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INFLUENCE OF BIOLOGICAL INDUCTORS ON THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF MICROBIAL METABOLITES

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The increasing antibiotic resistance is a severe concern for humanity. Co-cultivation of microorganisms is a promising method for obtaining new secondary antimicrobial metabolites. An effective strategy for co-cultivation of microorganisms involves the usage of certain biological inductors.

The *aim* of this review is to summarize existing scientific research in the literature related to the influence of physiologically different types of biological inductors on the synthesis and biological activity of microbial secondary metabolites.

An analysis of the literature has shown that in such studies, either live or inactivated cells of the inductor are added to the culture medium at significantly lower concentrations compared to the producer cells of the final metabolites, or the supernatant (filtrate) after cultivation of a competitive microorganism is used as an inductor.

According to the literature and our own experimental studies, the using inductors is an effective approach not only for intensifying the synthesis of bacteriocins, surfactants, and antibiotics, but also for increasing their biological activity. Additionally, it often leads to the production of novel antimicrobial compounds that are not typical for the producer.

However, the mechanisms of effect of inductors on the synthesis of biologically active secondary metabolites require further research, as the literature suggests that their introduction into the cultivation medium of producer does not always lead to an intensification of the synthesis of the final product. Moreover, the biological activity of secondary metabolites depends on the cultivation conditions of the producer, including the presence of biological inductors in the culture medium. Therefore, it is essential to conduct further research on the interaction between producers and competitive microorganisms to regulate the biological activity of the synthesised metabolites. In addition, there is a necessity to search for more cost-effective substrates for the biosynthesis of secondary metabolites, optimize the composition of the culture medium and expand the range of both pro- and eukaryotic inductors.

Key words: co-culture; inductor; physiological state of the inductor; antimicrobial metabolites.

In our previous publication [1], it was mentioned that the increase in antibiotic resistance of pathogenic microorganisms in recent decades has led the scientific community to research for novel environmentally friendly antimicrobial metabolites of natural origin with stable properties. One of the ways to solve this issue was the strategy of co-cultivation of microorganisms, in which the producer of practically valuable metabolites is cultivated together with competitive microorganisms. This is considered to be an effective strategy to induce producing by microorganisms secondary metabolites with increased antimicrobial activity or/and will stimulate the production of bioactive secondary metabolites, which cannot be obtained in the corresponding pure culture [1, 2].

Studies on the influence of competitive microorganisms on the synthesis of antimicrobial compounds can be divided into three categories:

1) both strains (the producer and the competitive microorganism) are introduced into the culture medium of antimicrobial metabolites producer in a 1:1 ratio, i.e. in almost the same concentration [2, 3];

2) live or inactivated inductor cells are added to the medium at a significantly lower concentration compared to the cells of the final metabolite producer [4–23];

3) the supernatant (filtrate) after cultivation of a competitive microorganism is used as an inductor [4, 21, 22, 24–29].

For each of these three categories of experiments, the corresponding terminology is used. The first category is the classical co-cultivation of two microorganisms, the cultivation of artificial microbial associations (consortia). Competitive microorganisms (or their supernatants) used in the second and third categories are called inductors or elicitors.

Related to the above stated, the aim of this review is to summarize current literature data on the effect of physiologically different types of biological inductors on the synthesis and biological activity of microbial metabolites.

Heat-inactivated inductors

There is information in the literature on the effect of heat-inactivated inductors on the synthesis and properties of bacteriocins [4], microbial surfactants [5–7], pigments [8–10], antibiotics [11], and other secondary metabolites [12–15].

Bacteriocins. It was found in [4] that the introduction of heat-inactivated *Staphylococcus aureus* ATCC 43090 cells (2 and 3% v/v) or *Bacillus* sp. cells (3% v/v) into the culture medium of the bacteriocin producer *Bacillus subtilis* NK16 was accompanied by a 2-4-fold increase in the synthesis of the final product compared to that established for the NK16 strain. The scientists suggested that one of the mechanisms for the increase in bacteriocin synthesis could be the recognition of certain proteins or receptors on the surface of inactivated inductor cell fragments and the implementation of a protective mechanism against a competitive microorganism. This was supported by the results of determining the antimicrobial activity of the synthesised bacteriocins against inductor cells (*S. aureus* ATCC 43090, *Bacillus* sp.): the growth inhibition zone was 25 and 23 mm, respectively. At the same time, without inductor cells, the growth inhibition zone was from 5 to 15 mm after treatment with the obtained bacteriocins.

Microbial surfactants. The researchers found [5] that the introduction of inactivated *Listeria monocytogenes* ATCC 7644 or *Aspergillus niger* IFL5 cells into the culture of *Bacillus* sp. P34 increased the synthesis of the antimicrobial lipopeptide iturin A by more than 2 times compared to that established for the P34 strain, but had virtually no effect on the synthesis of fengycins A and B. An interesting fact was that, despite the increased synthesis of lipopeptides, their antimicrobial activity was twice as low as that of those synthesized in the medium without inductor.

In the work [6], it is reported that the synthesis of iturin A by the *Bacillus amyloliquefaciens* P11 strain was increased by 0.5 and 3 times in the presence of heat-inactivated cells of *S. aureus* ATCC 25923 or *Aspergillus parasiticus* (strain number not provided), respectively. Furthermore, the introduction of inductors into the cultivation medium of *B. amyloliquefaciens* P11 was accompanied by the synthesis of new compounds not typical for the producer, such as subtilosin A and fengycin. However, the researchers did not specify their concentrations.

When inactivated *Candida albicans* SC 5314 yeast cells were added to *B. subtilis* RLID 12.1 culture medium, a 3–4-fold increase in the concentration of cyclic lipopeptides AF3 and AF5 was observed [7], which were characterized by high antifungal activity against *Candida auris* yeast, with minimum inhibitory concentrations (MIC) of 4–16 μg/ml.

Pigments. The effect of inactivated prokaryotic and yeast inductors on the synthesis of the antimicrobial pigment prodigiosin by actinobacteria of the genus *Streptomyces* and bacteria of the genus *Serratia* was studied by a few authors [8–10].

For example, researchers [8] found that the presence of inactivated *Escherichia coli*, *B. subtilis* or *Saccharomyces cerevisiae* cells (2–3%) in the culture medium of *Serratia marcescens* S23 was accompanied by a 7–9-fold increased production of this pigment compared to that of the S23 strain, moreover, the concentration of prodigiosin did not depend on the nature of the inductor (pro- or eukaryotic). The authors assumed that one of the mechanisms of induction is direct contact between the producer and the inductor cells, as they found no evidence of the participation of certain signal molecules in this process.

The authors in the study [9] demonstrated a 30–100% concentration increased of prodigiosin synthesis by *S. marcescens* (strain number not given) in the presence of the corresponding inductors (*E. coli, B. subtilis*, or *S. cerevisiae*), but compared to the studies described in work [8], the maximum induction of prodigiosin synthesis was observed in the presence of bacterial inductors.

The authors reported [10] that the introduction of heat-inactivated *Lactobacillus rhamnosus* LGG cells (0.5–1%) into the culture medium of actinobacteria *Streptomyces coelicolor* (strain number not given) was associated with an increased synthesis of prodigiosin up to 9.8 mg/l, which is 7 times higher than without the inductor. The authors hypothesised that the lactic acid bacteria lysis products could work as a precursor to the synthesis of the final product. It should be noted that the synthesis ability of *S. coelicolor* is significantly lower than that of *S. marcescens* [8, 9].

Antibiotics. The authors in the study [11] managed to significantly enhance the synthesis of the antibiotic phenazine by *Pseudomonas aeruginosa* (strain number not given) up to 43–300% by adding heat-inactivated *E. coli, B. subtilis*, and *S. cerevisiae* cells to the medium. *S. cerevisiae* yeast cells proved to be the most effective inductor, in the presence of which the phenazine concentration increased up to 30 mg/l. The determination of the antimicrobial activity of phenazine against the inductor cells showed that the growth inhibition zones of *E. coli, B. subtilis* and *S. cerevisiae* were 1.6, 2.9 and 4.3 mm, respectively.

Other secondary metabolites. During the cultivation of *Streptomyces* sp. RKND-216 in the presence of inactivated cells of *Alteromonas* sp. RKMC-009 or *Mycobacterium smegmatis* ATCC 120515, the production of two novel alkaloids was found: N-carbamoyl-2-hydroxy-3-methoxybenzamide and carbazoquinocin G [12]. The obtained metabolites did not show antimicrobial activity, but carbazoquinocin G was characterised by cytotoxic activity against breast cancer cell lines MCF7 and HTB26 (IC_{50} was 3.07 and 3.67 μM, respectively).

It was found in the work [13] that the introduction of heat-inactivated *S. aureus* cells into the culture of *Streptomyces* sp. MH-133 was accompanied by the synthesis of a complex of unidentified antibacterial metabolites that inhibited the growth of *S. aureus, E. coli, Klebsiella pneumonia*, *Enterobacter cloacae* (growth inhibition zones were 24, 22, 24 and 16 mm, respectively).

It is reported in studies [14, 15] about the effect of heat-inactivated inductors on the production of antimicrobial metabolites by micromycetes.

Six novel 16-residue peptaibols (acremopeptibodies A-F) were obtained from the culture of the micromycete *Acremonium* sp. IMB18-086 cultivated in the presence of autoclaved *Pseudomonas aeruginosa* cells [14]. Acremopeptabolites A and F showed antimicrobial activity against *S. aureus, B. subtilis, P. aeruginosa, Candida albicans*: the growth inhibition zones were 15, 16, 10 and 12 mm, respectively.

Other studies [15] showed that the introduction of autoclaved *P. aeruginosa* cells into the culture of *Chaetomium* sp. led to the production of four novel butenolide derivatives, as well as two analogues of shikimic acid (chetoisochorismine, shikimeran B), which were not observed in either the micromycete or inductor culture.

In Table 1, we summarised the data on the influence of heat-inactivated inductors on the production and the antimicrobial activity of secondary metabolites. These data indicate that the use of these inductors is a technologically simpler and effective method of not only intensifying the production of bacteriocins, surfactants, and antibiotics, but also increasing their biological activity, and is often accompanied by the synthesis of novel antimicrobial metabolites not typical for the producer.

Live inductors

There is scientific data showing that live cells of prokaryotic and eukaryotic inductors can affect the production and properties of bacteriocins [4, 16], surfactants [17, 18], pigments [8, 9, 19], antibiotics [11, 20–22] and other secondary metabolites [23].

Bacteriocins. It was shown in the work [4] that the introduction of live cells of *S. aureus* ATCC 43090 (0.5%), *E. coli* (0.2%) or *A. niger* (0.75%) into the culture medium of the bacteriocin producer *B. subtilis* NK16 caused an increase in the synthesis of the final product by 4–8 times compared to the rates without inductors. The produced bacteriocins exhibited high antimicrobial activity against *S. aureus* ATCC 4309, *E. coli* and *A. niger* cells: the growth inhibition zones were 27, 22 and 24 mm, respectively, and were 20–50% higher than when using bacteriocins synthesised without inductor.

Table 1

Effect of heat-inactivated inductors on the synthesis and antimicrobial activity of secondary metabolites

Producer	Carbon source	Biological inductor	Concentration (activity) of secondary metabolites		Test-cultures for determining antimicrobial activity	Antimicrobial activity	References
			without inductor	with an inductor			
1	2	3	4	5	6	7	8
Bacteriocins							
Bacillus subtilis NK16	Dextrose	*Staphylococcus aureus* ATCC 43090 / *Bacillus* sp. ATCC 6633	80 AU/ml	320 / 160 AU/ml	*Staphylococcus aureus* ATCC 43090	Growth inhibition zone of 25 mm (100 µg/disc)	4
					Bacillus sp. ATCC 6633	Growth inhibition zone of 23 mm (100 µg/disc)	
Microbial surfactants							
Bacillus sp. P34	Dextrose	*Listeria monocytogenes* ATCC 7644 / *Aspergillus niger* IFL5	Iturin A 100 mg/l	Iturin A 250 mg/l	*Aspergillus niger* IFL5	400 AU/ml*	5
					Listeria monocytogenes ATCC 7644	1600 AU/ml*	
Bacillus amyloliquefaciens P11	Dextrose	*Staphylococcus aureus* ATCC 25923 / *Listeria monocytogenes* ATCC 7644 / *Aspergillus parasiticus* **(strain number not given)**	Iturin A 100 mg/l	Iturin A 300 mg/l Surfactin** Subtilisin A** Fengycin**	*Staphylococcus aureus* ATCC 25923	1333 AU/ml*	6
					Listeria monocytogenes ATCC 7644	933 AU/ml*	
					Aspergillus parasiticus **(strain number not given)**	1600 AU/ml*	
Bacillus subtilis RLID 12.1	Glucose	*Candida albicans* SC 5314	AF3 441 mg/l	AF3 1280 mg/l	*Candida auris* **(strain number not given)**	MIC 4–10 µg/ml	7
			AF5 263 mg/l	AF5 960 mg/l	*Candida auris* **(strain number not given)**	MIC 4–16 µg/ml	
Pigment prodigiosin							
Serratia marcescens S23	Starch	*Escherichia coli* / *Bacillus subtilis* / *Saccharomyces cerevisiae* **(strain number not given)**	0.45 g/l	4.1 / 3.5 / 4.1 g/l	-----	N.d.	8

Table 1 (Continuend)

1	2	3	4	5	6	7	8
Serratia marcescens **(strain number not given)**	Trypton, yeast extract	*Bacillus subtilis* / *Escherichia coli* / *Saccharomyces c erevisiae* **(strain number not given)**	100 mg/ml	200 / 170 / 130 mg/ml	-----	N.d.	9
Streptomyces coelicolor **(strain number not given)**	Glucose	*Lactobacillus rhamnosus* LGG	1.4 mg/l	9.8 mg/l	-----	N.d.	10
Antibiotics							
Pseudomo-nas aeru-ginosa **(strain number not given)**	Trypton, yeast extract	*Escherichia coli* / *Bacillus subtilis* / *Saccharomyces cerevisiae* **(strain number not given)**	Phenazine 9.2 mg/l	Phenazine 13.4 / 19.4 / 30 mg/l	*Escherichia coli* **(strain number not given)**	Growth inhibition zone of 1.6 mm (200 µl/disc)	11
					Bacillus subtilis **(strain number not given)**	Growth inhibition zone of 2.9 mm (200 µl/disc)	
					Saccharomyces cerevisiae **(strain number not given)**	Growth inhibition zone of 4.6 mm (200 µl/disc)	
Other secondary metabolites							
Streptomyces sp. RKND-216	Dextrose	*Alteromonas* sp. RKMC-009 / *Mycobacterium smegmatis* ATCC 120515	N-carbamoyl-2-hydroxy-3-methoxybenzamide** carbazoquinocin G** (alkaloids)		-----	N.d.	12
Streptomyces sp. MH-133	Trypton, yeast extract	*Staphylococcus aureus* **(strain number not given)**	Complex of unidentified antibacterial metabolites		*Klebsiella pneumonia* **(strain number not given)**	Growth inhibition zone of 24 mm (100 µl/disc)	13
					Staphylococcus aureus **(strain number not given)**	Growth inhibition zone of 24 mm (100 µl/disc)	
					Escherichia coli ATCC 25922	Growth inhibition zone of 22 mm (100 µl/disc)	

Table 1 (End)

1	2	3	4	5	6	7	8
					Enterobacter cloacae **(strain number not given)**	Growth inhibition zone of 16 mm (100 µl/disc)	
Acremonium sp. IMB18-086	Rice	*Pseudomonas aeruginosa* ATCC 27853	Acremopeptaibols A-F** (16-residue peptaibols)		*Staphylococcus aureus* ATCC 33591	Growth inhibition zone of 15 mm	14
					Bacillus subtilis ATCC 6633	Growth inhibition zone of 16 mm	
					Candida albicans ATCC 10231	Growth inhibition zone of 12 mm	
					Pseudomonas aeruginosa ATCC 27853	Growth inhibition zone of 10 mm	
Chaetomium sp. **(strain number not given)**	Rice	*Pseudomonas aeruginosa* **(strain number not given)**	Hetobutenolide A, C** Methyl ester WF-3681** (butenolide derivatives) Hetoisochorismine** Shikimeran B** (shikimic acid analogues)		-----	N.d.	15

Notes. N.d. - not determined; * — activity was determined as the last dilution giving a growth inhibition zone and indicated in units of activity per millilitre; ** — synthesis of new compounds not typical for monoculture.

Other authors [16] found that paracin 1.7 production by *Lactobacillus paracasei* strain HD1-7 increased by almost 75% in the presence of live cells of *B. subtilis* ATCC 11774.

Microbial surfactants. There is information in the literature about the effect of live cells of prokaryotic [17] and eukaryotic [18] inductors on the synthesis of surfactants.

In work [17], the emulsifying activity of *S. marcescens* surfactants (strain number not given) was increased by 1.7–3.5 times when introduced into the culture medium of live *E. coli* or *S. aureus* cells. The surfactants synthesised in the presence of inductors showed antimicrobial activity against the test cultures of *S. aureus, K. pneumonia, E. coli, B. subtilis*: the growth inhibition zones were in the range of 14–16 mm.

The synthesis of iturin A by the producer *B. amyloliquefaciens* CX-20 increased by an average of 10% in the presence of live cells of the micromycetes *Aspergillus oryzae* 92011 or *Trametes* sp. 48424 [18].

Pigments. A number of studies reported the influence of live prokaryotic [8, 9, 19] and yeast [8, 9] inductors on the synthesis of pigments by bacteria of the genus *Pseudomonas* and *Serratia*.

The level of prodigiosin synthesised by *S. marcescens* S23 increased by 1.4–7 times by adding to the culture medium *E. coli, B. subtilis*, or *S. cerevisiae* cells [8], and the highest concentration of this particular metabolite (3.1 g/l) was achieved with the introduction of a yeast inductor.

In the study [9], it was found that the addition of live *S. cerevisiae* cells to the *S. marcescens* culture medium increased the synthesis of prodigiosin to 170 mg/ml, which is 70% above the level obtained when the producer was cultivated without an inductor. The use of prokaryotic inductors (*E. coli, B. subtilis*) resulted in an increasing of the final product synthesis by *S. marcescens* strain to 220–250 mg/ml, which is 50% higher than in case of using yeast inductors.

The authors in the work [19] found that the addition of live *S. aureus* (0.5, 0.75%), *K. pneumonia* (0.5, 0.75%), or *B. subtilis* (0.25, 0.5%) cells to the

P. aeruginosa culture medium increased the synthesis of the pyocyanin pigment in 2.3 times compared to the cultivation of the producer in the medium without inductors. Pyocyanin showed high antimicrobial activity against *S. aureus, K. pneumonia, B. subtilis*, and *E. coli* cells: growth inhibition zones were in the range of 26–38 mm.

Antibiotics. There is available data in literature about the influence of live prokaryotic cells [20, 11], yeast [20, 21, 11] and micromycetes [21, 22] on the synthesis of antibiotics by actinobacteria of the genus *Streptomyces*.

For instance, researchers [20] found that in the presence of live *Bacillus cereus* or *S. cerevisiae* cells, the production of valinomycin by *Streptomyces lavendulae* strain ACR-DA1 increased for 34–62% compared to the levels observed without inductor.

In the study [21], the concentration of rimocidin was increased by 42% by introducing the yeast inductor *S. cerevisiae* into the culture medium of the producer *Streptomyces rimosus* M527. When the micromycete *Fusarium oxysporum* f. sp. *cucumerinum* was used as an inductor, the antibiotic concentration almost twice increased compared to the values obtained without the inductor.

The authors reported [22] that the introduction of live cells of *A. niger* AS 3.6472 (0.2%) or *Penicillium chrysogenum* AS 3.5163 (0.4%) into the culture medium of *Streptomyces natalensis* HW-2 increased the production of the antibiotic natamycin by 25-36% compared to that of the HW-2 strain grown without micromycetes.

Other researchers [11] demonstrated that in the presence of live cells of the prokaryotes *B. subtilis, E. coli* and the yeast *S. cerevisiae*, the concentration of phenazine synthesised by *P. aeruginosa* was 80–145% higher than in the case of cultivation of the producer without inductors. The most effective inductor was *E. coli* cells, in the presence of which the concentration of phenazine increased to 18.8 mg/l, which is 2.5 times higher than without inductor. Phenazine showed antimicrobial activity against the inductor cells of *B. subtilis, E. coli, S. cerevisiae*: the growth inhibition zones of the tested cultures were 2.9, 1.6, 4.3 mm, respectively.

Other secondary metabolites. During the cultivation of *Saccharopolyspora erythraea* ATCC 31772 in the presence of cells of the micromycete *Fusarium pallidoroseum* ATCC 74289, three novel analogues of decalin-type tetraminic acids (N-demethylophiosetin, pallidorosetin A, pallidorosetin B) were identified [23].

In Table 2, we summarised the influence of live cell inductors on the synthesis and antimicrobial activity of secondary metabolites. These data indicated that the use of both prokaryotic and yeast and microbial inductors can increase the synthesis of bacteriocins, surfactants, antimicrobial pigments and antibiotics. The synthesis and the activity of the induced metabolites increased with the addition of live inductor cells, but almost did not depend on their nature (pro- or eukaryotic). In addition, the use of micromycetes as inductors proved to be an effective way to increase the synthesis of antibiotics.

Supernatant after cultivation of inductors

There is limited information in the literature regarding the impact of supernatant after cultivation of biological inductors on the synthesis and antimicrobial activity of secondary metabolites. Most of the research focuses on the induction of bacteriocin synthesis [4], pigments [24], surfactants [25], antibiotics [21, 22, 26–28], and other secondary metabolites [29].

Bacteriocins. In the study [4], it was found that the addition of supernatant after the cultivation of *S. aureus* ATCC 43090 (2 and 3%), *Bacillus* sp. ATCC 6633 (2 and 3%), *A. niger* (2 and 3%), or *S. cerevisiae* (3%) into the culture medium of bacteriocins producer *B. subtilis* NK16 was accompanied by a 2–4-fold increase in the synthesis of the final product compared to the controls without inductors. Bacteriocins exhibited high antimicrobial activity against cells of the inductor strains (*S. aureus* ATCC 43090, *Bacillus* sp. ATCC 6633, *A. niger*, and *S. cerevisiae)*: the growth inhibition zones were 27, 25, 25 and 21 mm, respectively.

Pigments. It was reported in the research [24] that the addition of supernatant after cultivation of the lactic acid bacteria *Leuconostoc mesenteroides* or *Lactobacillus plantarum* to the culture of *S. coelicolor* led to the production of the pigment prodigiosin, which is not typical for that microorganism.

Surfactants. The authors in the study [25] reported a 107.4% increase in

Table 2

Effect of live inductor cells on the synthesis and antimicrobial activity of secondary metabolites

Producer	Carbon source	Biological inductor	Concentration (activity) of secondary metabolites		Test-cultures for determining antimicrobial activity	Antimicrobial activity	References
			without inductor	with an inductor			
1	2	3	4	5	6	7	8
Bacteriocins							
Bacillus subtilis NK16	Dextrose	*Staphylococus aureus* ATCC 43090 / *Escherichia coli* / *Aspergillus niger* **(strain number not given)**	Bacteriocins 80 AU/ml	Bacteriocins 640 / 320 / 320 AU/ml	*Staphylococcus aureus* ATCC 43090	Growth inhibition zone of 27 mm (100 µl/disc)	4
					Escherichia coli **(strain number not given)**	Growth inhibition zone of 21 mm (100 µl/disc)	
					Aspergillus niger **(strain number not given)**	Growth inhibition zone of 21 mm (100 µl/disc)	
Lactobacillus paracasei HD1-7	Glucose	*Bacillus subtilis* ATCC 11774	Paracin 1.7 60 AU/ml	Paracin 1.7 105 AU/ml	-----	N.d.	16
Microbial surfactants							
Bacillus amyloliquefaciens CX-20	Glucose	*Aspergillus oryzae* 92011/ *Trametes* sp. 48424	Iturin A 1.74 g/l	Iturin A 1.88 / 1.95 g/l	-----	N.d.	18
Serratia marcescens **(strain number not given)**	Trypton, yeast extract	*Escherichia coli* / *Staphylococcus aureus* **(strain number not given)**	0.27 (units of emulsifying activity)	0.46 / 0.94 (units of emulsifying activity)	*Staphylococcus aureus* **(strain number not given)**	Growth inhibition zone of 14 mm (40 µg/disc)	17
					Klebsiella pneumonia **(strain number not given)**	Growth inhibition zone of 16 mm (40 µg/disc)	
					Escherichia coli **(strain number not given)**	Growth inhibition zone of 14 mm (40 µg/disc)	
					Bacillus subtilis **(strain number not given)**	Growth inhibition zone of 16 mm (40 µg/disc)	

Table 2 (Continued)

1	2	3	4	5	6	7	8
Antimicrobial pigments							
Pseudomonas aeruginosa **(strain number not given)**	Trypton, yeast extract	*Staphylococcus aureus* / *Klebsiella pneumonia* / *Bacillus subtilis* **(strain number not given)**	Pyocyanin 17 mg/ml	Pyocyanin 38 / 40 / 33 mg/ml	*Staphylococcus aureus* **(strain number not given)** *Bacillus subtilis* **(strain number not given)**	Growth inhibition zone of 34 mm (40 μg/disc) Growth inhibition zone of 28 mm (40 μg/disc)	19
					Escherichia coli **(strain number not given)**	Growth inhibition zone of 26 mm (40 μg/disc)	
					Klebsiella pneumonia **(strain number not given)**	Growth inhibition zone of 38 mm (40 μg/disc)	
Serratia marcescens S23	Starch	*Escherichia coli* / *Saccharomyces cerevisiae* / *Bacillus subtilis* **(strain number not given)**	Prodigiosin 0.45 g/l	Prodigiosin 2.5 / 3.1 / 0.65 g/l	-----	N.d.	8
Serratia marcescens **(strain number not given)**	Trypton, yeast extract	*Bacillus subtilis* / *Escherichia coli* / *Saccharomyces cerevisiae* **(strain number not given)**	Prodigiosin 100 mg/ml	Prodigiosin 250 / 220 / 170 mg/ml	-----	N.d.	9
Antibiotics							
Streptomyces lavendulae ACR-DA1	Dextrine	*Bacillus cereus* / *Saccharomyces cerevisiae* **(strain number not given)**	Valinomycin 50 mg/ml	Valinomycin 81 / 67 mg/ml	-----	N.d.	20
Streptomyces rimosus M527	Soybean flour, mannitol	*Saccharomyces cerevisiae* / *Fusarium oxysporum* f. sp. *cucumerinum*	Rimocidin 0.21 g/l	Rimocidin 0.3 / 0.39 g/l	-----	N.d.	21
Streptomyces natalensis HW-2	Glucose, maltose	*Aspergillus niger* AS 3.6472 / *Penicillium chrysogenum* AS3.5163	Natamycin 0.639 g/l	Natamycin 0.799 / 0.875 g/l	-----	N.d.	22

Table 2 (End)

1	2	3	4	5	6	7	8
Pseudomonas aeruginosa **(strain number not given)**	Trypton, yeast extract	*Escherichia coli*, або *Bacillus subtilis* / *Saccharomyces cerevisiae* **(strain number not given)**	Phenazine 7.6 mg/ml	Phenazine 18.8 / 13.8 / 14.5 mg/ml	*Escherichia coli* **(strain number not given)**	Growth inhibition zone of 1.6 mm (200 µl/disc)	11
					Bacillus subtilis **(strain number not given)**	Growth inhibition zone of 2.9 mm (200 µl/disc)	
					Saccharomyces cerevisiae **(strain number not given)**	Growth inhibition zone of 4.3 mm (200 µl/disc)	
Other secondary metabolites							
Saccharopolyspora erythraea ATCC 31772	Dextrose	*Fusarium pallidoroseum* ATCC 74289	N-Demethylophiosetin* Palidorosetin A* Palidorosetin B* (tetraminic acid analogues)	-----	-----	N.d.	23

Notes. N.d. — not determined; * — synthesis of new compounds not typical for monoculture.

were synthesized, minimum inhibitory concentrations of which against *B. subtilis* BT-2 and *S. aureus* BMC-1 were 5.6-11 times lower compared to those obtained for biosurfactants synthesized in a medium without the inductor.

In the study [32], it was found that the introduction of live *B. subtilis* BT-2 cells into the *R. erythropolis* culture medium with ethanol (2%, v/v) was accompanied by the synthesis of surfactants that were characterized by higher antimicrobial activity than surfactants synthesized in the medium without inductor. The minimum inhibitory concentrations against test-cultures of these biosurfactants were 6 µg/ml, which were 8 times lower than the values established for the preparations obtained without the inductor. In further research [33], heat-inactivated cells of *B. subtilis* BT-2 were used instead of live cells of the inductor. It was established that the antimicrobial activity of surfactants synthesized under such cultivation conditions was 16-32 times higher than that of preparations formed during the cultivation of IMV As-5017 strain in medium without an inductor.

The summarized information on the effect of live and inactivated *B. subtilis* BT-2 cells on the antimicrobial activity of *N. vaccinii* IMV B-7405, *A. calcoaceticus* IMV B-7241 and *R. erythropolis* IMV AS-5017 biosurfactants is shown in Table 4.

These data showed that the antimicrobial activity of surfactants (*R. erythropolis* IMV Ac-5017 [32, 33], *N. vaccinii* IMV B-7405 [30] and *A. calcoaceticus* IMV B-7241 [31]) was almost unaffected by the physiological state of the inductors (live or inactivated cells).

It should be noted that there are only few reports on the influence of inductors in various physiological states on the biological activity of microbial surfactants (see Tables 1–3). In contrast to those described in the available literature, the synthesis of the surfactants we have studied is based on low-cost substrates, including industrial waste (crude glycerol, used sunflower oil). Additionally, synthesized in the presence of biological inductors biosurfactants by *R. erythropolis* IMV Ac-5017, *N. vaccinii* IMV B-7405, and *A. calcoaceticus* IMV B-7241 showed exceptionally high antimicrobial activity (MIC values ranging from 0.85 to 20 µg/ml, see Table 4).

lipopeptide synthesis (name not given) by *Streptomyces bikiniensis* strain HD-087 in the presence of supernatant after cultivation of *Magnaporthe oryzae* Guy11. The authors suggested that one of the mechanisms of induction is the presence of fungal intermediates in the supernatant, which are precursors to the biosynthesis of fatty acids, the components of lipopeptides.

Antibiotics. The influence of the supernatant after inductor cultivation on the synthesis of antibiotics by actinobacteria of the genus *Streptomyces* was studied in [21, 22, 26–28]. Most of the articles are devoted to the synthesis of natamycin, and micromycete supernatant was used as an inductor in these studies.

For instance, the authors of [21] showed that the introduction of *F. oxysporum* f. sp. *cucumerinum* or *S. cerevisiae* supernatant into the *S. rimosus* M527 culture medium was accompanied by an increase in rimocidin synthesis by 42 and 72%, respectively, compared to the values without inductors.

In the work [22], it was found that the synthesis of natamycin by strain *S. natalensis* HW-2 increased by 1.3 to 3 times with the addition of supernatant of micromycetes *A. niger* AS 3.6472 (1.5 and 2%) or *P. chrysogenum* AS 3.5163 (1.5 and 2%). At the same time, the presence of *S. cerevisiae* AS 2.2081 supernatant (2.5%) in the culture medium of the producer had practically no effect on the synthesis of the antibiotic.

In the study [26], the synthesis of natamycin by *S. natalensis* HW-2 strain was increased by 32% when *P. chrysogenum* AS 3.5163 supernatant was added to the culture medium, which was caused by overexpression of the ilvH gene in the antibiotic producer under such culture conditions. In addition, the method of RNA sequencing showed changes in the transcriptome of *S. natalensis* HW-2 under the influence of the inductor supernatant. In further studies [27], it was found that when the concentration of *P. chrysogenum* AS 3.5163 supernatant was increased to 6%, and introduced into the *S. natalensis* HW-2 cultivation medium after 24 h from the start of the process, the concentration of natamycin doubled compared to cultivation without inductor.

In the presence of the supernatant after the cultivation of *A. niger* or *P. chrysogenum* (5%) in the cultivation medium of *Streptomyces natalus* N5, there was a 1.7- to 2-fold increase in the concentration of natamycin was observed compared to the values without inductors [28].

Other secondary metabolites. In 2020 [29], researchers isolated, but did not characterise, a group of antibacterial metabolites from the culture of *Promicromonospora kermanensis* DSM 45485 in the presence of *P. aeruginosa* UTMC 1404 supernatant. The obtained compounds exhibited antimicrobial activity against *S. aureus* UTMC 1401: the growth inhibition zone was 23 mm.

In Table 3, we summarised the effect of the supernatant after cultivation of biological inductors on the production and antimicrobial activity of secondary metabolites. As well as in the presence of live (see Table 1) or inactivated (see Table 2) inductor cells, the use of the supernatant led to an intensification of the synthesis of bacteriocins, surface-active lipopeptides, and antibiotics.

The effect of prokaryotic inductors on the antimicrobial activity of microbial surfactants of *Nocardia vaccinii* IMV B-7405, *Acinetobacter calcoaceticus* IMV B-7241 and *Rhodococcus erythropolis* IMV AS-5017

Our own experimental studies [30–33] have shown the possibility of regulating the antimicrobial activity of surfactants of *N. vaccinii* IMV B-7405, *A. calcoaceticus IMV* B-7241 and *R. erythropolis* IMV AS-5017 by introducing live and inactivated cells of *B. subtilis* BT-2 and *E. coli* IEM-1 into the medium with ethanol and industrial waste (waste sunflower oil, crude glycerol).

In the study [30], it was observed that the presence in medium of *N. vaccinii* IMV B-7405 cultivation with sunflower oil (2% v/v), both live and inactivated cells of *B. subtilis* BT-2 led to the production of biosurfactants, antimicrobial activity of which against test cultures (*B. subtilis* BT-2, *S. aureus* BMC-1) was 3-6 times higher compared to the levels established for biosurfactants synthesized under cultivation of strain IMV B-7405 without the inductors.

Similar patterns were demonstrated in studies with another biosurfactant producer — *A. calcoaceticus* IMV B-7241 [31]. The results showed that live cells of *B. subtilis* BT-2 were more effective inductors: in their presence in a cultivation medium containing crude glycerol (5% v/v), biosurfactants

Table 3

Effect of supernatant after cultivation of inductors on the synthesis and antimicrobial activity of secondary metabolites

Producer	Carbon source	Biological inductor	Concentration (activity) of secondary metabolites		Test-cultures for determining antimicrobial activity	Antimicrobial activity	References
			without inductor	with an inductor			
1	2	3	4	5	6	7	8
Bacteriocins							
Bacillus subtilis NK16	Dextrose	*Staphylococus aureus* ATCC 43090 / *Bacillus* sp. ATCC 6633 / *Saccharomyces cerevisiae* / *Aspergillus niger* **(strain number not given)**	Bacteriocins 80 AU/ml	Bacteriocins 160 / 160 / 320 / 160 AU/ml	*Staphylococcus aureus* ATCC 43090	Growth inhibition zone of 27 mm (100 µl/disc)	4
					Bacillus sp. ATCC 6633	Growth inhibition zone of 25 mm (100 µl/disc)	
					Saccharomyces cerevisiae	Growth inhibition zone of 25 mm (100 µl/disc)	
					Aspergillus niger	Growth inhibition zone of 21 mm (100 µl/disc)	
Antimicrobia pigments l							
Streptomyces coelicolor **(strain number not given)**	Dextrin, peptone	*Leuconostoc mesenteroides* / *Lactobacillus plantarum* **(strain number not given)**	Prodigiosin* (concentration not given)		-----	N.d.	24
Microbial surfactants							
Streptomyces bikiniensis HD-087	Starch, glucose	*Magnaporthe oryzae* Guy11	Lipopeptides 285.6 mg/l	Lipopeptides 531.3 mg/l	-----	N.d.	25
Antibiotics							
Streptomyces rimosus M527	Soybean flour, mannitol	*Saccharomyces cerevisiae* / *Fusarium oxysporum* f. sp. *cucumerinum*	Rimocidin 0.21 g/l	Rimocidin 0.36 / 0.3 g/l (polyene macrolide)	-----	N.d.	21

Table 3 (Continued)

1	2	3	4	5	6	7	8
Streptomyces natalensis HW-2	Glucose, maltose	*Saccharomyces cerevisiae* AS 2.2081 / *Aspergillus niger* AS 3.6472 / *Penicillium chrysogenum* AS 3.5163	Natamycin 0.639 g/l	Natamycin 0.7 / 1.62 / 1.84 g/l (polyethylene antibiotic)	----	N.d.	22
Streptomyces natalensis HW-2	Oat	*Penicillium chrysogenum* AS 3.5163	Natamycin 0.85 g/l	Natamycin 1.25 g/l	----	N.d.	26
Streptomyces natalus N5	Glucose	*Aspergillus niger* / *Penicillium chrysogenum* **(strain number not given)**	Natamycin 0.85 g/l	Natamycin 1.44 / 1.69 g/l	----	N.d.	28
Streptomyces natalensis HW-2	Glucose	*Penicillium chrysogenum* AS 3.5163	Natamycin 1.2 g/l	Natamycin 2.49 g/l	----	N.d.	27
Other secondary metabolites							
Promicromonospora kermanensis DSM 45485	Dextrose	*Pseudomonas aeruginosa* UTMC 1404	The name is not given (group of antibacterial metabolites)		*Staphylococcus aureus* UTMC 1401	Growth inhibition zone of 23 mm (50 µg/disc)	29

Notes. N.d. — not determined; * — synthesis of new compounds not typical for monoculture.

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Analysis of the published literature on the effect of biological inductors of various physiological states on the synthesis of antimicrobial secondary metabolites (see Tables 1–3) showed that the mechanisms responsible for increasing the synthesising ability of antimicrobial compound producers are currently unclear. The researchers identified some of them:

1) an increase in the synthesis of antimicrobial compounds as a protective mechanism against a competitive organism; the producer recognised particular proteins or receptors of inactivated inductor cells [4];

2) the presence of heat-inactivated inductor cells affected the expression of genes related to the synthesis of antimicrobial peptides [6];

3) the mechanism of interaction may be due to direct contacts between the cells [8];

4) inactivated inductor cells contain lysed compounds that can perform the role of precursors for metabolite production [10];

5) production of specific metabolites by fungi that stimulated transcriptional activation of a silent cluster of biosynthetic genes for the biosynthesis of antimicrobial compounds [27].

The available literature on the effect of biological inductors on the synthesis of antimicrobial compounds is much less than the literature concerning co-cultivation of microorganisms [1–3]. At the same time, the using biological inductors to obtain novel antimicrobial metabolites [12-15, 23, 29], increase the synthesis or activity of already known ones [4–11, 16–22, 25–28] is more technologically advanced, as such processes are easier to scale and implement (in particular, using inactivated inductor cells).

At the same time, it is necessary to pay attention to the costly growth substrates used for the biosynthesis of secondary metabolites. Obviously, the next stage of research should be devoted to finding lower-cost substrates for biosynthesis and optimising the composition of culture media. In addition, different scientists have often used the same biological inductors for different producers of various secondary metabolites. Expanding the range of both pro- and eukaryotic inductors should also be taken into account in further studies.

Table 4

Antimicrobial activity of microbial surfactants synthesized by *N. vaccinii* IMV B-7405, *A. calcoaceticus* IMV B-7241 and *R. erythropolis* IMV AS-5017 in the presence of live and inactivated *Bacillus subtilis* BT-2 cells

Producer	Carbon source	Physiological state of inductor cells	Test culture	Minimum inhibitory concentrations (μg/ml) of surfactants synthesized		References
				without inductor	with an inductor	
Nocardia vaccinii IMV B-7405	Used sunflower oil	Live	*Bacillus subtilis* BT-2	120	20	30
			Staphylococus aureus BMC-1	80	20	
		Heat-inactivated	*Bacillus subtilis* BT-2	120	40	
			Staphylococus aureus BMC-1	80	20	
Acinetobacter calcoaceticus IMV B-7241	Crude glycerol	Live	*Bacillus subtilis* BT-2	9.8	0.85	31
			Staphylococus aureus BMC-1	4.9	0.85	
		Heat-inactivated	*Bacillus subtilis* BT-2	9.8	2.2	
			Staphylococus aureus BMC-1	4.9	2.2	
Rhodococcus erythropolis IMV Ac-5017	Ethanol	Live	*Bacillus subtilis* BT-2	48	6	32
			Staphylococus aureus BMC-1	48	6	
		Heat-inactivated	*Bacillus subtilis* BT-2	96	3	33
			Staphylococus aureus BMC-1	48	3	

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ВПЛИВ БІОЛОГІЧНИХ ІНДУКТОРІВ НА СИНТЕЗ ТА БІОЛОГІЧНУ АКТИВНІСТЬ МІКРОБНИХ МЕТАБОЛІТІВ

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Зростаюча антибіотикорезистентність є серйозною проблемою для людства. Спільне (комбіноване) культивування мікроорганізмів є перспективним методом для отримання нових антимікробних метаболітів. Перспективним варіантом спільного культивування мікроорганізмів є використання так званих біологічних індукторів.

Мета огляду — узагальнення наявних у літературі наукових досліджень, що стосуються впливу фізіологічно різних типів біологічних індукторів на синтез та біологічну активність мікробних вторинних метаболітів.

Аналіз даних літератури показав, що у таких дослідженнях живі або інактивовані клітини індуктора вносять у середовище у значно нижчій концентрації порівняно з клітинами продуцента цільових метаболітів, або як індуктор використовують супернатант (фільтрат) після вирощування конкурентного мікроорганізму.

Згідно даних літератури і власних експериментальних досліджень використання індукторів є ефективним способом не тільки інтенсифікації синтезу бактеріоцинів, поверхнево-активних речовин, антибіотиків, а й підвищення їх біологічної активності, а також часто супроводжується утворенням нових антимікробних сполук, не характерних для продуцента.

Разом з тим потребують подальших досліджень механізми дії індукторів на синтез біологічно активних сполук, оскільки за даними літератури їх внесення у культуру продуцента не завжди супроводжувалося інтенсифікацією синтезу цільових продуктів. Крім того, біологічна активність вторинних метаболітів залежить від умов культивування продуцента, у тому числі від наявності біологічних індукторів у середовищі. Тому важливим є проведення подальших досліджень щодо взаємодії продуцентів з конкурентними мікроорганізмами для контролю біологічної активності синтезованих метаболітів. Необхідним є також пошук дешевших субстратів для біосинтезу вторинних метаболітів, оптимізація складу поживних середовищ і розширення спектру як про-, так і еукаріотичних індукторів.

Ключові слова: спільне культивування; індуктор; фізіологічний стан індуктора; антимікробні метаболіти.