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CHAPTER

c0019 # 19

Regulation and Role of Metal Ions in Secondary Metabolite Production by Microorganisms

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s0010 19.1 INTRODUCTION

p0115 Microbes are metabolically versatile and well-renowned for their ability to produce many bioactive secondary metabolites (SMs) with diverse biological activities. SMs are small, low molecular weight bioactive compounds that are naturally produced by numerous microbes, especially soil-dwelling bacteria, and fungi in response to environmental abiotic and biotic stimuli [1,2]. SMs exploited from these microbes for human therapeutics have a tremendous impact on society via their application in health, medicine, agriculture, and industry due to both detrimental (e.g., mycotoxins) and beneficial (e.g., antibiotics) effects on human endeavors [3,4]. The majority of clinically used pharmaceutical drugs are produced from microbes such as bacteria and fungi, as their genomes contain a large repertoire of SMs genes [5]. In microbes, several genes responsible for the biosynthesis of SMs are arranged in gene clusters, which are coordinately regulated by the cluster-specific transcription factors (TFs) [6,7]. With the remarkably rapid advancement in whole genomic sequencing technology, the genome sequences of many microbes such as *Streptomyces*, myxobacteria, and fungi have been decoded and it has become evident that each species consists of a large fraction of "silent" or "cryptic" biosynthetic gene clusters (BGCs) which are not expressed under standard laboratory culture conditions [8,9]. Significant research efforts of trying to unlock these unexplored cryptic BGCs have been made worldwide and in many cases successfully they have been

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accessed to identify unknown SMs using molecular, mathematical, and cultivation-based approaches [10–13]. The activation of these silent BGCs pathways can pave the way to the discovery of many novel bioactive SMs with the potential to rejuvenate stalled drug discovery pipelines. Strategies to activate these silent BGCs have been thus an area of major interest in recent years [14]. Up to now numerous strategies employing biological, chemical, or molecular elicitation have been implemented to induce silent BGCs [5,15–21]. Apart from genomic approaches, traditional approaches such as cocultivation (also called mixed fermentation) through an inducer and a recipient microorganism culture conditions and external cues have long been recognized as effective approached for inducing significant changes in the microbial metabolome [22,23]. In cocultivation, one attractive, affordable approach to induce cryptic BGCs involves the variation of culture media composition. The alteration of fermentation conditions, for instance through variation of macro- and micronutrient compositions in culture media, is a simple but very potent approach to activate the silent BGCs and to evaluate the metabolic potential of a microbial strain [24]. Besides the regulation within the silent BGCs, many environmental and nutritional factors control the biosynthesis of natural SMs, including nutrient concentrations, humidity, temperature, light, pH, and trace metals [4,8,25–27]. The influences of such factors are considered to be vital for optimization of the SM production. It has been appreciated for a long time that the chemical composition of the culture medium, and in particular the trace metals, can influence the production of SMs in microbes. The metals are one of the most crucial factors and their use serves as a promising approach for the activation of cryptic BGCs in microbes [28,29].

p0120 The regulatory effects of metals on SMs of microbes have been recognized for decades and have been well-documented for a variety of microorganisms [30–32]. For example, the role of iron in the regulation of diphtheria toxin production has been appreciated for more than 75 years [33]. SMs are often produced only within a limited range of culture conditions. Therefore, in order to observe/induce their production, one of the essential requirements is the presence of the appropriate trace metal to influence the metabolic processes through the global control of gene expression (Table 19.1), for example, iron regulation by Fur and DtxR. Additionally, a similar

t0010 **TABLE 19.1** Elicitation of Secondary Metabolite Production by Metal Ions in Microorganisms

Trace metal	*Microbes*	Secondary metabolite	Functions	References
Manganese (Mn)	*Streptomyces coelicolor*	Actinorhodin	Manganese caused a reduction in actinorhodin titers	[34]
	Streptomyces actuosus Z-10	Nosiheptide	$MnSO_4$ addition to the medium has a significant effect on production	[35]
	Streptomyces lomondensis S015	Lomofungin	$MnCl_2$ addition stimulated lomofungin biosynthesis	[36]
	Bacillus licheniformis ATCC 10716	Bacitracin	Manganese increasing the bacitracin synthetase activity	[37]
	Actinomycetes strain LAM2	Unknown antibiotic	Manganese plays an important role in growth and antibiotic production	[38]
	Aspergillus niger	Malformin	The addition of manganese inhibit the biosynthesis of malformin	[39]
	Penicillium urticae	Patulin	Manganese play an important role in patulin fermentation	[40,41]
	Streptoverticillium kitasatoensis	Leucomycin	$MnSO_4$ and $MnCl_2$ in high quantity suppressed the production of leucomycin	[42]
Copper (Cu)	*S. coelicolor*	Actinorhodin	Production decreased with the addition of Cu to the fermentation medium	[34]
	S. actuosus Z-10	Nosiheptide	Production decreased with the addition of $CuSO_4$ to the medium	[35]
	Streptomyces halstedii	Geosmin	Elevated concentrations of Cu prevented geosmin production	[43]
	Paraphaeosphaeria quadriseptata	Polyketide monocillin I	Copper increases the production of the polyketide monocillin I	[44]

(*Continued*)

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TABLE 19.1 (*Continued*)

Trace metal	*Microbes*	Secondary metabolite	Functions	References
Nickel (Ni)	*S. coelicolor*	Actinorhodin	The addition of nickel in cultures inhibited biosynthesis	[34]
	Streptomyces acidiscabies E13	Melanin-like pigment Unknown antibiotic	Synthesis induced by nickel supplementation Synthesis by mycelial fraction grown in nickel-supplemented medium	[45]
	Streptomyces ciscaucasicus PT1	Unknown antibiotic	When mycelial fraction grow in nickel-supplemented medium	[45]
	Streptomyces purpurascens	Unknown antibiotic	Produced by supernatant fraction in the presence of nickel	[45]
	Streptomyces lincolnensis	Unknown antibiotic	Biosynthesis by mycelial fraction in the presence of nickel	[45]
Iron (Fe)	*Streptomyces antibioticus*	Antimycin A	Iron inhibits the formation of siderophore-like secondary metabolites antimycin A	[46]
	Streptomycetes avermitilis K139	Nocardamine	Fe-dependent IdeR protein regulates the production of nocardamine by binding to the sidABCD operon	[47]
	Aspergillus terreus	Terrein	Lack of iron induced production	[48]
Zinc (Zn)	*Streptomyces flavotricini*	Streptothricin	Zinc (0.6 μM) concentration enhances the streptothricin production	[49]
	Streptomyces griseus	Candicidin	Zinc (500 μM) concentration produced maximum amount of candicidin	[50]
	Streptomyces cinnamonensis	Monensin	Zinc concentration inhibits the biosynthesis of monensin	[51]
	Aspergillus parasiticus	Versicolorin A Coelibactin	Zinc inhibits the biosynthesis of coelibactin	[52]
	Alternaria alternata	Alternariol and Alternariol methyl ether (AME)	AOH and AME production is absolutely dependent on zinc	[53]
	P. urticae	Patulin	—	[54]
	A. terreus	Lovastatin	Zinc influences the increased production of lovastatin	[34]
	Aspergillus ochraceus NRRL3174	Ochratoxin A	Zinc increases the biosynthesis of ochratoxin	[55,56]
	Penicillium citrinum	Citrinin	Zinc increases the biosynthesis of citrinin in idiophasic stage	[57]
	Streptomyces resistomycificus	Resistomycin	Zinc-binding site and its biosynthesis are catalyzed by RemF polyketide cyclase	[58]
	Sclerotium rolfsii	Scleroglucan	Zinc promotes the biosynthesis of scleroglucan	[59]
	Fusarium moniliforme	Fusarin C	Increases the biosynthesis of fusarin C	[60,61]
	Aspergillus glaucus	Aspergiolide	Inhibits the biosynthesis of aspergiolide	[62]
	Pseudomonas fluorescens	2,4-diacetylphloroglucinol (DAPG)	Actinorhodin production is inhibited by zinc	[43]
	S. griseus IMRU350	Candicidin	Biosynthesis of undecylprodigiosin is influenced by Zn^{2+} availability	[32]
	S. coelicolor	Undecylprodigiosin	Influenced by the amount of Zn	[63]
	S. halstedii	Nosiheptide	Production of nosiheptide is decreased upon addition of $ZnSO_4$	[64]

(*Continued*)

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TABLE 19.1 (*Continued*)

Trace metal	*Microbes*	Secondary metabolite	Functions	References
Cadmium	*A. parasiticus*	Versicolorin	Exposure of cadmium leads into inhibition of synthesis of versicolorin	[52]
	Rhizobium leguminosarum	Protein and glutathione syntheses	Inhibition of protein and glutathione syntheses	[65,66]
	Pseudomonas brassicacearum	Citric acid	Shift in metabolic pathway from citric acid to anaerobic metabolism	[67,68]
	Staphylococcus epidermis	Inositol phosphate metabolism	Cadmium also activates the inositol phosphate metabolism pathway which plays a crucial role in Ca^{2+} communications and cyclic ADP ribose pathway, which is a secondary messenger for mobilization of Ca^{2+}. Cadmium promotes biofilm formation at low concentration biofilm formation, activates the inositol phosphate metabolism and cyclic ADP ribose pathway necessary for mobilization of Ca^{2+}	[69]
Cobalt	*S. griseus*	Anthracyclin	Cobalt stimulates the production	[70]
	Streptomyces rishiriensis	Actinorhodin	Biosynthesis is increased by the addition of cobalt	[71]
	S. coelicolor	Prodigiosins, Undecylprodigiosins	High concentration of cobalt reduced the biosynthesis	[34]
	A. glaucus	Streptorubin B	Cobalt stimulates the biosynthesis and production of high molecular weight compound at higher concentration	[72]
		Coumermycin A1	Increases the production of coumeromycin A1	[71]
		Aspergiolide A	Increases the biosynthesis of aspergioloide A	[73,74]
	Fusarium graminearum	Acety deoxynivalenol	Cobalt ions stimulate the production of acety deoxynivalenol	[83]
		Spiramycins	Cobalt stimulates the production of spiramycin II and III	[83]
		Gentamycin	Increases the biosynthesis of gentamicin C1 and C2 and promotes the methylation	[75]
Scandium (Sc)	*Streptomyces* sp. YB-1	Naphthoquinone	Expression occurred in the presence of REEs	[76]
	S. coelicolor	Actinorhodin	Enhanced production occurred at 10–100 μM scandium concentrations	[77]
	S. antibioticus and *S. parvulus*	Actinomycin D	Antibiotic production by upregulating antibiotic activator transcripts and decrease in the bacterial alarmone ppGpp levels by binding of Sc to ribosome	[77]
	S. griseus	Streptomycin		
	Bacillus subtilis	Bacilysin	Effective in upregulating antibiotic production, Mechanism of action unknown	[9]
Lanthanum (La)	*S. coelicolor*	Actinorhodin	Low concentrations of lanthanum enhanced production and activated the expression of silent and poorly expressed genes belonging to nine secondary metabolite–biosynthetic gene clusters	[77]
Yttrium (Y), Cerium (Ce), and Europium (Eu)	*S. coelicolor*	Actinorhodin	Provokes antibiotic production	[77]

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type of other proteins may influence gene expression in response to the varying levels of other metal ions such as copper and zinc. The controls which regulate the production of SMs are essentially the same as the regulatory mechanisms found to operate in primary metabolism. The levels of induction, repression, or even inhibition are dependent on various types and the amount of metals in the culture media. Numerous reports have been published on the importance of metal ions in SM biosynthesis, particularly for antibiotics [78]. In some actinomycetes, it has been observed that the metal stress or exposure to metals in growth and culture conditions causes altered biosynthetic metabolic pathways leading to certain novel metabolites that are not formed in wild-type isolates during normal growth conditions. Further, the synthesis of different SM is enhanced when certain metal micronutrients are added to the fermentation medium of heavy metal tolerant microbial strains [45]. Their importance is also emphasized by the prediction that nearly 30% of all biosynthetic enzymes within the microbes interact with a metal cofactor [79,80]. Several metals with redox functions, such as Fe, Cu, Mn, Zn, Co, Ni, Mo, and Mg, are key factors for many microbial enzymes involved in the biosynthesis pathways of SMs. Besides them, many other metal micronutrients are also directly or indirectly involved in the secondary metabolism of microbes. Additionally, the enhanced SM production by the supplementation of metals in fermentation medium requires the better understanding of the metal homeostasis in a microbial cell, their roles in microbial physiology, and how they affect the overall fermentation processes. Metal availability in the medium appears to be the most critical factor for some fungal SM biosynthesis as well, with mycotoxins being the best-documented class. Cuero [81] revealed the effects of different metal ions supplementation on growth and toxin production by *Fusarium graminearum*, *F. moniliforme*, and *Aspergillus flavus* in broth cultures while Woodcook et al. [82] characterized the metal ion complexes of the mycotoxins sporidesmin A and gliotoxin by electro-spray ionization mass spectrometry.

p0125 The regulation of SM production is complicated and the biosynthetic pathways of most SM are not fully understood. It is known that stress-induced networks and numerous cellular systems control the production of SMs by microorganisms. Therefore this chapter deals with the role of metal ions in microbial SM production with an emphasis on the molecular biology of the microbial regulatory systems. The various important metal ions having a peculiar role in SM production are discussed in detail.

19.2 MANGANESE

s0015

p0130 Manganese (Mn) ions are an important nutrient for microbes and have been determined to be specifically involved in various cellular processes, such as SM production. Mn is clearly an important regulatory ion in microbes and plays an important role in the biosynthesis of SM products, like fatty acids and lipids [84,85]. It has been reported that Mn plays a significant role in the growth and antibiotic production by the actinomycetes strain LAM2 [38]. Mn^{2+} with other divalent ions, such as Cu^{2+} and Fe^{2+}, stimulate the biosynthesis of AK-111-81 antibiotic [86]. These ions also stimulate the production of polyenes [50]. Georgieva-Borisova [87] reported that Fe^{2+} and Mn^{2+} also play an important role in niphimycin production. Certain enzymes require Mn^{2+} as a cofactor which may be vital or an inhibitor of the synthesis of SM such as carotenoids synthesis [88]. Mn^{2+} also controls the expression of several manganese peroxidase isoenzymes at the transcription level [89]. The enzyme level of lignin peroxidase was also indirectly influenced by Mn^{2+} ions. Consequently, Mn is not only a mediator of lignin oxidation but also a regulatory agent of the expression of various components of the ligninolytic system of white rot fungi. It also lowers the production of aromatic SMs such as veratryl alcohol [90]. Cooper et al. [91] reported that the synthesis of a secondary metabolic lipopeptide and surfactin, by *Bacillus subtilis* required 1 μM Mn^{2+} or 1300 μM Fe^{2+}. However, the production of surfactin yield can be enhanced (10-fold) by the addition of 4 mmol/L Fe^{2+} ions [92] and the lipopeptide production also enhances (2.6-fold) by the addition of Mn^{2+} ions [93]. The synthesis of exotoxin A through *Pseudomonas aeruginosa* was suppressed by either addition of 1000 μM manganese sulfate, or 1000 μM copper sulfate, or 2 μM iron sulfate [94]. Similarly, the production of diphtheria exotoxin was suppressed by the addition of 2350 μM manganese, 500 μM cobalt, 120 μM copper, 3 μM iron, or 2350 μM nickel [95]. Moreover, Mn^{2+} stimulates growth and bulbiformin production by *B. subtilis* [96]. In contrast, Mn^{2+} had an inhibitory effect on torulene and torularhodin synthesis [97].

p0135 Manganese is revealed to be a vital factor for the regulation of the biosynthesis of 3-acetyl deoxynivalenol via *F. graminearum* [98]. However, the crucial effects of metal signaling on the biosynthesis of these metabolites had never been discussed at the molecular level, until Cuero et al. [99] investigated the molecular consequence of metals in the production of aflatoxin. Biosynthesis of the polyketide patulin from *Penicillium urticae* was reported

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to be increased in a medium that contained 140 μM Zn with 20 μM Mn [40]. In *Alternaria alternata*, 10 μM Zn is essential for the synthesis of alternariol, but upon the addition of 10 μM Mn, the yield was reported to be three-fold higher [53]. The production of bacitracin in the cell-free enzyme preparation from *Bacillus licheniformis* ATCC 10716 was dependent on the presence of many divalent ions such as Mn^{2+}, Mg^{2+}, Fe^{2+}, or Co^{2+} [37]. Several divalent metals have been required in restrictive amounts for the production of citric acid and in this process, Mn^{2+} plays a crucial role [100–102]. Röhr and Kubicek [103] discussed the contribution of Mn^{2+} deficiency in developing the intracellular conditions which lead to citric acid accumulation. Papagianni [102] studied the effects of some important fermentation parameters, for example, the effect of Mn concentrations in the medium was observed on the mycelial morphology of *Aspergillus niger* (citric acid producer) by the fractal geometry and was distinguished by a transition pellet, whereas in the Mn-free medium, two clumps formed, when the medium contained 10 μg/L $MnSO_4$, and finally free filamentous mycelium were obtained by the addition of 20 and 30 μg/L $MnSO_4$. Mycelial pellets formation is considered to be a the necessity for successful production of certain metabolites, such as the citric acids [104,105]. The addition of Mn at a minimum concentration (3 μg/L) significantly reduces the yield of citric acid under optimal conditions [106]. Bowes and Mattey [107] reported that the citric acid accumulation is enhanced by the addition of 10 mg/L Mn^{2+}. The influence of Mn^{2+} ions on protein synthesis was considered to play an importance role in the formation of cycloheximide (an inhibitor of de novo protein synthesis) and was found to recognize the effect of the addition of Mn^{2+}. The cellular metabolism of *A. niger* is influenced under Mn deficiency and/or nitrogen and phosphate limitation conditions. In Mn deficiency conditions, the breakdown of the protein showed a high intracellular NH_4^+ concentration which causes the inhibition of phosphofructokinase enzyme (a vital enzyme for the conversion of glucose and fructose into pyruvate), leading to a flux during glycolysis and citric acid formation [100,108]. It has been observed that the absence or limitation of Mn^{2+} is responsible for degradation of the protein and accumulation of NH_4^+ during citric acid fermentation [109].

p0140 Besides, Mn^{2+} deficiency has several other roles, for example, reducing the formation of the by-product oxalic acid. It has been reported that oxalate production is arbitrated by the Mn^{2+}-dependent enzyme oxaloacetate acetylhydrolase in a citric acid-producing strain of *A. niger* [110]. Fill et al. [111] reported that the medium composition supplemented with $CuSO_4$ and $MnSO_4$ sheltered verruculogen biosynthesis in *Penicillium brasilianum* and added proline to the production of a chain of cyclodepsipeptides which identified as JBIR 113, JBIR 114, and JBIR 115.

19.3 COPPER

s0020

p0145 Copper (Cu) is a redox active metal ion. Although it is potentially hazardous to a cell, it is also an essential cofactor in a variety of enzymes and electron-transport proteins [112]. Copper is necessary for the function of several oxidases and oxygenases with a vital role in secondary metabolism. Copper deficiency effectively inhibits the activities of diamine oxidase, which is crucial for the metabolism of the diamines putrescine and cadaverine [113], polyphenol oxidase, and superoxidase dismutase (Cu/ZnSOD) [114]. Copper-mediated metelloregulation appears to depend on two likely regulatory loci, CopY and CopZ. In the presence of Cu, CopY is released from its DNA binding sites [115], while CopZ acts as an activator by opposing the action of CopY [116]. However, the detailed interactions between these metelloregulators that are responsible for Cu regulation are not yet well understood [115]. AU:1

p0150 In *Streptomyces* the availability of Cu in the culture medium has a marked influence on the beginning of morphological differentiation and SM production, with both processes occurring practically simultaneously and possibly with common regulatory elements involved [112,117]. The bacterial system strongly regulates the cytoplasmic Cu concentrations to eliminate the toxic level of Cu while maintaining the adequate amount required for cuproprotein biosynthesis [118]. *Enterococcus hirae* is extremely resistant to Cu because of the presence of a four-gene operon, *copYZAB*. *CopA* and *CopB* are small DNA-binding repressors. In contrast, CopY and CopZ are small soluble proteins that share the same ferredoxin fold as the cytosolic metal-binding domains of the ATPases [119]. The dimer of CopY bound to four Cu^+ separates from the *copA* promoter and derepresses expression of the *copYZAB* operon which allows resistance to Cu toxicity [118]. In *Streptomyces chartreusis* IMRU 3962, the addition of $CuSO_4$ (0.03%) increased the production of antibiotics such as hydroheptin and chartreusin [120].

p0155 Trace metal elements such as Cu, Fe, and Zn have a regulatory effect at the cellular and molecular level on fungal growth and concomitant mycotoxin synthesis [121]. Koffler et al. [122] and Vaughn and Weinberg [123]

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reported that the specific concentration of Cu can be critical for the formation of penicillin and *Candida albicans* mycelia, respectively. The metal activates the enzyme oxidation of polyphenols to quinines and can thus be important in secondary metabolism in the cells of microorganisms. A range of concentrations of Cu between 0.01 and 1.0 μM ± GHL (Glycyl-L-histidyl-L-lysine) should be supplied to cells at various times during the growth and early stationary phase to identify the possible mediation of secondary metabolism and differentiation. The naphthoquinone production was supported by the addition of peptone and yeast extract, but Cu^{2+}, Mn^{2+}, and Zn^{2+} metals less than 50 mg/L were necessary for efficient production of naphthoquinone by *Fusarium verticillioides* [124]. Shamsudeen et al. [121] reported that 5 and 10 mg/L concentrations of Cu in organic (chelated) and inorganic forms in the basal (liquid) media were used for fungal growth and aflatoxin (AF) synthesis in laboratory conditions. Recently, Pan et al. [125] reported the role and mechanism of Cu as a "signaling molecule" to awaken the silent FA (fusaric acid) BGCs in Cu−FA production from the mangrove endophyte *Fusarium oxysporum* ZZF51 by comparing it with that of another endophyte *Fusarium sp*. B2, which produced FA but not Cu−FA in the same culture conditions. A lot of work has been done on trace metals with *A. niger* concerning the growth and citric acid production. Zinc, manganese, copper, iron, heavy metals, and alkaline metals have been revealed to affect both the fungal morphology and the citric acid production. Haq et al. [126] reported the effect of copper ions on mold morphology and citric acid productivity by *A. niger* by using molasses-based media. The addition of 2×10^{-5} M $CuSO_4$ to the fermentation medium reduced the Fe^{2+} concentration by counteracting its deleterious effects on fungal growth. The copper ions also induced a loose-pelleted form of growth, reduced the biomass concentration level, and increased the productivity of citric acid monohydrate.

19.4 NICKEL

s0025

p0160 Nickel (Ni) is an essential nutrient and enzyme cofactor for a diverse range of microorganisms [127]. However, nickel is merely required as a trace element and may be toxic to cells when present in excess [128,129]. Haferburg et al. [45] reported that the strain *Streptomyces acidiscabies* E13 induces the synthesis of a melanin-like pigment when it is given nickel supplementation. In contrast, nickel inhibited growth, pigment and antibiotic production by *Streptomyces galbus* [130]. In a similar type of study, the authors found that the mycelial fraction of *S. acidiscabies* showed antibiosis toward *Staphylococcus aureus* and *Mycobacterium smegmatis* when it grew in a soy−mannitol medium with nickel supplementation, while in the same medium the mycelial fraction of *Streptomyces ciscaucasicus* PT1 exhibited a potent antibiosis toward *C. albicans*. Furthermore, in the presence of a nickel-supplemented medium the mycelial fraction of *Streptomyces lincolnensis* and the supernatant fraction of *Streptomyces purpurascens* revealed effective antibiosis toward *S. aureus* and *Escherichia coli*, respectively [45]. In the case of *Streptomyces coelicolor*, the accumulation of nickel (more than 5 μg/mL) in the culture medium inhibited the growth and induced actinorhodin biosynthesis [34]. In contrast, the positive effects of Ni^{2+} supplementation on the production of coumermycin A1 antibiotic have been reported in *Streptomyces rishiriensis* [71]. The efflux of nickel in *S. coelicolor* is controlled by a newly illustrated metalloregulator NmtR of the ArsR/SmtB family, which regulates a putative Ni−Co-efflux pump NmtA [129]. Raza et al. [131] reported that Mn^{2+} and Ni^{2+} ions showed the most positive synergistic interactive affect on the production of fusaricidin-type antifungal compounds from *Paenibacillus polymyxa* SQR-21 followed by the positive interactive synergistic effect of Cu^{2+} and Ni^{2+} and then Mn^{2+} and Cu^{2+}.

19.5 CALCIUM

s0030

p0165 Calcium (Ca) plays an important role in the signal transduction pathways for fungal development and secondary metabolism, such as the diacylglycerol-dependent protein kinase C (IP3-DAG-PKC or PKC) pathway. The key component PKC phosphorylates the target regulatory proteins. PKC is activated by diacylglycerol and Ca^{2+} ions. Phospholipase C acts upstream of PKC and can respond to damage in the cell wall and breaks phosphoinositol phosphate into inositol-3-phosphate (IP3) and diacylglycerol. The *Aspergillus nidulans* genome encodes the two PKC-encoding genes *pkcA* and *pkcB*, which are both essential. *pkcA* also inhibits secondary metabolism by controlling the AnBH1 penicillin regulatory protein, which represses penicillin biosynthesis. Reducing the *pkcA* leads to an increase in penicillin production by sequestering AnBH1 to the cytoplasmic fraction and therefore relieving the expression of penicillin biosynthetic genes [132,133]. Endogenous Ca^{2+} homeostasis is required for

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cercosporin biosynthesis in *Cercospora nicotianae* [134]. Bromochlorogentisylquinones A (255) and B (256) are SMs of the marine fungus *Phoma herbarum*, isolated from the Korean red alga *Gloiopeitis tenax*, which was formed upon addition of calcium bromide to the culture medium, together with the known chlorogentisyl alcohol and gentisyl alcohol [135]. In addition, Ca^{2+} ions also identified as an inhibitory substance during efrotomycin synthesis in resting cells of *Nocradia lactamdurans* [136]. In a very similar way to bacteria, SM production in fungi is highly sensitive to inhibition by Ca^{2+} ions. Kalle and Khandekar [137] reported that dipicolinic acid synthesis by *Penicillium citreoviride* was highly sensitive to inhibition by Ca^{2+} ions in the culture medium.

19.6 CADMIUM

s0035

p0170 Cadmium (Cd) is a highly toxic nonessential trace metal like mercury with no physiological role. Many zinc-binding proteins can bind Cd^{2+} ions without significantly affecting their structures [138]. Therefore cadmium can serve as a substitute for Zn^{2+} in the regulation of secondary metabolism under laboratory conditions. Even after these mentioned roles of Cd^{2+}, not much information is available regarding its role in the regulation of secondary metabolite production from microbes. Failla and Niehaus [52] reported that the mutant strain of *Aspergillus parasiticus* grown in Zn^{2+}-deficient culture when supplemented with 1 μM Cd^{2+} resulted in a two-fold increase in vegetative growth and a >60-fold increase in the synthesis of versicolorin. *Pseudomonas brassicacearum* has been reported to switch from the citric acid cycle to an anaerobic metabolism in response to Cd^{2+} supplementation [67]. Recently, Wu et al. [68] reported the biofilm formation by *Staphylococcus epidermidis* at a low subtoxic concentration of Cd^{2+}. Similarly, Schue et al. [139] investigated the dose-dependent growth effects of Cd^{2+} on *Rhizobium alamii*, an exopolysaccharide (EPS)-producing bacterium that forms a biofilm on plant roots. The results revealed that Cd^{2+} alters mainly the bacterial metabolism in pathways producing sugars, purine, phosphate, Ca^{2+} signaling, and cell respiration. These modulations of the bacterial metabolism and switching to biofilms prevail in the adaptation of *R. alamii* to Cd^{2+}. However, in *Rhizobium leguminosarum* it was found that the exposure to Cd^{2+} leads to the inhibition of protein and glutathione syntheses [65,66]. The Cd^{2+} also activates the inositol phosphate metabolism pathway which plays a crucial role in Ca^{2+} communications and the cyclic ADP ribose pathway, which is a secondary messenger for the mobilization of Ca^{2+} [69].

19.7 ZINC

s0040

p0175 Zinc (Zn) is an important metal and has been reported to be involved in various biochemical reactions to serve as catalytic, structural, redox regulatory, and regulatory functions [140]. In microbes, just as for iron, zinc plays a crucial role in constituting the structural elements, stabilizing protein folds, and most importantly regulating the functions of various metabolic enzymes in the forms of the cofactors and coactivators involved in biosynthetic reactions. However, at higher concentrations Zn^{2+} is also harmful to microbes, affecting their various physiological processes. For example, it has been found that the transcriptional regulons express and require a femtomolar (fM) range of free zinc rather than the available intracellular concentrations of the millimolar range, which further reflects the zinc-binding capacity of Zur proteins and their sensitivity for effective gene regulation [141]. Therefore, it is necessary to tightly regulate the intracellular concentration of Zn over a small concentration range. The zinc homeostasis in the bacterial system is mainly accomplished through the coordinated expression of zinc uptake and zinc export having their own self-regulatory systems [142–144]. The mobilization of Zn for maintaining Zn homeostasis is regulated by Zn^{2+}-sensing metalloregulatory proteins, belonging to the well-known Fur family of metal-dependent regulators [144]. Moreover, Zur protein controls the mobilization of Zn in association with ribosomal proteins [145], and regulates the Zn transport preferably in the freely available form and represses the expression of target genes when available with bounded Zn(II). It has been reported that the secondary metabolic processes and differentiation by some actinomycetes require the adjustment of both Zn^{2+} and Fe^{3+}. The biosynthesis of antibiotic actinorhodin (ACT) and undecylprodigiosin (Red) in *S. coelicolor* A3(2) is influenced by the amount of Zn [63]. The molecular mechanism of the binding of vancomycin, an antibiotic frequently used against methicillin-resistant *S. aureus*, involves the sequestration of Zn^{2+} from bacterial cells, and therefore causing Zur-dependent starvation of Zn. The similar mechanism of Zn deficiency mediated by vancomycin was also reported from several other bacterial systems and the study was well demonstrated, as the

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exposure of vancomycin to *S. coelicolor* caused highly but transient upregulation of Zur regulons [146]. Similarly, the Zur-dependent regulation of coelibactin, a putative zincophore, was also reported in *S. coelicolor* [54,147].

p0180 Many enzymes playing a significant role in the production of specific SMs possess zinc-binding sites and Zn^{2+} acts as a cofactor for these enzymes. For example, resistomycin, produced by *Streptomyces resistomycificus*, contains a zinc-binding site and its biosynthesis is catalyzed by RemF polyketide cyclase which contains a zinc-binding site, and thus Zn^{2+} is necessary for the biosynthesis of resistomycin [58]. Liu et al. [50] reported the effect of Zn^{2+} along with iron and manganese on the biosynthesis of candicidin, a polyene macrolide antibiotic produced by *Streptomyces griseus* IMRU350. Further, Zn^{2+} plays a significant role in the biosynthesis of 2,4-diacetylphloroglucinol (DAPG), a secondary antimicrobial metabolite with Cu^{2+} and NH_4Mo^{2+} [32], and therefore functions as an important determinant in regulating the antimicrobial activity associated with biocontrol strain *Pseudomonas fluorescens* CHA0 [148]. However, in recombinant *E. coli* grown in Terrific Broth (TB medium), it was observed that Zn^{2+} supplementation improved the production of β-glucanase [64]. Paul and Banerjee [149] reported that the production of extracellular antifungal antibiotics through *S. galbus* was enhanced by the addition of 200 μM Zn^{2+}.

p0185 The SM production in various fungi is also dependent on the available amount of Zn^{2+}. The biosynthesis of various toxins, including a fusaric acid in *Fusarium vasinfectum* [150] and aflatoxin in *A. parasiticus* [151,152] and *A. flavus* [99], is well-regulated by Zn^{2+}. Moreover, in yeast the metabolic flux is highly determined and regulated by the available amount of Zn supplemented, and therefore the size of yeast flocs, as Zn supplementation shifts the carbon fluxes toward increased biosynthesis of ergosterol (28.6%) and trehalose (43.3%). In contrast, the biosynthesis of glycerol, protein, and tricarboxylic acid cycle significantly decreased by 37.7%, 19.5%, and 27.8%, respectively [153]. Several studies have revealed that for the initiation and regulation of secondary metabolism a well-defined concentration of Zn^{2+} is required. It has been demonstrated that for the efficient production of SM, the engaged cells must be competent and be in their temporal phase for mineral nutrient acquisition. This could be best exemplified by the abundant uptake of Zn^{2+} by *Candida utilis* in initial lag as well as late exponential stages [154]. In an another study, it was reported that the biosynthesis of polyketide versicolorin A in *A. parasiticus* is largely determined by exogenous Zn^{2+} supplementation and must be available at between 20 and 30 hours postinoculation during early vegetative growth [52]. Similarly, the biosynthesis of polyketidealternariol (AOH) and alternariol methyl ether (AME) is well affected by the available amounts of Zn^{2+}, as it was observed that the adequate amount of 10−100 μM Zn^{2+} is required for the maximal biosynthesis of alternariol. In contrast, the minimum biosynthesis starts at 1 μM amount of available Zn^{2+} [53]. Likewise, *P. urticae* requires 140 μM Zn^{2+} along with 20 μM manganese for the biosynthesis of the polyketide patulin [40].

p0190 Maggon et al. [155] investigated the relationship between primary and secondary metabolism with reference to aflatoxin production by *A. flavus* and *A. parasiticus* and reported the enhanced stimulation of aflatoxin production by the supplementation of Zn^{2+}. Several workers have reported that 0.4−2 mg/L Zn^{2+} in the medium induced the fungal aflatoxin biosynthesis [151,156−158]. However, for *A. flavus* the requirement of Zn^{2+} was as high as 50 mg/L [159]. Cocucci and Rossi [160] showed the effect of Zn^{2+} deficiency on growth morphology and metabolism in *Rhodotorula gracilis*. In one study, Wold and Suzuki [60] reported the regulatory function of Zn^{2+} in citric acid production by *A. niger*. In *F. moniliforme* it has been reported that the biosynthesis of fusarin C is strongly dependent on the concentration of Zn^{2+} and glucose. As in the submerged culture when Zn^{2+} is supplemented with 90 g/L glucose (ample carbon substrate) both ethanol and fusarin C were produced, whereas at the lower concentration of glucose (30 g/L) and Zn^{2+} (5 ppb) fusarin C biosynthesis was inhibited [61]. Jia et al. [55] reported the effect of Zn^{2+} on the biosynthesis of lovastatin in *Aspergillus terreus* and found that Zn^{2+} influences the production of lovastatin by regulating the action of certain key enzymes, such as Lov D or LoV, involved in the secondary biosynthetic pathway. Mühlencoert et al. [56] reported the effect of Zn^{2+} on the ochratoxin A production and found that the addition of 0.2 mg/L Zn^{2+} to the culture filtrate at pH 6.5 increased the yield in biomass by 50% as well as for ochratoxin A (OTA) production in *Aspergillus ochraceus* NRRL3174.

p0195 Citrinin, a secondary *O*-heterocyclic metabolite, is produced by *Penicillium citrinum* VKM F1079 in idiophasic stage and its production is stimulated by the addition of Zn^{2+} [57]. In some fungi the production of some EPSs is regulated by medium supplementation of Zn^{2+} metal. For example, the biosynthesis of scleroglucan, an extracellular branched β-1,3-β-1,6-glucan in *Sclerotium rolfsii* ATCC 15205, is regulated by a high-affinity Zn^{2+} uptake system [59]. Cai et al. [62] reported the inhibition of aspergiolide biosynthesis in the marine fungus *Aspergillus glaucus* in the presence of Zn^{2+}. Several microorganisms require mineral nutrients such as Fe^{2+}, Mg^{2+}, and Zn^{2+} ions for the biosynthesis of pigments, as their available amounts play a significant role and have been shown to be one of the important factors for pigment biosynthesis [161]. In this context, Mendentsev and Akimenko [162] reported the enhanced biosynthesis of naphthoquinone in the presence of trace metal ions.

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Moreover, Boonyaprani et al. (2008) also evaluated the potential of *F. verticillioides* for naphthoquinone pigment production by using different growth media and found that the amendments of metals (K^+, Na^+, Mn^{2+}, Cu^{2+}, Fe^{2+}, and Zn^{2+}) were necessary for its efficient production. The biosynthesis of antibiotics and pigment production in mycophilic fungus *Hypomyces rosellus* 94/77 is well-determined by the presence of mineral trace metal ions including Mg^{2+}, Mn^{2+}, and Fe^{2+} [163]. However, the pigment production in fungi is negatively regulated by supplemented Zn^{2+} as, it was demonstrated that Zn^{2+} causes a detrimental effect on the production of SMs having polyketide structures and bearing red-, yellow-, and orange-colored pigmentations produced by *Monascus ruber* when grown under different culture conditions [164].

p0200 Zinc also plays a significant role in citric acid production. Shu and Johnson [165] reported optimal levels of Zn and Fe at 0.3 and 1.3 ppm, respectively, for the induction of silent BGCs concerning the growth and citric acid production in *A. niger*. It has been suggested that the involvement of trace metal ions (Fe and Zn) could be associated with diverging the carbon source inbetween biomass and citric acid [166]. The addition of Zn^{2+} to the microbial cultures at accumulation phase led into their reversion back to the growing phase [60]. Moreover, the stimulatory effect of Zn^{2+} on the biosynthesis of beta-carotene and the inhibitory response on the biosynthesis of torulene and torularhodin is also reported [97].

19.8 COBALT

s0045

p0205 Cobalt (Co) is an important transition metal as it acts as a cofactor for vitamin B_{12}-dependent enzymes. The role of cobalt in SM production has been well demonstrated in a variety of microbes and there are several reports of Co^{2+}-mediated regulation of antibiotic production from actinomyces. In certain actinomycetes, it has been reported that Co^{2+} shifts the general pathway of secondary metabolite production toward the production of specific SM. Ashy et al. [83] reported the biosynthesis of spiramycins I and increased antibiotic yield at the concentration of 0.5 g/dm^3 $Co(NO_3)_2$. However, at higher concentrations of the trace metals the microbial activities were shifted toward the production of spiramycin II and III, in addition to the spiramycin I. In one more study, it was reported that Co^{2+} stimulates the methylation of aminoglycosides antibiotics, particularly the biosynthesis of gentamicin [167]. Thus the biosynthesis of gentamicin C2 and gentamicin C1, but not C1a or C2b, are cobalt dependent [75]. The bacterium *S. coelicolor* M145 in the presence of 0.7 mM Co^{2+} produces certain volatile compounds like prodigiosins, undecylprodigiosin, and streptorubin B [72]. It has been reported that supplementation of a high amount of Co^{2+} in the medium resulted in the increase in growth parameters with a simultaneous reduction in the biosynthesis of actinorhodin in *S. coelicolor* [34]. Claridge et al. [71] described an increment in the production of coumermycin A1 by over 93%, after adding Co^{2+} to the culture medium of *S. rishiriensis*. Gräfe et al. [70] reported the stimulating effect of Co^{2+} on the A-factor induction of anthracycline production in *S. griseus*. However, still the studies on the effect of cobalt in *Streptomyces* are rather limited.

p0210 In yeast and molds, it has been reported that supplementing the medium with trace metal ions such as Co, Fe, Zn, Fe, Al, and Cu has been found to increase microbial carotenoid production [88,97], and has been shown to have selective influences on carotenoids biosynthesis. It was suggested that the involvement of trace metals have some possible activation and deactivation effects on the enzymes required for biosynthesis of these carotenoids. Of these enzymes, particularly specific desaturases have been found to be involved in the biosynthesis of carotenoids [97]. Another possible activation mechanism that has been reported is that the generation of active oxygenic free radicals is provoked by trace metal ions which in turn leads to the production of protective carotenoid metabolites that reduce the negative behavior of free radicals. The same strategy was also reported in several pigment-forming microbes for the biosynthesis of pigments [168,169].

p0215 Aspergiolide A is a promising anthraquinone derivative with a naphtha [1,2,3-de] chromene-2,7-dione skeleton produced by a marine-derived filamentous fungus *A. glaucus* HB 1−19 [170]. The biosynthesis of aspergiolide A in the presence of a medium supplemented with 0.052 mM Co^{2+} was reported in *A. glaucus* HB 1−19 [62]. Ding et al. [73] reported the stimulation of a novel hybrid polyketide-terpenoid, aspergstressin from the culture broth of strain *Aspergillus* sp. WU 243 by the stimulation of Co^{2+} ions. Tsuyuki et al. [74] reported the effect of cobalt chloride ($CoCl_2$) on the production of trichothecenes and ergosterol in *F. graminearum* and found that the addition of 3−30 μM $CoCl_2$ into a liquid culture strongly enhanced the production of acetyl deoxynivalenol.

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19.9 IRON

s0050

p0220 Iron (Fe) is recognized as the most vital metal ion in cellular metabolism for bacteria as well as fungi by being a cofactor for many enzymes [171,172]. Antibiotic production involves a very significant role for iron [173] and the working mechanism of Fe regulation can be best understood in *E. coli* (Fur regulon) and *Corynebacterium diphtheria* (DtxR regulon) [33]. IdeR repressor proteins and their ortholog DtxR, which depend mainly on Fe are well-known to regulate iron metabolism, as well as siderophore production and Fe-absorbing genes in bacteria ([174,175]). IdeR is reported to induce the high production of nocardamine by combining to the sidABCD operon in *Streptomyces avermitilis* K139 under enormous iron stress state [47]. Recently, Park et al. [176] discovered the relationship between nonG ortholog TetR family transcriptional regulator from *S. puniceus* Act1085 and IdeR protein that regulates nocardamine production in *S. avermitilis* K139 by binding to the sidABCD operon.

p0225 Fungal growth at the cellular and molecular level as well as concomitant mycotoxin synthesis is also guided by iron. An increase in the production of aflatoxin by Fe salts was reported by several studies [99,177,178]. CBC (CCAAT-binding complex) composed of three proteins (HapB, HapC, and HapE), combines various physiological signs that provide statistics about the redox level and iron distress [179,180]. This combination gets merged to the CCAAT boxes in the promotion of penicillin biosynthetic genes, being essential for the expression of penicillin in *A. nidulans* by deploying a positive regulatory impact on gene expression for both *ipnA* and *aatA* [181]. The iron-regulatory protein, HapX is dependent on the iron availability and the links to the CBC complex under iron-scarce conditions [180]. This linkage leads to the investiture of genes involved in iron procurement, such as siderophore biosynthesis genes. However, Gressler et al. [48] found out that the shortage of iron in *A. terreus* culture stimulates terrein (phytotoxin) production depending on the iron response regulator HapX which controls siderophore biosynthesis. In different bacteria, such as *S. coelicolor*, iron is very important for growth, and its scarcity results in impaired differentiation and SM production while iron availability facilitates developmental genes [182–184]. In *Streptomyces spp*., the production of actinomycin, neomycin, steptomycin, and chloramphenicol requires iron [185]. Azasteroidal, an antifungal antibiotic from *Geotrichum flavo-brunneum* was enhanced by 10% through adding just 0.2% iron [186]. By submerged fermentation, the bacterial culture of *Nocardia mediterranea* ATCC 13685 was used to produce antitubercular antibiotic rifamycin; it was also observed that 100 ppm of iron had upscaling effects on the rifamycin production [187].

p0230 Lin et al. [188] reported that the lipopeptide antibiotic iturin A production was increased in *Bacillus amyloliquefaciens* B128 due to ferrous ion. The results of ferrous ion compared to those reported for ferric ion (trivalent iron at 0.25–1.0 mM) significantly increased the antibiotic zwittermicin A production from the cultivation of Bacillus *cereus* UW85 [189]. The results also cross-verify the previous reports that suggest that iron supplement strategies enhanced surfactin production from *B. subtilis* [92]. In *P. fluorescens*, phenazine-1-carboxylic acid (PCA) production is increased in the presence of iron or magnesium [30,190]. Raza et al. [191] studies the alteration in the production of fusaricidin-type antimicrobial compounds by *P. polymyxa* SQR-21 with different concentrations of iron and reported that its concentration increased by 33%–49%, but only up to 50 μM Fe^{3+}, while the highest level of Fe^{3+} was inhibitory.

19.10 RARE-EARTH ELEMENTS

s0055

p0235 Despite the immense importance of rare-earth elements (REEs) in the different chemical industries, comparatively little is known about their biological effects in microbes. Since REEs are ubiquitously distributed around the world, it is conceivable that microbes have gained the ability to use the low levels of these elements during their long course of evolution, possibly as a means of adapting their physiology with respect to prevailing environmental conditions. In recent years, the regulation of gene expression by REEs have been an active area of research and REEs have been shown to be involved in the biosynthesis and overproduction of SMs, particularly antibiotics, through activation of silent BGCs in microbes. Notably, these elements were effective in activating SM silent BGCs in *Streptomyces*. In recent years, while investigating the effects of metals on bacterial physiology, some REEs such as lanthanides, scandium (Sc), and lanthanum (La), were discovered to induce increased expression of silent BGCs in several *Streptomyces* spp. through an as-yet undetermined, guanosine pentaphosphate- or tetraphosphate-dependent pathway. This bacterial alarmone provoked by REEs is considered to be essential for antibiotic overproduction [77,192]. Kawai et al. [77] reported an increase in antibiotic production (2–25-fold) in *S. coelicolor* (an actinorhodin producer), *Streptomyces antibioticus* (an actinomycin producer), and *S. griseus*

(a streptomycin producer) cultures upon supplementation of effective concentrations of REEs. Other REEs such as yttrium (Y), lanthanum (La), cerium (Ce), and europium (Eu) can also provoke actinorhodin production in *S. coelicolor* but differ in the order of magnitude, however, the effect of Sc^{3+} was most pronounced. The effects of Sc^{3+} during production was observed to be exerted at the level of transcription of pathway-specific positive regulatory genes, as demonstrated by marked upregulation of *act II*-ORF4. In addition, Sc^{3+} was also found to be effective in activating the dormant ability to produce actinorhodin in *Streptomyces lividans*. In another study, Tanaka et al. [192] found that low concentrations of Sc or La induced the expression of nine BGCs (2.5–12-fold) in *S. coelicolor* culture. The results of the current study also revealed that REEs (except for promethium (Pm)) increased the production of compound 4 in *S. coelicolor* A3(2). However, the most effective were Sc^{3+} and La^{3+}, which altered the transcription of 17 SM silent BGCs [9,192,193]. The ability of REEs (especially Sc^{3+}) to enhance enzyme production and secondary metabolism was also observed in *B. subtilis*. The supplementation of Sc^{3+} to the culture medium induces the production of bacilysin at the transcriptional level [194]. Although still the exact sites of action of REEs are unknown, it is thought that they might bind to bacterial ribosomes [19,77,193].

19.11 OTHER METALS

s0060

p0240 Several other divalent cations, such as Ba and Ca, have been demonstrated to act as stimulants for the growth of *Rhodotorula glutinis* and carotenoid production. These trace elements have been shown to exert a selective influence on the carotenoid profile in *R. graminis* to enhance the total carotenoid content (mg/L) about two times. Raza et al. [131] reported that Ca^{2+} ions and their interactive effects with other metals (Ni^{2+}, Mn^{2+}, and Cu^{2+}) inhibited the production of antifungal compounds by *P. polymyxa* SQR-21. Al^{3+} had a stimulatory effect on beta-carotene synthesis [97]. Abbas and Edwards [34] by using *S. coelicolor* for actinorhodin production reported that mercury was highly toxic followed by lead; both tended to inhibit growth and antibiotic titers to a similar extent. Unexpectedly, chromium and calcium resulted in enhance growth but a reduction in antibiotic production. The production of antifungal compound, 2,4-diacetylphloroglucinol (DAPG) through fluorescent pseudomonad, *Pseudomonasjessenii*, can be enhanced upto 125 mg/L after optimizing the concentration of metal ions the culture medium with Zn^{2+}, Mn^{2+} and MoO_4^{2-} at 83, 42 and 135 μM respectively, using response surface methodology [195]. Similarly, Duffy and Defago [32] reported the enhanced production of DAPG using *P. fluorescens* and a medium amended with Zn^{2+} and NH_4Mo^{2+}. Lin et al. [188] reported that when *B. amyloliquefaciens* B128 was grown on a nutrient broth medium, the concentration of iturin A was about 12.58 mg/L. In contrast, Mg^{2+} ions can significantly affect the production of antifungal compounds. Raza et al. [191] studied the effect of Mg^{2+} ions on the production of fusaricidin-type antifungal compounds by *P. polymyxa* SQR-21 in fermentation media. The results indicated that Mg^{2+} positively affected the growth and significantly increased the production of antifungal compounds through the relative expression of *fusA* gene. Additionally, a synergistic positive effect of Mg^{2+} and Fe^{3+} on the fusaricidins production was also observed. Similarly, Vasudeva et al. [196] reported that Mg^{2+} (>1.25 mM) also increased the growth of *B. subtilis* as well as bulbiformin production. In contrast, $MgSO_4$ (>2 mM) concentration increases the antibiotic iturin A synthesis by *B. amyloliquefaciens* B128 [188]. Only iron and magnesium salts caused significant enhancement of iturin A production. However, iron sulfate caused a much larger increase in iturin A production than the magnesium salt. Although there is much information on the various roles of Mg^{2+} in bacterial cells [197], it is not often an inhibitor at physiological concentrations.

p0245 Numerous studies reveal that silver nanoparticles (>two-fold) repress SM synthesis in several mycotoxins-producing filamentous fungi [198,199]. Mitra et al. [200] reported that in silver nanoparticles an amendment in growth medium containing *A. parasiticus* resulted in a significant decrease in transcript levels of five aflatoxin genes and at least two key global regulators of secondary metabolism, laeA and veA. In addition, the results also confirmed the feasibility of silver nanoparticles to inhibit fungal secondary metabolism at nonlethal concentrations.

19.12 CONCLUSION AND FUTURE PROSPECT

s0065

p0250 Production of SM by microbes and their extraction for commercial interest is not new. It has been predicted that microbes are considerably diversified in the production of SM and have been credited with producing an impressive amount of metabolites that have been characterized based on their chemical structure, complexity,

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and the physiological functions. However, only 10% of the metabolites are known for human and animal welfare. Today, with the knowledge of the rich microbial diversity of metabolites available, it has been necessary to unravel, identify, and characterize these microbes in order to maximize production from new microbial species and to develop sophisticated methodologies for stimulating the production of SMs from currently available microbes for commercial exploitation in an economically feasible and environment-friendly manner. It has been reported that the microbial SM production is well effected by production costs and other environmental issues. Moreover, the dwindling fossil fuel reserves have been considered to be the major driving force in searching for the efficient methods of microbial fermentations.

p0255 Due to the advancement in biotechnological tools and techniques, it has now become possible to manipulate the entire microbial factories for commercial exploitation of these metabolites. Moreover, the researchers are interested in developing novel strains of SM-producing microbes for basic research and industrial applications that could be superseded for making the novel metabolites. The genetic variation that exists between the microbes, their physiological characteristics, and the comprehensive knowledge about the biochemical pathways involved have provided new directions and have proven to be of enormous importance for SM production. The *in-silico* modeling approaches, when compared and correlated with metabolic flux analysis studies, have provided an in-depth understanding of the physiological mechanisms of the microbes involved, fermentation pathways, and the mechanisms that lead to the production of these SMs. The rational strain engineering approaches have been limited by the physiological complexity of the microbes. In contrast, the approaches for random mutagenesis have been restricted by the screening and selection of the concerned microbes, and require the readily accessible phenotypic identification of the product-forming microbial species.

p0260 Furthermore, the genome sequences available for many microbial species have accelerated this mechanism for rapid identification of metabolic pathways, the concerned regulatory genes and their promoters, and the diversity of metabolic (catabolic and anabolic enzymes) available for biocatalysis. This available information, when compiled and correlated with the data available from microarray and proteomics approaches, could lead to the identification of the expression of functional gene products under different environmental conditions such as in the presence of differing concentrations of metal ions. The comprehensive and in-depth knowledge about the role of trace metals in the pathways for secondary metabolite biosynthesis will definitely increase the screening and high-throughput culturing of the microbes and will have the potential to accelerate the development of novel, efficient, cost-effective, and environment-friendly fermentation systems.

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Further Reading

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Abstract

Microorganisms are widely recognized for their ability to produce a wealth of natural products with structural complexity and diverse biological activities having discrete pharmaceutical and biotechnological applications. In microbes, several genes responsible for the biosynthesis of secondary metabolites are arranged in gene clusters, which are coordinately regulated by the cluster-specific transcription factors. Nevertheless, a large fraction of secondary metabolites encoded within the microbial genomes remains unexplored probably because these genes are not expressed under classical laboratory conditions. Significant research has been done in the recent years to unlock/induce these undiscovered cryptic biosynthetic gene clusters and in many cases successfully accessed to identify unknown secondary metabolites by employing biological, chemical and molecular elicitation strategies. However, cultivation-based approaches specifically, cocultivation by subjecting an inducer and a recipient microorganism culture conditions as well as external cues has long been recognized as an effective strategy to activate cryptic biosynthetic gene clusters and inducing significant changes in the microbial metabolome. Under this traditional strategy, the alteration by the mean of variation in metal ions composition is the simplest and most effective approach to provoke the expression of unexpressed or poorly expressed cryptic biosynthetic gene clusters and to realize the metabolic potential of a microbial strain under fermentation conditions. It has been appreciated for a long time that the trace metals are one of the most crucial factors which influence the production of secondary metabolites in microbes. However, the lack of precise information on the regulation of biosynthetic machinery by metal ions signals makes the research on stimulating cryptic gene clusters a challenging task. In this sense, the application of multidisciplinary approach such as genome mining, gene expression analyses with elicitation approaches with the help of bioinformatic algorithms tools can help in identification, activation and exploration of the full chemical diversity of various putative cryptic gene clusters which can provide a new avenue to the treasure trove of secondary metabolites from microorganisms. This traditional strategy can pave the way to the discovery of a plethora of secondary metabolites for pharmaceutical applications with the potential to rejuvenate stalled drug discovery pipelines. Hence this review highlights the ascribed role of metal ions in regulation of secondary metabolite production by microorganisms during fermentation processes.

Keywords: Microbes; metal ions; essential nutrient; regulation; secondary metabolites; biosynthetic gene clusters