Biological inducers as regulators of secondary metabolite biosynthesis in actinobacteria

Anastasiia Okhmakevych[1], Tetiana Pirog[1,2]

1 – National University of Food Technologies, Kyiv, Ukraine
2 – Institute of Microbiology and Virology, National Academy of Sciences of Ukraine, Kyiv, Ukraine

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Corresponding author:

Tetiana Pirog
E-mail: tapirog@nuft.edu.ua

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Abstract

Introduction. The aim of this review is to summarise available information on secondary metabolite production by actinobacteria in the presence of biological inducers in culture media.

Materials and methods. A systematic search of scientific publications was conducted, primarily using PubMed and Google Scholar, to identify studies on the cultivation of actinobacteria in the presence of biological inducers from the earliest available reports up to 2025.

Results and discussion. With the development of biotechnology, unconventional methods of cultivating producers alongside other microorganisms or inducers are attracting increasing attention. Cultivating actinobacteria with biological inducers can lead to increased concentration and/or activity of synthesised secondary metabolites, as well as to the production of practically valuable metabolites that are not characteristic of monocultures.

Actinobacteria, bacteria, fungi, and yeasts are used as biological inducers, mainly in the form of living cells, although supernatants and inactivated cells are also employed. Among the possible mechanisms of induction, the most commonly highlighted are intercellular interactions between producers and inducers, as well as the effect of inducer signalling molecules on the biosynthesis of secondary metabolites; however, this aspect remains insufficiently studied and requires deeper molecular and physiological investigation.

Actinobacteria are cultivated with inducers in the laboratory mainly in flasks on shakers, although some researchers also use laboratory bioreactors, indicating the potential for process scale-up. Different nutrient media are often applied for the preparation of microbial inocula and for biosynthesis, which requires further optimisation for scaling-up to the industrial level. Not all authors provide a detailed description of preparing inocula of actinobacteria and other microorganisms, which makes it difficult to determine whether the cultivation was indeed performed with an inducer and limits reproducibility of the results. Furthermore, not all studies investigate the biological activity of the secondary metabolites obtained, which requires further study, as the feasibility of their industrial production and their potential practical applications largely depend on this.

Conclusions. The co-cultivation of actinobacteria with biological inducers represents a promising biotechnological strategy for enhancing and diversifying the production of secondary metabolites. However, the underlying mechanisms of induction and intercellular interactions remain insufficiently understood and further study is needed to identify effective inducers and optimise conditions.

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Introduction

Microbial products are increasingly being explored for medical applications, as it has been established that only 0.1–1% of all microorganisms have been successfully cultivated under laboratory conditions, while their diversity remains virtually limitless (Adnani et al., 2017; Alhadrami et al., 2021). Actinobacteria are prolific producers of secondary microbial metabolites and can be classified into members of the genus *Streptomyces* and rare, non-*Streptomyces* actinomycetes, possessing dozens of biosynthetic genes (Hoshino et al., 2018a; Liang et al., 2020). Their metabolic repertoire includes, among others, antibiotics (Boruta et al., 2021; Shamikh et al., 2020), alkaloids (Maglangit et al., 2020; Shamikh et al., 2020), and polyketides (Hoshino et al., 2016; Wang et al., 2014).

A considerable number of valuable microbial metabolites are now known; however, some exhibit low biological activity, occur at low concentrations, or are not synthesised at all under standard laboratory conditions, making it important to explore strategies to overcome these limitations (Maimone et al., 2021).

Conventional approaches to modulating the biosynthesis process include altering the composition of the nutrient media, adjusting temperature and pH (Alam et al., 2022), as well as refining strains through metabolic engineering techniques (Singh et al., 2023). Concurrently, with the advancement of applied biotechnologies, the use of mixed cultures has attracted increasing attention (Khedkar et al., 2025). In our study (Pirog et al., 2023), we have highlighted that the concepts of co-cultivation "with competitive microorganisms" and "with biological inducers" are distinct: in the former, inocula are introduced at nearly equal concentrations, whereas in the latter, the producer is applied at a substantially higher concentration than the inducer. In our previous review (Pirog et al., 2025), we examined the impact of competitive microorganisms on the synthesis of secondary metabolites by actinobacteria; in this review, we focus on the role of biological inducers.

The earliest reports on the impact of biological inducers on the synthesis of secondary metabolites by actinobacteria date back to 2008–2011. Initially, these were sporadic studies (Kurosawa et al., 2008; Onaka et al., 2011); however, in recent years, there has been a noticeable increase in such research (Selegato et al., 2023).

Cultivation of producers of antimicrobial secondary metabolites with competitive microorganisms or inducers may result in (Wang et al., 2021): alterations in metabolite concentration and/or antimicrobial activity; production of metabolites not typically observed in monocultures; or absence of metabolites normally formed in monoculture. Studies (Liang et al., 2020; Song et al., 2020) indicate that producers respond differently to various inducers in the culture media, and no consistent patterns in secondary metabolite formation have been identified, meaning that the induction mechanism underlying co-cultivation remains poorly understood. Furthermore, there is no guarantee that the metabolites obtained will possess the desired biological activity, so each approach to co-cultivating microorganisms or cultivating them with inducers should be thoroughly investigated and analysed.

The aim of this study is to summarise the literature on the biosynthesis of practically important secondary metabolites by actinobacteria in the presence of biological inducers, considering their various physiological states (living cells, inactivated cells, or supernatant).

The objectives of this study are to search for, analyse, and summarise the findings of international colleagues regarding the influence of biological inducers on the synthesis of secondary metabolites by actinobacteria and their biological activity, as well as on the production of metabolites not typically observed in the producer monoculture.

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Materials and methods

A systematic search of scientific publications was conducted, primarily using PubMed and Google Scholar databases, with keywords including "actinobacteria," "secondary metabolites," "co-culture," "inducer," "elisitor," and "microbial interactions." Articles published from 2008 to 2025 were selected. Only studies reporting secondary metabolite production in the presence of biological inducers were included. Relevant studies were summarised and analysed.

Results and discussion

Synthesis of metabolites not characteristic of monocultures

In the available literature, the vast majority of studies on the cultivation of actinobacteria with inducers, resulting in the synthesis of new metabolites, focus on the use of other actinobacteria containing mycolic acids and belonging to the genera *Tsukamurella*, *Rhodococcus*, *Gordonia*, and *Nocardia* (see Table 1).

Table 1

Cultivation of actinobacteria in the presence of inducers: synthesis of metabolites not characteristic of monocultures

Producer + inducer	Synthesised metabolites	Antimicrobial activity	Cytotoxic and other activity	Sources
Inducers - other actinobacteria				
Streptomyces lividans TK23 + *Tsukamurella pulmonis* TP-B0596 (living cells)	Red pigment UPG*	–	–	Onaka et al., 2011
S.coelicolor S522 + *T. pulmonis* TP-B0596 (living cells)	Antibiotic alchivemycin A	MIC (μg/mL) against: *Micrococcus luteus* TP-B100 – 0.06; *Bacillus subtilis* ATCC 6633 – 40; *Staphylococcus aureus* 209P JC-1, *Escherichia coli* NIHJ JC-2, *Candida albicans* TP-F0176 - > 50	–	Onaka et al., 2011
Gordonia sp. KMC005 + *S. tendae* KMC006 (living cells)	Gordonic acid (yellow polyketide glycosid)	GIZ (mm) 10 μg/disc: *M. luteus* KCCM11548 – 2.5; *Enterococcus hirae* KCCM11768 -1.5	–	Park et al., 2017
Umezawaea sp. RD066910 + *T. pulmonis* TP-B0596 (living cells)	Antibiotic umezawamide A	GIZ, 5 μg/disc: *C. albicans* – 1.7 mm; Diameter of GIZ (10 μg/disc): *B. cereus, S. aureus* sensitive to methicillin, *E. coli* (not reported)	–	Hoshino et al., 2018b

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Producer + inducer	Synthesised metabolites	Antimicrobial activity	Cytotoxic and other activity	Sources
	Antibiotic umezawamide B	Diameter of GIZ (10 µg/disc): *C. albicans, B. cereus, S. aureus* sensitive to methicillin, *E. coli* - not reported	–	
Actinosynnema mirum NBRC 14064 + *T. pulmonis* TP-B0596 (living cells)	Antibiotics mirilactams C, D, E	Absence of antimicrobial activity against *C. albicans, B. cereus, S. aureus* sensitive to methicillin (strain numbers not specified)	Cytotoxic activity against cervical cancer, MCF-7 breast cancer, A549 lung cancer cells, starting from 100 µM	Hoshino et al., 2018c
Micromonospora sp. WMMB-235 + *Rhodococcus* sp. WMMA-185 (living cells)	Antibiotic keyicin	Inhibition of growth of *Mycobacterium* sp. WM MB-235, *Rhodococcus* sp. WMMA-185 (degree of inhibition not reported); MIC (µg/mL) against *B. subtilis* – 8; *S. aureus* sensitive to methicillin (strain numbers not specified) - 2	–	Adnani et al., 2015, 2017
Streptomyces nigrescens HEK616 + *T. pulmonis* TP-B0596 (living cells)	Lipidic metabolite SA-9n*	GIZ, mm (30 µg/disc): *B. subtilis* NBRC 3134 – 12; *S. aureus* NBRC 13276 – 10. Growth inhibition zone, mm (100 µg/disc): *E. coli* NBRC 3972 - 10	–	Sugiyama et al., 2016
Streptomyces sp. CJ5 + *T. pulmonis* TP-B0596 (living cells)	Chojalactones A, B and C (butanolides)	Absence of antimicrobial activity against *B. subtilis, S.aureus,* and *C. albicans* (strain numbers not specified)	IC_{50} 18–28 µM Moderate cytotoxic activity against P388 mouse leukemia cells	Hoshino et al., 2015a
Catenuloplanes sp. RD067331 + *T. pulmonis* TP-B0596 (living cells)	*Catenulobactin* A (heterocyclic peptide)	–	Moderate cytotoxic activity against P388 mouse leukemia cells (IC_{50} 22.4 µM)	Hoshino et al., 2018a
	Catenulobactin B (heterocyclic peptide)	–	Cytotoxic activity against P388 mouse leukemia cells ($IC_{50} \geq 100$ µM)	
Streptomyces padanus MITKK-103 + *Rhodococcus fascians* 307 (living cells)	Antibiotic RSM* A	GIZ, mm (30 µg/disc): *S. padanus* MITKK-103 – 15; *E. coli*-8; *S. aureus*-9; *B. subtilis*–8; *Helicobacter pylori* -10	Absence of activity against HL-60 human leukemia cells	Kurosawa et al., 2008; 2010

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Producer + inducer	Synthesised metabolites	Antimicrobial activity	Cytotoxic and other activity	Sources
S. padanus MITKK-103 +*R. fascians* 307 (living cells)	Antibiotic RSM* B	GIZ, mm (30 µg/disc): *S. padanus* MITKK-103 – 18; *E. coli*–12; *S. aureus*-14; *B. subtilis*–14; *H. pylori* -18	Absence of activity against HL-60 human leukemia cells	Kurosawa et al., 2008; Kurosawa et al., 2010
Streptomyces sp. RKND-216 + *Mycobacterium smegmatis* ATCC 12051 (living and inactivated cells)	CBQ* G	Absence of antimicrobial activity against *S. aureus* resistant to methicillin ATCC 33591, *E. faecium* F379 resistant to vancomycin E, *S. warneri* ATCC 17917, *Proteus vulgaris* ATCC 12454, and *C. albicans* ATCC 14035	Selective cytotoxic activity against MCF-7 and HTB26 breast cancer cells (IC_{50} 3.07 and 3.67 µM)	Liang et al., 2020
Streptomyces sp. NZ-6 + *T. pulmonis* TP-B0596 (living cells)	Niizalactams A, B (multicyclic macrolactams)	Absence of GIZ against *C. albicans*, *B. subtilis*, and *Saccharomyces cereviciae*	Absence of activity against P388 mouse leukemia cells	Hoshino et al., 2015b
Streptomyces sp. TAKO-2 + *T. pulmonis* TP-B0596 (living cells)	Aromatic polyketides julichrome Q_6 and julichrome $Q_{8.8}$	–	–	Hoshino et al., 2016
S. nigrescens HEK616 + *T. pulmonis* TP-B0596 (living cells)	Alkaloids 5aTHQs*	MIC (µM) against *Schizosaccharomyces pombe* JY1 – 6.3	–	Sugiyama et al., 2015
Streptomyces sp. KUSC_F05 + *T. pulmonis* TP-B0596 (living cells)	LCA* A-D (cyclic hexapeptides)	MIC (µM) against *B. subtilis* IFO3134 -100; absence of antimicrobial activity against *S. aureus* IFO13276, *E. coli* IFO3972, *Pseudomonas aeruginosa* IFO169	Absence of activity against HT1080 human fibrosarcoma cells at 100 µM	Jiang et al., 2021
Streptomyces cinnamoneus NBRC 13823 + *T. pulmonis* (strain number not specified) (living cells)	*Arcyriaflavin* E (alkaloid)	–	Cytotoxic activity against P388 mouse leukemia cells (IC_{50} 39 µM)	Hoshino et al., 2015c
Micromonospora wenchangensis HEK-797 + *T. pulmonis* TPB0596 (living cells)	Dracolactams A i B (macrolactams)	Absence of antimicrobial activity against *C. albicans*, *B. cereus, S. aureus* resistant to methicillin, *T. pulmonis* (strain numbers not specified)	Absence of activity against P388 mouse leukemia cells	Hoshino et al., 2017

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Producer + inducer	Synthesised metabolites	Antimicrobial activity	Cytotoxic and other activity	Sources
Micromonospora sp. UA17 + *Gordonia* sp. UA19 (living cells)	Complex of metabolites, including piperidine derivative MY 336a, antibiotic *chlorocardicin,* antibiotic WS 5995-A, neocopiamycin A	MIC (µg/mL) against: *S. aureus* NCTC 8325 – 8.6; *Enterococcus faecalis* (strain number not specified) – 7.4; *C. albicans* 5314 – 6.4	Activity against *Trypanosoma brucei* TC221 (MIC > 100 µg/mL)	Shamikh et al., 2020
Micromonospora sp. UA17 + *Nocardia* sp. UA 23 (living cells)	Complex of metabolites, including antibiotic chicamycin B, libramycin-A, alkaloids	MIC (µg/mL) against: *S. aureus* NCTC 8325 – 4.2; *E. faecalis* (strain number not specified) – 3.9; *C. albicans* 5314 – 3.8	Activity against *T. brucei* TC221 (MIC > 100 µg/mL)	
Streptomyces sp. UR23 + *Nocardia* sp. UR27 (living cells)	During growth on ISP2 agar medium: bafilomycins D and A1, aggreceride A, salbostatin During growth in ISP2 liquid medium: lipstatin, trichostatic acid, trichostatin A, terreusinol, platenolide II	–	Activity of metabolites synthesised on agar and in liquid media against *T. brucei* (strain number not specified) (IC_{50} 4.6 and 2.4 µg/mL, respectively)	Gamaleldin et al., 2020
Micromonospora sp. UR17 + *Nocardia* sp. UR27 (living cells)	During growth on ISP2 agar medium: neihumicin, *antascomicins* D and C. During growth in ISP2 liquid medium: geldanamycin, 2-HPAA*, daidzein, GTRI-02	–	Activity of metabolites synthesised on agar and in liquid media against *T. brucei* (IC_{50} 2.7 and 2.5 µg/mL, respectively)	Gamaleldin et al., 2020
Nocardiopsis sp. UR17 + *Nocardia* sp. UR27 (living cells)	During growth on ISP2 agar medium: MPC *, 5-HPA* During growth in ISP2 liquid medium: Forphenicine	–	Activity of metabolites against *T. brucei* (strain number not specified) (IC_{50} ≥ 100 µg/mL)	Gamaleldin et al., 2020

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Producer + inducer	Synthesised metabolites	Antimicrobial activity	Cytotoxic and other activity	Sources
Inducers – other bacteria				
Streptomyces sp. RKND-216 +*Alteromonas* sp. RKMC-009 (living and inactivated cells)	NC-DHBA *	–	Low activity against kidney CCL-81 cells, MCF-7 and HTB26 breast cancer cells, and HCT116 colon cancer cells (IC_{50} ≥ 32 mg/mL)	Liang et al., 2020
Inducers – fungi				
Streptomyces lunalinharesii A54A +*Rhizoctonia solani* (strain number not specified) (living cells)	Complex of new unknown metabolites, including the DFO* siderophores and anisomycin derivatives	Inhibition of growth of *R. solani* (strain number not specified) – 88,43 % (extract concentration 500 mg/µL)	–	Maimone, et al., 2021
Streptomyces sp. CMB-StM0423 + *Aspergillus* sp. CMB-AsM0423 (living cells)	Heronapyrrole B	Diameter of GIZ for *A.* sp. CMB-AsM0423 – not reported	–	Khalil, et al., 2019

Notes: «–» – data not reported; GIZ - growth inhibition zones, **UPG* – undecylprodigiosin; SA-9n - streptoaminal-9n; *RSM – rhodostreptomycin; CBQ – carbazoquinocin;* 5aTHQs - 5-alkyl-1,2,3,4-tetrahydroquinolines; *LCA – longicatenamides;* 2-HPAA - 2-hydroxyphenylacetic acid; MPC - methyl pyrrole-2-carboxylate; 5-HPA – 5-hydroxypicolinic acid; NC-DHBA - N-carbamoyl-2,3-dihydroxybenzamide; DFO – desferrioxamine.

Data from Table 1 also indicate that living cells of other organisms are most commonly employed to induce the synthesis of metabolites not typically observed in monocultures. Liang and co-authors (2020) used living and inactivated cells of *M. smegmatis* ATCC 12051 and *Alteromonas* sp. RKMC-009, and suggested that the presence of inactivated cells in the medium reduces the number of potential secondary metabolites of the inducers that could act as chemical signals on the producer, thereby limiting the induction of new metabolites.

In contrast, when living inducer cells are used, competition for carbon and nitrogen sources in the culture medium occurs, which can act as a trigger for the activation of silent biosynthetic pathways.

Not all authors have described in detail the procedure for introducing the inocula prior to the synthesis of secondary metabolites, which makes it difficult to determine whether the cultivation was carried out with an inducer or with competitive microorganisms. For example, Sugiyama et al. (2015, 2016) do not specify the ratio in which the inocula of *S. nigrescens* HEK616 and *T. pulmonis* TP-B0596 were introduced for the synthesis of the natural lipidic metabolite streptoaminal-9n and 5-alkyl-1,2,3,4-tetrahydroquinoline alkaloids. We consider that in these studies *T. pulmonis* TP-B0596 was used as an inducer, as numerous similar articles report that the inocula of *Tsukamurella* actinobacteria were added in significantly smaller

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amounts than that of the producers. In Liang et al. (2020), the inocula of the producer *Streptomyces* sp. RKND-216 and the inducers *M. smegmatis* ATCC 12051 and *Alteromonas* sp. RKMC-009 were introduced into the medium in equal amounts; however, this also constitutes cultivation with inducers, since the producer was introduced 72 hours earlier, resulting in a higher biomass.

Among the possible mechanisms inducing the synthesis of new metabolites, the following can be distinguished: (1) Mycolic acid stimulating biosynthesis pathways in actinobacteria (Shamikh et al., 2020); (2) Mycolic acid triggering biosynthetic routes in producer strains, alongside intercellular interactions with inducers (Hoshino et al., 2018c; Onaka et al., 2011); (3) Specific inducer compounds acting without direct cellular contact (Adnani et al., 2017; Maimone, et al., 2021); (4) Horizontal transfer of plasmid DNA resulting in formation of recombinant strains (Kurosawa et al., 2010); (5) Modification of precursors of target product biosynthesis by an inducer (Hoshino et al., 2017); (6) Inducer-stimulating NO synthesis, which mediates transcriptional activation of silent gene clusters (Khalil, et al., 2019).

Secondary metabolites of actinobacteria synthesised in the presence of inducers are mostly characterised by antimicrobial activity. These include the antibiotics alchivemycin A (Onaka et al., 2011), keyicin (Adnani et al., 2017), rhodostreptomycins A and B (Kurosawa et al., 2008), complexes of antibiotic-containing (Shamikh et al., 2020) and new unknown metabolites (Maimone et al., 2021), gordonic acid (Park et al., 2017), the lipid metabolite streptoaminal-9n (Sugiyama et al., 2016), alkaloids 5-alkyl-1,2,3,4-tetrahydroquinolines (Sugiyama et al., 2015), and longicatenamides A–D (Jiang et al., 2021). All these compounds showed antimicrobial activity against various pathogens, supported by specific data. Such secondary metabolites can be considered as potential antiseptic agents for pharmacological and medical use.

In some studies (Hoshino et al., 2018b; Khalil et al., 2019), the diameters of the growth inhibition zones for test cultures were not reported, but the authors noted that umezawamides A and B and heronapyrrole B also exhibit antimicrobial activity.

New metabolites of actinobacteria obtained in the presence of inducers in the culture media may also exhibit cytotoxic or anti-trypanosomal activity. The antibiotics mirilactams C, D, and E (Hoshino et al., 2018c), chojalactones A, B, and C (Hoshino et al., 2015a), and carbazoquinocin G (Liang et al., 2020) showed no antimicrobial activity, but displayed cytotoxic effects against cancer cells, making them potential antitumour agents.

The use of different nutrient media for inoculum growth and cultivation may complicate process scaling to an industrial level. For example, in Hoshino et al. (2018b, c), the inocula was grown on A-3M medium, while cultivation was carried out on V-22 medium. In contrast, Park et al. (2017) and Liang et al. (2020) used the same medium for both purposes (YM-liquid and ISP2m, respectively) making the process technologically feasible for industrial-scale production.

Overall, the technology of cultivating actinobacteria with biological inducers to produce new metabolites appears promising for practical applications, but further data and optimisation of the production process are required.

Effect on metabolite synthesis

As a result of cultivating actinobacteria together with inducers, the concentration of synthesised secondary metabolites may also increase. Representatives of the genus *Streptomyces* are most frequently used as producers in such studies, but Ma et al. (2020) also report the cultivation of rare actinomycetes *Rhodococcus equi* CGMCC14861 together with a prokaryotic inducer. Biological inducers include living cells (Sharma et al., 2017; Yu et al.,

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2015), supernatant (Ma et al., 2020; Shi et al., 2017), and inactivated cells (Song et al., 2020). In Wang et al. (2017), *Penicillium chrysogenum* AS 3.5163 was used as an inducer in a rather original physiological state – the evaporated ethyl acetate extract of the supernatant, which, to our knowledge, has not been reported previously in the available literature. The target products are most often antibiotics, such as natamycin (Shi et al., 2017; Wang et al., 2017), valinomycin (Sharma et al., 2017), and rimocidin (Song et al., 2020). Summary information is provided in Table 2.

Table 2

Cultivation of actinobacteria in the presence of inducers: effects on metabolite synthesis

Producer + inducer	Synthesised metabolites	Concentration		Sources
		With inducer	Without inducer	
Inducers - other actinobacteria				
S. lividans TK23 + *T. pulmonis* TP-B0596 (living cells)	Red pigment actinorhodin	1.9×10^2 μM	0.2 μM	Onaka et al., 2011
Streptomyces sp. NZ-6 + *T. pulmonis* TP-B0596 (living cells)	Niizalactam C (multicyclic macrolactam)	1.3 mg/10 L	in 5 times lower	Hoshino et al., 2015b
Inducers – other bacteria				
R. equi CGMCC14861 + *Staphylococcus* sp. MC7 (living cells, supernatant)	Chitin deacetylase	2,974.05± 208.3 U/mL (living cells); 3,153.90 ± 161.49 U/mL (supernatant)	157.61 U/mL	Ma et al., 2020
S. sp. CGMCC4.7185 + *B. mycoides* GMCC1.197 (living cells)	*N-Ac-Trp, bacillamides A and B	14.9 mg/L, 3 mg/L, 13.7 mg/L, respectively	much lower without inducer	Yu et al., 2015
Inducers – fungi				
S. natalensis HW-2 + *P. chrysogenum* AS 3.5163 (evaporated ethyl acetate extract of supernatant)	Antibiotic natamycin	2.49 g/L	1.33 g/L	Wang et al., 2017
S. natalensis HW-2 + *A. niger* AS 3.6472 (living cells, supernatant)	Antibiotic natamycin	0.799 g/L (living cells), 1.62 g/L (supernatant)	0.639 g/L	Wang et al., 2013
S. natalensis HW-2 + *P. chrysogenum* AS 3.5163 (living cells, supernatant)	Antibiotic natamycin	0.975 g/L (living cells), 1.84 g/L (supernatant)	0.639 g/L	Wang et al., 2013
S. natalensis HW-2 + *Aspergillus oryzae* AS 3.2068 (living cells, supernatant)	Antibiotic natamycin	No effect (living cells), inhibition of synthesis (supernatant)	0.639 g/L	Wang et al., 2013
Streptomyces natalus N5 + *A. niger* (strain number not specified, supernatant)	Antibiotic natamycin	1.44 g/L	67% lower	Shi et al., 2017

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Producer + inducer	Synthesised metabolites	Concentration		Sources
		With inducer	Without inducer	
S. natalus N5 + *P. chrysogenum,* supernatant	Antibiotic natamycin	1.42 g/L	66% lower	Shi et al., 2017
S. lavendulae ACR-DA1+ *T. velutinum* (living cells)	Antibiotic valinomycin	26.3 g/L	50 mg/L	Sharma et al., 2017
S. noursei ATCC 11455 + *P. rubens* ATCC 28089 (living cells)	DFO-E, DHXC * and argvalin	Increase in concentration	-	Boruta et al., 2023
Inducers – yeasts				
S. natalensis HW-2 + *S. cerevisiae* AS 2.2081 (living cells, supernatant)	Antibiotic natamycin	No effect	0.639 g/L	Wang et al., 2013
S. natalus N5 + *S. cerevisiae* (strain number not specified, supernatant)	Antibiotic natamycin	Increase in concentration	-	Shi et al., 2017
S. lavendulae ACR-DA1 + *S. cerevisiae* (living cells)	Antibiotic valinomycin	67 mg/L	50 mg/L	Sharma et al., 2017
Streptomyces rimosus M527 + *S. cerevisiae* A3 (supernatant, living and inactivated cells)	Antibiotic rimocidin	0.37 g/L (supernatant), 0.3 g/L (living cells), slight increase (inactivated cells)	0.21 g/L	Song et al., 2020

Notes: «–» – data not reported; *N-Ac-Trp - N-acetyltryptamine; DFO-E - desferrioxamine E; DHXC – deshydroxynocardamine

The article (Ma et al., 2020) describes an atypical case of successful cultivation of actinobacteria with an inducer, as living cells and the corresponding supernatant of *Staphylococcus* sp. MC7 were added to the culture medium at higher concentrations than the inoculum of the producer *R. equi* CGMCC14861 (4:1 and 7:5, respectively), resulting in the synthesis of chitin deacetylase at higher concentrations than when the inocula were added in other ratios. In a study by Boruta et al. (2023), although the inocula of *Streptomyces noursei* ATCC 11455 and *Penicillium rubens* ATCC 28089 were added simultaneously, actinomycetes predominated in the total biomass; therefore, in our opinion, this also constitutes cultivation with an inducer.

The presence of the same inducer in the media can lead to multiple effects simultaneously. For example, Onaka et al. (2011) reported that the cultivation of *S. lividans* TK23 together with living cells of *T. pulmonis* TP- B0596 was accompanied by an increase in the concentration of the red pigment actinorhodin and the synthesis of a new pigment, undecylprodigiosin. A similar situation was described by Hoshino et al. (2015b), where cultivation of *Streptomyces* sp. NZ-6 in a medium containing *T. pulmonis* TP-B0596 resulted in an increase in the concentration of niizalactam C and the synthesis of niizalactams A and B, which are not observed in monoculture.

The effect of biological inducers on the synthesis of secondary metabolites by actinobacteria is not always positive. For instance, the presence of living cells of *Aspergillus oryzae* AS 3.2068 and *S. cerevisiae* AS 2.2081, as well as their corresponding supernatants, in the culture medium of *Streptomyces natalensis* HW-2 did not affect the concentration of natamycin (Wang et al.,

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2013). Similarly, the cultivation of *Streptomyces lavendulae* ACR-DA1 with living cells of *Trichoderma velutinum* (strain number not specified) was accompanied by a decrease in valinomycin concentration by 23.7 g/L.

Among the possible mechanisms of induction, the authors highlight the influence of mycolic acid on the induction of biosynthetic pathways in producers, as well as the intercellular interaction of actinobacteria with inducers (Onaka et al., 2011), and the action of extracellular signalling substances produced by an inducer (Ma et al., 2020).

Yu and co-authors (2015) abstractly refer to induction as an "inter-species crosstalk strategy," whereas Wang and co-authors (2017) suggest that the increase in natamycin concentration in *S. natalensis* may represent a protective response to the presence of fungi in the culture medium, mediated by changes in the permeability of the producer's membrane and the influx of extracellular calcium as an activator of enzymes involved in antibiotic biosynthesis.

Not all authors have investigated changes in the antimicrobial and cytotoxic activities of synthesised metabolites in the presence of inducers, which raises questions about the cost-effectiveness of the technology of cultivation with inducers for the industrial production of bioproducts. Hoshino and colleagues (Hoshino et al., 2015b) examined the biological activity of niizalactam C; however, this metabolite exhibited neither antimicrobial activity against *C. albicans, B. subtilis*, and *S. cereviciae* (strain numbers not specified), nor cytotoxic activity against P388 mouse leukaemia cells.

Regarding culture media, not all authors described the experimental preparation procedures in detail. For instance, Yu et al. (2015) do not specify the medium used for cultivating *Streptomyces* sp. CGMCC4.7185 with *Bacillus mycoides* CGMCC1.197, and Sharma et al. (2017) do not indicate the medium used for preparing inocula.

Wang and co-authors (2017) employed different nutrient media for the preparation of the inocula of *S. natalensis* HW-2 and *P. chrysogenum* AS 3.5163, which could potentially complicate the scaling-up of the technology to an industrial level.

On the other hand, in the study by Boruta et al. (2023), the cultivation of *S. noursei* ATCC 11455 with an inducer was performed in a laboratory bioreactor rather than in shaking flasks, which may facilitate the scaling-up to an industrial production level.

Therefore, the technology of cultivating actinobacteria with inducers to obtain target products in higher concentrations is both interesting and promising, but requires further in-depth investigation.

Effect on the synthesis and activity of metabolites

The cultivation of actinobacteria in the presence of inducers can simultaneously produce multiple effects on the same metabolites, such as increased concentration and enhanced antimicrobial activity, which is commercially attractive. We identified two such studies (Patin et al., 2018; Sung et al., 2017). The summarised data are shown in Table 3.

The study of *Streptomyces* sp. PTY087I2 cultivation with different bacteria as inducers (Sung et al., 2017) illustrates that each combination of microorganisms must be investigated separately. Thus, in the presence of living cells of *B. subtilis* ATCC 6051, methicillin-resistant *S. aureus* ATCC BAA-1717, and *P. aeruginosa* ATCC 15442 in the culture medium, antibiotics with enhanced antimicrobial activity were synthesised. By contrast, in the presence of methicillin-sensitive *S. aureus* ATCC BAA-1718, no changes in the biological activity of the synthesised metabolites were observed compared with antibiotics produced in monoculture.

From a practical perspective, it is difficult to estimate the concentrations of synthesised secondary metabolites, as Sung and colleagues (Sung et al., 2017) reported the areas under the peaks obtained by liquid chromatography-mass spectrometry, and Patin and his team (Patin et al., 2018) presented graphs showing the variation of peak areas over time. Moreover, the latter study

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does not provide specific values for the growth inhibition zones of test cultures on agar-based medium, nor is the cause of their inhibition clarified.

In the article by Sung et al. (2017), the authors suggest that a possible mechanism for the increased concentration and antimicrobial activity of the antibiotic complex is an ecological stressor, i.e., competition between microorganisms for substrate and space. However, Patin et al. (2018) describe the ecological relevance of induction as "often speculative," since most producers and inducers were isolated from different environments and are unlikely to interact in nature.

Table 3

Cultivation of actinobacteria in the presence of inducers: effects on metabolite synthesis and activity

Producer + inducer	Synthesised metabolites	Effects on concentration and biological activity	Sources
Inducers – other bacteria			
Streptomyces sp. PTY087I2 + *B. subtilis* ATCC 6051 (living cells)	Antibiotics granaticin, granatomycin D, dihydrogranaticin B	Increase in concentration by 10.9–13.8-fold. Reduction in MIC (μg/mL) by 4-fold against *B. subtilis* ATCC 6051, 2-fold against methicillin-sensitive *S. aureus* ATCC BAA-1718 and methicillin-resistant *S. aureus* ATCC BAA-1717, with no change against *P. aeruginosa* ATCC 15442	Sung et al., 2017
Streptomyces sp. PTY087I2 + *S. aureus* sensitive to methicillin ATCC BAA-1718 (living cells)	Antibiotics granaticin, granatomycin D, dihydrogranaticin B	Increase in concentration by 2–73.3-fold. No change in antimicrobial activity against *B. subtilis* ATCC 6051, methicillin-sensitive *S. aureus* ATCC BAA-1718, methicillin-resistant *S. aureus* ATCC BAA-1717, and *P. aeruginosa* ATCC 15442	Sung et al., 2017
Streptomyces sp. PTY087I2 + *S. aureus* resistant to methicillin ATCC BAA-1717 (living cells)	Antibiotics granaticin, granatomycin D, dihydrogranaticin B	Increase in concentration by 15.6–25.9-fold. Reduction in MIC (μg/mL) by 16-fold against *B. subtilis* ATCC 6051, 4-fold against methicillin-sensitive *S. aureus* ATCC BAA-1718, 8-fold against methicillin-resistant *S. aureus* ATCC BAA-1717, with no change against *P. aeruginosa* ATCC 15442	Sung et al., 2017
Streptomyces sp. PTY087I2 + *P. aeruginosa* ATCC 15442 (living cells)	Antibiotics granaticin, granatomycin D, dihydrogranaticin B	Increase in concentration by 3.8–7.3-fold. Reduction in MIC (μg/mL) by 4-fold against *B. subtilis* ATCC 6051, methicillin-sensitive *S. aureus* ATCC BAA-1718, and methicillin-resistant *S. aureus* ATCC BAA-1717, with no change against *P. aeruginosa* ATCC 15442	Sung et al., 2017
Salinispora tropica CNY-681 +*Vibrio* sp. CUA-759, (living cells, supernatant)	Lomaiviticin (glycoside), sioxanthin (carotenoid pigment)	Increase in concentrations. Increase in antimicrobial activity of the metabolite complex (living cells), with a slight increase in antimicrobial activity of the metabolite complex (supernatant) against 12 test cultures.	Patin et al., 2018

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The available scientific literature also reports the cultivation of *Streptomyces* sp. 2-85 with *Cladosporium* sp. 3-22 (Liu et al., 2024), which was accompanied by the synthesis of a borrelidin complex and its derivatives, with antimicrobial activity increasing by 36.67 and 42.86% against *B. subtilis* ATCC6633 and *Saprolegnia parasitica* YG438, respectively, compared with the control. In addition, four metabolites not observed in the *Streptomyces* sp. 2-85 monoculture were detected, alongside a 7-30-fold increase in the concentration of other metabolites. This study describes an atypical method of culturing the secondary metabolite producer *Streptomyces* sp. 2-85 with other microorganisms, as the inocula of actinobacteria and fungi were prepared together in equal proportions rather than separately, with *Cladosporium* sp. 3-22 dominating the overall biomass.

Therefore, the cultivation of actinobacteria with biological inducers, which is accompanied by multiple simultaneous effects, is commercially attractive but requires further investigation and clarification.

Effect on metabolite activity

The effect of eukaryotic and prokaryotic inducers in the culture media of *Rhodococcus erythropolis* IMV Ac-5017 and *Nocardia vaccinii* IMV B-7405 on the biological activity of surfactants synthesised under these conditions was studied in detail at the Department of Biotechnology and Microbiology, National University of Food Technologies (Table 4).

Table 4

Cultivation of actinobacteria in the presence of inducers: effect on surfactant activity

Producer + inducer	Effect on antimicrobial activity	Effect on antibiofilm activity	Sources
R. erythropolis IMV Ac-5017 + *S. cerevisiae* BTM-1 (living cells)	Increase in antimicrobial activity by 7.5–30 times against bacteria (*E. coli* IEM-1, *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *B. subtilis* BT-2) and by 60–240 times against yeasts (*C. albicans* D-6, *C. utilis* BVS-65, *S. cerevisiae* BTM-1)	Increase in antibiofilm activity by 9.1–45.4% against bacteria (*E. coli* IEM-1, *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *B. subtilis* BT-2) and by 27.1–58.9% against yeasts (*C. albicans* D-6, *C. utilis* BVS-65, *S. cerevisiae* BTM-1), as well as by 3–26 and 6–29% against dual-species bacterial and bacterial–yeast biofilms, respectively	Okhmakevych et al., 2025
R. erythropolis IMV Ac-5017 + *S. cerevisiae* BTM-1 (inactivated cells)	Increase in antimicrobial activity by 1.8-3.5 times against bacteria (*E. coli* IEM-1, *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *B. subtilis* BT-2) and by 7.1-14.1 times against yeasts (*C. albicans* D-6, *C. utilis* BVS-65, *S. cerevisiae* BTM-1)	Increase in antibiofilm activity by 1.2-23.8% against bacteria (*E. coli* IEM-1, *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *B. subtilis* BT-2) and by 12.1-45.4% against yeasts (*C. albicans* D-6, *C. utilis* BVS-65, *S. cerevisiae* BTM-1), as well as by 1-14 and 2-15% against dual-species bacterial and bacterial–yeast biofilms, respectively	Okhmakevych et al., 2025

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Producer + inducer	Effect on antimicrobial activity	Effect on antibiofilm activity	Sources
R. erythropolis IMV Ac-5017 + *S. cerevisiae* BTM-1 (supernatant)	Increase in antimicrobial activity by 3.6-7.3 times against bacteria (*E. coli* IEM-1, *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *B. subtilis* BT-2) and by 29.1-14.5 times against yeasts (*C. albicans* D-6, *C.utilis* BVS-65, *S. cerevisiae* BTM-1)	Increase in antibiofilm activity by 13.3-38.4% against bacteria (*E. coli* IEM-1, *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *B. subtilis* BT-2) and by 26.7-51% against yeasts (*C. albicans* D-6, *C. utilis* BVS-65, *S. cerevisiae* BTM-1), as well as by 1-22 and 7-26% against dual-species bacterial and bacterial–yeast biofilms, respectively	Okhmakevych et al., 2025
R. erythropolis IMV Ac-5017 + *E. coli* IEM-1 (living cells)	Increase in antimicrobial activity by 4-16 times against *E. coli* IEM-1, *S. aureus* BMS-1, *B. subtilis* BT-2	Increase in antibiofilm activity by 3.8-16.6% against *B. subtilis* BT-2	Pirog et al., 2020a
R. erythropolis IMV Ac-5017 +*B.subtilis* BT-2 (living cells)	Increase in antimicrobial activity by 8 times against *E. coli* IEM-1, *S. aureus* BMS-1, *B. subtilis* BT-2	Increase in antibiofilm activity by 15.3-23.7% against *B. subtilis* BT-2; by 2.6-20.8% against *C. utilis* BVS-65	Pirog et al., 2020a
N.vaccinii IMV B-7405 + *E. coli* IEM-1 (living cells)	Increase in antimicrobial activity by 4-16, 3.3-6.25, and 2.9-5.8 times for surfactants, synthesised on biodiesel production waste, refined sunflower oil, and fried sunflower oil, respectively, against *E. coli* IEM-1, *B. subtilis* BT-2, *S. aureus* BMS-1, *P. vulgaris* PA-12, *Pseudomonas* sp. MI-2, *E. cloaceae* C-8	Increase in antibiofilm activity by 11-23% against *E. coli* IEM-1; by 19-31% against *B. subtilis* BT-2; by 10-28% against *Pseudomonas* sp. MI-2; and by 8-22% against *S. aureus* BMS-1	Pirog et al., 2020b
N. vaccinii IMV B-7405 + *E. coli* IEM-1 (inactivated cells)	Increase in antimicrobial activity by 3.3-13.3, 5-10, and 3.5-7 times for surfactants, synthesised on biodiesel production waste, refined sunflower oil, and fried sunflower oil, respectively, against *E. coli* IEM-1, *B. subtilis* BT-2, *S. aureus* BMS-1, *P. vulgaris* PA-12, *Pseudomonas* sp. MI-2, *E. cloaceae* C-8	Increase in antibiofilm activity by 10-24% against *E. coli* IEM-1; by 17-29% against *B. subtilis* BT-2; by 11-30% against *Pseudomonas* sp. MI-2; by 14-24% against *S. aureus* BMS-1	Pirog et al., 2020b

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Producer + inducer	Effect on antimicrobial activity	Effect on antibiofilm activity	Sources
N. vaccinii IMV B-7405 + *B. subtilis* BT-2 (living cells)	Increase in antimicrobial activity by 2.9-5.7, 3.3-6.7, and 4-8 times for surfactants, synthesised on biodiesel production waste, refined sunflower oil, and fried sunflower oil, respectively, against *E. coli* IEM-1, *B. subtilis* BT-2, *S. aureus* BMS-1, *P. vulgaris* PA-12, *Pseudomonas* sp. MI-2, *E. cloaceae* C-8	Increase in antibiofilm activity by 18-25% against *E. coli* IEM-1; by 23-34% against *B. subtilis* BT-2; by 14-33% against *Pseudomonas* sp. MI-2; and by 20-26% against *S. aureus* BMS-1	Pirog et al., 2020b
N. vaccinii IMV B-7405 + *B. subtilis* BT-2 (inactivated cells)	Increase in antimicrobial activity by 2.5-5, 2.9-5.7, and 2-8 times for surfactants, synthesised on biodiesel production waste, refined sunflower oil, and fried sunflower oil, respectively, against *E. coli* IEM-1, *B. subtilis* BT-2, *S. aureus* BMS-1, *P. vulgaris* PA-12, *Pseudomonas* sp. MI-2, *E. cloaceae* C-8	Increase in antibiofilm activity by 16-21% against *E. coli* IEM-1; by 20-33% against *B. subtilis* BT-2; by 17-35% against *Pseudomonas* sp. MI-2; and by 17-28% against *S. aureus* BMS-1	Pirog et al., 2020b

Thus, it was reported that the surfactants of *R. erythropolis* IMV Ac-5017, synthesised in the presence of living *Saccharomyces* yeast cells, exhibited higher antimicrobial and antibiofilm activity against single- and dual-species biofilms compared with surfactants synthesised in the presence of inactivated *Saccharomyces* cells or the corresponding supernatant (Okhmakevych et al., 2025). It is suggested that both intercellular and biochemical interactions between the surfactant-producing strain and the inducer are important for induction. Furthermore, in comparison with data reported by Pirog et al. (2020a), it is suggested that changes in the inducer also affect the specificity of the activity of the synthesised antimicrobial compounds.

Okhmakevych et al. (2025) and Pirog et al. (2020a) focused on surfactant synthesis exclusively in ethanol-containing media; therefore, further research on alternative substrates, such as technical glycerol or waste sunflower oil, is required. In Pirog et al. (2020a), inoculum preparation of *E. coli* IEM-1 and *B. subtilis* BT-2 was performed on agar medium, which may complicate scaling up the laboratory technology to an industrial level.

Pirog et al. (2020b) investigated the cultivation of *N. vaccinii* IMV B-7405 in the presence of prokaryotic inducers, resulting in the synthesis of surfactants with higher biological activity against bacterial test cultures compared with those obtained without inducers. However, the effects of eukaryotic inducers on surfactant activity and their impact on yeast test cultures were not evaluated, which warrants further investigation.

Therefore, the technology of cultivating actinomycetes with prokaryotic and eukaryotic inducers to enhance the antimicrobial and antibiofilm activity of the synthesised secondary metabolites is potentially attractive for application in the pharmaceutical industry and medicine, but further research is still required.

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Actinobacteria as inducers

Actinobacteria can act not only as producers of secondary metabolites but also as inducers, for example, stimulating the synthesis of metabolites that are not characteristic of fungal monocultures. Stroe et al. (2020) showed that cultivation of *Aspergillus fumigatus* ATCC 46645 with living *Streptomyces rapamycinicus* cells (strain number not specified) or with the corresponding supernatant was accompanied by fumigermin synthesis. Wakefield et al. (2017) demonstrated that cultivation of *A. fumigatus* MR2012 in a medium containing living *Streptomyces leeuwenhoekii* C34 cells resulted in the formation of luteoride D, pseurotin G, terezine D, and 11-O-methylpseurotin A, none of which are typical of fungal monocultures.

Selegato et al. (2023) distinguished two types of induction: single-culture activation and multispecies induction. Whereas the former is widely reported in the scientific literature, the latter remains relatively rare. Wakefield et al. (2017) described bilateral microbial crosstalk occurring within the same cultivation flask, as the concentrations of chaxapeptin and nocardiamin produced by *S. leeuwenhoekii* C34 increased during interaction with the fungus. However, the biological activity of the metabolites formed was not investigated, which raises questions regarding their potential practical applications. Stroe et al. (2020) prepared the fungal inoculum in minimal AMM medium and the actinobacterial inoculum in M79 medium, an approach that may complicate process scaling to the production level.

Therefore, the use of actinobacteria as inducers also requires further investigation and optimisation.

Conclusions

Technologies for cultivating actinobacteria with biological inducers to obtain metabolites that are not characteristic of monocultures, or metabolites with higher concentrations and/or enhanced biological activity, are highly promising. However, the mechanisms by which inducers influence the biosynthesis of secondary metabolites remain insufficiently studied and require further investigation. Additional research is also needed to evaluate the antimicrobial, antibiofilm, cytotoxic, and antitrypanosomal activities of secondary metabolites synthesised in the presence of inducers, as these properties largely determine the feasibility of their industrial production and practical applications. Furthermore, optimisation of nutrient media for both inoculum preparation and metabolite biosynthesis is necessary, since the use of a single medium is more practical and economically advantageous for industrial-scale production. Finally, approaches in which an inducer promotes the synthesis of a complex of metabolites rather than a single product appear especially promising, as they may facilitate the development of integrated industrial technologies for the production of actinobacterial secondary metabolites.

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Author identifiers ORCID

Anastasiia Okhmakevych 0009-0004-3849-1543

Tetiana Pirog 0000-0002-3873-2253

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