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Research Article

The Effect of Streptomyces-Derived Bioactive Compounds on IL-6 Levels Exploring Antimicrobial and Anti-inflammatory Properties in Bacterial Infections

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A B S T R A C T

Background: Streptomyces, a genus of Actinomycetes, are known for their ability to produce bioactive compounds, including antibiotics, with significant applications in medicine and agriculture.

Objective: This study's aim is to investigate the effects of extracellular extracts from Streptomyces spp. on the inflammatory response, specifically interleukin-6 (IL-6), in various bacterial infection models.

Methods: Through 16S rRNA gene sequencing, the T2 strain was identified and shown to share a high similarity with S. actinomycinicus. Phylogenetic analysis confirmed its close evolutionary relationship with other species in the Streptomyces genus.

Results: The study found that IL-6 levels were significantly elevated in infections caused by both sensitive and resistant bacterial strains, with resistant strains showing the highest inflammatory response. Post-infection treatment with Streptomyces extracts effectively reduced IL-6 levels in sensitive bacterial infections, demonstrating the extract's potential antimicrobial properties. However, the treatment had limited effectiveness in resistant infections, as indicated by persistent high IL-6 levels. The extract alone did not significantly alter IL-6 levels, suggesting anti-inflammatory properties without triggering an immune response.

Conclusion: Streptomyces extracts may reduce bacterial load and inflammation in infections, but limited effectiveness on resistant strains necessitates further research for more potent antibiotic-resistant treatments.

Keywords: Streptomyces Actinomycetes, IL-6, ELISA, 16S rRNA

Introduction

Streptomyces, a genus within the Actinomycetes order, are prokaryotic microorganisms that exhibit characteristics of both bacteria and fungi. A distinguishing feature of actinomycetes is their ability to undergo complex morphological differentiation, forming hyphae and spore structures, often associated with their filamentous growth pattern. These microorganisms are widely recognized for their capacity to produce an array of bioactive compounds, including antibiotics such as streptomycin, erythromycin, and tetracycline. These compounds have significant applications in both medicine and agriculture, where they contribute to infection control and crop protection.[1] The versatile metabolic capabilities of Streptomyces make them invaluable in the pharmaceutical, agricultural, and industrial sectors. Researchers are actively investigating the potential of these organisms to produce novel bioactive compounds and enzymes with various applications.[2] In particular, the secondary metabolites produced by Streptomyces play a critical role in defense mechanisms, such as inhibiting the growth of pathogens. Numerous studies have reported the antibacterial, anticandidal, anti-inflammatory, and anticancer properties of secondary metabolites isolated from actinomycetes.[3,4] One of the key challenges in leveraging microbial extracts for drug development is the identification of novel bacterial strains capable of producing bioactive secondary metabolites. Many environmental niches remain unexplored, presenting opportunities for the discovery of new actinomycetes with unique metabolic pathways. By focusing on these untapped resources, researchers can enhance the diversity of bioactive compounds available for therapeutic use.[5] In the context of immune modulation, interleukins (ILs) play a pivotal role in regulating the immune response. These cytokines, produced by white blood cells and other immune cells, facilitate the growth and differentiation of T and B lymphocytes. Interleukins like IL-6 are integral to the immune system's function and have been implicated in both autoimmune diseases and immune deficiencies. They also influence the effectiveness of vaccines by stimulating the activation and proliferation of immune cells.[6] This study aims to investigate the effect of extracellular extracts from Streptomyces spp. on the pro fortress cytokine interleukin 6 (IL-6) in bacterial infection models. The primary focus is to evaluate whether these extracts can modulate IL-6 levels, particularly in infections caused by sensitive and resistant bacterial strains. By doing so, the study seeks to explore the potential of Streptomyces extracts as antimicrobial agents and their influence on the immune response.

Materials and Methods

Study design

The anti-inflammatory and antibacterial effects of extracellular extracts obtained from Streptomyces on IL-6 levels in bacterial infections were examined in this controlled, randomized experimental trial. In order to guarantee the reliability and repeatability of the findings, each of the six groups of 18 healthy adult albino rats was tested three times. There was a control group, two groups that received either sensitive or resistant Escherichia coli infections, a group that received simply extract, and two groups that received either sensitive or resistant treatments after the infection.

Study Duration

In order to provide sufficient time for infection formation, therapy delivery, and monitoring of inflammatory responses, the trial was conducted across four months, from January 1, 2024, to April 30, 2024. We set out to test the Streptomyces extract's ability to modulate IL-6 levels in a variety of infection settings, with the hope of learning more about its therapeutic and preventative uses.

This study was designed as a controlled, randomized experiment using 18 albino rats, divided into six groups with three rats each, including triplicates for every group. The duration of the study was 5 weeks, chosen to adequately assess the inflammatory response and treatment effects.

Molecular Identification and Sequence Alignment of Streptomyces actinomycinicus Strain T2.

The partial 16S rRNA gene of the Streptomyces actinomycinicus strain T2 was sequenced to establish its phylogenetic relationship within the Streptomyces genus. The sequence, spanning nucleotides 504 to 914 (Sequence ID: LC310927.1), was analysed using BLASTn to compare it against the GenBank database.

Study Groups

1. **Control Group:** No infection or treatment.
2. **Sensitive Bacteria Group:** Infected with Escherichia coli, a common UTI-causing bacterium.
3. **Resistant Bacteria Group:** Infected with a resistant strain of Escherichia coli.
4. **Extract Only Group:** No infection, treated with Streptomyces extract.
5. **Post-Infection Sensitive Treatment Group:** Infected with sensitive E. coli, treated with the extract starting two days post-infection.
6. **Post-Infection Resistant Treatment Group:** Infected with resistant E. coli, treated with the extract starting two days post-infection.

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Experimental Procedure

1. **Preparation and Acclimatisation:** The albino rats were acclimatized to laboratory conditions for one week prior to the experiment. They were provided with food and water ad libitum.
2. **Infection Process:** Rats in the Sensitive and Resistant Bacteria Groups were inoculated with their respective strains of E. coli via intravesical instillation under sterile conditions.
3. **Treatment Administration**

- The Extract Only Group received Streptomyces extract orally at a predetermined dosage daily for the duration of the experiment.
- The post-infection Sensitive and resistant treatment groups started receiving the extract orally at the same dosage two days after infection and continued treatment daily.

4. **Monitoring and Maintenance:** All animals were monitored daily for any signs of infection, distress, or behavioural changes, and weight was recorded throughout the study.
5. **Sample Collection:** After the 5-week study period, the rats were anaesthetized, and blood samples were collected via cardiac puncture for serum analysis.
6. **Serum Analysis:** Serum IL-6 levels were measured using an ELISA kit (Sunglong Biotech, China) to assess the inflammatory response.

Measurement of IL-6 Levels

The IL-6 levels in the serum were measured using the sandwich enzyme-linked immunesorbent assay (ELISA) technology. A 96-well plate was pre-coated with an anti-IL-6 antibody. Horseradish peroxidase (HRP)-conjugated IL-6 antibodies were added, and after washing, tetramethylbenzidine (TMB) substrates were used to produce a blue colour reaction, turning yellow after adding an acidic stop solution. The optical density (O.D.) was measured at 450 nm using a microplate reader, and IL-6 concentrations were calculated.

Ethical Considerations: This study was conducted following the ethical guidelines obtained from the institutional ethics committee of Al-Nahrain University 754/2/2 is available upon request. All efforts were made to minimise animal suffering, and proper care was given throughout the study.

Statistical Analysis: IL-6 levels were recorded in triplicates for each group and statistically analysed using standard curve ELISA techniques, and the data were analysed using GraphPad prism software to determine the significance of differences between groups in which P. value <0.05 considered significant differences between the studied groups.

Results

Molecular Identification and Phylogenetic Analysis

The results revealed that the 16S rRNA gene sequence of the T2 strain was closely related to the members of the Streptomyces genus. The T2 strain shared the highest 16S rRNA gene sequence similarity with S. actinomycinicus CMU-RKDM30 (96.86%). Based on the study of the 16S rRNA gene sequence and phylogenetic relationship, T2 was found to belong to the same clade as S. actinomycinicus CMU-RKDM30. The full-length 16S rRNA gene of T2 shared a 99.86% sequence similarity with S. actinomycinicus CMU-RKDM30, indicating that they belong to the same species. The alignment revealed a high degree of similarity with the 16S rRNA gene sequence of S. actinomycinicus strain CMU-RKDM30, with a score of 619 bits, an E-value of 4e-175, and a sequence identity of 94%. Out of 412 nucleotides, 387 were identical, with only 3 gaps, indicating a very close relationship as shown in figure 1.

Effect of extracellular extract of Streptomyces spp. on proinflammatory interleukin

The mean IL-6 levels for the control group were 32.14±2.86 ng/mL; the control group serves as a baseline for comparison with other experimental conditions. The sensitive bacteria group exhibited significantly higher IL-6 levels, with a mean of 57.33±3.96 ng/mL. The p-value for this group, when compared to the control, was 0.0257, indicating a statistically significant increase in IL-6 levels. Similarly, the resistant bacteria group showed elevated IL-6 levels, with a mean of 61.1±2.45 ng/mL. This increase was also statistically significant, as evidenced by a p-value of 0.0059. The extract-only group had a mean IL-6 level of 24.94±2.66. The p-value for this group was 0.26, indicating no significant difference compared to the control group. For the post-infection sensitive treatment group, the mean IL-6 level was 44.38±2.95 ng/mL. The p-value was 0.102, suggesting no significant difference from the control group. Finally, the post-infection resistant treatment group exhibited a mean IL-6 level of 54.3±2.94 ng/mL. The p-value for this group was 0.0187, indicating a statistically significant increase in IL-6 levels compared to the control group. As it is fully described in Table 1.

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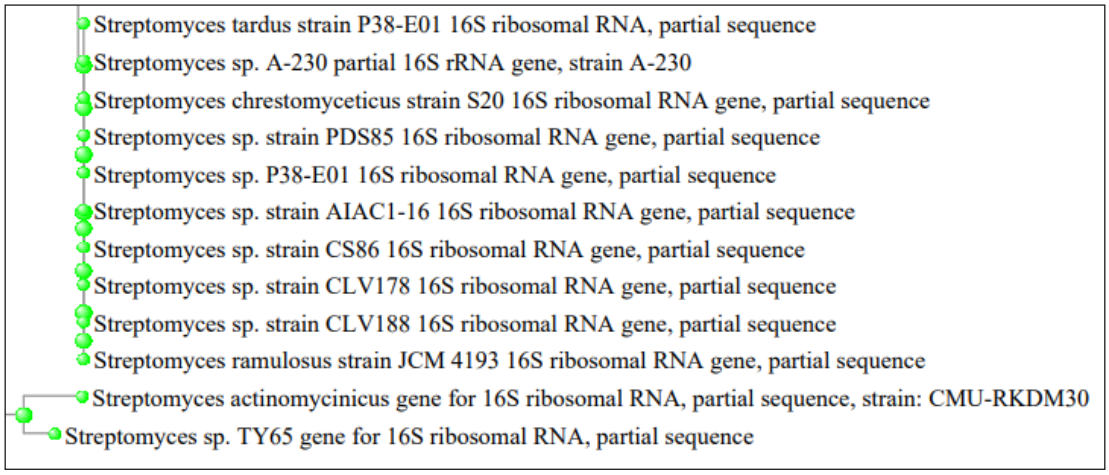

Figure 1.A phylogenetic tree was constructed using relative 16S rRNA gene sequences to illustrate the evolutionary relationships among different species of -Streptomyces

Table 1.The effect of Streptomyces extracellular extracts on IL-6 levels

Group	IL-6 Levels (ng/mL) Mean±SE	CI 95%	P-Value
Control	32.14 ± 2.86 a	(19.84, 44.43)	1 NS
Sensitive Bacteria	57.33 ± 3.96 b	(40.29, 74.37)	0.0257 *
Resistant Bacteria	61.1 ± 2.45 b	(50.58, 71.62)	0.0059 **
Extract Only	27.94 ± 3.66 a	(15.51, 36.37)	0.2624 NS
Post-Infection Sensitive Treatment	44.38 ± 2.95 b	(31.7, 57.06)	0.1028 NS
Post-Infection Resistant Treatment	54.3 ± 2.94 b	(41.66, 66.93)	0.0187 *

Different letters in column means significance differences; NS; Not significant (p>0.05); *:P<0.05; ** :p<0.01.

Discussion

This study examined the inflammatory response, specifically IL-6 levels, under various conditions, including control, sensitive and resistant bacterial infections, and post-infection treatments. Both bacterial groups demonstrated significantly higher IL-6 levels compared to the control, indicating a strong inflammatory response. The elevated IL-6 levels are consistent with previous findings that associate bacterial infections with increased production of proinflammatory cytokines, such as IL-6, as part of the body's immune defence.[7] However, the extract-only group showed no significant difference in IL-6 levels, suggesting potential anti-inflammatory properties. This result supports earlier studies suggesting that certain Streptomyces extracts possess anti-inflammatory capabilities without triggering excessive immune responses.[8] The post-infection sensitive treatment group showed no significant difference in IL-6 levels compared to the control, suggesting that the Streptomyces extract was effective in mitigating inflammation in sensitive bacterial infections. Similar findings have been reported by other studies showing that Streptomyces-derived compounds can effectively reduce bacterial loads and modulate immune responses in bacterial infections.[9,10] These results align with the hypothesis that appropriate antimicrobial treatments can reduce inflammation by lowering the bacterial burden.[11] Conversely, the post-infection resistant treatment group continued to exhibit elevated IL-6 levels, similar to the untreated resistant group. This finding highlights the challenge of treating infections caused by antibiotic-resistant strains, which often provoke sustained inflammatory responses even after treatment. These results are comparable to those observed in studies of other resistant bacterial infections, where conventional treatments fail to adequately control inflammation.[12] This underscores the growing concern over antibiotic resistance in clinical settings and the need for innovative therapeutic approaches.[13] The persistence of high IL-6 levels in the resistant treatment group suggests that current treatments may be inadequate in managing inflammation in resistant infections. Similar results have been observed in studies of multidrug-resistant bacterial infections, where standard antimicrobial therapies fail to reduce cytokine levels, leading to prolonged inflammatory responses.[14] Future research should focus on identifying

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alternative treatments or adjunct therapies that can effectively target resistant bacterial strains and reduce the associated inflammatory response.[15] Furthermore, the antimicrobial properties of Streptomyces extracts, as observed in this study, align with previous findings that certain Streptomyces species produce secondary metabolites with potent antimicrobial effects.[16] These findings are consistent with research demonstrating that Streptomyces-derived compounds, such as streptomycin, have been successful in inhibiting the growth of various pathogens, including resistant strains.[17]

The study's limitations include the small sample size and the short duration of the experiment, which may affect the generalisability of the results. Additionally, the focus on a single cytokine, IL-6, limits the scope of immune response analysis. However, the findings highlight the potential of Streptomyces extracts in reducing bacterial load and inflammation in sensitive bacterial infections. Further research is necessary to enhance the potency of these extracts, particularly against resistant strains, and to explore their use in combination therapies to address the growing issue of antibiotic resistance.

Conclusions

This study demonstrated that the T2 strain of Streptomyces is closely related to S. actinomycinicus, with high sequence similarity, confirming its identification within the same species. The extracellular extract of Streptomyces spp. significantly modulated IL-6 levels, reducing inflammation in sensitive bacterial infections but showing limited effectiveness against resistant strains. These findings highlight the potential antimicrobial and anti-inflammatory properties of Streptomyces extracts, particularly in treating sensitive infections, and emphasise the need for further research to enhance their efficacy against resistant bacteria.

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Units of measurement used in this study:

- Concentration of IL-6: Nanograms per millilitre (ng/mL)
- Length of DNA sequences: Base pairs or nucleotides (bp or nt)
- Optical Density: Nanometres (nm) for absorbance readings (e.g., 450 nm)
- Weight: Grams (g), typically for the rats
- Time: Minutes (min), Hours (h), Days (d), or Weeks (wks)
- Volume: Microlitres (µL) or millilitres (mL)

Conflicts of Interest: None

Sources of Funding: None

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

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