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Cultivation Conditions and Optimization Strategies for Antibiotic-Producing Microorganisms: Focus on Actinomycetes

Tofiq Aliyev, Aysel Memmedova
[1] Aliyev, T. Nakhchivan State University, Azerbaijan. Email: tofiqaliyev3001@gmail.com. ORCID: https://orcid.org/0009-0008-0138-7493
[2] Mammadova, A. T., Master's student in Biotechnology, Nakhchivan State University. Email: mammadliasel011@cloud.com, ORCID: https://orcid.org/0009-0009-4658-5407
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Abstract; Antibiotics remain indispensable for treating bacterial infections, yet accelerating antimicrobial resistance is reducing their clinical effectiveness and increasing the demand for reliable, high-yield production. Because most major antibiotics originate from microbial secondary metabolism, understanding and controlling cultivation conditions is essential for both laboratory reproducibility and industrial-scale fermentation.

This review analyzes cultivation and process factors that determine antibiotic productivity in antibiotic-producing microorganisms, with emphasis on actinomycetes (especially *Streptomyces*). The findings highlight how undefined (complex) media can support growth but reduce comparability, whereas defined media improve control and interpretation of physiological responses. Carbon and nitrogen sources strongly shape pathway activation through catabolite and nitrogen regulation, while pH and temperature influence morphology, enzyme activity, and the timing of entry into idiophase. Evidence also supports roles for lipid and fatty-acid components in selected systems, as well as precursor feeding strategies and feedback inhibition (retroinhibition) that can either enhance or suppress biosynthesis depending on pathway control. Inoculum age, mycelial state, aeration/hydrodynamics, and typical fermentation durations (often multi-day) further determine yield stability.

Optimizing these upstream variables can improve productivity and batch-to-batch reproducibility and supports future research integrating omics-guided optimization and metabolic engineering.

***Keywords**: Actinomycetes; Streptomyces; nutrient medium optimization; secondary metabolism*

1. INTRODUCTION

Antibiotics remain central to modern medicine, yet their effectiveness is increasingly undermined by antimicrobial resistance (AMR). AMR is recognized as a major global health threat that reduces the ability to treat common infections and increases the risk of severe outcomes. Recent global surveillance summaries and fact sheets emphasize that resistance is widespread and rising across multiple pathogen–drug combinations, reinforcing the need for both new antimicrobial agents and more efficient production of existing ones.

Microorganisms are the primary natural source of clinically useful antibiotics. Soil-derived bacteria—especially actinobacteria/actinomycetes (notably *Streptomyces*)—have historically yielded a large share of naturally derived antibiotics, while filamentous fungi and other bacteria also contribute important drug classes. Their metabolic diversity and ecological competitiveness explain why microbial secondary metabolites became foundational to antibacterial therapy.

Antibiotic output is not fixed; it depends strongly on cultivation and bioprocess conditions because many antibiotic pathways are part of secondary metabolism and are tightly regulated. Reviews of *Streptomyces* biology show that antibiotic gene clusters are controlled by complex regulatory networks and respond to nutritional and physiological signals. Consequently, parameters such as carbon and nitrogen sources, pH, precursor supply, aeration/hydrodynamics, and inoculum state can shift metabolism toward or away from productive antibiotic biosynthesis.

This article reviews cultivation conditions for antibiotic-producing microorganisms with emphasis on actinomycetes, synthesizing evidence on (i) defined versus complex media, (ii) carbon–nitrogen balance, (iii) pH and key environmental controls, (iv) precursor feeding and feedback regulation, and (v) inoculum and process monitoring factors that influence productivity. By organizing the literature around controllable variables, the paper aims to support more reproducible laboratory cultivation and more rational optimization for industrial fermentation, thereby contributing to improved yield and consistent production quality.

2. MATERIALS AND METHODS

Methodology of the review

A structured narrative review approach was used. Literature was searched in Scopus, PubMed, Web of Science, and Google Scholar.

Search keywords (examples):
“antibiotic-producing microorganisms”, “actinomycetes” OR “Streptomyces”, “secondary metabolism regulation”, “fermentation medium optimization”, “carbon source regulation”, “nitrogen source”, “pH”, “precursor feeding”, “inoculum”, “submerged aerobic fermentation”.

Inclusion criteria:

- **Time window:** primarily 2000–2026 for reviews and mechanistic studies; older “classic” sources were included when they are foundational to fermentation/secondary-metabolism concepts.
- **Language:** English.
- **Study types:** peer-reviewed reviews, primary experimental studies on cultivation variables and regulation of antibiotic biosynthesis, and (where relevant) authoritative surveillance/position documents on AMR.
- **Exclusion:** non-peer-reviewed items lacking methodological detail; studies not linking cultivation/bioprocess variables to antibiotic yield, regulation, or reproducibility.

Synthesis approach:
Findings were extracted and grouped by controllable variables and their reported effects on production: (1) nutrient medium type (defined vs complex), (2) carbon source and repression, (3) nitrogen source and ammonium effects, (4) pH and environmental parameters, (5) lipid/fatty-acid contributions (where applicable), (6) precursor feeding and feedback inhibition, (7) inoculum physiology and process monitoring, and (8) strain improvement strategies when directly connected to cultivation outcomes.

Reporting guideline (optional but recommended):
Although this is not a full systematic review, the structure of reporting (search description, inclusion

logic, and synthesis transparency) was aligned where practical with PRISMA 2020 principles for clarity and reproducibility.

3. RESULTS OF THE REVIEW

1) Producers and ecological sources

Soil ecosystems are a major reservoir of antibiotic producers, particularly actinomycetes; selective isolation strategies often exploit the ecological advantage and metabolic diversity of these organisms. Many *Streptomyces* species are prolific natural-product producers, which explains their central role in antibiotic discovery and industrial production.

2) Nutrient media: natural vs synthetic (defined)

Early screening and initial production frequently rely on **complex (undefined) media** derived from agricultural materials (e.g., starch products, bran, peptones). These can support robust growth but suffer from **batch-to-batch variability** in composition, which reduces reproducibility and complicates physiological interpretation and scale-up control. In contrast, **defined/synthetic media** improve comparability, mechanistic interpretation, and tighter process control—especially important when optimizing secondary metabolite production.

3) Carbon and nitrogen sources

Carbon source selection is a dominant lever because readily metabolized sugars can trigger **carbon catabolite repression**, delaying or suppressing antibiotic pathways, while slower/alternative carbon sources can favor entry into idiophase. This effect is widely documented in *Streptomyces* regulatory networks.

A specific example reported in *Streptomyces antibioticus* showed that a mixture containing **~0.1% glucose with 1% galactose** supported production behavior consistent with rapid glucose utilization followed by a shift to galactose metabolism, aligning with the broader concept that staged carbon utilization can promote secondary metabolism.

Nitrogen source form and concentration also shape antibiotic output: nitrate salts and other "milder" nitrogen regimes are often used in actinomycete media design, while high ammonium can repress secondary metabolism in many systems (strain-dependent).

4) pH and temperature

Temperature around **~28 °C** is common for many actinomycete fermentations (strain- and product-specific), reflecting their mesophilic physiology and typical industrial practice. pH effects are more nuanced: some processes run near neutral, while selective isolation or specialized groups (including acid-tolerant/acidophilic actinomycetes) can involve **lower pH** to limit competing microbes. Therefore, statements such as "pH 4.0–4.5" should be presented as **context-specific** (e.g., selective isolation or particular strains), not as a universal optimum for all actinomycetes.

5) Lipids and fatty acids

Lipid availability can influence membrane properties and precursor supply for some antibiotic pathways. In cephalosporin-producing fungi (historically *Cephalosporium/Acremonium* systems), supplementation with lipid components (e.g., oleate-related inputs) has been reported to modulate production, consistent with the broader observation that fatty acid metabolism can interact with secondary metabolite yield in certain producers.

6) Amino acids, ammonium regulation, and metabolic control

Nitrogen assimilation routes help explain why ammonium effects can differ by condition. In many microbes, high ammonium can favor assimilation via glutamate dehydrogenase (GDH), while ammonium limitation increases reliance on the GS/GOGAT (glutamine synthetase/glutamate synthase) system. These shifts alter intracellular nitrogen status and can impact regulatory signals that gate secondary metabolism and antibiotic biosynthetic gene expression.

7) Precursors and feedback inhibition (retroinhibition)

Precursor feeding and pathway feedback are central to β-lactam productivity. Penicillin biosynthesis begins with formation of the tripeptide ACV from α-aminoadipate, cysteine, and valine, establishing α-aminoadipate availability as a key node. Classic and modern work also shows lysine-linked feedback control (e.g., via homocitrate synthase regulation) that can indirectly reduce α-aminoadipate flux and thereby constrain penicillin formation.

8) Inoculum and bioprocess control

Inoculum quality (age, physiological state, and morphology) influences downstream fermentation because it shapes growth kinetics, pellet/filament structure, oxygen transfer, and the timing of transition into idiophase. Reviews and process studies emphasize that monitoring and controlling variables related to respiration/oxygen demand, hydrodynamics, and morphology can improve reproducibility and support scale-up. Fermentation durations vary by organism/product, but industrial submerged aerobic antibiotic processes commonly operate across multi-day windows (often about ~5–10 days, depending on the system).

9) Strain improvement approaches

Classical strain improvement remains important in industry: iterative selection, random mutagenesis (e.g., UV or ionizing radiation), and screening can increase yield, and modern approaches add genome-guided strategies (omics, metabolic engineering) to target bottlenecks more precisely. In penicillin systems, for example, omics-era reviews document how genetic and regulatory understanding supports rational improvement beyond purely random mutation.

4. DISCUSSION

Overall, the literature supports a consistent interpretation: antibiotic production is not simply a function of "more growth," but of regulated secondary metabolism that emerges when nutrients, energy status, and global regulators align to activate biosynthetic gene clusters. Carbon and nitrogen are particularly powerful because they control both metabolic flux (precursor supply) and transcriptional programs (catabolite repression, nitrogen repression, stress responses), which jointly determine when and how strongly the idiophase begins.

From an industrial viewpoint, reproducibility and scale-up are often limited by variability in complex raw materials and by morphology-dependent oxygen transfer. Moving from undefined to more controlled media components, documenting raw material quality, and measuring physiological proxies (e.g., OUR/CER, off-gas analytics) can reduce batch failures and improve comparability across labs and production sites.

The nitrogen-control findings also explain why "more nitrogen" can paradoxically reduce yields: ammonium assimilation strategy, intracellular nitrogen signaling, and downstream repression mechanisms can shift the cell away from antibiotic pathway commitment. Similarly, precursor feeding can help only when it respects pathway control logic—otherwise feedback inhibition or pathway imbalance can negate the intended benefit.

Finally, connecting production to the resistance context: improving yields and process robustness can support better access and reduce shortages, but it does not substitute for stewardship. Higher productivity is most valuable when coupled with (i) responsible clinical use, (ii) quality-assured manufacturing, and (iii) continued discovery of new scaffolds/strains to stay ahead of resistance trends.

Downstream formulation innovations: liposomal anti-infectives

Liposomal delivery can improve pharmacology by increasing stability, changing tissue distribution, and reducing toxicity for certain agents. A well-known example is liposomal amphotericin B, which has a substantially improved toxicity profile compared with conventional amphotericin B formulations.

For antibacterial therapy, liposomal amikacin for inhalation is an approved/regulated product in some regions (e.g., ARIKAYCE liposomal), illustrating that liposomes can be clinically feasible for targeted delivery where conventional dosing is limited by toxicity or distribution.

However, liposomal products are not "simple substitutions": small differences in liposome composition and physical properties can alter performance, creating manufacturing, comparability, and regulatory challenges. This is why regulators explicitly warn against substituting liposomal formulations without demonstrating equivalence.

5. CONCLUSION

Cultivation optimization is a primary driver of antibiotic productivity because it governs the timing and intensity of secondary metabolism through media composition, carbon/nitrogen regulation, pH/temperature, precursor availability, and inoculum physiology.
For industry, reproducible yields depend on controlled media inputs, morphology-aware oxygen transfer, and monitoring strategies that track physiological state—not just biomass.
Future work should prioritize (1) omics-guided optimization to identify bottlenecks, (2) metabolic engineering paired with robust bioprocess control, and (3) standardized reporting of media/raw-material variability and key control parameters to improve comparability and scale-up success.

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