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Effect of nutrients and culture conditions on antibiotic synthesis in Streptomycetes

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ABSTRACT

Antibiotics are important secondary metabolites that produced through complex biosynthetic pathways by some microorganisms in specific conditions. They have been the best option for many infectious diseases in the past decades. Diversity of antibiotic groups makes them to be effective for a wide range of microbial infections. These valuable compounds are produced mostly by genus Streptomyces in specific conditions. Optimization of medium composition and fermentation process are of vital importance in pharmaceutical industries for increasing antibiotic production in large scale and minimization of operating costs. This review aims to communicate about different factors affecting on antibiotic synthesis in streptomycetes..

INTRODUCTION

Antibiotics are of the most important secondary metabolites produced by microorganisms and specifically inhibit the growth of other bacteria or fungi or destroy them. Their specific action on particular groups of living organisms makes them valuable compounds in medical and agricultural uses [1]. Many researchers have become interested in antibiotics because of their diversity, complexity and specific biological functions. Among microorganisms, streptomyces is the largest antibiotic-producing genus including gram positive aerobic filamentous bacteria and of medical and industrial importance.

Many experimental studies have focused on various methods such as optimization of growth conditions (pH, temperature, aeration) and medium composition (carbon, nitrogen and phosphate sources), for increasing antibiotic production in different strains. Determination of factors influence on synthesis of antibiotics would be very beneficial for designing rational methods for better yields of antibiotic production. like other secondary metabolites, antibiotics are often produced after rapid growth phase of microorganisms and during their stationary phase as a result of carbon or nitrogen limitation [2]. This occurs at a time when one of the key nutrients i.e carbon, nitrogen or phosphate depleted and results in slow growth rate [3].

EFFECT OF CARBON SOURCE

Antibiotic synthesis strongly related to components and their concentrations in culture media. Carbon source usually constitute the major part of a culture media and because of this, it has been the subject of many studies on optimization antibiotic production. Simply metabolizable carbon sources generally repress production of many antibiotics [4]. Glucose and other carbohydrates have an adverse effect on antibiotic synthesis when using as the sole carbon source [5]. It has reported that glucose decreases production of oleandomycin [6], avilamycin [7], nystatin [8], Spiramycin [9] ,Neomycin [10]. In many cases, it has reported that glucose suppress the enzymes involved in antibiotic biosynthesis. For instance, glucose has an adverse effect on phenoxazinone synthetas and N-acetyl kanamycin amidohydrolase action, two enzymes in biosynthetic pathways of actinomycin and kanamycin respectively [11], [12].

Negative effect of carbohydrates, can be related to effect of growth rate on antibiotic biosynthesis. Studies on fermentation media, showing that polysaccharides are generally the best carbon sources for antibiotic production as they support a slow growth rate which is desirable for antibiotic production (Table 1).

EFFECT OF NITROGEN SOURCE

Many Studies have proved that antibiotic synthesis strongly related to nature and concentration of nitrogen source in culture of strptomycetes. Quickly metabolizable nitrogen sources, usually

Table 1: Best carbon sources for antibiotic production by different microorganisms

Carbon source	Antibiotic	Microorganism	Reference
Lactose	AK-111-81	*Streptomyces hygroscopicus*	[2]
Starch	Tylosin	*Streptomyces fradiae*	[13]
Blackstrap molasses	Oxytetracycline	*Streptomyces rimosus*	[14]
Dextrin	Spiramycin	*Streptomyces ambofaciens*	[15]
Starch	Kanamycin	*Streptomyces kanamyceticus*	[16]
Glycerol	Clavulanic acid	*Streptomyces clavuligerus*	[17]
Dextrose	Kanamycin	*Streptomyces kanamyceticus*	[18]
Starch	Antifungal antibiotics	*Streptomyces rimosus*	[19]
Starch	Nystatin	*Streptomyce noursei*	[20]

decrease antibiotic production in different microorganisms as well as streptomycetes [21]. Different studies have shown that complex nitrogen sources such as soybean meal, corn steep liquor and yeast extract can increase the production of antibiotics produced by Streptomycetes which can be attributed to slow decomposition of these compounds in the medium [22,23,24]. It seems using inorganic nitrogen sources which lead to high ammonium concentrations in culture medium, suppress antibiotic production in many microorganisms. As a result of this, medium containing ammonium salts as the sole nitrogen sources are not suitable for antibiotic production and supplemented with high concentrations of complex nitrogen sources in antibiotic production industries. Table 2 shows best nitrogen sources for antibiotic production in microorganisms.

EFFECT OF PHOSPHATE SOURCE

Phosphate is one of the crucial components for growth of living organisms as it is essential for biosynthesis of DNA, RNA and proteins. It also involves in respiration, energy metabolism and transport [31]. Phosphate controls biosynthesis of secondary metabolites in streptomycetes and other microorganisms. High concentrations of Phosphate, inhibits secondary metabolites production while favored growth of microorganisms [32]. Many antibiotics are produced only when phosphate is the growth limiting nutrient [33]. In many cases, antibiotic synthesis starts after depletion of phosphate source. When phosphate concentration decreases slowly in the fermentation medium, microorganisms starts to produce metabolites to survive against their rivals [34]. Phosphate concentration more that 10 mM suppress antibiotic biosynthesis in most microorganisms [9].

Additional amounts of inorganic phosphate suppress the actinomycin and tetracycline biosynthesis [35]. In addition, biosynthesis of many antibiotics such as actinhorhodin [36], tetracycline and actinomycin [35], candicidin [37-38], undecylprodigiosin [39], Tylosine [40], Spiramycin[9], avilamycin [7], animomycin [41-42] negatively controlled by phosphate.

EFFECT OF OXYGEN

Most of antibiotic-producing microorganisms are aerobic microorganism. Thus oxygen supply has a great impact on their growth and antibiotic production. As a consequence of this, aeration is one of the important factors considered in optimization of fermentation condition for antibiotic production. The importance of dissolved oxygen (DO) concentrations on antibiotic production has been established in different fermentations [29,43,44,45]. It has shown that effect of oxygen limitation on secondary metabolites production is similar to substrate limitations and stimulates production of antibiotics in most streptomycetes. Oxygen limitation induces erythromycin production in *S.erythreae* while this antibiotic also could be excreted in oxygen sufficiency [46]. production of cephamicin c by *streptomyces clavuligeus*, revealed when dissolved oxygen levels is held close to saturation in exponential growth phase, antibiotic synthesis and its duration increase [47].

Based on Chen and his coworkers studies, oxygen has a significant impact on biosynthetic enzymes involved in antibiotic production. In tylosin production by *Streptomyces fradiae*, the growth rate and antibiotic yield were significantly lower at low dissolved oxygen concentration, compared to high DO [48]. Similarly, in kanamycin production by 3 mutants of *Streptomyces kanamyceticus* sufficient aeration was one of the key factors for

Table 2: Best nitrogen sources for antibiotic production in different microorganisms

Nitrogen source	Antibiotic	Microorganism	Reference
Ammonium succinate	AK-111-81	*Streptomyces hygroscopicus*	[2]
Aspartic acid	Olendomycin	*Streptomyces antibioticus*	[6]
Malt extract	Neomycin	*Streptomyces fradiae*	[10]
Urea	Oxytetracycline	*Streptomyces rimosus*	[14]
Soytone	Kanamycin	*Streptomyces kanamyceticus*	[16]
Yeast extract	Avermectin	*Streptomyces avermitilis*	[22]
Aspartate	Clavulanic acid	*Streptomyces clavuligerus*	[25]
Yeast extract and beef extraxt mixture	Natamycin	*Streptomyces natalensis*	[26]
Soybean meal	Tylosin	*Streptomyces fradiae*	[27]
Soybean meal	Actinomycin	*Streptomyces sindenesis*	[28]
Malt extract	A new antibiotic	*Streptomyces albovinaceus*	[29]
Soybean meal	Anisomycin	*Streptomyces griseolus*	[30]

Table 3: Inducers of antibiotic synthesis in different microorganisms

Inducer	Antibiotic	Microorganism	Reference
5,5-diethylbarbituric acid	Galirubins	*Streptomyces galilaeus*	[49]
Phenyl acetic acid	Tetracyclin	*Streptomyces aureofaciens*	[50]
Valine	Tylosine	*Streptomyces fradia*	[51]
Arginine	Clavulanic acid	*Streptomyces clavuligerus*	[52]
Propanol	Erythromycin	*Streptomyces erythreus*	[53]
Soybean oil	Spiramycin	*Streptomyces ambofaciens*	[54]
Vegetable oils	Cephamycin-C	*Streptomyces sp.P6621*	[55]
Rapeseed oil	Erythromycin	*Saccharopolysporaerythraea*	[56]
Propyl alcohol	Spiramycin	*Streptomyces ambofaciens*	[54]

better yields [16]. All these results demonstrate the importance of controlling DO in fermentation medium for better yields of antibiotics.

EFFECT OF TEMPERATURE

Temperature affects on growth rate and enzymetic reactions involved in metabolite synthesis [57]. The optimum temperature for growth of most streptomycetes is close to 30^{0}C. However, maximum antibiotic production might occur at a same or different temperature. The optimum temperature for growth and antibiotic production in *Streptomyces aureofaciens* MY18 and *Streptomyces roseviolaceus* MR13 was 30 ^{0}C [58]. Similarly, the best temperature for neomycin, kanamycin and anicomycin production by *Streptomyces fradiae*, *Streptomyces kanamyceticus* and *Streptomyces griseolus* is 30 ^{0}C [16],[10],[30]. Monamycin and erythromycin production at 26^{0}Cand 33^{0}C were maximum and the optimum temperature for antifungal antibiotics production by *Streptomyces rimosus* is 28^{0}C ([59],[60],[19]). Nevertheless, antibiotic production might happen on higher temperatures in specific streptomycetes. For instance, maximum granaticin production, a polyketide-derived antibiotic occurs at 45 ^{0}C [61].

EFFECT OF pH

pH has a significant impact on growth kinetics of microorganisms as enzymes activities in producing strains are strongly sensitive to its changes [62]. Most of bacterial strains have their optimum growth on neutral environments. As a result of this, most antibiotics are optimally produced in pH close to 7.0. For instance, granaticin production was highest when initial pH of culture medium adjusted between 6.5 and 7.0 [63]. Similarly, maximum antibiotic production by *S.albovinaceus* was observed at pH 7.2 and optimum pH for oxytetracycline production was 7.0 ([29],[64]. However, for some antibiotic fermentation such as kanamycin production by *Streptomyces kanamyceticus* pH above 8 is favored [16].

EFFECT OF INDUCTION

Induction of antibiotic synthesis occurs when specific compounds are added to fermentation broth during growth phase of microorganism. Addition of precursors of antibiotic biosynthesis to the fermentation broth can induce antibiotic production. Amino acids are precursors of most antibiotics and added to media in industrial processes [65],[66]. Short-chain fatty acids are also the precursors of macrolide antibiotics and provided from addition of vegetable oils into culture medium [67],[68]. However, in some cases, induction could be done by substances other than precursors [23]. Table 3 illustrates some of the inducers of antibiotic synthesis in different strains.

INHIBITION OF ANTIBIOTIC BIOSYNTHESIS

Duration of antibiotic synthesis varies in different strains and different environmental conditions. In streptomycetes, production phase usually is longer than exponential growth phase [7], [46], [53], [69].

Studies have shown some antibiotics including candihexin, chloramphenicol and staphylomycin among many others inhibit enzymes involved in their synthesis [69,70,71]. Therefore, cessation of antibiotic bio synthesis may be the result of accumulation of antibiotic in culture media and their inhibitory effect on biosynthetic enzymes.

CONCLUSION

Identification of factors affecting on antibiotic synthesis is of great importance in pharmaceutical industries. It provides strategies for increasing antibiotic production through optimization of growth and physiologic conditions. Using cheap complex substrates significantly influence on economics of processes and lead to reducing total costs. In addition, it leads to more rational studies for genetic manipulation in order to strain improvement.

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