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Sustainable Approach Towards Multiple Drug Resistance: Exploring the Antiswarming Potential of Actinobacteria in Search of Novel Metabolites.

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KEYWORDS

Antimicrobial resistance, SDG 3, SDG 9, Quorum sensing, Actinobacteria, Anti-swarming, *Proteus mirabilis*

ABSTRACT:

Introduction: Antimicrobial resistance (AMR) occurs when pathogenic microorganisms—bacteria, viruses, fungi, and parasites—develop mechanisms that reduce their susceptibility to antimicrobial agents, such as antibiotics, antivirals, antifungals, and antiparasitic drugs. This compromises therapeutic efficacy, accelerates the dissemination of infections, increases disease severity, and raises mortality rates. Rare actinobacteria, beyond the genus *Streptomyces,* harbour diverse biosynthetic gene clusters (BGCs) that biosynthesise novel secondary metabolites with potent activity against multidrug-resistant (MDR) pathogens. These BGCs counter resistance via efflux inhibitors and carbapenemase antagonists, as well as quorum-sensing disruptors (QSIs) that impede biofilm formation without inducing resistance. Actinobacteria-derived drug development primarily aligns with UN Sustainable Development Goal 3 (SDG 3)—"Ensure healthy lives and promote well-being for all at all ages"—through targets 3.3 (ending epidemics of communicable diseases via novel antimicrobials) and 3.d (strengthening global health risk capacity against antimicrobial resistance threats) and **SDG 9** (Industry, Innovation, Infrastructure) by advancing biotechnological pipelines for bioactive metabolites.

Objectives. Exploration of quorum inhibition activity of rare actinobacteria against pathogenic bacteria, *Proteus Mirabilis*, and uncover a previously unreported profile of antimicrobial and anticancer bioactive metabolites.

Methods: Rare actinobacterium isolated from a soil sample was used in this study. Its genetic characterisation was confirmed using 16s RNA sequencing. A crude extract was collected by growing the isolate in PDB media, and its antimicrobial activity was assessed against *Proteus mirabilis.* Crude extract was obtained using ethyl acetate solvent. The LC-MS method was used for the characterisation of the presence of bioactive metabolites.

Results: LC MS profiling identified 5 major constituents, of which two have anticancer activity. This compound has never been reported to be produced by this rare actinobacteria.

Conclusions: This study expands the potent anticancer and antimicrobial compounds of rare actinobacteria, *Amycolatopsis thermoflava,* along with unique anti-swarming potential. These findings support further bioactivity assays (cytotoxicity) to evaluate therapeutic potential and may inform isolation and structure-activity relationship studies.

1. **Introduction** In 2019, bacterial AMR directly resulted in 1.27 million global deaths and was associated with 4.95 million additional fatalities, with projections estimating up to 10 million annual deaths by 2050 in the absence of robust stewardship interventions. (Hosaka et al., 2024) The escalating antimicrobial resistance (AMR) crisis underscores an urgent imperative for innovative alternative therapeutics, as conventional antibiotics exhibit waning efficacy against multidrug-resistant (MDR) pathogens amid stagnant pipelines for novel agents.(Singha et al., 2024) Compounding factors,

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including antimicrobial overuse, misuse, and inadequate stewardship, precipitate therapeutic failures across infections, surgical prophylaxis, and oncological interventions. Antimicrobial peptides (AMPs) that destabilise microbial membranes with minimal induction of resistance, and quorum-sensing inhibitors (QSIs) that attenuate virulence factor expression, biofilm maturation, and intercellular communication without conferring bactericidal selection pressure, thereby circumventing resistance escalation through non-lethal interference with bacterial pathogenesis signalling cascades, can be promising alternative therapies.

Actinobacteria are aerobic, gram-positive, filamentous, soil-dwelling bacteria with exceptional metabolic diversity and are a rich source of several useful bioactive natural products, such as polyketides containing repeated (–CH2–CO–) groups, and peptides, represent 20% of pharmaceutical drugs in the market along with many well-known antibiotics such as erythromycin, kanamycin, streptomycin, tetracycline, and vancomycin. From the current scenario of multiple drug resistance capacity of pathogenic microorganisms, focus is shifted to the isolation of novel bioactive compounds from the non-*Streptomyces* group, also known as rare actinobacteria. (Khanna Kapur et al., 2011)(Ezeobiora et al., 2022)(Parra et al., 2023).

New groups of rare actinobacteria and novel metabolites from these actinobacteria are gaining importance as they curb infection without killing the pathogenic organisms. Bacterial quorum sensing (QS), a pivotal cell-to-cell communication paradigm, orchestrates virulence factor expression and swarming motility, facilitating pathogen dissemination and infection exacerbation. Amid escalating antimicrobial resistance (AMR) to conventional antibiotics, quorum-sensing inhibitors (QSIs) emerge as promising antivirulence agents, attenuating biofilm formation and pathogenesis sans selective pressure, thereby reinstating therapeutic efficacy. (Nashikkar et al., 2011)(Devaraj et al., 2017) (Miao et al., 2017) In the present study, the purification and characterisation of the bioactive metabolite from one potent, rare actinobacterium selected from a previous study were carried out. This isolate was identified by 16S rRNA gene sequencing as *Amycolatopsis thermoflava N1165(T),* and it was deposited in the GenBank with the accession no. KI421511.

The present study is the first report of quorum inhibition activity of *Proteus mirabilis* by the isolate SNN 6, which was later identified as *Amycolatopsis thermoflava N1165(T),* along with LC MS profiling of the isolate *Amycolatopsis thermoflava N1165(T).*

2. Objectives: The primary objective of the study was to identify the antiquorum-sensing ability of the isolate SNN 6, *Amycolatopsis thermoflava N1165(T),* followed by in-depth LC-MS analysis of the ethyl acetate extract of the isolate and characterise its metabolite constituents. The rationale behind this research is to identify the potential antiquorum-sensing ability of rare actinobacteria SNN 6 (*Amycolatopsis thermoflava N1165(T)*) and to explore its full metabolite spectrum.

2. Materials and Methods

2.1 Chemicals and media

All chemicals and solvents were of analytical grade and purchased from Merck, Germany and culture media from Hi-media, Mumbai, India.

2.2 Test organisms

The target strain, *Proteus mirabilis* 425, used for screening antimicrobial activity, was procured from Microbial Type Culture Collection (MTCC), IMTECH, Chandigarh, India.

3. Methods

3.1 Production of the metabolite - Selected potent isolate SNN 6 was grown in potato dextrose broth and incubated in a rotary shaker incubator (REMI CIS-24 BL) at 130 rpm at 28 °C for 8 to 15 days.(Ribeiro et al., 2025)

3.2 Extraction of metabolite - A crude antimicrobial compound was recovered from the cell and broth extracts by the solvent extraction method using the solvent ethyl acetate. (Chakraborty et al., 2015) (Krenn & Biol Graz, 2019)

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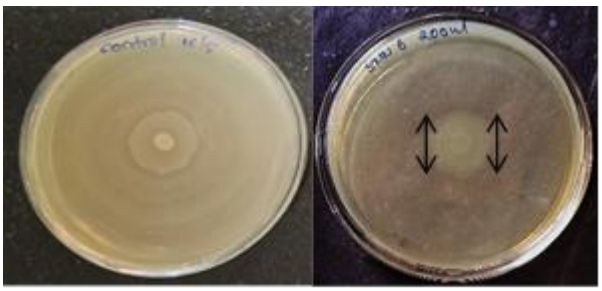
3.3 Swarming inhibition studies – Anti-swarming potential of the bioactive compounds from rare actinobacteria SNN 6, on the swarming motility of *Proteus mirabilis* was studied. 5 ul of an overnight-grown culture of *Proteus mirabilis* was centrally inoculated on swarm agar plates containing various concentrations of the compounds. Two control plates were set up for the experiment; one containing no additives and termed the positive control, and the other containing Ethyl acetate and termed the solvent control. The plates were incubated for 20 h at 37 °C. The diameter of the zone of inhibition was measured and compared to the control. (Godbole et al., 2023) (Bundale et al., 2025).

3.4 Spectral studies Liquid chromatography mass spectrometry (LC–MS) analysis was performed using a Thermo Scientific Vanquish ultra-high-performance liquid chromatography (UHPLC) system (Thermo Fisher Scientific, USA)(Shinwari et al., 2013) (Forner et al., 2013) equipped with a pump module, autosampler, and column compartment, coupled to a Thermo Scientific Q Exactive Plus Orbitrap mass spectrometer (Thermo Fisher Scientific, USA) fitted with a heated electrospray ionisation (HESI) source operated in positive ion mode**.** Chromatographic separation was conducted at a column temperature of 40 °C with a flow rate of 0.300 mL min^{-1}. The mobile phases consisted of 0.1% formic acid in water (A), methanol (B), and acetonitrile (C). The mass spectrometer was operated in Full MS/data-dependent MS^2 (dd-MS^2) acquisition mode with a resolving power of 70,000 for Full MS and 17,500 for MS/MS.

4. Result and Discussion

4.1 Antiswarming Studies -From the previous studies, the crude extract of rare isolate SNN 6 exhibited anti-swarming activity against *Proteus mirabilis.* (Bundale et al., 2025) . In the present study, 70% inhibition of the swarm zone was observed when the compound was used at a concentration of 0.5mg/ml, which is a further study added to the research.

4.2 Compound Identification and LC-MS Chromatogram. The crude extract was subjected to compound profiling to identify the bioactive constituents. The LC-MS analysis of the extract revealed the presence of multiple bioactive compounds, identified based on their retention times and mass spectral data. As described in Figure 1, the total ion chromatogram (TIC) was obtained by UHPLC–Orbitrap MS in positive ion mode**.** Peaks show compound separation over 30 min, with early elution of polar analytes (1–5 min), major components between 13–20 min (base peak at 16.26 min), and late elution of non-polar compounds (20–30 min) (Figure 1).



Control swarm plate Swarm inhibition at 0.5mg/ml

4.2 Spectral Studies - This chromatogram elutes multiple LC peaks between 1 and 30 min, with major components eluting around 9.49, 13.56, 15.31, 16.26, 17.86, and 18.9 min, indicating a mixture of several abundant metabolites separated under this 30 min gradient. The chromatogram in Figure 1 shows the six most distinct peaks, indicating a complex mixture of metabolites in the extract. Among these compounds, the major constituents were observed at retention times corresponding to significant peak areas. The most prominent compounds detected with the corresponding peaks were Eslicarbazepine (C15H14 N2O2) RT 9.49, Indole (C8H7N) RT 10.32, Chrysin (C15H10O4), NP-011548 (Oleic acid), NP-009092 (C19H22O3) RT 15.31, and are known for their pharmacological properties as anti-inflammatory, antioxidant, and antimicrobial activities. Additionally, among the minor bioactive constituents, several compounds like Palmitic acid (C16H32O2), and 4-Chloro-N-(2,6-dimethyl-1-piperidinyl)-3-(dimethylsulfamoyl)-N methylbenzamide and Genistein(C15H10O5), were identified that may contribute synergistically to the overall bioactivity of the extract.

Overall, the mass spectrum in Figure 1 demonstrated a rich chemical profile, suggesting its suitability for further biological screening and potential pharmaceutical applications

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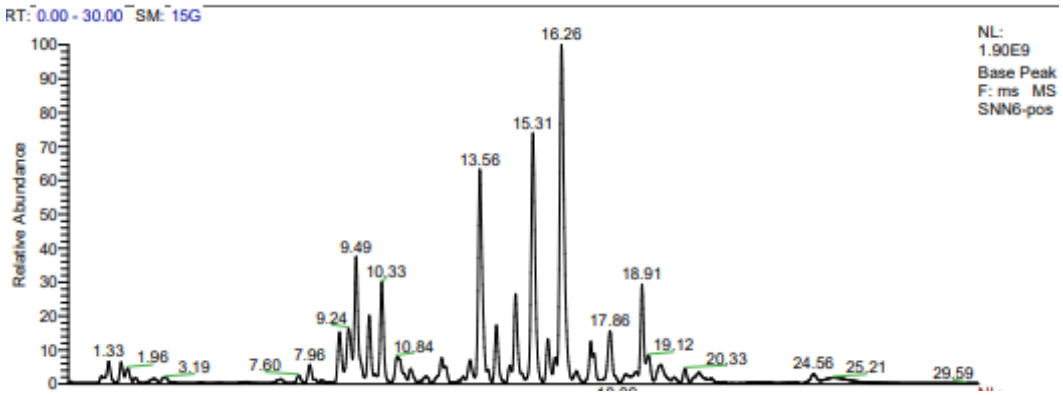

Figure 1 LCMS DATA OF ISOLATE SNN 6

The organic extract of the sample was subjected to compound profiling to identify the bioactive metabolite constituents. As mentioned in Table 1 of LC-MS analysis of the crude extract revealed the presence of multiple bioactive compounds, identified based on their retention times and mass spectral data. The chromatogram displayed in Figure 1 shows the highest distinct peaks, indicating a complex mixture of bioactive compounds within the extract. Among these identified compounds, the major constituents were observed at retention times corresponding to significant peak areas. The most prominent compounds included Eslicarbazepine, Indole, Chrysin, Oleic acid, and NP-009092. Eslicarbazepine is a well-known antiepileptic drug belonging to the dibenzazepine group with anticancer potentials.(Afsordeh et al., 2024a)

Sr. No.	Name of the Compound	Molecular Formula	Molecular Weight	Retention Time	Reported Activity
1	Eslicarbazepine	C15 H14 N2 O2	254	9.49	Anticancer activity,(Afsordeh et al., 2024)
2	Indole	C8H7N	117	10.32	Anticancer activity, (Gaur et al., 2022)
3	Formononetin	C16 H12 O4	268.26	12.64	Anticancer activity(Tay et al., 2019a)
4	NP-009092	C19H22O3	240.34	15.37	Anticancer activity,
5	NP-011548 (Oleic acid)	C18 H34 O3	298.46	16.27	Anticancer activity, antimicrobial activity(Jiang et al., 2017)
6	Chrysin	C15 H10 O4	254.24	10.92	Anticancer activity(Salari et al., 2022)Antimicrobial

Table No. 1 Major Components identified and their corresponding activities

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Discussion - For generations, *Actinobacteria* have been regarded as an important source of various bioactive secondary metabolites with rich chemical and bioactive diversities.(Parra et al., 2023) To date, among the 22,500 biologically active compounds obtained from microbes, 45% are from *Actinobacteria,* 38% are from fungi, and 17% are from other bacteria(Shrestha et al., 2021). However, because of the emergence of multidrug-resistant bacteria, researchers have turned to rare *Actinobacteria* to develop novel antibiotics. (Lazzarini, A., Cavaletti, L., Toppo, G. *et al.*). *Amycolatopsis thermoflava* is an aerobic, gram-positive, non-acid, alcohol-fast, non-motile actinobacterium that forms an extensively branched substrate mycelium. The aerial mycelium is white, and the substrate mycelium is yellow. (Chun et al., 1999). The genus *Amycolatopsis* is regarded as an important source of diverse valuable bioactive natural products, covering many antibiotics. (Stackebrandt et al., 1997). The ethyl acetate extract of SNN 6 showed a broad spectrum of antibiotic properties against tested bacteria in different ranges and demonstrated the largest inhibition zone at 0.5mg/ml. Hence, this strain could be a potential candidate for new drug development.

As per the LC MS peak (Retention time 9.49 minutes), compound Eslicarbazepine(C1H14N2O2) is identified (Figure 1). Eslicarbazepine (Dibenzazepine carboxamides), a classical VGSC-blocking antiepileptic agent, also acts as a mood stabiliser and, as recent *in vitro* and *in vivo* studies indicate, a promising anticancer drug-repurposing candidate (Afsordeh et al., 2025). ESL offers a strategic advantage by potentially bypassing the high costs and extended timelines associated with the new anticancer drug development. Future research should focus on further exploring these compounds in diverse cancer models, elucidating their precise mechanisms of action, optimising dosing regimens, and advancing toward pilot clinical trials.(Afsordeh et al., 2024b)

Indole, a low molecular weight compound (C8H7N) is identified at 10.32 R.T. (Figure 1). Cancer remains the second most common cause of mortality. The indole ring system—owing to its favourable bioavailability, distinct chemical reactivity, and diverse pharmacological profile—has emerged as a key scaffold for modern targeted anticancer therapy, as evidenced by the clinical approval of multiple indole-based agents, including panobinostat, alectinib, sunitinib, Osimertinib, anlotinib, and nintedanib by U.S. (F.D.A.) (Dhiman et al., 2022). Nitrogen-based heterocycles play a pivotal role in modern anticancer drug discovery, with indole serving as a core scaffold shared by numerous FDA-approved agents. Because of this broad mechanistic repertoire and consistent pharmacological performance, indole is widely recognised as a privileged structural template for designing new anticancer candidates.(Gaur et al., 2022)

Formononetin is an isoflavone-type phytoestrogen predominantly distributed in leguminous and Fabaceae plants and occurs at relatively high levels in cow's milk, soybeans, and sunflower-derived foods. It is also present, usually in lower amounts, in various fruits and vegetables such as grapes, berries, beans, celery, chickpeas, ferns, and related plant-derived products. Contemporary pharmacological studies indicate that formononetin exerts multiple health-promoting effects, including antioxidant, anti-inflammatory, cardiometabolic, and potential anticancer activities.(Ong et al., 2019). This compound is identified at 12.64 R.T. in Figure 1 with the formula C16H12O4. Formononetin regulates various transcription factors and growth-factor-mediated oncogenic pathways, consequently alleviating the possible causes of chronic inflammation that are linked to cancer survival of neoplastic cells and their resistance against chemotherapy.(Tay et al., 2019b)

NP-006255 (C17 H26 O4) at R.T. 15.31, like Gingerol (Zingiberaceae family), is a dietary compound that can be found in several plants. Its major phenolic component is the [6]- gingerol, which has antitumor, antimutagenic, antioxidant, anti-apoptotic, anti-inflammatory, cardio- and hepatoprotective properties. (Brahmachari, 2019).

NP-011548 (Oleic acid), at R.T. 16.27 (C18 H34 O3), has shown anticancer effects in many types of cancers, such as prostate, breast and colorectal cancer, and Oleic Acid is commonly administered in combination with chemotherapy.(Jiang et al., 2017) The oleic acid–derived microbial extracts displayed stronger broad-spectrum antimicrobial effects than pure oleic acid, and one fraction (extract 2) additionally showed promising cytotoxicity against A549 lung cancer cells, with an IC50 of 62.5 µg/ml comparable to cisplatin, warranting further anticancer evaluation. (Todorov et al., 2019).

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Chrysin R.T. 10.92 (C15 H10 O4), this naturally occurring flavonoid shows broad bioactivity, including anticancer effects, but its therapeutic use is hampered by low solubility and poor bioavailability; strategic introduction of amine, amide, ester, or alkoxy substituents on the flavone core can significantly modulate and often enhance its biological profile.(Shahbaz et al., 2023)

This bioactive compound has attracted interest for its favourable safety profile and anticancer potential, acting through multiple mechanisms, notably triggering apoptosis and suppressing tumour cell proliferation, angiogenesis, metastasis, and cell-cycle progression. (Sood et al., 2024)

The LC–MS characterisation of the unknown extract uncovered a constellation of pharmacologically relevant scaffolds—Eslicarbazepine, indole, formononetin, gingerol-like NP-006255, oleic acid (NP-011548), and chrysin—collectively defining a rich, multitarget bioactive matrix. Eslicarbazepine exemplifies a clinically deployed dibenzazepine carboxamide with emerging onco-therapeutic promise, supporting a drug repurposing strategy that can accelerate translation by leveraging its established safety and pharmacokinetic profile. The presence of indole further anchors the extract within contemporary anticancer medicinal chemistry, as this nitrogen heterocycle is widely recognised as a privileged core for targeted agents and rational analogue design. Formononetin(Aliya et al., 2023) and chrysin contribute complementary flavonoid pharmacology, including modulation of apoptosis, proliferation, angiogenesis, and inflammatory signalling, thereby impacting tumour progression(Tay et al., 2019b) and potential therapy resistance. Meanwhile, gingerol-type NP-006255 and oleic-acid–based NP-011548 add antitumor, anti-inflammatory, and antimicrobial dimensions, consistent with the reported ability of gingerols and oleic acid to interfere with NF-KB and PTEN/AKT/mTOR signalling axes.

Notably, compounds such as Eslicarbazepine and Formononetin exhibited multiple biological actions, making them promising candidates for drug development. In addition, these compounds from *Amycolotopsis* either have novelty or limited prior reporting, thereby indicating potential for new drug discovery or pharmacological exploration. These findings provide a valuable foundation for further preclinical and clinical investigations. The biological insights gathered emphasise the medicinal significance of actinobacterial metabolites and their role in the development of therapeutic agents. This study contributes to the growing field of natural product pharmacology and underscores the importance of research in identifying effective, bioactive compounds.

Considering this chemical diversity of the metabolites, future work will prioritise advanced spectroscopic and chromatographic refinement—targeted MS/MS, multidimensional NMR, and preparative LC—to isolate and structurally confirm the principal bioactive constituents, enabling a transition from complex mixtures to well-defined single-entity candidates. These purified leads can then be subjected to detailed mechanistic, in vivo efficacy, and formulation studies, with the overarching aim of utilising this extract as a tractable platform for the development of next-generation anticancer and anti-infective agents. Future studies are warranted to elucidate their detailed molecular structures, bioactivity profiles, and therapeutic potential. This metabolite exploration not only enhances our understanding of the chemical diversity but also contributes to the expanding repository of natural bioactive compounds with promising biotechnological relevance

Conclusion: Pathogenic microorganisms primarily regulate the expression of virulence genes using QS systems. The indirect role of QS in the emergence of multiple drug resistance (MDR) in microbial pathogens necessitates the finding of alternative antimicrobial therapies that target QS and inhibit the same. A related phenomenon of quorum-sensing inhibition (QSI), performed by small inhibitor molecules called quorum-sensing inhibitors (QSIs), can efficiently reduce gene expression regulated by quorum sensing. In accordance with this, these small molecules from the extract of SNN 6 have a very good quorum inhibition potential against *Proteus mirabilis*, a uropathogenic organism.

The present study successfully demonstrated the potential of *Amycolotopsis thermoflava* extract through a comprehensive in vitro evaluation. The extract exhibited promising antimicrobial properties, supporting its therapeutic applications. Moreover, LC-MS analysis

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identified bioactive compounds, including six major prominent peaks of bioactive compounds mentioned in Figure 1. Out of these six, four bioactive compounds show high intensity peaks and observed pharmacological effects and have not been reported yet for *Amycolotopsis thermoflava* extract. These findings validate the use of *Amycolotopsis thermoflava* and emphasise its relevance in modern phytomedicine. Despite the encouraging results, further research is essential to establish a more comprehensive understanding of the extract's mechanisms of action. Future studies should focus on the isolation and structural elucidation of individual active compounds, followed by detailed in vivo pharmacological evaluations and toxicity profiling. Additionally, exploring the synergistic interactions among constituents could pave the way for developing standardised formulations with enhanced efficacy. The integration of molecular docking and computational biology approaches may also help in predicting biological targets and improving drug development strategies. LCMS analysis has revealed a diverse array of bioactive compounds with significant therapeutic potential. These constituents are reported to exhibit a broad spectrum of biological activities, including antimicrobial, anti-inflammatory, antioxidant, and anticancer properties. The results of this study not only validate the medicinal value but also provide a scientific basis for its continued exploration as a source of natural drug candidates. Moreover, the identification of key compounds through LC-MS profiling enhances our understanding of the actinobacterial extract's biochemical composition and paves the way for further pharmacological studies.

Future research should aim to isolate and characterise these compounds in greater detail, explore their mechanisms of action, and assess their therapeutic efficacy through in vivo studies and clinical trials. *A. thermoflava* remains a promising candidate for natural product drug discovery, and the insights from this study contribute meaningfully to the growing body of knowledge. In conclusion, *Amycolotopsis thermoflava* extract has shown remarkable inhibition of the swarming potential of *Proteus mirabilis*, which is a first report here, and it holds significant promise as a source of novel therapeutic agents. With advanced research and clinical validation, it could contribute to the development of effective treatments for various health conditions. Further purified compound can be extracted and commercially it can be utilised as a coating agent on catheters or further instruments as a quorum inhibitory agent, or further commercial applications can be done with respect to the well-being of humans.

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Declaration of competing interest: The authors declare that they have no competing interests or other personal relationships that could have appeared to influence the work reported in this research paper.

Author contributions: Credit

Nisha D. Margode Conceptualisation, methodology, data curation, formal analysis, writing-original draft and visualisation.

Dr Sunita Bundale: Supervision, Conceptualisation, investigation, data curation, formal analysis, visualisation. Editing.

Dr Varaprasad Kolla: Supervision, Conceptualisation, investigation, formal analysis, and visualisation.

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Ethics in Publishing. In conducting and publishing this study, all research procedures adhered strictly to ethical standards, ensuring accurate data representation, proper acknowledgement of sources, and avoidance of any form of data manipulation or fabrication. The authors affirm that the work is original, unpublished, and not under consideration elsewhere, and that all contributors have been appropriately credited for their roles in the study.

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