Journal of Biosciences and Medicines, 2025, 13(4), 141-151
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Switch-On Time for Act Gene Expression and Switch-Off Time of the 16S rRNA Gene for Optimization Production of Actinorhodin Antibiotic by *Streptomyces coelicolor strain* ATCC 10147

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How to cite this paper: Mahasneh, I.A., Ahmady, I.M., Mahfood, M., Algatham, N., Awad, M. and Hazaymeh, I. (2025) Switch-On Time for Act Gene Expression and Switch-Off Time of the 16S rRNA Gene for Optimization Production of Actinorhodin Antibiotic by *Streptomyces coelicolor strain* ATCC 10147. *Journal of Biosciences and Medicines*, **13**, 141-151.
https://doi.org/10.4236/jbm.2025.134013

Received: March 6, 2025
Accepted: April 12, 2025
Published: April 15, 2025

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Abstract

The aim of the study was to determine the switch-on time for Act gene expression and switch-off time of the 16S rRNA gene for optimization production of the actinorhodin antibiotic by *Streptomyces coelicolor strain* ATCC 10147. The full sequence of 1804 bp of the 16SrRNA gene of the *S. coelicolor strain* ATCC 10147 was determined, and its phylogenetic tree is given with 99.9% homology to the closest sister strains, *S. coelicolor strain*s M1154 and A3(2). The expression switch-on time of the Act gene was determined to be after 34 h of growth, whereas the switch-off time of 16S rRNA was determined to be at 120 h of growth by the addition of chloramphenicol, which blocks the RNA enzyme peptidyl transferase center, which is located at the lower tips (acceptor ends) of the A- and P-site tRNAs, where it binds to the residues A2451 and A2452 in the 23S rRNA (component of 50S) and prevents the attachment of aminoacyl transferase to the ribosomal subunit, which inhibits peptide bond formation. The optimum growth conditions for actinorhodin production were determined in liquid growth as nutrient broth as a C-source (1% starch), N-source (K_2NO_3), P-source (K_2PO_4), Fe-source ($FeCl_3$-EDTA), shaking speed (200 rpm), pH 7.0, 28˚C, and aerobic conditions. The extracellular and intracellular actinorhodin reached 165 mg^{-1} and 88 mg^{-1}, respectively. The optimum growth of the strain on solid media was on nutrient agar plus 1% starch. For production of the antibiotic droplets on the colony's surface, the strain was cultured on potato dextrose agar (PDA) for 5 days before several droplets (3 -

5) appeared on the top of each colony. The actinorhodin activity was tested against the international MRSA control strain *Staphylococcus aureus* ATCC 25923 and the local MR *Bacillus cereus* strain. The inhibition zones were 21 mm and 24 mm for the MRSA control strain *Staphylococcus aureus* ATCC 25923 and the local MR *Bacillus cereus* strain, respectively. The MIC of the actinorhodin antibiotic was 2.0 ug/ml and 4.0 ug/ml for the MRSA control strain *Staphylococcus aureus* ATCC 25923 and the local MR *Bacillus cereus* strain. The results are novel on the ON/OFF switching of interplay regulation of gene expression for optimization of actinorhodin antibiotic production by *S. coelicolor strain* ATCC 10147. The results also provide evidence of optimization of actinorhodin antibiotic production using cheap starch as a C-source to produce a highly effective antibiotic against MRSA and the MAR pathogens.

Keywords

Sequencing of 16 SrRNA Genes, Actinorhodin Antibiotic Production, *S. coelicolor strain* ATCC 10147, Multi-Resistant Pathogens, Phylogenetic Tree

1. Introduction

Currently, there is a worldwide urgent need to produce a new generation of antibiotics against the increasing global crisis of multi-antibiotic resistant (MAR) pathogens, known as superbugs, which are the causative agents of nosocomial infections in worldwide hospitals. For instance, after the World Health Organization (WHO) published a list of bacteria for which new antibiotics were urgently needed in 2017 and this year, 2025, WHO determined the production of antibiotics against multi-resistant MR bacteria is among the top priorities for this year, 2025 (https://www.who.int) [1]. The most recent Global Antimicrobial Surveillance System (GLASS) by the World Health Organization (WHO) reveals a significant prevalence of AMR among a population of 500,000 individuals diagnosed with bacterial illnesses in 22 different countries [2]. Furthermore, the most comprehensive global estimates of the MAR have been reported as posing a major threat to human health around the world on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen-drug combinations in select locations [3]-[5]. Multi-antibiotic resistance (MAR) is a critical global health issue driven by antibiotic misuse and overuse in various sectors, leading to the emergence of antibiotic-resistant "priority pathogens" that pose the greatest threat to human health. The biotechnological importance of *Streptomyces* as producers for the majority of the broad-spectrum commercial antibiotics in use today keeps them as the main natural stock for screening programs [6]-[8]. Therefore, the aim of the study was to determine the switch-on time for Act gene expression and switch-off time of the 16S rRNA gene for optimization production of actinorhodin antibiotic by *Streptomyces coelicolor strain* ATCC 10147.

2. Materials and Methods

2.1. Bacterial Source

Streptomyces coelicolor strain ATCC 10147 (Muller) Waksman and Henrici was imported from the American (https://www.atcc.org/products/10147) on May 2023 with all documentations as needed for the export certificate of origin.

2.2. Growth Conditions and Characteristics

For maintenance and experimental sub-culturing, *Streptomyces coelicolor* ATCC 10147 was grown in ATCC Medium 1877: ISP Medium 1 broth according to manufacturer instruction (HiMedia, India) and then incubated at 26˚C - 28˚C in a shaking incubator under aerobic conditions. The components of the ATCC medium, 1877 ISP Medium 1, as dissolved in 1.0 L distilled water, were tryptone (BD 211705) (5.0 gm), yeast extract (3.0 gm), and agar (if necessary) (15.0 gm). Adjust the medium for a final pH of 7.0 - 7.2 before autoclaving at 121˚C for 15 minutes. A 50% glycerol stock was prepared and stored at −80˚C for further investigation. For growth characterization and genomic DNA extraction, *Streptomyces coelicolor* ATCC 10147 was grown in ISP Medium 1 agar (from HiMedia, India) and incubated for 5 - 7 days at 28˚C under aerobic conditions until full growth was attained, as the aerial mycelia became abundant and medium gray whilst the vegetative mycelia were blue-gray with a blue soluble pigment.

2.3. Genomic DNA Extraction and 16S rRNA Gene Amplification

Genomic DNA was extracted from 1 ml of pure bacterial culture using the Isolate II Genomic DNA kit (Bioline, BIO-52066) according to the manufacturer's protocol. The purity and concentration of extracted genomic DNA were assessed using the NanoDrop One Microvolume UV-Vis Spectrophotometer (Thermo Fisher Scientific). To amplify the 16S rRNA gene, the MicroSEQ Full Gene 16S rDNA PCR Kit (Thermo Fisher Scientific, 4349155) was used. In brief, 60 ng of genomic DNA was used in three separate PCR reactions, thereby amplifying three overlapping fragments to ensure that a high-quality and full-length gene sequence was obtained. PCR was carried out according to the following conditions: 95˚C for 10 minutes; 30 cycles of 95˚C for 30 seconds, 60˚C for 30 seconds, and 72˚C for 45 seconds, followed by a final extension at 72˚C for 10 minutes. Generated amplicons were then verified by visualizing them on a 2% agarose gel. Moreover, 5 ul of each PCR product was treated with ExoSAP-IT PCR Product Cleanup Reagent (Thermo Fisher Scientific, 78200.200.UL) according to the supplied protocol and used for sequencing.

2.4. 16S rRNA Gene Sequencing

Sequencing reactions were conducted via the MicroSEQ Full Gene 16S rDNA Sequencing Kit (Thermo Fisher Scientific, 4347484) according to the manufacturer's protocol. In short, each of the three purified PCR products was sequenced using both their respective forward and reverse primers, resulting in six reactions. Se-

quencing reactions were carried out using the following conditions: 25 cycles of 96˚C for 10 seconds, 50˚C for 5 seconds, and 60˚C for 4 minutes. Sequencing reactions were then purified using the ethanol/EDTA/sodium acetate precipitation method. Afterward, capillary sequencing was carried out by the Genetic Analyzer 3500 (Applied Biosystems, Thermo Fisher Scientific, USA). Obtained forward and reverse sequences were then analyzed using the Sequencing Analysis Software 6 (Applied Biosystems, Thermo Fisher Scientific, USA) and assembled into one contiguous sequence using the CAP3 software (https://doua.prabi.fr/software/cap3). Finally, the assembled sequence was aligned to published sequences using the Basic Local Alignment Search Tool (BLAST) (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

2.5. Pairwise Sequence Alignment

The full gene sequence of the bacterial strain extracted was aligned automatically using the BLAST tool against the gene libraries available for bacterial species in the NCBI (https://www.ncbi.nlm.nih.gov/), Sanger Institute (https://www.sanger.ac.uk/), DDBJ (https://www.ddbj.nig.ac.jp/index-e.html), and EMBL-EBI GeneBank (https://www.ebi.ac.uk/) databases.

2.6. Multiple Sequence Alignment

The phylogenetic analysis was constructed using the neighbor-joining tree of the isolated strain using BLAST and CLUSTAL W (1.83) available in the following international gene banks: National Center for Biotechnology Information (NCBI), International Nucleotide Sequence Databases (INSD) (DDBJ GenBank), and EMBL-EBI Bank (European Bioinformatics Institute and the European Molecular Biology Laboratory). The closely related homologous strains were identified, retrieved, and compared to the sequence of the strain extracted, using CLUSTAL W (version 3.2) available on the Biology StudyBench (https://www.ncbi.nlm.nih.gov/).

2.7. Statistical Criteria for Species Identification

Genotyping identification of species through sequence similarity was determined based on the international diagnostic criteria as set by the international gene banks (International Nucleotide Sequence Databases (INSD) (DDBJ GenBank), EMBL-EBI Bank (European Bioinformatics Institute and the European Molecular Biology Laboratory), and the National Center for Biotechnology Information (NCBI), where if the difference between the query and the compared strain is 1% - 1.5% (14 - 22 bp), 1.5% - 5.0% (23 - 72 bp), and 5.0% - 7.0% (72 - 98 bp), then the query strain should be given to the same species, genus, or a different genus, respectively.

2.8. Determination of Actinorhodin Antibiotic

The production of antibiotics by the present strain was determined as described earlier [9] and as follows: 10 ml of the culture broth were taken and centrifuged at 200 rpm for 10 minutes, resulting in having two portions: the supernatant (extra-

cellular actinorhodin) and the cells pellet (cellular actinorhodin). Then, 1.0 ml of 1 N KOH was added to the supernatant, and pH was adjusted to 8.0 before extracellular actinorhodin was determined by measuring the absorption at A640 nm. For the cellular actinorhodin, it was extracted by the addition of 10 ml of 1 N KOH to the pellet, centrifuged at 2000 rpm for 10 minutes, and the pH was adjusted to 8.0 before cellular actinorhodin was determined by measuring the absorption at A640 nm. For statistical assurance, 4 replicates were used for the mean value calculation. For production of the antibiotic droplets on the surface of the colonies, the strain was cultured on potato dextrose agar (PDA) and incubated for several days.

2.9. Antibiotic Activity of the Actinorhodin Antibiotic

The antimicrobial assay for the strain antibiotics was conducted using both the inhibition zone method and the minimum inhibition concentration. The actinorhodin activity was tested against the multi-antibiotic resistant (MAR) control strain *Staphylococcus aureus* ATCC 25923 and the local MAR *Bacillus cereus* strain using the agar well diffusion method [10]. The MAR strains were grown overnight on nutrient agar plates at 37˚C before four colonies were collected by using a sterile loop and resuspended in 2 ml saline solution, vortexed to obtain a homogenous mixture. The suspension was adjusted to the 0.5 McFarland standard (~1.5×10^8 CFU/ml) and tested for antibacterial activity using agar well diffusion [11]. For statistical assurance, 4 replicates were used for the mean value calculation.

The actinorhodin supernatant was collected from the grown *Streptomyces coelicolor strain* ATCC 10147 in 250-ml Erlenmeyer flasks that contained 150 ml of starch casein broth with supplements. The flasks were incubated for 8 days at 28˚C and 150 rpm, and cultures were later centrifuged at 10,000 rpm for 10 mins, and the cell-free supernatant was used to determine the antimicrobial activity against the MAR strains using the agar-well diffusion method on Mueller Hinton agar plates (Lab M, UK). The sterile 6 mm Whatman filter paper discs were soaked in 50 µl of the extract, and the same quantity was introduced into the bored holes on separate agar plates. The plates (4 replicates) were incubated overnight at 37˚C for 24 hours, and the inhibition zones were measured using a ruler, and the mean values were interpreted as sensitive, intermediate, and resistant according to the Clinical and Laboratory Standard Institute (CLSI) CLSI M100-Ed35 [12].

2.10. Determination of the Minimum Inhibition Concentration (MIC) and Biochemical Characteristics Using the VITEK-2 System

The minimum inhibition concentration (MIC) and biochemical characteristics were conducted using the VITEK® SOLUTIONS—Complete automated ID/AST platform (https://www.biomerieux.com/). Bacterial strains were grown overnight on nutrient agar at 37˚C. By using a sterile loop, four to five colonies were collected and resuspended in 2 ml saline solution. The density of the colonies was checked using a DensiCHEK Plus device; the reading should range from 0.58 to 0.62. The mixture was put on the cassette, and VITEK 2 Identification card Gram-

Negative (ID GN) cards and VITEK 2 Identification card Gram-Positive (ID GP) cards were placed accordingly. Samples were placed in a VITEK 2 Compact device.

3. Results

3.1. Morphological and Growth Characteristics

The optimum growth of the strain on solid media was on nutrient agar plus 1% starch. Aerial mycelia are abundant and medium-gray. After 7 days of incubation, bacteria were grown with gray, chalky aerial mycelia and blue vegetative mycelia. Vegetative mycelia are blue-gray with a blue soluble pigment. The morphology of colony growth was typically similar to that of *S. coelicolor*, where it showed the actinorhodin production and then its conspicuous red color diffusion in the media after 48 h of growth. The strain was exposed to the most notable test for the *S. coelicolor* by the red-blue acid-base test. Thus, the colonies that become red-purple because of actinorhodin production were rapidly turned blue on fuming the colonies with ammonia, consistent with the known pH indicator properties of the compounds (Figure 1).

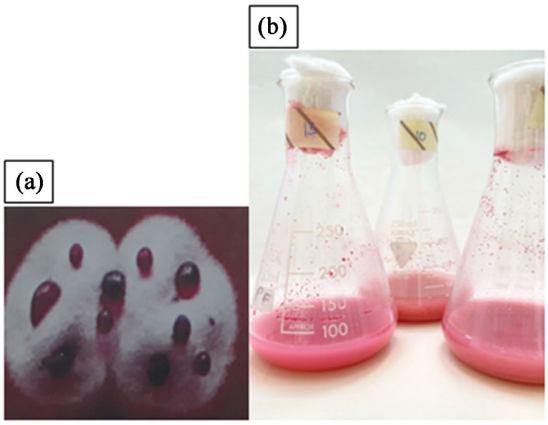

Figure 1. Growth of *S. coelicolor strain* ATCC 10147 on nutrient agar with 1% starch (a) and in nutrient broth with 1% starch (b).

3.2. Phylogenetic Tree and Genotyping of the *S. coelicolor strain* ATCC 10147

The full sequence (1804 bp) of the 16SrRNA gene of the *S. coelicolor strain* ATCC 10147 was determined (Figure 2), and its phylogenetic tree is given with 99.9% homology to the closest sister strains, *S. coelicolor strain*s M1154 and A3(2) (Figure 3).

3.3. Expression Switch-On/Off Time of the Act Gene and Optimization Production of Actinorhodin by *S. coelicolor* ATCC 10147

The expression switch-on time of the Act gene was determined to be 34 h, whereas the switch-off time of 16S rRNA was 120 h growth by the addition of chloramphenicol blocking the RNA enzyme peptidyl transferase center, which is located

Streptomyces coelicolor ATCC full gene sequencing length (1804)

>Contig1
TTCGTCCCAATCGCCAGTCCCACCTTCGACAGCTCCCTCCCACAAGGGGTTGGGCCACCG
GCTTCGGGTGTTACCGACTTTCGTGACGTGACGGGCGGTGTGTACAAGGCCCGGGAACGT
ATTCACCGCAGCAATGCTGATCTGCGATTACTAGCGACTCCGACTTCATGGGGTCGAGTT
GCAGACCCCAATCCGAACTGAGACCGGCTTTTTGAGATTCGCTCCACCTTGCGGTATCGC
AGCTCATTGTACCGGCCATTGTAGCACGTGTGCAGCCCAAGACATAAGGGGCATGATGAC
TTGACGTCGTCCCCACCTTCCTCCGAGTTGACCCCGGCGGTCTCCCGTGAGTCCCCAACA
CCCCGAAGGGCTTGCTGGCAACACGGGACAAGGGTTGCGCTCGTTGCGGGACTTAACCCA
ACATCTCACGACACGAGCTGACGACAGCCATGCACCACCTGTACACCGACCACAAGGGGG
GCACCATCTCTGATGCTTTCCGGTGTATGTCAAGCCTTGGTAAGGTTCTTCGCGTTGCGT
CGAATTAAGCCACATGCTCCGCCGCTTGTGCGGGCCCCCGTCAATTCCTTTGAGTTTTAG
CCTTGCGGCCGTACTCCCCAGGCGGGGCACTTAATGCGTTAGCTGCGGCACGGACAACGT
GGAATGTTGCCCACACCTAGTGCCCACCGTTTACGGCGTGGACTACCAGGGTATCTAATC
CTGTTCGCTCCCCACGCTTTCGCTCCTCAGCGTCAGTATCGGCCCAGAGATCCGCCTTCG
CCACCGGTGTTCCTCCTGATATCTGCGCATTTCACCGCTACACCAGGAATTCCGATCTCC
CCTACCGAACTCTAGCCTGCCCGTATCGACTGCAGACCCGGGGTTAAGCCCCGGGCTTTC
ACAACCGACGTGACAAGCCGCCTACGAGCTCTTTACGCCCAATAATTCCGGACAACGCTT
GCGCCCTACGTATTACCGCGGCTGCTGGCACGTAGTTAGCCGGCGCTTCTTCTGCAGGTA
CCGTCACTTTCGCTTCTTCCCTGCTGAAAGAGGTTTACAACCCGAAGGCCGTCATCCCTC
ACGCGGCGTCGCTGCATCAGGCTTTCGCCCATTGTGCAATATTCCCCACTGCTGCCTCCC
GTAGGAGTCTGGGCCGTGTCTCAGTCCCAGTGTGGCCGGTCGCCCTCTCAGGCCGGCTAC
CCGTCGTCGCCTTGGTGAGCCATTACCTCACCAACAAGCTGATAGGCCGCGGGCTCATCC
TTCACCGCCGGAGCTTTCGAACCTCGCAGATGCCTGCRAGGGTCAGTATCCGGTATTAGA
CCCCGTTTCCAGGGCTTGTCCCAGAGTGAAGGGCAGATTGCCCACGTGTTACTCACCCGT
TCGCCACTAATCCCCACCGAAGTGGTTCATCGTTCGACTTGCATGTGTTAAGCACGCCGC
CAGCGTTCGTCCTGAGCCAGG

Figure 2. Full sequence of the 16S rRNA gene of *Streptomyces coelicolor strain* ATCC 10147.

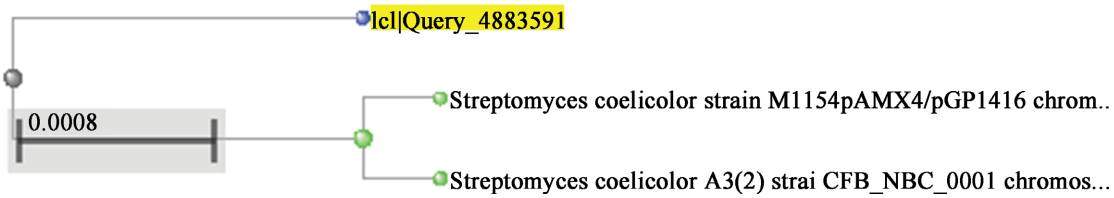

Figure 3. Phylogenetic tree of *Streptomyces coelicolor strain* ATCC 10147 with the top two sister strains with 99.9% homology as constructed by the neighbor-joining method.

at the lower tips (acceptor ends) of the A- and P-site tRNAs, where it binds to the residues A2451 and A2452 in the 23S rRNA (component of 50S) and prevents the attachment of aminoacyl transferase to the ribosomal subunit, which inhibits peptide bond formation (**Figure 4**). The optimum growth conditions for actinorhodin production were determined in liquid growth as: nutrient broth as C-source (1% starch), N-source (K_2NO_3), P-source (K_2PO_4), Fe-source ($FeCl_3$-EDTA), shaking speed (200 rpm), pH 7.0, 28˚C, and aerobic conditions. The extracellular and intracellular actinorhodin reached 165 mg^{-1} and 88 mg^{-1}, respectively. The optimum growth of the strain on solid media was on nutrient agar plus 1% starch. For production of the antibiotic droplets on the colony's surface, the strain was cultured on potato dextrose agar (PDA) for 5 days before several droplets (3 - 5) appeared on the top of each colony.

3.4. Actinorhodin Activity against MAR and MRSA

The inhibition zone activity against both the international MRSA control strain

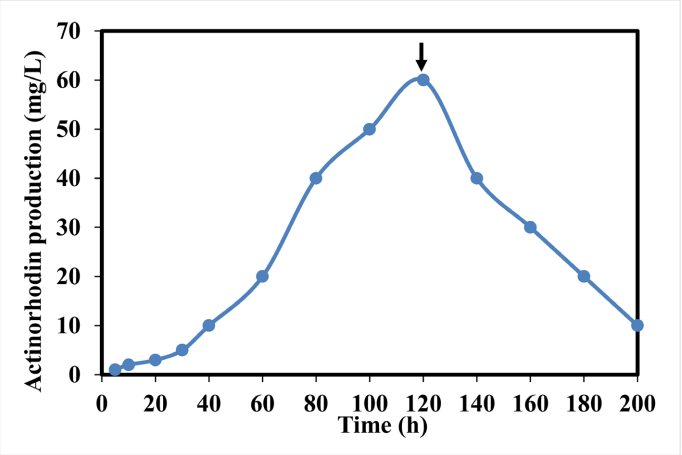

Figure 4. Expression switch-on time of the Act gene cluster and switch-off time of 16S rRNA gene (arrow indicate chloramphenicol addition) for optimization of actinorhodin antibiotic production by *S. coelicolor strain* ATCC 10147.

Staphylococcus aureus ATCC 25923 and the local MAR *Bacillus cereus* strain was 21 mm and 24 mm for both strains, respectively. The MIC of the actinorhodin antibiotic were 2.0 μg/ml and 4.0 μg/ml for the MRSA control strain *Staphylococcus aureus* ATCC 25923 and local MAR *Bacillus cereus* strain, respectively.

The actinorhodin activity was tested against the international MRSA control strain *Staphylococcus aureus* ATCC 25923 and the local MR *Bacillus cereus* strain. The inhibition zones were 21 mm and 24 mm for the MR control strain *Staphylococcus aureus* ATCC 25923 and the local MR *Bacillus cereus* strain, respectively. The MIC of the actinorhodin antibiotic was 2.0 ug/ml and 4.0 ug/ml for the MR control strain *Staphylococcus aureus* ATCC 25923 and the local MR *Bacillus cereus* strain.

4. Discussion

The results are novel on the ON/OFF switching of interplay regulation of gene expression for optimization of actinorhodin antibiotic production by *S. coelicolor strain* ATCC 10147. The results also provide evidence of production optimization using cheap starch as a C-source to produce a highly effective antibiotic against the MRSA and MAR pathogens. The results show the synchronization induction & synergistic ability to control the expression switching board of the interplay regulation for optimization of actinorhodin antibiotic production.

The 16S rRNA sequence of *S. coelicolor strain* ATCC 10147 and its position on the phylogenetic tree revealed the closest sister strains are *S. coelicolor strain*s M1154 and A3(2), with a homology of 99.9% in the international GeneBanks NCBI (www.ncbi.nlm.nih.gov), Sanger Institute (http://www.sanger.ac.uk), DDBJ (http://www.ddbj.nig.ac.jp), and EMBL-EBI GeneBank (http://www.ebi.ac.uk) databases.

The expression switch-on time of the Act gene was determined to be after 34 h of growth, whereas the switch-off time of 16S rRNA was determined to be at 120 h

of growth by the addition of chloramphenicol, which blocks the RNA enzyme peptidyl transferase center, which is located at the lower tips (acceptor ends) of the A- and P-site tRNAs, where it binds to the residues A2451 and A2452 in the 23S rRNA (component of 50S) and prevents the attachment of aminoacyl transferase to the ribosomal subunit, which inhibits peptide bond formation [13]. The results also provide evidence of optimization of actinorhodin antibiotic production using cheap starch as a C-source to produce a highly effective antibiotic against MRSA and the MAR pathogens. The actinorhodin antibiotic production was similar to that reported by other strains of *Streptomyces* [6]-[8] [14]-[16]. The antibiotic potency of the actinorhodin activity was high against the MRSA control strain *Staphylococcus aureus* ATCC 25923 and local MAR *pathogenic* strains. *Bacillus cereus* is considered a relatively common cause of gastroenteritis worldwide as a food poisoning causative pathogen that occurs when it produces toxins, causing two types of gastrointestinal illness, such as vomiting and diarrhea. *B. cereus* grows in food that has been improperly stored; therefore, proper food handling, especially after cooking, will help prevent illnesses caused by this microorganism. For instance, in Canada, over 36,000 cases of foodborne illness due to *B. cereus* were estimated to have occurred in 2006.

5. Conclusion

The results are novel on the ON/OFF switching of interplay regulation of gene expression for optimization of actinorhodin antibiotic production by *S. coelicolor strain* ATCC 10147. The results also provide evidence of production optimization using cheap starch as a C-source to produce a highly effective antibiotic against the MRSA and MAR pathogens. The results show the synchronization induction & synergistic ability to control the expression switching board of the interplay regulation for optimization of actinorhodin antibiotic production.

Authors' Contributions

IAM: Conceptualization, design, phylogenetic analysis, writing up manuscript and intellectual content, project administration and supervision, investigation and methodology. **IMA:** Experiments, investigation, and results presentation. **MM:** Sequencing the 16SrRNA gene.

Funding

There was no funding or financial support, as the present study did not require any type of funding support.

Availability of Data and Materials

The data will be available on request.

Acknowledgements

The authors would like to thank the University of Sharjah for providing the labor-

atory facilities and the University Hospital of Sharjah (UHS) for providing the MAR bacterial strains.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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