[34,35] Sekgranaticin, granaticins A, B and methyl granaticinate were extracted from soil containing Streptomyces sp. 166 that was discovered in the Tibetan mountains of China. The cytotoxicity of the compounds against HCT-116 cell lines of colon, breast and lung cancer was assessed.[36]

Streptomyces sp. KCB13F030, a terrestrial actinomycetes, produced three novel glycoside chemicals. Among the chemicals are 2-methylaminobenzoyl 6-deoxy-α-l-talopyranoside, ulleungoside and naphthomycinoside. Uleungoside showed notable cytotoxicity with an IC50 value of 9.3 µM against multiple cancer cell lines, including SW480.[37] The terrestrial Streptomyces sp. NEAU-L3 produces tetracenoquinocin A, an anthracycline metabolite. Three cancer cell lines from humans liver, lung and colon were employed to assess its cytotoxicity. The HCT-116 colon cancer cell line was subjected to significant cytotoxicity from the chemical (IC50=20.82 µM).[38]

ANTICANCER COMPOUNDS FROM ENDOPHYTIC ACTINOMYCETES

Endophytic actinomycetes, which are considered emerging reservoirs of bioactive compounds, have garnered significant interest over the years. Several publications have shown that endophytic streptomycetes can produce chemicals with strong anticancer characteristics that have the potential to be turned into chemotherapeutic medicines.[39] This distinct category of actinomycetes has demonstrated significant potential for generating a broad spectrum of secondary chemicals with varied biological characteristics.

Scientists have found more than 200 new bioactive secondary metabolites from this group of bacteria. These have a lot of different chemical structures, but most of them are alkaloids, polyketides, flavonoids and terpenoids.[39] This review discusses several significant compounds derived from endophytic actinomycetes. New glycosylated piericidin compounds were discovered upon the isolation of Streptomyces sp. KIB-H1083 from the traditional medicinal plant *Diaphasiastrum veitchii*. Several cell lines, including HL-60, SMMC-7721, A-549 and MCF-7, were subjected to the cytotoxic effects of this drug. It exhibited the least potency against the SW480 CRC cell line, with an IC50 value of 32.59 µM.[39] One naturally occurring compound is 2, 3-dihydro-2, 2-dimethyl-4 (1H)-quinazolinone, which is produced by the endophytic bacteria Streptomyces sp. (Table 3).

Moreover, cardamine is not produced by the *Streptomyces cattleya* isolate that is obtained from the Brazilian plant *Lychnophora ericoides*. Significant cytotoxicity has been shown by these substances against a number of cell lines, including SF-295, MDA-MB435, HL-60 and HCT-8. In particular, 1.10 µg/mL was shown to have the IC50 value for the HCT-8 colon cancer cell line.[40]

Misamycin is an anthracycline-class chemical produced by the endophyte Streptomyces sp. YIM66403, which was isolated from the root of the traditional Chinese medicinal plant *Isodon eriocalyx*. Moreover, a variety of human cancer cell types have been demonstrated to be effectively destroyed by the chemical, with the colorectal cancer cell line SW4801 having an IC50 value of 9.75 µM.[41]

FDA APPROVED DRUGS OF ACTINOMYCETES

The primary natural compound synthesizers of β-lactones are actinomycetes, although they are also present in higher plants and mammals. Four members make up heterocycles called β-lactones, which are highly reactive. They have a tendency to undergo nucleophilic assault by serine, threonine or cysteine residues.

As a result, the creation of stable covalent adducts with -lactones can easily inhibit enzymes that have these activated catalytic nucleophiles. Lipases and proteases are the specific targets of β-lactones. Currently orlistat is the sole β-lactone molecule derived from lipstatin that has been successfully introduced into the pharmaceutical market. A terrestrial Streptomyces strain's extracts yielded lipstatin, which showed a potent inhibitory effect on pancreatic lipase. A saturated derivative of lipstatin orlistat is an anti-obesity drug that is marketed under the name Xenical.[42]

Midostaurin

The source of midostaurin was an isolated marine actinomycetes. This multitarget kinase inhibitor is used to treat adult patients with newly diagnosed acute myeloid leukemia (AML) who have the FLT3 genetic mutation. Initially, it was identified as a possible wide-ranging antineoplastic drug capable of targeting several types of solid and hematopoietic malignancies. Approved on April 28, 2017, this treatment has demonstrated an improvement in the overall survival rate of patients with AML when used in conjunction with chemotherapeutic drugs.[41,43,44]

Mitomycin C

Japanese microbiologists first discovered mitomycin, an antineoplastic antibiotic, from cultures of *Streptomyces caespitosus* in the 1950s. Mitomycin's unique mechanism of action has made it a valuable tool in cancer treatment, particularly in the management of certain types of solid tumors. It has been demonstrated that it can effectively stop the development and division of cancer cells by interfering with the synthesis of DNA and inhibiting the production of RNA and proteins. As a result, mitomycin has been utilized in combination with additional chemotherapy medications to increase their efficacy and improve patient outcomes.

Mitomycin is approved to treat a number of malignancies, including neoplasms of the gastrointestinal tract, bladder and breast, including colon cancer. It was also authorized for use in April 2020 in cases of LG-UTUC or low-grade upper tract urothelial carcinoma. Because of its cross-linking properties, it is also employed as an adjuvant in procedures for ab externo glaucoma. In one notable study, the effects of irinotecan and mitomycin C together were investigated in the treatment of colorectal cancer. This combination therapy yielded highly favorable outcomes and was well-tolerated, as seen by other trials.[45,46]

Salinomycin

Salinomycin is synthesized by Streptomyces albus. Being over one hundred times more effective than paclitaxel, a medication that is frequently used to treat breast cancer makes it a special anti-cancer agent. Later studies going in this direction show strong evidence that salinomycin has an effect on cancer stem cells (CSCs) of different types of cancer cells and also works to eliminate cancer cells' resistance to chemotherapy. These data suggest that salinomycin has great potential as an effective medicine for preventing and treating cancer.[47-49]

Doxorubicin

Doxorubicin (DXR), commonly known as adriamycin, is an anthracycline chemical derived from Streptomyces peucetius. This is an oncology drug employed for the treatment of cancer. These diseases include acute lymphoma, Kaposi's sarcoma, lymphocytic leukemia, breast cancer and bladder cancer. It is commonly used in combination with several chemotherapeutic medications. Doxorubicin is administered intravenously. Doxorubicin pegylated liposomal, marketed as Caelyx, is expressly prescribed by doctors in the European Union to treat AIDS-related Kaposi's sarcoma, breast cancer and ovarian cancer.

Bortezomib is recommended as part of a combination therapy for multiple myeloma. When combined with cyclophosphamide, doxorubicin hydrochloride, also known as Myocet liposomal, is indicated for the treatment of breast cancer.[50] Doxorubicin interferes with the synthesis of macromolecules by intercalating with DNA. This inhibits topoisomerase II, an enzyme that unravels tightly wrapped DNA to enable transcription. Doxorubicin inhibits the release of the DNA double helix by stabilizing the topoisomerase II complex. The compound has already broken the DNA chain, allowing for copying. This effectively puts an end to the replicating process.[51,52]

Everolimus

Everolimus is a compound derived from sirolimus, which is a type of macrocyclic lactone. Sirolimus was first discovered in *Streptomyces hygroscopicus*. Everolimus decreases the occurrence of acute and chronic rejection in individuals who have received kidney or heart transplants. When treating colorectal cancer that has metastasized to other parts of the body, the combination of everolimus and medications such as bevacizumab and mFOLFOX-6 has proven to be highly successful. These findings have been observed throughout the clinical trial phase.[53,54]

Paclitaxel

Paclitaxel is a widely recognized chemotherapeutic drug that has a distinct method of action against cancer. It is widely regarded as one of the most efficacious natural anticancer medications now accessible.[55] *Kitasatospora sp* an endophytic actinomycete that was isolated from *Taxus baccata*, was used to make the medicine. Breast cancer, bladder squamous cell carcinoma and colorectal cancer have all been treated extensively using paclitaxel. It has also been used to treat diseases like AIDS, head and neck malignancies and small-cell and non-small-cell lung carcinomas.[56] Paclitaxel has the unusual capacity to induce tubulin assembly into microtubules and impede their disintegration, in contrast to other anticancer medicines that bind to tubulin. This activity significantly reduces cancer cell proliferation while also inhibiting mitosis and cell cycle progression.[55] It is also used to treat axon regeneration, inflammation, renal and hepatic fibrosis, skin conditions and coronary heart disease. Moreover, scientific trials exploring its potential for treating degenerative neurological disorders are presently being conducted.[57]

Sirolimus

Sirolimus, also referred to as rapamycin, is an antibiotic of the macrocyclic lactone class. Its source is the soil in the Vai Atari region of Rapa Nui, which was found to contain *Streptomyces hygroscopicus* (Easter Island).[58] Initially, it was isolated and recognized as a powerful antifungal substance that effectively combats candida infections. However, subsequent research revealed its remarkable abilities to suppress tumors and the immune system, leading to intensive investigations as an immunosuppressive and anticancer agent.[59] Its primary function is to inhibit the mammalian target of rapamycin (mTOR), a protein kinase that regulates cell proliferation, survival and growth. Since mTOR has been shown to

regulate longevity and maintain appropriate glucose balance, it is an important therapeutic target for a variety of ailments. The targeting of mTOR has garnered significant attention, particularly in the field of cancer research, due to the constitutive activation of mTOR signalling pathways in several forms of human cancer.[60]

The derivatives of this substance have the ability to effectively address a diverse array of medical conditions, including diabetes, tuberous sclerosis, neurodegenerative disorders and various others. In addition to its therapeutic effects, this chemical has also been shown to possess anti-CRC capabilities.[60]

Table 1: Anticancer compounds from marine derived actinobacteria.

S. no.	Compound	Organism	Activity	Reference
1	Arenicolide	*Salinispora arenicola*	Human colon	Wu et al[23]
2	Chalcomycin	*Streptomyces sp*	Human cervix carcinomo	Gupta et al[24], Ward et al[25]
3	(R)- 10, methyl 6 undercanolide, Chartreusin	*Streptomyces sp*	Gastric adenocarcinoma Heptocarcinomo, Breast cancer	Stritzke et al[26]
4	Chinikomycin	*Streptomyces sp*	Mammary cancer and renal cancer	Li et al[27]
5	Altemicidin	*S. sioyaensis*	Murine lymphoid leukemia and carcinoma cell line	Takahashi et al[28]

Table 2: Anticancer compounds from terrestrial actinobacteria.

S. no.	Compound	Organism	Activity	Reference
1	1 - (1H – indol -3 –yl – propane -12, 3 – triol, Chromomycin SA	*Streptomyces sp.*	HeLa cancer	Aftab et al[29]
2	Benzoxazole	*Streptomyces sp.*	Gastric adenocarcinoma MCF-7, HepG2	Sommer et al [30]
3	Di – (2- ethylhexyl) phthalate	*S. mirabilis*	MCF -7, HepG2, human colon carcinoma cell line, HCT116	EI – Sayed et al[31]
4	Pradicimin	*Amycolatopsis sp*	Human colon cancer	Bauermeister et al[32], Almeida et al[33]
5	Sekgranatic granaticins A, B Methyl granticinate	*Streptomyces sp.*	Lung cancer, breast cancer, colon cancer	Lv et al[34]
6	Ulleungoside, 2 methylaminobenzoyl 6-deoxy-α-l-talopyranoside, naphthomycinoside	*Streptomyces sp.*	Several cancer cell lines	Son et al[35]
7	Tetracenoquinocin A, Anthracycline	*Streptomyces sp.*	Lung cancer, liver cancer, human cancer, colon cancer	Lu et al[36]

Table 3: Anticancer compounds from endophytic actinobacteria.

S. no.	Compound	Organism	Plant source	Activity	Reference
1	Pipericidins	*Streptomyces* sp.	*Diaphasiastrum veitchii*	HL–60, SMMC -772, MCF-7	Shang et al[37]
2	2, 3-dihydro-2, 2-dimethyl-4 (1H)-quinazolinone	*Streptomyces* sp.	Brazilian plant *Lychnophora ericoides*	Colon cancer	Conti et al[38]
3	Nocardamine	*S. cattleya*	Brazilian plant *Lychnophora ericoides*	Colon cancer	Conti et al[38]
4	Misamycin	*Streptomyces* sp.	*Isodon eriocalyx*	Several human cancer cell line colorectal cancer cell line	Li et al[39]

CONCLUSION

This review offers a thorough examination of the current body of information regarding the biology of the phylum Actinobacteria and the applications of its components in various cancer forms. Actinomycetes, particularly Streptomyces, have attracted a lot of attention in the last 70 years because of their remarkable ability to synthesize a wide range of bioactive chemicals, including anticancer drugs. Moreover, comprehending the biosynthetic routes of these established drugs might offer valuable insight into their mechanisms of action and potential targets for pharmaceutical development. Also, finding new biosynthetic gene clusters can make it possible to make one-of-a-kind molecules with different shapes and functions, which increases the number of possible cancer treatment options.

Compounds produced from Actinomycetes have demonstrated encouraging outcomes in the treatment of cancer, either as alone therapies or in combination with other medicines. Combination therapy is a widely used strategy in cancer treatment that aims to improve treatment efficacy, mitigate medication resistance and limit adverse effects. Compounds originating from actinomycetes, due to their varied structures and modes of action, can serve as valuable elements in combination therapy protocols for cancer.

Future research on actinomycetes medications in combination with other commercially available medications will be required. The advancement of more specialized and patient-specific cancer therapeutic options may be facilitated by this research. Furthermore, doing research on the substances derived from actinomycetes when combined with existing treatments can provide insights into their synergistic effects and enhance patient results.

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