Investigation of Meropenem (Meronem) and Marine Streptomyces to Inhibit Shiga Toxin Producing E. Coli and Oxidation Process

Anushka1 , T.Visha1,a)

1Anu Health Centre, Chennai, Tamilnadu, India

Corresponding Author: a)[vishhh131@gmail.com](mailto:vishhh131@gmail.com)

**Abstract:** Shiga-toxin producing meropenem resistant *Escherichia coli* (STEC) are zoonotic foodborne pathogens responsible for severe human illnesses, including haemolytic uraemic syndrome (HUS). This study investigates the antioxidant and lactate dehydrogenase (LDH) inhibitory activities of polyphenols extracted from marine-derived *Streptomyces sp*. The Streptomyces strain exhibited unique morphological and chemo-taxonomical characteristics, confirming its classification. LDH activity assays revealed a dose-dependent inhibition, with the highest concentration (100 µg/ml) reducing LDH activity by 51%. Antioxidant assays demonstrated that the polyphenol extract exhibited significant scavenging activities against DPPH and lipid peroxidation (LPO), with maximal activities of 47% and 51.49% at 100 µg/ml, respectively. Additionally, the reducing power assay showed increased activity with higher concentrations, peaking at 61.04% at 100 µg/ml. The polyphenol extracts also demonstrated substantial antibiofilm activity against Shiga toxin-producing *E. coli*, significantly reducing biofilm formation in a time-dependent manner. These findings suggest that polyphenols from Streptomyces possess potent antioxidant, LDH inhibitory, and antibiofilm properties, highlighting their potential therapeutic applications in managing oxidative stress-related conditions and bacterial infections

**Keywords:** *Escherichia coli;*  lactate dehydrogenase; Antioxidant; Biofilm

# Introduction

Shiga toxin-producing *Escherichia coli* (STEC) are zoonotic pathogens transmitted through food, known to cause significant illnesses in humans. In 2018, over 8,000 cases of STEC infections were documented across Europe, with more than one-third of the patients requiring hospitalization and additional medical care [(Efsa, 2019)](https://paperpile.com/c/tj9cjx/bIvnY). Both enterohemorrhagic *E. coli* (EHEC) and other related strains fall under the broader classification of STEC [(Goldstein et al., 2021)](https://paperpile.com/c/tj9cjx/aFnQW). These bacteria pose a considerable threat to public health due to their ability to cause gastrointestinal outbreaks and severe complications like haemolytic uraemic syndrome (HUS), a potentially fatal systemic disorder [(Byrne et al., 2015)](https://paperpile.com/c/tj9cjx/erbny). STEC is characterized by the presence of genes encoding Shiga toxins—Stx1 and Stx2 located on bacteriophages integrated into their genomes. These toxins are further categorized into subtypes, including Stx1a–1d and Stx2a 2g, with Stx2a being most frequently linked to severe clinical outcomes [(EFSA BIOHAZ Panel et al., 2020)](https://paperpile.com/c/tj9cjx/4SWcW). Polyphenols, known for their antioxidant capabilities, are secondary metabolites that neutralize free radicals and influence oxidative stress-related biological pathways [(Rudrapal et al., 2022)](https://paperpile.com/c/tj9cjx/bBkoK) [(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/tj9cjx/i080H+HFYuX+Qjwmx) Actinobacteria, particularly marine-derived species, continue to garner scientific interest due to their potential in producing novel bioactive compounds with therapeutic value. This bacterial phylum is highly adaptive, thriving in various environmental niches through a complex life cycle and sophisticated defense strategies, especially within the genus *Streptomyces* [*(Thye et al., 2022)*](https://paperpile.com/c/tj9cjx/nO5lu); [(Law et al., 2019)](https://paperpile.com/c/tj9cjx/vLUgk) [(Ramakrishnan et al., 2023; Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/tj9cjx/u75FI+b1li7+dhFc8). The largest genus in the  phylum Actinobacteria is *Streptomyces*, the largest genus within Actinobacteria, plays a vital role in global health by producing a majority of antibiotics currently used to treat infectious diseases in both animals and humans [(Quinn et al., 2020)](https://paperpile.com/c/tj9cjx/VRxg6) [(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/tj9cjx/eV8JT+XrCGg+4Jhw0)

# Materials and methods

Marine sediment samples were obtained from the coastal region of Tuticorin, Tamil Nadu, using a Van Veen grab sampler. These samples were placed into sterile containers and promptly transported to the Marine Biomedical Lab and Environmental Toxicology Unit. Once received, the samples were subjected to air drying for 48 hours, followed by an additional 12 hours of sun drying. After drying, the sediments were finely ground using a mortar and pestle.To isolate actinobacteria, the samples were cultured on KUA medium supplemented with 10 µg/ml each of cycloheximide and nalidixic acid to inhibit fungal and bacterial contamination. Serial dilutions were performed, and aliquots were spread onto the medium and incubated for seven days at room temperature. Colony-forming units (CFU) per gram of sediment were calculated to estimate the actinobacterial population. Distinct colonies were selected and subcultured to obtain pure isolates for further study. Identification of isolates followed the guidelines of the International Streptomyces Project (ISP), including assessments of morphological characteristics (such as aerial mycelium color, spore chain arrangement), pigment production, and utilization of various carbon sources. Chemotaxonomic traits were also considered for classification [(Noufal et al., 2022)](https://paperpile.com/c/tj9cjx/wkyat).The antimicrobial properties of meropenem and extracts from *Streptomyces* were analyzed by determining the minimum inhibitory concentration (MIC). Concentrations tested ranged from 10 to 100 mg/ml for meropenem, and from 250 to 1000 µg/ml for *Streptomyces* extracts.To assess antioxidant activity, the DPPH radical scavenging method was employed, based on the procedure described by [(S B et al., 2023)](https://paperpile.com/c/tj9cjx/6splg). Samples were incubated at 37°C for 30 minutes in the dark, and absorbance was measured at 517 nm. The inhibition percentage was calculated using the formula:

Percentage of Inhibition (I %) = (A blank - A sample) / A blank ×100

where A\_blank refers to the absorbance of the control and A\_sample to that of the test sample. Ascorbic acid served as a reference standard, and tests were carried out in triplicate. Lipid peroxidation inhibition was evaluated using crude mangrove extracts (0.5–3 mg/ml), mixed with 2 ml of 20% trichloroacetic acid and 2 ml of 0.67% thiobarbituric acid. This mixture was heated at 100°C for 10 minutes in a water bath, cooled to room temperature, and centrifuged at 3,000 rpm for 20 minutes. Absorbance was then measured at 532 nm, and the percentage of inhibition was calculated as described previously, using ascorbic acid as a positive control [(Subaraman et al., 2022)](https://paperpile.com/c/tj9cjx/3BDrt). The reducing power of the extracts was determined using a modified version of the method by [(Roy et al., 2022)](https://paperpile.com/c/tj9cjx/nM8v0). One milliliter of extract (25–100 mg/ml) was combined with 2.5 ml of 1% potassium ferricyanide and 2.5 ml of a benzene:chloroform mixture, then incubated at 50°C for 20 minutes. Afterward, 2.5 ml of 10% trichloroacetic acid was added, and the mixture was centrifuged at 10,000 rpm for 10 minutes. The upper layer was mixed with 0.5 ml of 0.1% FeCl₃ and 2.5 ml of distilled water. Absorbance was recorded at 700 nm to determine the reducing capability. For biofilm analysis, overnight *E. coli* cultures were incubated for 24 to 96 hours at 37°C to facilitate biofilm development. After incubation, non-adherent cells were removed by washing, and the remaining biofilms were stained with acridine orange and propidium iodide. Samples were then examined under a confocal laser scanning microscope at 40x magnification.

# Results

The morphological examination of *Streptomyces* sp. showed various distinguishing characteristics. The aerial mycelium was white, and the strain produced no melanoid, soluble, or reverse pigments, which is usual for the *Streptomyces genus* (Table 1). The lack of these pigments was constant across all test circumstances, indicating a stable phenotype. Chemotaxonomical examination of the cell wall composition provided additional evidence for the strain's categorization within the Streptomyces genus. The cell wall contained LL-diaminopimelic acid (LL-DAP) and glycine, but DL-DAP, alanine, lysine, and ornithine were lacking. This unique peptidoglycan structure is seen in numerous Streptomyces species. Whole-cell sugar analysis revealed the lack of arabinose, galactose, xylose, madurose, and ribose, indicating an unusual sugar pattern. This distinct metabolic profile reflects the genus diversity. The cell wall was classified as Type I, which is common for actinomycetes. Spore morphology was found to be spiral, which supports the identification as *Streptomyces.*  Biochemical characteristics of the pathogen were given in (Table 2).

**Table 1.** Morphological and other taxonomical characteristics of marine actinobacteria

|  |  |
| --- | --- |
| **Morphological observation** | **Result** |
| A.M.Color | Present |
| Mel.Pigment | + |
| Sol.Pigment | - |
| Rev.pigment | + |
| Cell wall amino acid | |
| LL-DAP | + |
| DL-DAP | - |
| Glycine | + |
| Alanine | - |
| Lysine | - |
| Ornithine | - |
| Whole cell sugar | |
| Arabinose | - |
| Galactose | - |
| xylose | - |
| Madurose | - |
| Ribose | - |
| Sugar pattern | N.C |
| Cell Wall type | I |
| Spore morphology | Spiral |
| Index | *Streptomyces* sp. |

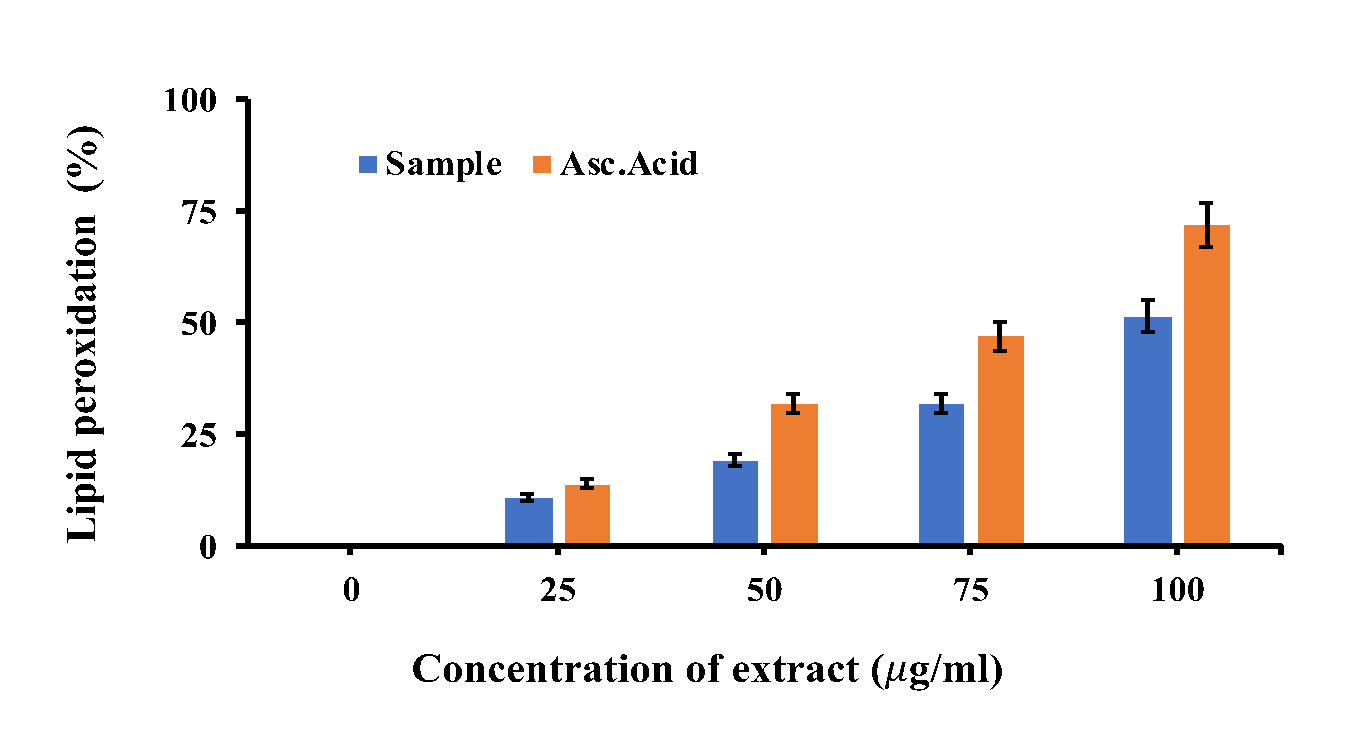
**Table 2.** Biochemical characteristics of *E.coli*

|  |  |
| --- | --- |
| Gram stain | Negative |
| Shape | Rod |
| Motility | Positive |
| Indole | Positive |
| MR | Positive |
| VP | Positive |
| Citrate | Negative |
| TSI | Negative |
| Oxidase | Negative |
| Catalase | Positive |
| Urease | Negative |
| Lactose | Positive |
| Maltose | Positive |
| Sucrose | Variable |
| Xylose | Variable |
| Starch | Positive |
| Inositol | Negative |
| Genus | *Escherichia* |
| Species | coli |

The present study examined the DPPH scavenging activity of polyphenols, using ascorbic acid as a reference due to its high antioxidant content. At a low dosage of 25μg/ml, the polyphenol sample demonstrated 8% scavenging activity(Nikalje et al., 2024), while standard ascorbic acid had 19.58% activity. Increasing the concentration to 50μg/ml resulted in 15% scavenging activity, compared to 39.37% for ascorbic acid. At 75μg/ml, polyphenol showed 32% scavenging activity, whereas ascorbic acid showed 56.29% activity. The highest measured concentration (100μg/ml) of polyphenol showed the highest scavenging activity (47%), whereas ascorbic acid had a value of 74.68%(Chehelgerdi et al., 2023). These results indicate that polyphenol exhibits dose-dependent antioxidant activity, although lower than ascorbic acid, indicating its potential as a natural antioxidant agent (Graph 2).

**Graph 2.** DPPH antioxidant activity

At a low concentration of 25µg/ml, the sample exhibited 11.04% scavenging activity, whereas the standard ascorbic acid showed 14% scavenging activity, serving as a reference. As the sample concentration increased, there was an observed tendency for scavenging activity to rise. The highest scavenging activity was observed at a high concentration of 100µg/ml, reaching 51.49%, while the standard ascorbic acid demonstrated 72% scavenging activity (Graph 3). These findings suggest a potential for the sample to exhibit lipid peroxidation (LPO) antioxidant activity, particularly at higher concentrations.



**Graph 3.** Lipid peroxidation activity

Antibiofilm activity of the extract of *Streptomyces* has been evaluated against Shiga toxin-producing *Escherichia coli* was investigated over time. At 24 hours, the untreated control had a biofilm cell count of around 1012CFU/mL. *Streptomyces* extract treatment decreased cell count to approximately 9×104CFU/mL. At 48 hours, the control cell count grew to roughly 2×106CFU/ml, while extract treatments resulted in cell counts of around 1.5×106 CFU/ml. Extract treatment decreased the cell count to approximately 8×106 CFU/ml, while the control biofilm cell count reached around 107 CFU/ml after 72 hours. After 96 hours, the control cell count reached an average of around 107 CFU/ml. The polyphenol treatments significantly decreased biofilm development to around 2×106CFU/ml (Fig. 1). These decreases were statistically significant (p < 0.05), suggesting that polyphenols have the ability to reduce biofilm-associated illnesses by efficiently inhibiting biofilm formation in a time-dependent manner in *E. coli* that produces Shiga toxin.



**Figure 1**. Antibiofilm activity of the extract of *Streptomyces*

# Discussion

Recent studies have increasingly highlighted the antioxidant and antibacterial potential of actinomycetes, particularly from the *Streptomyces* genus. These microorganisms, isolated from diverse environments such as marine sediments and forest soils, have shown significant biological activity, supporting their relevance in the search for natural therapeutic agents. For instance, research conducted by [(Mesrian et al., 2021)](https://paperpile.com/c/tj9cjx/7084Q) evealed that crude extracts from actinomycete strains HV11.P3 and SCA54.P2 were effective in neutralizing DPPH free radicals, with IC₅₀ values of 231.08 µg/mL and 369.3 µg/mL, respectively, indicating their moderate antioxidant potential. Similarly, [(Chang et al., 2021)](https://paperpile.com/c/tj9cjx/qC4di) iisolated five novel *p*-terphenyl derivatives from a marine sediment-derived *Streptomyces* strain, among which one compound demonstrated not only antibacterial effects but also potential free radical scavenging activity. The production of melanin pigments by *Streptomyces* species, particularly those sourced from marine ecosystems, has also been associated with antioxidant capabilities. In a previous study, [(Sheefaa & Sivaperumal, 2022)](https://paperpile.com/c/tj9cjx/BQni9) demonstrated that these pigmented compounds had strong DPPH radical scavenging properties, pointing to their role in oxidative stress mitigation. Further support comes from [(Wu et al., 2024)](https://paperpile.com/c/tj9cjx/7lV3l) who reported that polyphenols derived from *Streptomyces* could suppress heme protein-induced lipid oxidation in muscle-based foods, positioning these compounds as viable natural antioxidants in food preservation. Terrestrial strains such as *Streptomyces* sp. FR7, isolated from forest soils, have also demonstrated considerable antioxidant capacity [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/tj9cjx/2QC8m+OBCrl+msHTo)).According to Weslati et al. (2023) FR7 exhibited not only high DPPH scavenging activity but also protected yeast cells from oxidative stress, underlining its promise as a source of antioxidant and antimicrobial agents [(Weslati et al., 2023)](https://paperpile.com/c/tj9cjx/ZVd9o). In addition to microbial polyphenols, plant-derived food-borne polyphenols (FPPs) have also drawn attention. Zhang et al. (2024) reported that FPPs can inhibit lipid peroxidation in biological membranes through activation of the Nrf2/GPx4 antioxidant pathway. This mechanism strengthens the case for polyphenols as effective therapeutic agents in oxidative stress-related conditions [(Zhang et al., 2024)](https://paperpile.com/c/tj9cjx/PaX2X). Mangrove-derived *Streptomyces* strains also contribute to this growing body of evidence. Kemung et al. (2020) found that *Streptomyces* sp. MUSC 14 exhibited strong antioxidant activity, which was positively correlated with its phenolic content [(Kemung et al., 2020)](https://paperpile.com/c/tj9cjx/ceqV8). Similarly, Ganta et al. (2021) reported that melanin produced by marine *Streptomyces* strains possessed notable antioxidant properties, reinforcing the role of phenolic compounds in oxidative defense [(Ganta et al., 2021)](https://paperpile.com/c/tj9cjx/2ETOu). The strain *Streptomyces cellulosae* TES17 also demonstrated high antioxidant activity, with reducing power largely attributed to its phenolic constituents [(Rani et al., 2018)](https://paperpile.com/c/tj9cjx/k0nfk). Additional strains like OS-6 and TES-25 have been found to generate secondary metabolites rich in polyphenolic compounds, which contribute to their potent antioxidant effects [(Kaur & Arora, 2017)](https://paperpile.com/c/tj9cjx/pJcpM).Beyond antioxidant properties, several *Streptomyces* strains have shown capacity to inhibit bacterial biofilms. [(Neamah et al., 2020)](https://paperpile.com/c/tj9cjx/UgN4w) found that crude extracts of *Streptomyces* sdLi were effective in suppressing *Escherichia coli* biofilm formation, with ethyl acetate extracts showing the strongest activity. This was supported by Oberoi et al. (2020), who noted similar inhibitory effects against bacterial biofilms using ethyl acetate fractions of *Streptomyces* [(Oberoi et al., 2020)](https://paperpile.com/c/tj9cjx/3alYC)[(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/tj9cjx/zmVXa+UqrVO+Bw9VE)[(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/tj9cjx/zmVXa+UqrVO+Bw9VE+3l0Pc).Moreover, phenolic compounds have been studied for their predictive antibiofilm behavior. Stepanov et al. (2022) developed a model to evaluate the antibiofilm potential of natural phenolics, adding a computational approach to screening bioactive molecules [(Stepanov et al., 2022)](https://paperpile.com/c/tj9cjx/jlgPm). Mukaide et al. (2022) further demonstrated that Thai propolis exhibited significant antibacterial and antibiofilm activity against *E. coli*, aligning with the role of natural compounds in microbial control [(Mukaide et al., 2022)](https://paperpile.com/c/tj9cjx/I0DN1). Additionally, Ryandini et al. (2021) isolated bioactive metabolites from *Streptomyces* SA32 that showed antibacterial efficacy against *E. coli*  [(Ryandini et al., 2021)](https://paperpile.com/c/tj9cjx/mPIkC), while Bhandari et al. (2021) documented the inhibitory effects of medicinal plant extracts—particularly polyphenols—on both bacterial growth and biofilm formation [(Bhandari et al., 2021)](https://paperpile.com/c/tj9cjx/RtvnA) [(*Evaluation Composite Restoration Posterior Teeth Proanthocyanidin Pretreatment Liner Using Fédération Dentaire Internationale Criteria: Split-Mouth Randomized Controlled Trial*, n.d.; Pranati et al., 2021; Sakthi & Department of Public Health Dentistry, 2021)](https://paperpile.com/c/tj9cjx/K4chC+2qGbI+9Mp3E)[(G. & Ganapathy, 2022; Kumar & Ramesh, 2021)](https://paperpile.com/c/tj9cjx/xGcN0+abtkL))Collectively, these findings underscore the therapeutic relevance of both microbial and plant-derived polyphenols. Their ability to act as antioxidants and interfere with bacterial biofilm formation makes them promising candidates for further pharmaceutical and food industry applications.

# Conclusion

This study shows that polyphenol extracts from marine-derived Streptomyces sp. have a strong bioactive potential. The polyphenol extract inhibited LDH activity in a dose-dependent manner, showing that it has the capacity to modulate cellular metabolism. The antioxidant studies indicated significant scavenging activity against DPPH radicals and lipid peroxidation, demonstrating the extract's ability to reduce oxidative stress. Furthermore, the polyphenol extract had high reducing properties and efficiently prevented biofilm formation by Shiga toxin-producing Escherichia coli. These findings imply that Streptomyces polyphenols may be potential candidates for the development of natural antioxidant and antibacterial drugs. Additional study is needed to understand the processes behind these bioactivities and to investigate the therapeutic potential of Streptomyces-derived polyphenols in clinical applications.

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