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Actinomycetes And Their Medicinal Properties

Munashe Nigel Kashitigu[a], Aditya Prakash Sahu[a], Suchitra Ku Panigrahy[a]

[a]Department of Biotechnology, Faculty of Science, Kalinga University, Raipur-492101, Chhattisgarh, INDIA.

Abstract

Actinomycetes are a diverse group of Gram-positive bacteria known for their ability to produce a wide variety of bioactive secondary metabolites with significant medicinal properties. These microorganisms play a critical role in the development of antibiotics, anticancer agents, immunosuppressants, antioxidants, and anti-inflammatory compounds. Notably, Actinomycetes such as *Streptomyces* species have been the source of life-saving antibiotics like streptomycin, erythromycin, and vancomycin, which have revolutionized the treatment of infectious diseases. The ecological and evolutionary significance of Actinomycetes in producing these bioactive compounds for survival and competition further underscores their importance. Despite these advances made, several challenges such as difficulties in culturing, the rise of antibiotic resistance, and limited exploration of Actinomycetes in understudied environments limits its widespread use. This paper delves into the various therapeutic compounds produced by Actinomycetes, ranging from anticancer drugs like doxorubicin and bleomycin to immunosuppressants like rapamycin, demonstrate the far-reaching implications of Actinomycetes in modern medicine. A future research direction includes exploration of the underexplored species, optimizing metabolite production, and developing combination therapies. Overall, Actinomycetes remain an invaluable resource for combating emerging health challenges, and continued investment in research and innovation is essential to harness their full potential for medical and industrial applications.

Keywords: Actinomycetes; Medical; Industrial; cancer; diabetes

1. Introduction

Natural products have been used to treat diseases for thousands of years, and have been useful sources of bioactive compounds in the pharmaceutical industry as a leading compound for drug discovery (Kang, 2019; panigrahy et al. 2019).

Actinomycetes are a diverse group of Gram-positive, filamentous bacteria, that have long been recognized as one of the most prolific sources of bioactive secondary metabolites. These (Zhou, 2020) microorganisms, which inhabit a wide range of environments from nutrient-rich soils to extreme habitats, have played a pivotal role in the development of modern medicine. The discovery of key antibiotics such as streptomycin not only revolutionized the treatment of bacterial infections but also underscored the immense therapeutic potential embedded within these organisms (Chater, 2017). Over the decades, these bacteria have been credited with producing over 70% of naturally derived antibiotics, demonstrating their unparalleled capacity to generate potent bioactive compounds (Smith, 2021;Olano 2014). Their role extends beyond antimicrobials, as actinomycetes have also yielded compounds with antifungal, anticancer, and immunosuppressive properties, making them indispensable in the fight against a myriad of diseases (Singh 2020).

Actinomycetes can be used as a template for synthesising new drugs to treat complex diseases. Actinomycetes (Actinobacteria) have been widely researched for their application within the biotechnology and pharmaceutical industry and they have been found to have a wide range of potential with the antimicrobial, anticancer, antiviral, and anti-inflammatory activities. Thus, according to (Berdy, 2017) exploring natural sources like actinomycetes, renowned for their ability to produce diverse bioactive compounds, offers a promising avenue for developing novel drugs to safeguard human life and improve global health outcomes.

1.1. Taxonomy and diversity of Actinomycetes

Actinomycetes belong to the order Actinomycetales and are characterized by their filamentous, branching morphology, which often causes them to be mistaken for fungi (O'Brien, 2019). They are ubiquitous, thriving in diverse ecological niches including soils, marine environments, and even extreme habitats such as deserts and high-altitude regions. This wide distribution contributes to their vast genetic diversity and metabolic versatility (Doe, 2020). Environmental pressures in these varied habitats drive the evolution of unique biosynthetic pathways, enabling actinomycetes to produce an extensive spectrum of secondary metabolites with diverse chemical structures and biological activities.

1.3. Biology of Actinomycetes

Actinomycetes, members of the Actinomycetales order within the phylum Actinobacteria, are a diverse group of Gram-positive bacteria characterized by their high guanine-cytosine content and varied morphologies. They inhabit a wide range of environments from alkaline, organic-rich soils to aquatic and even saline habitats (Zhao, 2019). Morphologically, these organisms display significant variation, some adopt a coccoid or rod-like shape, while others, such as species in the Streptomyces genus, form a

complex branched mycelium. Genetically, the capacity of actinomycetes to produce bioactive secondary metabolites is encoded within their genomes in long operons, which include both coding and regulatory sequences. These gene clusters, which orchestrate the synthesis, modification and export of various compounds, are highly responsive to environmental cues like nutrient levels, the presence of competing microorganisms, and overall cell density (Horsburgh, 2017).

Beyond their well-known role in producing antibiotics, actinomycete metabolites serve multiple ecological functions. Although traditionally viewed as antimicrobial agents that kill competing bacteria, these molecules also act as signalling compounds, modulate biofilm formation, and can influence gene expression within both the producer and neighbouring organisms (Goh, 2020). This multifunctionality is particularly evident in soil ecosystems, where many actinomycete-derived antibiotics have been isolated from environments with intense microbial competition. Such compounds not only provide a competitive edge by suppressing rival species but also contribute to the complex communication networks that shape microbial communities (Challis, 2018).

1.2. Biosynthetic capabilities and mechanisms

The extraordinary biosynthetic potential of actinomycetes is largely attributed to their complex enzymatic systems, particularly polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPS). These multi-modular enzymes are capable of assembling intricate molecules that serve as antibiotics, antifungals, anticancer agents, and immunosuppressants (Liu, 2018). Many actinomycete biosynthetic gene clusters remain “cryptic” or silent under standard laboratory conditions, representing an untapped reservoir of novel compounds. Recent advancements in genomic and metabolomic technologies, alongside synthetic biology tools such as CRISPR-Cas9, are now being employed to activate these silent pathways, thereby expanding our understanding and utilization of actinomycete-derived metabolites (Katz, 2016).

Combining historical knowledge, cutting-edge genomics, and innovative culturing approaches has unveiled new avenues of their medicinal potential. This review examines the extensive research on actinomycetes, addresses current challenges in leveraging their biosynthetic capabilities, and outlines future directions for discovering next-generation therapeutics.

This chemical diversity arises from their complex biosynthetic pathways, which are orchestrated by multi-modular enzymes such as polyketide synthases and non-ribosomal peptide synthetases. These pathways are often conserved among different genera, underscoring the evolutionary significance of their metabolic strategies. The broad spectrum of compounds produced by actinomycetes remains an important tool in addressing contemporary medical challenges, especially as novel drug-resistant pathogens emerge (Baltz, 2018).

2. Medicinal Properties and Therapeutic Applications

The contribution of actinomycete to antibiotic development has been the cornerstone of modern antimicrobial therapy, addressing life-threatening bacterial infections (Bérdy, 2012). Moreover, emerging research suggests that actinomycete-derived metabolites may offer novel therapeutic avenues for managing chronic conditions, such as diabetes and inflammatory disorders, through mechanisms involving antioxidant and anti-inflammatory effects.

2.1. Actinomycetes as a source of antibiotics

The discovery and development of antibiotics marked a turning point in modern medicine, fundamentally altering the treatment of bacterial infections. Before the clinical use of antibiotics, diseases such as pneumonia, typhoid fever, and gonorrhea were often fatal due to the lack of effective therapies.

Early research in antibiotics established that natural products derived from microorganisms could be harnessed to treat infectious diseases (Rein, 2019;Ghosh 2020). The pioneering work in the mid-20th century led to the discovery of many antibiotics, predominantly from actinomycetes, a group of Gram-positive, filamentous bacteria. These organisms became renowned for producing a vast array of secondary metabolites, with over 70% of naturally derived antibiotics originating from this group (Zhang, 2019). Their ability to generate structurally diverse molecules not only revolutionized clinical treatments but also spurred extensive research into their potential as a source of new therapeutic agents (Zhu, 2021).

. The antibiotics produced by Actinomycetes target specific prokaryotic systems, such as cell wall biosynthesis, protein synthesis, and DNA replication, while sparing eukaryotic cells. This specificity is due to the structural and functional differences between prokaryotic and eukaryotic cells, particularly in key targets like ribosomes, cell walls, and metabolic pathways.

a. Antibiotics from Actinomycetes That Target Ribosomes

Ribosomes, the cellular machinery responsible for protein synthesis, represent a critical target for antibiotics produced by actinomycetes. Notably, bacterial ribosomes are structurally distinct from those of eukaryotes being smaller (70S versus 80S), with differences in their composition and RNA sequences (Harms, 2018). This variation allows antibiotics to selectively target bacterial ribosomes without adversely affecting human cells.

Among the antibiotics produced by actinomycetes, aminoglycosides, such as streptomycin and neomycin, are the key examples. These compounds, primarily synthesized by species like *Streptomyces griseus* and certain *Micromonospora*, function by binding to the 16S rRNA within the 30S subunit. This binding disrupts protein synthesis by causing misreading of mRNA, although bacteria may develop resistance through enzymatic modifications of the drug or by reducing its uptake (Wilson, 2022).

Tetracyclines, including oxytetracycline and chlortetracycline, are another important class produced by actinomycetes such as *Streptomyces aureofaciens* and *Streptomyces rimosus*. These antibiotics act by attaching to the 30S ribosomal subunit, thereby blocking the attachment of tRNA to the ribosome and halting protein production (Wilson, 2022;Wilson 2016). Resistance to tetracyclines can emerge via efflux pumps or the presence of ribosomal protection proteins that interfere with the binding of drug.

Macrolides, like erythromycin and spiramycin, are produced by *Streptomyces erythreus* and *Streptomyces ambofaciens*. They exert their antibacterial effect by binding to the 50S ribosomal subunit, which inhibits the translocation step during protein synthesis. Resistance to macrolides is often due to modifications of the ribosome, such as methylation, or the action of efflux pumps that reduce intracellular drug concentration (Roberts 2016). Similarly, lincosamides, exemplified by lincomycin and its more potent derivative clindamycin from *Streptomyces lincolnensis*, target the 50S subunit and share resistance mechanisms akin to those of macrolides, primarily through ribosomal methylation.

Together, these various classes of ribosome-targeting antibiotics illustrate the sophisticated strategies that actinomycetes employ to disrupt bacterial protein synthesis, highlighting the evolving resistance mechanisms that challenge their clinical efficacy.

b. Actinomycetes breaking down bacterial walls

Cell wall-targeting antibiotics from actinomycetes hit the bacterial cell wall, mainly the peptidoglycan layer causing the cell to burst and die. β-lactams, such as penicillins and cephalosporins, are produced by strains like *Streptomyces clavuligerus* and *Streptomyces cattleya*. They block the transpeptidase enzymes which cross-link the peptidoglycan strands, maintaining the cell wall's strength (Bush, 2019). But, as we know, bacteria can fight back by producing β-lactamase enzymes or by altering their penicillin-binding proteins. On the other hand, glycopeptides like vancomycin, made by *Amycolatopsis orientalis*, bind directly to the D-Ala-D-Ala ends of peptidoglycan precursors, effectively stopping the cell wall from being built. However, some bacteria manage to dodge this attack by changing these D-Ala-D-Ala sequences to D-Ala-D-Lactate, reducing the drug's effectiveness (Reynolds, 2019).

c. Actinomycetes and Their Role in Targeting Bacterial DNA and RNA

Actinomycetes target bacterial DNA and RNA by disrupting essential genetic processes required for survival (Binda, 2020). These antibiotics interfere with key enzymatic activities, ultimately halting bacterial replication and transcription. Antibiotics that target these macromolecules exhibit potent bactericidal effects, making them valuable in treating resistant bacterial infections. Actinomycetes-derived antibiotics such as ansamycins and aminocoumarins exploit vulnerabilities in bacterial nucleic acid metabolism, providing a powerful means of microbial control.

Ansamycins, including rifamycin, are a notable class of DNA and RNA-targeting antibiotics derived from *Amycolatopsis mediterranei* and *Micromonospora* species. These compounds function by inhibiting DNA-dependent RNA polymerase, an enzyme crucial for bacterial transcription. By binding to the β-subunit of RNA polymerase, rifamycin prevents the synthesis of messenger RNA (mRNA),

effectively stopping protein production and leading to bacterial cell death (Surette, 2021). However, resistance can arise through mutations in the RNA polymerase gene, altering the binding site and reducing the antibiotic's effectiveness. Despite this challenge, rifamycin and its derivatives remain widely used, particularly in treating tuberculosis and other mycobacterial infections.

Aminocoumarins, another class of DNA-targeting antibiotics, include novobiocin, which is produced by *Streptomyces niveus* and *Streptomyces spheroids* act by inhibiting DNA gyrase, which maintains DNA supercoiling during replication. Without proper supercoiling, bacterial DNA becomes dysfunctional, leading to replication failure and cell death (Schmutz, 2003).

2.2. Antidiabetic Potential of Actinomycetes

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to either insufficient insulin production (Type 1 diabetes) or insulin resistance (Type 2 diabetes). The increasing global prevalence of diabetes has driven extensive research into novel therapeutic agents, particularly from natural sources (Panigrahy et al.2023) Actinomycetes, a group of filamentous Gram-positive bacteria, have gained significant attention due to their ability to synthesize bioactive secondary metabolites with medicinal properties. Among their many therapeutic potentials, Actinomycetes have demonstrated promising antidiabetic activities by targeting key metabolic pathways associated with glucose homeostasis (Bérdy, 2012; Li, 2023).

These microorganisms produce various compounds that function as alpha-glucosidase inhibitors, alpha-amylase inhibitors, insulin mimetics, antioxidants, and anti-inflammatory agents. Such bioactive molecules have the potential to regulate blood glucose levels, improve insulin sensitivity, and reduce diabetes-associated complications. The discovery and application of these metabolites could contribute to the development of new natural antidiabetic drugs, providing alternative treatment options for patients with diabetes.

a. Alpha-Glucosidase Inhibitors: Regulating Postprandial Glucose Levels

Alpha-glucosidase is a key enzyme located in the small intestine that facilitates the breakdown of complex carbohydrates into simple sugars for absorption into the bloodstream. Inhibiting this enzyme can slow glucose absorption and prevent sudden spikes in blood sugar levels after meals (Singh R. K., 2020). Actinomycetes have been found to produce compounds with alpha-glucosidase inhibitory properties, functioning similarly to commercially available drugs like acarbose, voglibose, and miglitol.

In comparison to existing synthetic alpha-amylase inhibitors, natural inhibitors from Actinomycetes exhibit strong potential due to their stability, bioavailability, and reduced toxicity (Zhang M. M., 2019). These inhibitors not only help in glucose regulation but also have additional health benefits, such as improving gut microbiota balance and promoting metabolic health.

Several species within the *Streptomyces* genus have been identified as producers of alpha-glucosidase inhibitors. These natural inhibitors have shown comparable or superior activity to synthetic drugs,

making them potential candidates for diabetes treatment. The inhibition of alpha-glucosidase effectively reduces the glycemic index of carbohydrate-rich foods, improving glucose control in diabetic individuals. Moreover, these natural inhibitors have fewer reported side effects compared to synthetic drugs, which often cause gastrointestinal discomfort (Gupta, 2020).

Actinomycetes, particularly *Actinoplanes* species, are also known to produce acarbose-like molecules,

b. Alpha-Amylase Inhibitors: Slowing Starch Digestion

Alpha-amylase is another crucial enzyme involved in carbohydrate metabolism, breaking down starch into maltose and glucose for absorption. Inhibiting this enzyme helps slow down glucose release, preventing sharp increase in blood sugar levels. *Actinoplanes* and *Streptomyces* species have been reported to produce bioactive compounds with alpha-amylase inhibitory effects. These metabolites interfere with starch digestion, delaying glucose absorption and helping maintain stable blood sugar levels (Kumar, 2019).

2.3. Anticancer Agents from Actinomycetes

Actinomycetes are a remarkable source of bioactive compounds with medicinal properties, particularly in the field of cancer treatment. These bacteria produce several potent anticancer agents, with doxorubicin and bleomycin being among the most well-known and widely used. Both of these compounds are derived from species of *Streptomyces*, a genus that has proven to be invaluable in the development of cancer therapies. The biosynthetic pathways responsible for the production of these drugs are highly complex, involving intricate enzymatic processes that convert simple precursors into bioactive molecules capable of inhibiting cancer cell growth (Bérdy, 2016).

Doxorubicin, produced by *Streptomyces peucetius*, is synthesized via a polyketide biosynthetic pathway, a process that assembles its structure by linking acetate and propionate units into a complex polycyclic ring system (Zhang M. M., 2019). The biosynthetic pathway begins with the *deoxysugar transferase* enzyme, which plays a pivotal role in forming the anthracycline structure that is critical for the drug's anticancer activity. The final molecule is further modified through the addition of sugar groups, which enhance its stability and allow it to intercalate into the DNA of tumor cells. By inserting itself between DNA base pairs, doxorubicin disrupts the DNA’s double helix, leading to DNA damage that prevents replication and transcription (Hertweck, 2016). Additionally, doxorubicin induces oxidative stress, producing reactive oxygen species (ROS) that exacerbate the damage to cancer cells, ultimately resulting in cell death. The biosynthetic pathway behind doxorubicin is essential for its effectiveness as it enables the production of this highly specific and potent anticancer agent.

Similarly, bleomycin, derived from *Streptomyces verticillus*, follows a non-ribosomal peptide synthetase (NRPS) pathway for its biosynthesis. This pathway is unique because it assembles the compound without the involvement of ribosomes, using a series of highly specialized enzymes. The final product, bleomycin, is a glycopeptide antibiotic that binds to DNA and causes strand breaks by interacting with oxygen and metal ions, leading to the generation of free radicals that cleave the DNA. These breaks

prevent the cancer cells from replicating and induce apoptosis, or programmed cell death. Bleomycin is particularly effective in treating solid tumors like testicular cancer and Hodgkin's lymphoma (Olano, 2017), though its clinical use is limited due to the risk of lung toxicity. Understanding the biosynthetic pathway of bleomycin provides valuable insights into how such compounds can be optimized for better therapeutic outcomes, minimizing side effects while maximizing efficacy.

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The anticancer potential of Actinomycetes extends beyond doxorubicin and bleomycin. Researchers continue to explore the biosynthetic pathways of various other compounds produced by these microorganisms. Studies from (Bérdy, 2012) are uncovering new bioactive metabolites that show promise as adjuncts to existing treatments or as alternatives with fewer side effects.

2.4. Antioxidant Activity: Combating Oxidative Stress in metabolic disorders

Oxidative stress is a major factor in the development of chronic diseases, including diabetes, cardiovascular diseases, and neurodegenerative conditions like Alzheimer's disease. Chronic diseases generates excess reactive oxygen species (ROS), leading to cellular damage and inflammation (Panigrahy et al. 2017). Actinomycetes have proven to be an abundant source of antioxidant compounds,

including carotenoids, flavonoids, and phenolic compounds, all of which help mitigate the harmful effects of oxidative stress on cells and tissues (Kumar, 2019;singh 2020).

Certain *Streptomyces-derived* metabolites have been reported to exhibit strong antioxidant activities (Zhang M. M., 2019).

Actinomycetes produce a variety of antioxidant compounds, including phenolics, flavonoids, and other redox-active metabolites. These compounds help in neutralizing ROS, thereby protecting cells from oxidative damage. By reducing oxidative stress, Actinomycetes-derived antioxidants contribute to improved beta-cell survival, enhanced insulin sensitivity, and reduced complications in diabetic patients (Lenzen, 2017).

The biosynthesis of carotenoids, such as beta-carotene and lycopene, occurs through the isoprenoid biosynthetic pathway, specifically the mevalonate pathway. In *Streptomyces* species, enzymes like geranylgeranyl pyrophosphate synthase and phytoene synthase play key roles in catalyzing the formation of the isoprenoid precursors, which are then converted into carotenoids. These compounds are known for their potent antioxidant properties, neutralizing free radicals that can cause oxidative damage to cells. Carotenoids are particularly beneficial for protecting the cardiovascular system, as they reduce oxidative stress that leads to the formation of arterial plaques, thereby lowering the risk of heart disease. They also prevent oxidative DNA damage, which has been linked to cancer development (Eggersdorfer, 2018).

Flavonoids and phenolic compounds are produced through the shikimate pathway, a fundamental biochemical pathway in plants and Actinomycetes that leads to the production of aromatic amino acids and their derivatives. The key enzymes involved in the synthesis of flavonoids include chalcone synthase and flavonoid synthase, which catalyze the formation of the basic flavonoid structure, which is later modified into specific antioxidant compounds like quercetin. Quercetin, a widely known flavonoid, has demonstrated strong antioxidant activity, helping to neutralize free radicals and reduce inflammation. Phenolic compounds, which are also derived from the shikimate pathway, are produced by enzymes such as phenylalanine ammonia-lyase. These compounds are crucial for protecting cells from oxidative damage, especially in conditions like diabetes, where oxidative stress contributes to insulin resistance and glucose metabolism impairment (Gupta, 2020).

Antioxidants derived from Actinomycetes also show neuroprotective effects. In diseases like Alzheimer's, where oxidative damage accelerates the degeneration of brain cells, these antioxidants have the potential to slow the progression of the disease. Overall, the antioxidant compounds produced by Actinomycetes provide promising therapeutic avenues for treating oxidative stress-related diseases.

2.8. Enzyme Inhibitors from Actinomycetes

Actinomycetes are also known for producing enzyme inhibitors that target metabolic processes in the body. These inhibitors act on enzymes like proteases and lipases, which are involved in the breakdown

of proteins and fats, respectively. By inhibiting these enzymes, Actinomycetes-derived compounds can help manage conditions such as obesity, diabetes, and hyperlipidemia.

Protease inhibitors, like novobiocin, produced by *Streptomyces niveus*, block the activity of proteases, which regulate protein turnover. By inhibiting protease activity, novobiocin reduces fat accumulation, making it useful in managing obesity (Olano 2014). Similarly, lipase inhibitors prevent the breakdown of fats, helping reduce lipid levels in the blood, which can be beneficial in managing hyperlipidemia and diabetes. The biosynthetic pathways that produce these enzyme inhibitors typically involve non-ribosomal peptide synthetase (NRPS) systems, which assemble the inhibitors into their active forms.

These inhibitors present a valuable opportunity for developing new treatments for metabolic disorders by improving insulin sensitivity, regulating fat metabolism, and reducing the risk of cardiovascular diseases. Actinomycetes-derived enzyme inhibitors could play a key role in combating the growing global health concerns of obesity and diabetes (Yaribeygi H. S., 2020).

4. Current Challenges and future prospectus

Despite these promising advances, challenges persist in fully harnessing the potential of Actinomycetes for drug discovery. Culturing certain Actinomycetes strains in laboratory settings remains difficult, as many species have stringent growth requirements and are not easily cultivated on conventional media. Furthermore, the rise of antibiotic resistance poses a significant challenge, as it diminishes the effectiveness of current drugs and necessitates the discovery of new drug targets. Additionally, many Actinomycetes species have yet to be explored, particularly those found in understudied environments like marine ecosystems or extreme habitats, where they may produce unique and unexplored metabolites. Advanced techniques, such as genome mining, metagenomics, and synthetic biology, are essential tools to unlock the full potential of Actinomycetes. These methods can help identify cryptic gene clusters responsible for the production of undiscovered bioactive compounds and optimize the conditions under which these metabolites are produced.

Looking ahead, the future of Actinomycetes research holds vast promise. The exploration of underexplored species and environments for new bioactive compounds is a key priority, as many Actinomycetes strains are still untapped. The integration of genomics and metabolomics will further aid in identifying hidden gene clusters and optimizing the production of valuable metabolites. The development of combination therapies, which leverage multiple Actinomycetes-derived compounds, could enhance the efficacy of treatments, particularly in cancer and infectious disease management. Additionally, Actinomycetes may play a central role in personalized medicine and microbiome-based therapies, where their unique metabolites could be tailored to individual patients. Interdisciplinary approaches, combining expertise in microbiology, chemistry, and bioinformatics, will be key to accelerating drug discovery and ensuring that the full potential of Actinomycetes is realized.

5. Conclusion

Actinomycetes, a diverse group of filamentous bacteria, have long been recognized for their significant role in the production of bioactive secondary metabolites. These microorganisms have shown a remarkable ability to produce a wide array of medicinal compounds with antibiotic, anticancer, antidiabetic, immunosuppressant, and antioxidant properties. Through the intricate biosynthetic pathways involving polyketides, non-ribosomal peptides, and glycosylated compounds, Actinomycetes synthesize complex molecules that are not only critical for their survival but also serve as essential therapeutic agents for humans. The evolution of these pathways highlights their ecological significance, as these metabolites provide a competitive advantage by inhibiting the growth of other microbes and defending against environmental stressors.

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