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Original article

Extraction, Identification, and In Silico Analysis Bioactive Compound of *Streptomyces bungoensis* strain 15721 from *Euphorbia* sp. Rhizosphere as Antibacterial and Antiviral Drugs Candidates

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Abstract

Actinomycetes are a group of bacteria that display an important role in their ability to produce secondary metabolites in the form of bioactive compounds with various chemical structures and biological activities. Thousands of bioactive compounds have been isolated and characterized. These compounds have been developed into medicines for the treatment of various diseases in humans and animal problems. Antibiotic resistance is still a major global health challenge. This involves the transfer of bacteria and genes between humans, animal and the environment. The next stage after the exploration of antimicrobial potential is the extraction and purification of the components of bioactive compounds. Therefore, the extraction and identification of actinomycetes bioactive compounds is very important especially in the development of new candidates for antibiotics. *Streptomyces bungoensis* strain 15721 was previously isolated from *Euphorbia* sp. Rhizosphere. The methodology comprises from the preparation of the isolate, production and extraction of bioactive compound, antibacterial test and GC-MS analysis. Crude extract showed an average of 12 mm inhibition zone against *Escherichia coli* ATCC 8739. There are seven bioactive compounds from *Streptomyces bungoensis* strain 15721. These compounds were Dibutoxy (Dimethyl) Silane, Naphthalene, Butane, 1,1-Dibutoxy, Heneicosane, 2,6,10,14-Tetramethyl-Hexadecane, Icosane and Nonadecane. Bioactive compounds were then analyzed in silico with molecular docking. In silico studies showed that bioactive compounds have very good antibacterial activity with different binding energies, inhibition constants, and protein-ligand interactions. Three compound 2,6,10,14-Tetramethyl-Hexadecane, Naphtalene, and Butane, 1,1 dibutoxy showed promising antibacterial and antiviral activity. These compounds should be further investigated for future antibacterial and antiviral candidates.

Keywords: Bioactive Compound, Extraction, GC-MS, In silico, Molecular Docking, *Streptomyces bungoensis* strain 15721, 2,6,10,14-Tetramethyl-Hexadecane, Naphthalene, Butane, 1,1 dibutoxy

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Introduction

Natural products also known as bioactive molecules are one of the important sources of current drugs and new drug candidates. These bioactive molecules derived from living organisms: plants, animals, and microorganisms. Microorganisms have been proven to be a productive source as a producer of secondary metabolite bioactive compounds to date (Abdel-Razek et al., 2020).

Actinomycetes serve as a crucial source of secondary metabolites, including antibiotics and various active natural compounds. Several widely recognized antibiotics, including streptomycin, oxytetracycline, and tetracycline, are synthesized by actinomycetes. Antibiotics have different methods of action against microorganisms: they block protein synthesis, nucleic acid synthesis, and cell wall formation. For decades, actinomycetes have played a critical role in clinical treatment for major diseases such as pathogenic bacterial infections, serving as one of the most important sources of novel discoveries. (Yi et al., 2025). Approximately 75% of all bioactive compounds produced to date come from this group of bacteria. Many of these compounds have been successfully isolated and transformed into valuable pharmaceuticals and other natural synthetic compounds with antifungal, antibacterial, and chemotherapeutic properties (Khalid et al., 2024).

Akbar et al., (2017) reported that their research succeeded in isolating 24 species of actinomycetes and 15 of them had antifungal bioactive compounds that could inhibit the growth of *Candida albicans*. Other study reported that quercetin 3-O-glucoside derivatives were successfully extracted and purified from *Strepomyses antibioticus*. demonstrated antimicrobial activity against *Staphylococcus aureus* ATCC6538, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC-7839, *Candida albicans*, *Fusarium moniliforme*, *Aspergillus niger*, and *Aspergillus flavus* (Sholkamy, Ahmed, et al., 2020). Other study also reported the production of antimicrobial and antinematicidal activity towards selected microbial pathogens such as *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Salmonella typhi*, *Bacillus subtilis*, *Proteus vulgaris*, *Shigella flexineri*, *Candida albicans*, *Fusarium* sp. and a nematode, *Meloidogyne incognita* (Sholkamy, Muthukrishnan, et al., 2020).

Antibiotic resistance remains major global health challenge. It involves transfer of bacteria and genes between humans, animal dan the environment. Despite barriers restrict its flow of bacteria and genes, pathogens

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oftenly acquire new resistance factors form other species (Larsson & Flach, 2021). Moreover, genetic adaptation of bacteria to natural environments may drive resistance evoution where antibiotic resistance occure without antibiotic exposure (Knöppel et al., 2017).

Exploration of actinomycetes from the rhizosphere of succulent plants has been carried out and several potential isolates have been obtained with antimicrobial activity. The next stage after the exploration of antimicrobial potential is the extraction and purification of the components of bioactive compounds. Therefore, the extraction and idemtification of actinomycetes bioactive compounds is very important especially in the development of new candidates for antibiotics.

Methods

Isolate preparation

Steptomyces bungoensis strain 15721 was isolated from *Euphorbia* sp. rhizosphere (Zulaika et al., 2021). This isolate was recovered from stock culture, inoculated on Starch Casein Nitrate Agar (SCNA) incubated for 7 days at 28 ± 2°C (Sholkamy, Ahmed, et al., 2020).

Production of bioactive compound

Isolate on SCNA inoculated to fifty ml starter broth Starch Casein Nitrate Broth (SCNB) incubated in shaker 120 rpm for five days at 30 °C. Five ml of starter inoculated to the fermentation broth. Afterward, incubated at 30 °C, 120 rpm for 7 days (pH 7.0). Culture filtrate was collected for extraction bioactive compound (Sholkamy, Ahmed, et al., 2020).

Extraction of bioactive compound

Culture filtrate was extracted with n-Butanol and centrifugeed at 10.000 rpm (Kawuri & Darmayasa, 2019a) supernatant was collected and separated. Solvent was added to supernatant in the ratio of 1:1 (v:v). The mixture was then shaken in separating funnel and settle at room temperature for 15 minutes. Afterwards, continued with evaporation process at 40 °C. The crude extract then tested for antibacterial activity.

Antibacterial test of bioactive compound

100 µl crude extract was tested for antimicrobial activity using agar well-diffusion method on Nutrient Agar triple plate (Khattab et al., 2016). *Escherichia coli* ATCC 8739 was used to test antibacterial activity. Streptomycin sulfate 30 ppm was used as the antibiotic control.

Identification of bioactive compound

Bioactive compounds were identified by using Gas chromatography-mass Spectrometer (GC-MS) (Kawuri & Darmayasa, 2019a).

In silico Analysis

In silico molecular docking computational studies were carried out using an Intel Core i3-1115G4 computer with 8 GB RAM. The software used is MarvinSketch 15.5.11, Chimera 1.10.2, PyMol 2.3.3, Discovery studio V21.1.0.20298, Autodock 4.2. and way2drug.com. The materials used are bioactive compounds in butanol extract, negative control (butanol), positive control (Streptomycin-antibacterial) and (oseltamivir-antiviral H1N1) as well as antibacterial and antiviral macromolecular targets with the PDB ID code respectively 1JIJ (crystal structure of *S . Aureus* TyrRs) and 3TI6 (crystal structure of H1NI neuraminidase).

Results

The crude extract of *Streptomyces bungoensis strain* 15721 showed antibacterial activity at a volume of 100 µL The Inhibition zone range from 11 to 11.5 mm as shown in Table 1. Various bioactive compound were detected in n-Butanol extract. Nine bioactive compounds were detected from *Streptomyces bungoensis* strain 15721 crude extract (Table 2). The most abundant was Naphtalene (41.44 %), whereas the least Dibutoxy (Dimethyl) Silane (2.01 %).

Table 1. Antibacterial activity against *Escherichia coli* ATCC 8739

Tested compound	Plate Number	Zone of inhibition (mm)
Crude Extract *Steptomyces bungoensis* strain 15721	One	11
	Two	11.5
	Three	11.5
Mean		12
Streptomycin sulfate 30 ppm	One	16
	Two	15.5
	Three	14.5
Mean		15.33
n-Butanol	One	15
	Two	13.5
	Three	12.5
Mean		13.67

Table 2. Bioactive Compound detected in n-Butanol extract of *Streptomyces bungoensis* strain 15721

Bioactive Compound	Retention Time	Compositition (%)
Dibutoxy (Dimethyl) Silane	6.393	2,01
Naphthalene	6.393	41,44
Butane, 1,1-Dibutoxy	8.813	18,43
Heneicosane	10.130	3,25
2,6,10,14- Tetramethyl-Hexadecane	30.058	14,34
Icosane	31.030	6,08
Nonadecane	31.520	3,27

In silico molecular docking was carried out to determine and analyze the interactions between bioactive compounds as ligands and protein macromolecules. The docking results showed that three out of seven bioactive compounds in butanol extract had antibacterial and antiviral activity based on binding energy values, namely 2,6,10,14-tetramethyl-hexadecane, naphthalene and butane,1,1-dibutoxy. In addition, the inhibition constant (Ki) is inversely related to binding energy, the lower the binding energy value, the smaller the Ki value. This means that the ligand-protein complex is more stable, which has a major impact on its activity (Table 3 and Table 4).

Tabel 3. Results of Molecular Docking of Bioactive Compounds from Butanol Extract as an Antibacterial

No	Bioactive Compound	Molecular Weight (gr/mol)	Binding energy (kkal/mol)	Inhibition Constant (Ki) (µM)
1	2,6,10,14-tetrame-thyl-hexadecane	282,5	-7,86	1,74
2	Naphthalene	128,169	-5,97	41,72
3	Butane,1,1-dibu-toxy	216,36	-4,97	229,32
4	Streptomycin (Positive Control)	581,6	-11,44	0,00415
5	n-Butanol (Nega-tive Control)	74,12	-2,90	7490

Tabel 4. Results of Molecular Docking of Bioactive Compounds from Butanol Extract as an antiviral

No	Bioactive Com-pound	Molecular Wieght (gr/mol)	Binding energy (kkal/mol)	Inhibition Constant (Ki) (µM)
1	2,6,10,14-tetrame-thyl-hexadecane	282,5	-5,34	122,53
2	Naphthalene	128,169	-4,96	231,42
3	Butane,1,1-dibutoxy	216,36	-4,15	914,1
4	Oseltamivir (Positive Control)	312,40	-7,71	2,24
5	n-Butanol (Negative Control)	74,12	-2,77	9270

The negative control butanol formed hydrogen bonds with amino acids GLN190 in the TyrRs protein and GLU119, ARG156 in the neuraminidase protein. Meanwhile, the positive control streptomycin formed hydrogen bonds with amino acids TYR36, GLY38, GLY49, THR75, TYR170, GLN190, and GLN196, while oseltamivir formed hydrogen bonds with amino acids ARG118 and TYR406. Images of the interaction between bioactive compounds, negative control, and positive controls with target proteinsTyrRs and Neuraminidase are shown in in Figures 1 and 2.

Discussion

Crude extract of *Steptomyces* species have been reported to have antibacterial activity on *E. coli* and *Staphylococcus aureus* (Khattab et al., 2016). Other research on *Streptomyces olivaceus* LEP7 crude extract also showed inhibition zone to *E. coli*, *Pseudomonas aeruginosa*, *S. aureus*, *Klebsiella* sp., *Acinetobacter* sp. and *Candida* sp. (Rajaram et al., 2020).

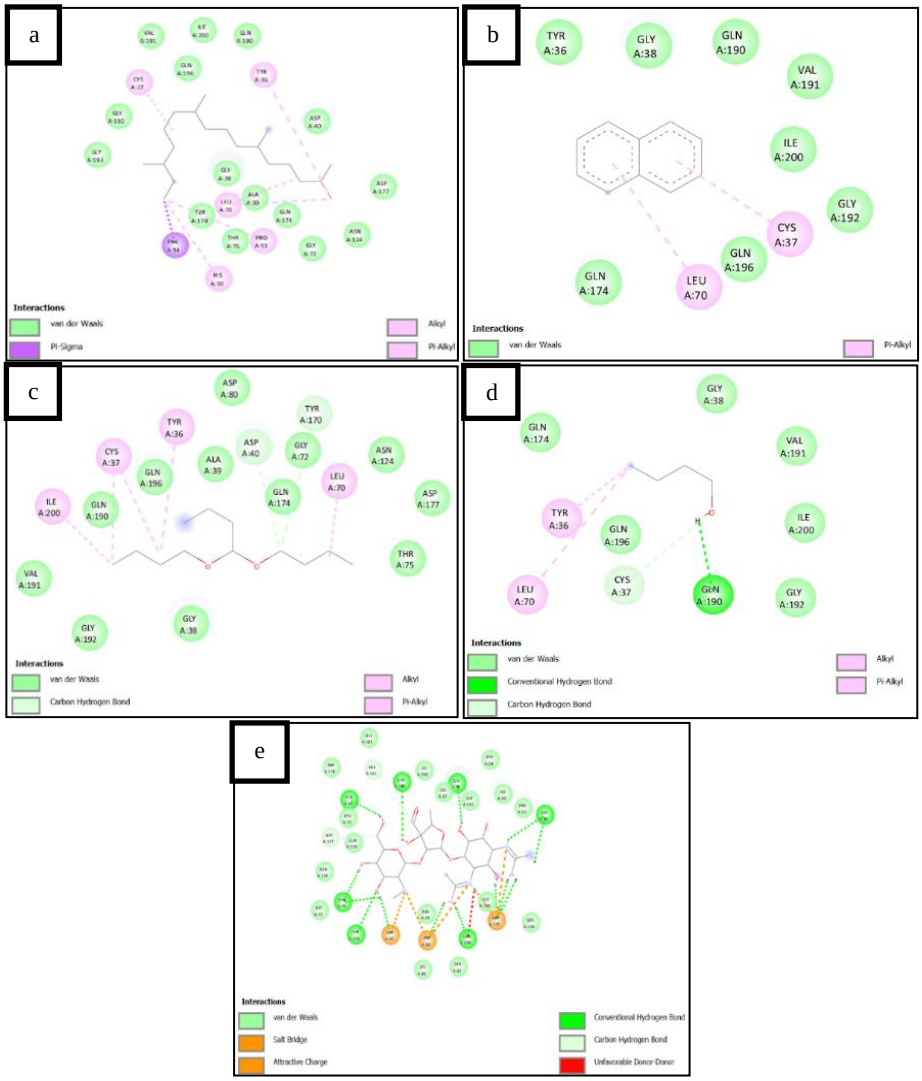

Figure 1. Interaction of ligand compounds with TyrRs proteins (a. 2,6,10,14-tetramethyl-hexadecane; b. Naphthalene; c. Butane,1,1-dibutoxy), negative control (d. butanol) and positive control (e. streptomycin)

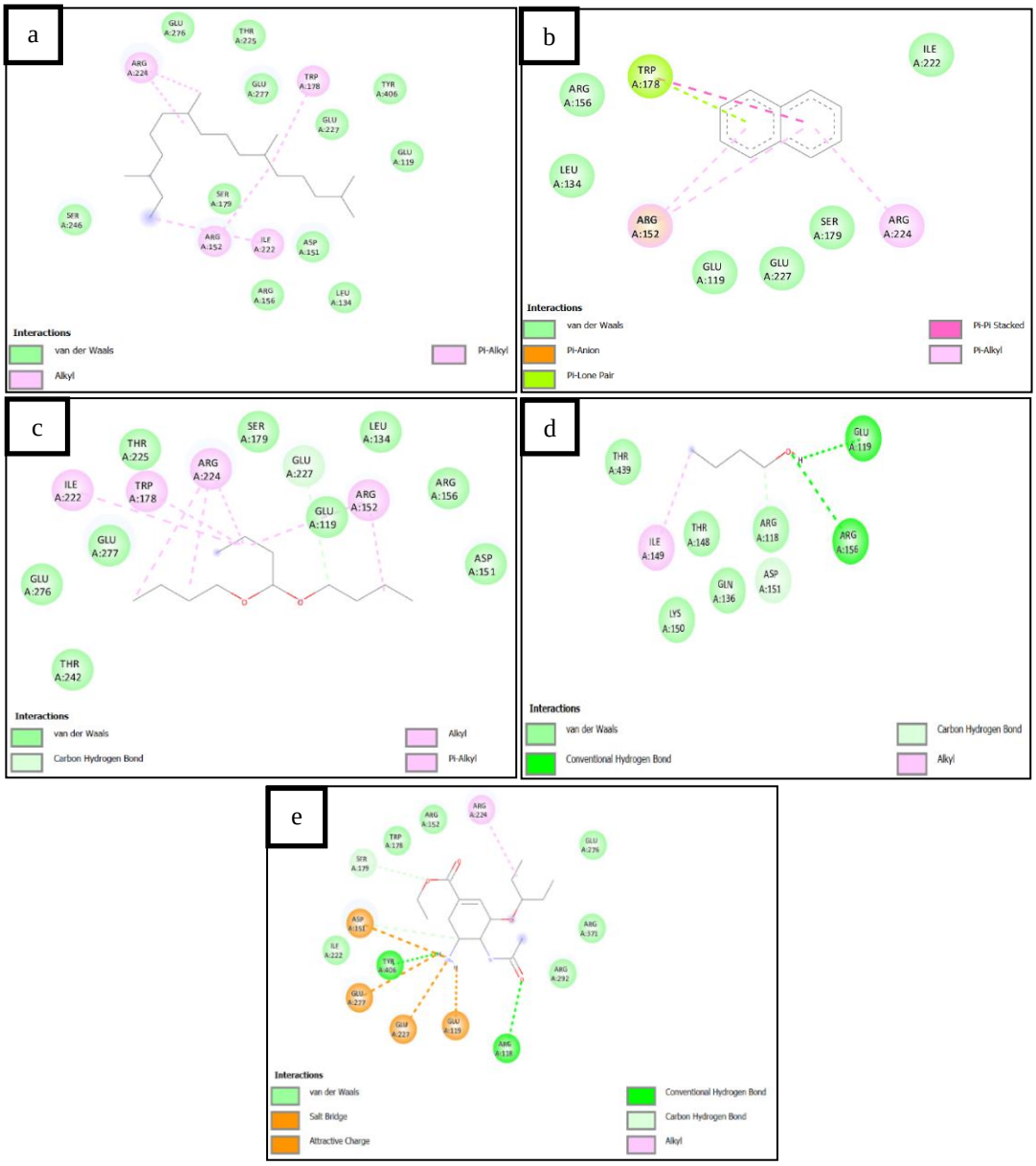

Figure 2. Interaction of ligand compounds with Neuraminidase proteins (a. 2,6,10,14-tetramethyl-hexadecane; b. Naphthalene; c. Butane,1,1-dibutoxy), negative control (d. butanol) and positive control (e. oseltamivir))

Gass chromatpraphy-mass spectrometry (GC-MS) is a reliable method to identify bioactive components. In this technique there are nine major bioactive compounds with various retention time. These bioactive compound displayed antibacterial properties. Six out of seven bioactive compounds were reported previously to have antimicrobial activities. These compounds are butane,1,1-dibutoxy; nonadecane; heneicosane; icosane; 2,6,10,14-tetramethyl-hexadecane and naphthalene.

Butane, 1,1-Dibutoxy has been reported to have potent antagonist activity against *Vibrio anguillarum* (Kawuri & Darmayasa, 2019a, 2019b; Wijayanti & Dewi, 2022) Nonadecane was reported to have antimicrobial activity. Reported by Naeim et al., (2020) crude extract from *Centaurea pumilio* L was tested against ten reference bacterial strains and sixteen clinical strains from ICUs Alexandria. The ten reference strains were *Acinetobacter baumannii* ATCC 17978, *Escherichia coli* ATCC 8739, *Enterococcus faecalis* ATCC 29212, *Enterobacter aerogenes* ATCC 13048, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 9027, *Proteus mirabilis* ATCC 14153, *Salmonella enterica* ATCC 14028, *Staphylococcus aureus* ATCC 6538, and *Candida albicans* ATCC 10231. These strains were obtained from the Microbiological Resources Centre (MIRCEN), Faculty of Agriculture, Ain Shams University, Cairo, Egypt. The sixteen clinical strains identified were *Enterococcus faecalis*, *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus mutans*, *Bacillus pumilus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Salmonella enterica* serovar Typhi, *Stenotrophomonas maltophilia*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter* sp, and *Candida albicans*. Extract showed antimicrobial activity against the reference and clinical strains with minimum inhibitory concentration (MIC) values of 31.25–125 and 31.25–125 µg/mL (Naeim et al., 2020).

Heneicosane has been reported to have antimicrobial effect on pathogenic microorganisms. Heneicosane extracted from *Plumbago zeylanica* was used for measuring the antimicrobial activity. Heneicosane exhibited excellent antimicrobial activity against *Streptococcus pneumonia* with inhibition zone 31 ± 0.64 mm. It was also tested against *Aspergillus fumigatus* and showed inhibition zone 29 ± 0.86 mm at 10 µg/ml concentration (Vanitha et al., 2020).

Icosane also reported having antimicrobial activities. Crude extract from *Streptomyces anulatus* NEAE-94 exhibit inhibition zone against *Staphylococcus aureus* NRRL B-313, multidrug-resistant *Staphylococcus aureus* and *Bacillus subtilis* NRRL B-543 (El-Naggar et al., 2017). Antifungal activities of eicosane was effective against *Rhizoctonia solani* AG-3 strain KX852461 (Ahsan et al., 2017).

Other research demonstrates icosane and 2,6,10,14-Tetramethyl-Hexadecane exhibit antimicrobial activities. The two bioactive compounds were extracted from *Streptomyces cuspidosporus* SA4. The crude extract of *S. cuspidosporus* SA4 was shown antibacterial activity against *E. coli, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella flexneri, S. aureus, Bacillus subtilis* and no activity against *Pseudomonas aeruginosa.* Various range of antifungal activity was observed for *Aspergillus niger, Aspergillus flavus, Candida albicans,* and *Fusarium sp.* at concentration 75 µg (Sholkamy, Muthukrishnan, et al., 2020).

Naphthalene had been reported to have antibacterial, antifungal and antimalarial activity. (Kalariya et al., 2022) reported a synthesized novel amide-coupled naphthalene. These derivatives were evaluated for their antibacterial, antifungal and anti-malarial actions Among all, 4g derivatives exhibited excellent antibacterial activity at MIC values ranging between 12.5 and 100 µg/mL against *E. coli, P. aeruginosa, S. aureus* and *Streptococcus pyogenes.* The antifungal assay revealed that compounds 4c, 4f and 4l were most effective (MIC - 250 µg/mL) against *C. albicans* compared to standard drug griseofulvin. Compounds 4h and 4l manifested moderately active anti-malarial action, with mean IC50 of 0.47 and 0.48 µg/mL, respectively (Kalariya et al., 2022).

In silico molecular docking is carried out to determine and analyse interactions between bioactive compounds as ligands and protein macromolecules. The docking results show that three out of seven bioactive compounds in butanol extract have potential activity as both the best antibacterial and antiviral based on binding energy values, namely 2,6,10,14-tetramethyl-hexadecane, naphthalene and butane,1,1-dibutoxy. Apart from that, the value of the inhibition constant (Ki) is directly proportional to the energy, the lower the binding energy value, the smaller the Ki value, meaning that the interaction between the ligand-protein complex will be more stable, which has a big impact on its activity.

According to Dolgonosov (2017), the lower the binding energy, the higher the stability of the complex. The bonds formed by bioactive compounds with amino acids are van der Waals bonds, due to the nature of the compounds tending to be hydrophobic, indicating that the hydrophobic bonds are quite strong. The negative control (butanol) forms hydrogen bonds with amino acids GLN190 in the TyrRs protein and GLU119, ARG156 in the neuraminidase protein. Meanwhile, the positive control streptomycin formed hydrogen bonds with amino acids TYR36, GLY38, GLY49, THR75, TYR170, GLN190, GLN196 and oseltamivir with amino acids ARG118, TYR406.

The bioactive compound demonstrates potent antibacterial activity, as evidenced by both in silico and in vitro analyses. This activity is attributed to its inhibitory effect on the enzyme tyrosyl-tRNA synthetase (TyrRS), which plays a critical role in bacterial cell viability (Skupińska et al., 2017). TyrRS is a member of the aminoacyl-tRNA synthetase family, its functions by recognizing both the corresponding tRNA molecules and specific amino acid structures. This process is essential for translating genetic information encoded in nucleic acids into functional protein structures (Sun et al., 2017).

Molecular docking investigations of bioactive compounds derived from *Streptomyces* sp. as tyrosyl-tRNA synthetase (TyrRS) inhibitors are limited (Bhandari et al., 2022). Some existing studies predominantly evaluate these bioactive compounds from various source as inhibitors of aminoacyl-tRNA synthetases (Asiri, 2020; Gupta, 2017; Saha et al., 2018). Bhandari et al. (2022) reported *Streptomyces* species_SB10 displayed antibacterial activity against *S. aureus* in vitro. Molecular docking result suggests three bioactive compounds from *Streptomyces* species_SB10 namely brevianamide F, essramycin, cyclo (L-Phe-L-Ala), and cyclo (L-Val-L-Phe), as potent inhibitors for target proteins TyrRS with significant binding energy and appropriate interactions.

Furthermore, this compound demonstrates potential antiviral activity against the H1N1 virus through the inhibition of neuraminidase (NA) protein. NA of H1N1 (influenza A) viruses plays a distinct role in viral replication and has a highly conserved catalytic site (Kumar et al., 2025). NA is an appealing target for the development of therapeutics against influenza A viruses (Gubareva & Mohan, 2022; Sadati et al., 2019). The viral enzyme NA expressed on the surface of type A virus particles and infected cells. Thus, makes it readily accessible to antiviral agents and antibiodies (Gubareva & Mohan, 2022). Numerous sialic-based antiviral agents competitively bind to the NA cavity and are marketed worldwide for the treatment of Influenza A infection (Gitto et al., 2025). Four NA inhibitors are now licensed in various parts of the world namely zanamivir, oseltamivir, peramivir, and laninamivir to treat influenza A and B infections (Gubareva & Mohan, 2022).

Numerous studies have reported the identification of bioactive compounds from diverse plant sources, followed by in silico evaluations to assess their inhibitory potential against NA (Boora et al., 2026; Luo et al., 2020; Mando & Moussa, 2024; Wang et al., 2023; Wu et al., 2026). Nevertheless, there has been limited research on bioactive compounds derived from *Streptomyces* sp. that function as NA inhibitors to date (Amrani et al., 2024; Chen et al., 2025). Chen et al., (2025) research demonstrated that bioactive compounds derived from *Streptomyces ardesiacus* exhibit potential inhibitory activity against influenza A (H1N1). Four key compounds, 1-acetyl-β-

carboline, 1H-indole-3-carbaldehyde, anthranilic acid, and indole-3-carboxylic acidwere successfully isolated, and their chemical structures were elucidated using nuclear magnetic resonance (NMR) spectroscopy. The bioactive compound 1-acetyl-β-carboline exhibited the most prominent antiviral activity, with an IC_{50} value of 9.71 µg/mL in the anti-influenza assay. The molecular docking results demonstrated that 1-acetyl-β-carboline exhibited binding affinities comparable to Tamiflu, the positive control drug (Chen et al., 2025). In addition, Amrani et al., (2024) reported the antiviral potential of *Streptomyces* sp. KSF 103, isolated from Kuala Sat, Jerantut, Pahang, against the Influenza A virus. In silico analysis by molecular docking tools such as AutoDock Vina and PyMOL analyse the interactions of four compounds – hypoxanthine, vitamin D, purine, and aminocaproic acid – against Influenza A virus proteins. Moreover, Root Mean Square Deviation (RMSD) dynamic analyses demonstrated that the highest-ranked ligand–protein complexes exhibit structural stability under physiological conditions. Collectively, these findings highlight *Streptomyces* sp. KSF 103 as a promising candidate for the discovery and development of novel antiviral agents against influenza (Amrani et al., 2024).

The results of this study emphasize key aspects of current research in antimicrobial and antiviral drug development, focusing on targeted inhibition of vital enzymes like tyrosyl-tRNA synthetase (TyrRS) and viral neuraminidase (NA). Additionally, it underscores the significant contribution of natural products from microorganisms in tackling major global health issues. These findings contribute to accumulating evidence that metabolites derived from actinomycetes remain a valuable and significant source for the development of novel and advanced therapeutic agents. that metabolites from actinomycetes continue to be an important source for creating new and advanced therapeutic treatments.

Despite these promising findings, several limitations should be acknowledged. The use of crude extract limits the identification of specific active compounds, and the study was conducted on a single bacterial strain. Additionally, GC-MS analysis may not detect all bioactive metabolites, and molecular docking results require further experimental validation. Future studies should focus on isolating and characterizing individual bioactive compounds, evaluating their activity against a wider range of pathogen and validating their mechanisms of actions through experimental assays. The integration of advances analytical techniques such as Liquid Chromatography-Mass Spectrometry (LC-MS), NMR, along with toxicity and pharmacological studies, will be essential to fully explore the therapeutic potential of these bioactive compounds.

Conclusion

There are seven bioactive compounds from *Streptomyces bungoensis* strain 15721. In silico studies showed that bioactive compounds have very good antibacterial activity with different binding energies, inhibition constants, and protein-ligand interactions. Three compounds 2,6,10,14-tetramethyl-hexadecane, Naphtalene, and Butane, 1,1 dibutoxy show promising antibacterial and antiviral activity. These compounds should be further investigated for future antibacterial and antiviral candidates.

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