



# Anticancer property of marine coral-derived *Streptomyces* sp. SS162 against A549 lung adenocarcinoma cancer cells

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## ABSTRACT

The genus *Streptomyces* is one of the most important sources producing a huge amount of secondary metabolites applied in the pharmaceutical industry nowadays, especially in cancer treatment. In this study, the anticancer effect of *Streptomyces* sp. SS162 isolated from marine corals was investigated utilizing a 3-(4,5-dimethylthazol-2yl)-2,5-diphenyl tetrazolium-bromide cytotoxicity assay. The results showed that the SS162-cultured medium caused a significant inhibitory effect (64.63%) on the A549 lung carcinoma cell line among various cancer cell lines while being less toxic to normal fibroblasts. The effect of the SS162-cultured medium was in a time-dependent manner. After 24 hours of treatment, A549 cells shrank, expressed round morphology, and lost the adhesion to the culture surface, leading to the deceleration of cell proliferation that has not been reported in other works. Regarding cytotoxic mechanism, SS162-cultured medium inhibited A549 cancer cell growth via the 2.75-fold downregulation of microtubule-associated *TPX2* mRNA level and the 2.78-fold upregulation of cyclin-dependent-kinase-inhibitor *CDKN1B* expression. Notably, the antiproliferative capacity of *Streptomyces* sp. via the downregulation of *TPX2* level was reported here for the first time. After the extraction of SS162-cultured medium by ethyl acetate solvent, the crude extract could also suppress the proliferation of A549 cells with an  $IC_{50}$  value of 407.38  $\mu\text{g/ml}$  and a selectivity index greater than 2.5 implying a specific effect on cancer cells. These findings proved the effect of *Streptomyces* sp. SS162 against lung cancer and simultaneously provided a suggestion that SS162-cultured medium could be potential for discovering novel anticancer agents.

## INTRODUCTION

*Streptomyces* belongs to Gram-positive bacteria, having a high guanine and cytosine (GC) content of 72.5% in its genome and being recognized by colony morphology and filamentous growth during its life cycle (Chater *et al.*, 2010). *Streptomyces* is known as the largest genus of the phylum actinobacteria and a promising source for discovering novel bioactive secondary metabolites contributing to the pharmaceutical industry (Lee *et al.*, 2019). These secondary metabolites possess varied properties containing antibiotic (Bekiesch *et al.*, 2020; Toumatia *et al.*, 2015), antitumor (Shen *et al.*, 2021), antimalarial (Nugraha *et al.*, 2020), and immunosuppressive activity (Yashiro *et al.*, 2019).

In particular, *Streptomyces* is responsible for producing approximately two-thirds of antibiotics used in current medicine, with major classes such as aminoglycosides, anthracyclines,  $\beta$ -lactams, glycopeptides, and macrolides (Barka *et al.*, 2016; Fernández-Martínez *et al.*, 2014; Petković *et al.*, 2017; Quinn *et al.*, 2020; Takano *et al.*, 2016). Notably, there are various antitumor antibiotics derived from *Streptomyces* that have been utilized in clinical treatment, including bleomycin (Shen *et al.*, 2001), mitomycin (Tiran *et al.*, 2020), doxorubicin (Benjanuwattra *et al.*, 2020), and dactinomycin (Schink *et al.*, 2020). Several studies reported that *Streptomyces* possesses different gene clusters encoding multiple polyketide and nonribosomal peptide synthases responsible for secondary metabolite biosynthesis, including antitumor constituents (Risidian *et al.*, 2019; Tang *et al.*, 2004). In fact, the research of cancer treatment attracts more and more interest due to challenges relating to tumor relapse, metastasis, drug resistance, and serious side effects on the whole body system that lower the life quality and expectancy of patients. Therefore, current Food and Drug Administration-approved

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chemotherapeutic drugs indicate the importance of research and discovery of various novel anticancer compounds from natural sources, including from different strains of *Streptomyces*.

The increase in exploration from different habitats on earth helps to isolate new taxa of *Streptomyces*. Some areas in Vietnam have been explored as sources of microbial biodiversity with newly discovered strains of *Streptomyces* that produce substances owning anticancer potential (Nguyen *et al.*, 2020; Quach *et al.*, 2021; Vu *et al.*, 2018). In that tendency, *Streptomyces* sp. SS162, recently collected from marine corals in distant islands of central Vietnam, was cultured in a liquid medium and then evaluated for biological activities. Following the initial screening, *Streptomyces* sp. SS162 exhibited antibacterial activity against the shrimp pathogen *Vibrio parahaemolyticus* (Chuong Hoang Nguyen, unpublished data), causing acute hepatopancreatic necrosis disease, which would seriously affect shrimp farming. To broaden exploring other activities of this species, the anticancer capacity of *Streptomyces* sp. SS162 would be investigated on varied cancer cell lines; then, the cytotoxic mechanism was preliminarily evaluated.

## MATERIALS AND METHODS

### Materials

*Streptomyces* sp. SS162 was isolated from the coral sample collected at Central Reef, Spratly Islands (GPS: 8° 55'51"N, 112° 21'11"E) by the Centre for Research and Application in Bioscience (Ho Chi Minh City, Vietnam). The isolated colonies were maintained as a suspension in 40% (v/v) glycerol, stored at -20°C.

### SS162-cultured medium preparation

First, the suspension of *Streptomyces* sp. SS162 from -20°C preservation was streaked on MPE agar medium (calcium carbonate: 4 g/l; glucose: 20 g/l; sodium chloride: 5 g/l; soybean flour: 5 g/l; agar: 20 g/l), incubating at 30°C within 3–5 days. Next, isolated colonies were picked up and grown in 20 ml of FM3 medium (yeast extract: 5 g/l; starch: 20 g/l; soybean flour: 15 g/l; peptone: 2 g/l; calcium carbonate: 4 g/l; sodium chloride: 18 g/l) for 3 days at 30°C, as a starting inoculum prior to the fermentation process. The fermentation was carried out in 300 ml of FM3 medium supplemented with 5% (v/v) starting inoculum and shaken at 200 rpm for 8 days at 30°C. Then, the biomass was discarded by centrifugation at 10,000 rpm for 10 minutes and the supernatant fluid was stored at -30°C. For cytotoxicity assay, the supernatant fluid was thawed at room temperature and filtered by a sterile 0.22 µm membrane.

### Cell line maintenance and growth condition

Cell lines included A549 (human lung carcinoma, ATCC CCL-185), SiHa (human cervical squamous cell carcinoma, ATCC HTB-35), Caov-3 (human ovarian carcinoma, ATCC HTB-75), NCI-N87 (human gastric carcinoma, ATCC CRL-5822), HL-60 (human acute promyelocytic leukemia, ATCC CCL-240), and BJ-5ta (human normal fibroblasts, ATCC CRL-4001). A549 cells were cultured in Dulbecco's modified Eagle's medium (DMEM)-F12 medium (Sigma-Aldrich, Germany), supplemented with 10% (v/v) fetal bovine serum (FBS) (Sigma-Aldrich, Germany). Caov-3 and BJ-5ta

cell lines were cultured in DMEM high glucose medium (Sigma-Aldrich, Germany), supplemented with 10% (v/v) FBS. NCI-N87 and HL-60 cell lines were cultured in Roswell Park Memorial Institute 1640 medium (Sigma-Aldrich, Germany), supplemented with 10% (v/v) FBS. SiHa cell line was cultured in Eagle's minimum essential medium (Sigma-Aldrich, Germany), supplemented with 10% (v/v) FBS (Sigma-Aldrich, Germany). Antibiotic antimycotic solution (100 U/ml penicillin, 100 µg/ml streptomycin, and 250 ng/ml amphotericin B) (Sigma-Aldrich, Germany) was also added to the medium to prevent contamination. All cell lines were cultured in humidified 5% CO<sub>2</sub> atmosphere at 37°C in a cell incubator (Esco, Singapore).

### Screening of cytotoxicity of SS162-cultured medium on human cancer cell lines

The cytotoxic effects of *Streptomyces* sp. SS162-cultured medium on human cancer lines was evaluated using 3-(4,5-dimethylthazol-2-yl)-2,5-diphenyl tetrazolium-bromide (MTT) assay. First, adherent cells were detached from the culture surface using 0.25% trypsin-0.53 mM Ethylenediamine tetraacetic acid (Sigma-Aldrich, Germany). These cells were centrifuged and the cell density was identified. Then, an amount of  $1 \times 10^4$  cells was added to each well of a 96-well plate (SPL, Korea). For adherent cells, the cells were left to attach overnight, while the suspension cells were incubated within 1 hour for the reconstitution. After that, the medium was removed and replaced with 95 µl of fresh medium. Next, 5 µl of SS162-cultured medium [ratio 1:20 (v/v)] was added to each well. Nontreated control samples were treated with noncultured FM3 medium. After 48 hours, 5 µl of MTT (5 mg/ml) (Sigma-Aldrich, Germany) was coincubated for 4 hours. Next, 60 µl of lysis buffer [30% (w/v) SDS, 0.03 N HCl] and 90 µl of dimethyl sulfoxide (DMSO) [99.9% (v/v)] were added to each well. The plates were shaken at 850 rpm for 10 minutes, and the optical densities were measured at a wavelength of 550 nm. These experiments were repeated at least in triplicate. The growth inhibition was calculated by the following formula:

$$\text{Growth inhibition (\%)} = \frac{(1 - (\text{OD}_{\text{Treated}} - \text{OD}_{\text{Blank}}) / (\text{OD}_{\text{Non-treated}} - \text{OD}_{\text{Blank}})) \times 100}{1}$$

### Evaluation of the anticancer activity of SS162-cultured medium on A549 cell line

#### Analysis of cell growth and morphology

A549 cells at a density of  $1 \times 10^4$  cells/well were treated with SS162-cultured medium [ratio 1:20 (v/v)]. Noncultured FM3 medium was used for nontreated control samples. MTT assay was utilized to analyze cell densities of treated and nontreated control samples at different time points of 24, 48, 72, and 96 hours. The morphology of A549 cells treated with SS162-cultured medium was recorded by inverted microscope Nikon Eclipse TiU (Nikon, Japan).

#### Total RNA extraction and quantitative real-time PCR (qPCR)

A549 cells were treated with SS162-cultured medium and noncultured FM3 medium (nontreated control). Total RNA was collected by using TriSure Kit (Bioline, UK). After that, 500 ng of total RNA was used for reverse transcription with

Tetro cDNA Synthesis Kit and Oligo-dT primers (Bioline, UK). Real-time PCR was conducted using SensiFAST™ HRM Kit (Bioline, UK), primers (Phu Sa, Viet Nam), and 1 µl of cDNA template. Primer sequences were referred to previous studies: *CDKN1B* (F) 5'-AGACTGATCCGTCGGACAGC, (R) 5'-CACAGAACCGGCATTTGGG; *TPX2* (F) 5'-ACATCTGAACTACGAAAGCATCC, (R) 5'-GGCTTAAC AATGGTACATCCCTTA; *CCNE1* (F) 5'-AAATGGCC AAAATCGACAGG, (R) 5'-CGAGGCTTGACGTTGA GTT; *CCND1* (F) 5'-TGAAGGAGACCATCCCCCTG, (R) 5'-TGTTCAATGAAATCGTGCGG; *PCNA* (F) 5'-TTTGGTG CAGCTCACCTG, (R) 5'-CGCGTTATCTTCGGCCCTTA; *MKI67* (F) 5'-TGTGCCTGCTCGACCCTACA, (R) 5'-TGAAA TAGCGATGTGACATGTGCT; *ACTB* (F) 5'-TCCTGTGG CATCCACGAAACT, (R) 5'-GAAGCATTGCGGTGGA CGAT (Amatori *et al.*, 2017; Lee *et al.*, 2012; Xiang *et al.*, 2012).  $\beta$ -Actin (*ACTB*) was used as a reference gene. The reactions were performed by LightCycler 96 instrument (Roche Diagnostics, Germany). The following thermal profile was applied: 1 cycle at 95°C for 3 minutes, 40 cycles at 95°C for 5 seconds, 55°C for 10 seconds, and 72°C for 5 seconds. The targeted mRNA expression was normalized to the expression of reference gene  $\beta$ -actin (*ACTB*) and evaluated in comparison between treated and nontreated samples by the  $2^{-\Delta\Delta Ct}$  method. The experiment was conducted in triplicate.

#### Ethyl acetate (EA) extraction of SS162-cultured medium

The SS162-cultured medium was extracted by EA solvent [ratio 1:1 (v/v)] for 24 hours, which was continually repeated until the color of the solvent remained unchanged. Next, the extract was concentrated and excluded the solvent by the rotary evaporator. The efficiency of EA extraction is 0.047% (0.047 g/100 ml of SS162-cultured medium). Finally, the EA extract was weighed, dissolved in DMSO solvent [99.9% (v/v)], and diluted to gain experimental concentrations (0.2–1,000 µg/ml) for cytotoxicity assay.

#### Gas chromatography-mass spectroscopy (GC-MS) analysis

The GC-MS analysis was conducted following the protocol of the previous study (Tangjitjaroenkun *et al.*, 2021). The SS162-EA extract was dissolved in acetone solvent and then analyzed in an Agilent Technologies 6890N GC coupled to an Agilent 5973 inert mass selective detector. The GC capillary column was HP-5MS (30 m × 0.25 mm × i.d., 0.25 µm film thickness 0.25 µm). The column temperature was increased from 70°C to 300°C (4°C/minute). The carrier gas was helium, with a column flow rate of 1 ml/minute. The mass selective detector was operated in electron ionization mode at 70 eV with a mass range from 40 to 400 amu. The compounds were identified by comparing them with NIST 14 Library.

#### Data analysis

Statistical analysis and graphs were performed using GraphPad Prism 8 software (USA). All data were analyzed by unpaired Student's *t*-test or one-way ANOVA test. The statistically significant differences were determined at  $p \leq 0.05$ . Data were presented as mean ± SD.

## RESULTS

### The morphological features of *Streptomyces* sp. SS162

The morphological features of *Streptomyces* sp. SS162 grown on MPE agar medium was observed. Specifically, this species developed under the form of colonies with white mycelium, accompanied by undulate, opaque, and dry characteristics (Fig. 1A). The images by scanning electron microscope also revealed that aerial mycelium developed into short, straight to flexuous spore chains, the spore surface is regular and smooth, and the spore length is approximately 1.2–1.5 µm (Fig. 1B).

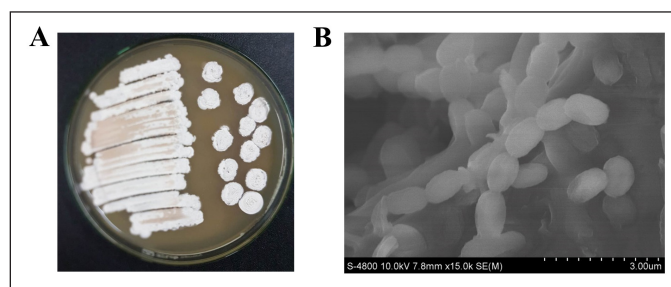
### Cytotoxicity of *Streptomyces* sp. SS162-cultured medium on different cancer cell lines

The cytotoxicity of SS162-cultured medium against various types of cancer cells was investigated using an MTT assay. The results showed that the growth inhibition percentages induced by SS162-cultured medium after 48 hours of incubation toward the A549 lung carcinoma cell line, SiHa cervical carcinoma cell line, NCI-N87 gastric carcinoma cell line, Caov-3 ovary carcinoma cell line, and HL-60 acute promyelocytic leukemia cell line were 64.63%, 51.73%, 36.73%, 17.66%, and 10.27%, respectively, while that toward BJ-5ta normal fibroblast cell line was 32.62% (Fig. 2A). Notably, the inhibition percentage of SS162-cultured medium on A549 lung cancer cells was two times that of BJ-5ta normal cells proving selective activity of SS162-cultured medium on this cancer cell line. In addition, the cell morphology of treated groups was significantly different from nontreated cells (Fig. 2B). Among the tested cancer cell lines, the inhibitory effect on the A549 cell line presented as the highest; thus, the effect of *Streptomyces* sp. SS162-cultured medium on A549 cells was favorable for the comprehensive investigation.

### Anticancer activity of SS162-cultured medium on A549 cell line

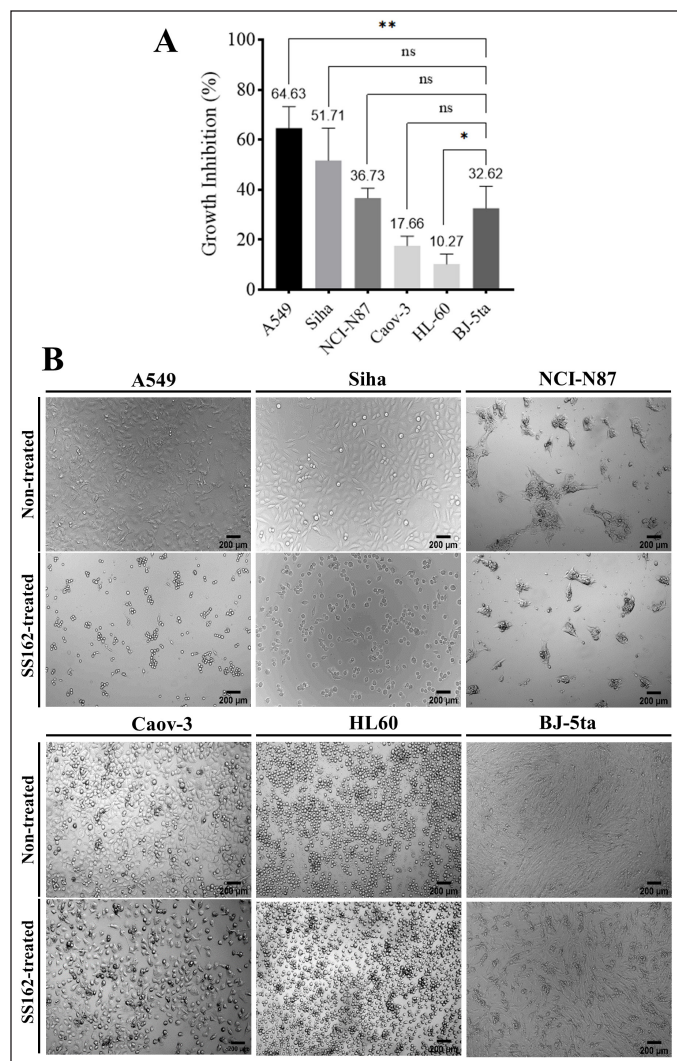
#### Analysis of A549 cell growth and morphology

The cell density of the treated sample was altered in a time-dependent manner, as evidenced by OD<sub>550</sub> values from 0 to 96 hours (Fig. 3A). For treated A549 cells, the OD<sub>550</sub> value was unchanged within 48 hours, then increasing by 1.4 and 1.6 times at 72 and 96 hours, respectively (Fig. 3A). On the other hand, for nontreated A549 cells, this value rose by 2.2, 2.8, and 3.2 times at 48, 72, and 96 hours, respectively. The growth-



**Figure 1.** Morphological features of *Streptomyces* sp. SS162 on MPE agar medium. (A) SS162's colony morphology. (B) SS162's spore-chain morphology was observed with scanning electron microscopy.

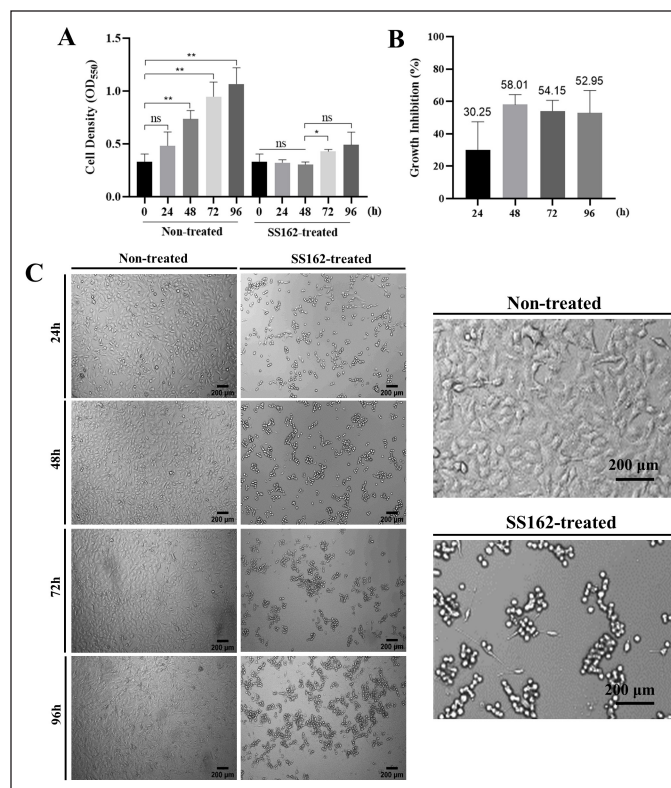




**Figure 2.** Cytotoxicity of *Streptomyces* sp. SS162-cultured medium against different cell lines. (A) Growth inhibition of SS162-cultured medium on cell lines. Data were expressed as mean  $\pm$  SD of at least three independent experiments. Statistical differences were analyzed by one-way ANOVA (\* $p \leq 0.05$ ; \*\* $p \leq 0.01$ ; ns,  $p > 0.05$ ). (B) Morphological changes of different cell lines induced by SS162-cultured medium. Scale bars: 200  $\mu$ m.

inhibitory percentage increased from 30.25% at 24 hours to 58.01% at 48 hours and then fluctuated at approximately 50% until 96 hours (Fig. 3B).

Besides, the image results also showed that cellular morphology changed after being treated with an SS162-cultured medium. The treated A549 cells had changes in their appearance immediately after the exposure. To be more specific, these cells began to round and detach from the culture surface and adjacent cells while maintaining the cell membrane's intactness (Fig. 3C). In contrast, nontreated A549 cells were adherent on the culture surface with the characteristics of healthy epithelial cells (Fig. 3C). Interestingly, nonadherent round morphology was expressed during the experimental 96-hour period (Fig. 3C). Therefore, the SS162-cultured medium could inhibit the cell proliferation which might be related to the change in interactions between cell and extracellular matrix (ECM).



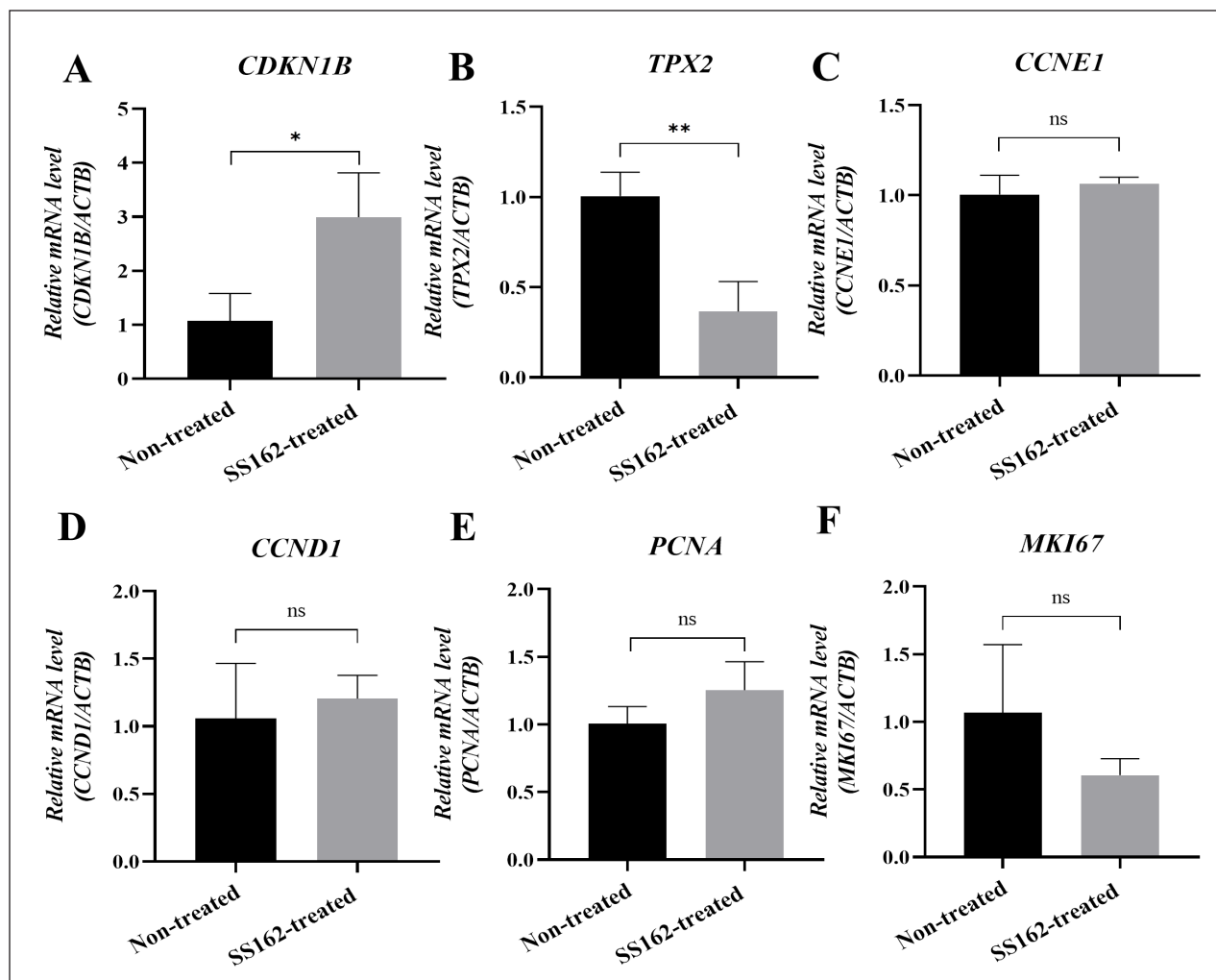
**Figure 3.** Time-dependent effect of *Streptomyces* sp. SS162-cultured medium against A549 cell line. (A) Cell densities of treated and nontreated control samples during the time. Data were expressed as mean  $\pm$  SD of at least three independent experiments. The statistical differences were analyzed by unpaired two-tailed Student's *t*-tests (\* $p \leq 0.05$ ; \*\* $p \leq 0.01$ ; ns,  $p > 0.05$ ). (B) The growth-inhibitory percentages of SS162-cultured medium on A549 cells during the time. (C) Optical images of SS162-treated A549 cells at different time points. Scale bars: 200  $\mu$ m.

**Effect of SS162-cultured medium on mRNA expression**

To identify the underlying molecular mechanism of the SS162-cultured medium on A549 cells' proliferation, the mRNA expression levels of genes involved in cell cycle progression, such as *CDKN1B*, *TPX2*, *CCNE1*, *CCND1*, *PCNA*, and *MKI67*, were examined (Fig. 4A–F). The results showed that *CDKN1B* expression in the treated A549 cells was 2.78-fold higher than that in nontreated control samples (Fig. 4A), while there was a decrease in *TPX2* mRNA level by 2.75-fold following the treatment (Fig. 4B). Besides, a 1.77-fold decline in *MKI67* level of treated samples was also observed despite no statistically significant difference when compared with control samples (Fig. 4F). However, *CCNE1*, *CCND1*, and *PCNA* mRNA levels expressed no significant changes (Fig. 4C–E). In brief, the proliferative inhibition of A549 cells induced by the SS162-cultured medium was related to the upregulation of *CDKN1B* expression and downregulation of *TPX2* expression.

**Anticancer effect of EA extract on A549 cell line**

To investigate whether bioactive constituents in SS162-cultured medium could concentrate in EA fraction after the extraction, the cytotoxicity of this fraction was evaluated



**Figure 4.** The effect of *Streptomyces* sp. SS162-cultured medium on mRNA expression levels in A549 cells. (A–F) Quantitative real-time PCR analysis of genes in treated A549 cells, including *CDKN1B*, *TPX2*, *CCNE1*, *CCND1*, *PCNA*, and *MKI67*. Data were expressed as mean  $\pm$  SD of three independent experiments. The statistical differences were analyzed by unpaired two-tailed Student's *t*-tests (\* $p \leq 0.05$ ; \*\* $p \leq 0.01$ ; ns,  $p > 0.05$ ).

on A549 cells with experimental concentrations ranging from 0.2 to 1,000  $\mu\text{g/ml}$ . As shown in Figure 5A, the effect of the SS162-EA extract was concentration-dependent. At the 1,000  $\mu\text{g/ml}$  concentration, the growth inhibition reached the highest value at 95.4%. The inhibitory percentages decreased following the decline of extract concentration. For concentrations lower than 15.6  $\mu\text{g/ml}$ , the inhibition appeared insignificantly. The 50% growth-inhibitory concentration of SS162-EA extract was 407.38  $\mu\text{g/ml}$ . In the meantime, normal human fibroblasts were less sensitive to SS162-EA extract treatment than A549 cells since the growth-inhibitory percentage for BJ-5ta cells just reached 49.4% at 1,000  $\mu\text{g/ml}$  (Fig. 5A).

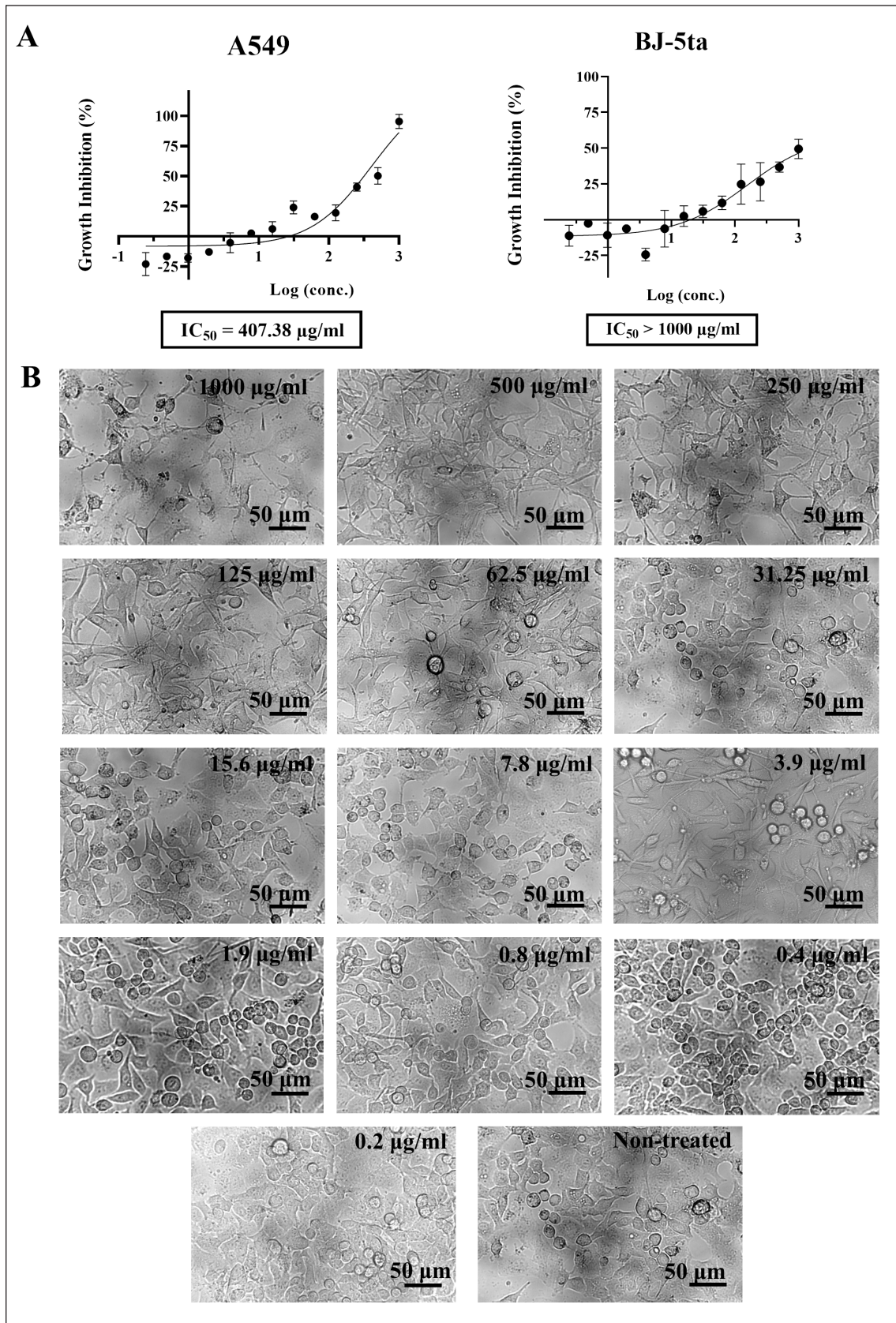
Regarding cell morphology, treated cells presented typical features of cell death at the concentration of 1,000  $\mu\text{g/ml}$ . For concentrations of 250 and 500  $\mu\text{g/ml}$ , the cell density exhibited lower than that of the nontreated control sample. However, unlike samples treated with SS162-cultured medium, nonadherent round morphology was not observed in those treated with SS162-EA extract at experimental concentrations.

Therefore, it is suggested that different substances present in the SS162-cultured medium might contribute to the anticancer activity of *Streptomyces* sp. SS162, besides the constituents, is concentrated in SS162-EA extract. To sum up, along with the MTT cytotoxicity assay, the images of cell morphology supported that SS162-EA extract could inhibit the proliferative capacity of A549 cells.

#### GC-MS analysis of SS162-EA extract

The chemical constituents in the SS162-EA extract were analyzed using the GC-MS method. The GC-MS chromatogram revealed that there were 23 compounds identified in the extract (Fig. 6), accompanied by retention time, molecular formula, molecular weight, and area, which are listed in Table 1. Among them, n-hexadecanoic acid (12.58%), 9,12-octadecadienoic acid (Z,Z)- (67.96%), octadecanoic acid (8.91%), and 3-chrysenamine (1.67%) take the major account in the extract, while the others presented at low percentages (<1%).





**Figure 5.** The cytotoxic effect of SS162-EA extract on A549 cells. (A) The growth-inhibitory percentages of SS162-EA concentrations on A549 cells and BJ-5ta normal fibroblasts. Data were expressed as mean  $\pm$  SD of three independent experiments. (B) The morphology of A549 cells treated with SS162-EA concentrations. Scale bars: 50  $\mu\text{m}$ .

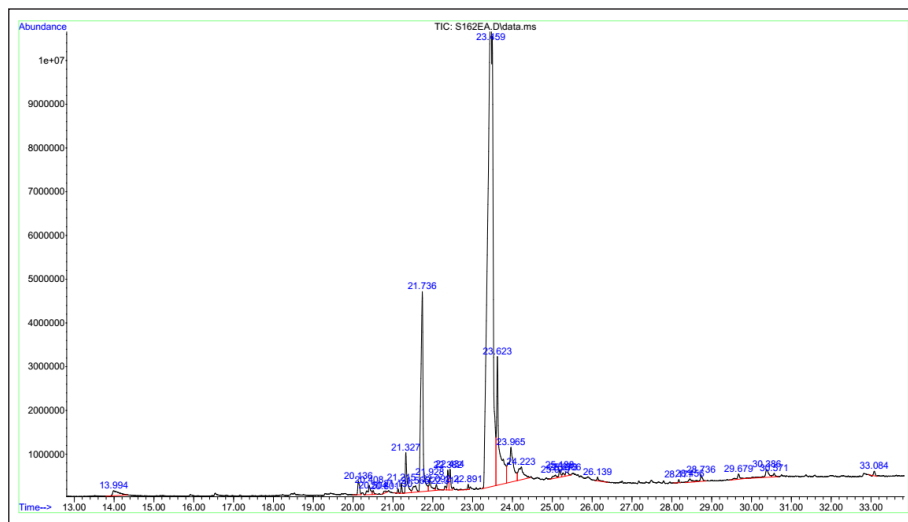


Figure 6. GC-MS chromatogram of SS162-EA extract.

## DISCUSSION

In this study, the preliminary screening indicated anticancer activity of *Streptomyces* sp. SS162 strain isolated from marine corals, in which SS162-cultured medium displayed inhibitory activity toward different human cancer cell lines. The highest cytotoxic activity was against the A549 lung carcinoma cell line, with growth inhibition of 64.63% after 48 hours of incubation. Meanwhile, SiHa and NCI-N87 suffered moderate cytotoxicity with 51.73% and 36.73% inhibition, respectively. Other cancer cell lines consisting of Caov-3 and HL-60 experienced weak cytotoxic activity (<20%). Notably, the SS162-cultured medium expressed less toxicity to the BJ-5ta normal cell line (32.62%) than A549 cells (64.63%), implying the selective activity on this cancer cell line. A bioactive agent causing toxicity on cancer cells while being unharmed to normal cells is also an important highlight since current chemotherapies usually cause serious side effects on patients despite the remarkable killing effect on tumor cells (Oun *et al.*, 2018). Therefore, the selectivity of tested agents on cancer cells is also an important target for determining promising candidates (Fahmy and Abdel-Tawab, 2021; Tan *et al.*, 2015); thus, *Streptomyces* sp. SS162 was opted for further investigation.

Regarding the A549 cell line, the SS162-cultured medium caused a proliferative inhibition on these cells during the experimental 96-hour period. After the treatment, the A549 cells became round immediately and detached from adjacent cells and the culture surface while their plasma membrane's integrity was maintained. Compared to a former study, Kumar *et al.* (2021) demonstrated the alteration of A549 cells, such as the round morphology, reduction in cell size, and cytoskeleton aggregation after being treated with *Streptomyces* sp. strain 196's extract, and these cells were induced apoptotic cell death later (Kumar *et al.*, 2021). In the current study, the SS162-cultured medium impeded the adhesion and proliferation of A549 cells; however, the cells did not experience the induction of apoptosis during experimental time. To the best of our knowledge, this phenomenon has not been reported in other works yet. The adhesion of cells to the ECM through receptors is one of the

dominant checkpoints for cell cycle progression to control proliferation, differentiation, and migration (Moreno-Layseca and Streuli, 2014). Integrin, known as a cell-surface receptor, can mediate and interact with ECM proteins to construct cellular morphology and induce the activation of various proliferative signaling pathways, such as PI3K/Akt (Sun *et al.*, 2019), ERK/MAP (Ho *et al.*, 2020), or Rho/ROCK (Streuli and Akhtar, 2009), related to drug resistance of chemotherapeutic agents. It is hypothesized that secondary metabolites presenting in the SS162-cultured medium could affect integrin-ECM interaction, causing the loss of A549 cells' adhesion and, thereby, affecting cell proliferation afterward.

Our quantitative reverse transcription-PCR data indicated a 2.75-fold decrease in *TPX2* mRNA level in treated A549 cells. This is correlated with previous results showing that a decrease in *TPX2* expression led to mitotic arrest (Hsu *et al.*, 2017). *TPX2* is identified as a prominent interactor triggering the interaction between Aurora A kinase and microtubules of the spindle apparatus during early mitosis (Grover *et al.*, 2012b). Therefore, the correlation between the downregulation of *TPX2* mRNA level and mitotic errors would disrupt cell cycle progression and prevent proliferation, which could become a potential therapeutic strategy for cancer treatment (Grover *et al.*, 2012a; Zhang *et al.*, 2018). In this study, the SS162-cultured medium decreased *TPX2* mRNA level, which could be related to the proliferative inhibition of A549 lung cancer cells. Interestingly, the antiproliferative capacity of *Streptomyces* sp. via the downregulation of *TPX2* was reported here for the first time. In addition, *CDKN1B* mRNA expression in A549 cells treated with SS162-cultured medium increased significantly, 2.78-fold higher than in nontreated samples. Cell cycle checkpoint is a prominent mechanism to control cell proliferation, differentiation, and cell death, which depends on the activation of cyclin-dependent kinase families (CDK) (Dickson and Schwartz, 2009). To ensure the cell transition from quiescence to proliferation, the interaction between CDK and cyclin needs to be triggered. In contrast, the proteins blocking this interaction can be listed as CDKN4, CDKN1A,

**Table 1.** Chemical compounds identified in the SS162-EA extract by GC-MS analysis.

No.	Compound name	Retention time	Area	Formula	Molecular weight
1	Pentadecanoic acid	20.409	0.60	C <sub>15</sub> H <sub>30</sub> O <sub>2</sub>	242.3975
2	Tyrosol, acetate	20.803	0.11	C <sub>10</sub> H <sub>12</sub> O <sub>3</sub>	180.2005
3	{4-Methoxy-2-[(trimethylsilyl)oxy]phenyl}(4-methylphenyl)methanone	21.130	0.10	C <sub>17</sub> H <sub>20</sub> O <sub>3</sub> Si	300.42
4	Pentadecanoic acid, dimethyl	21.215	0.25	C <sub>17</sub> H <sub>34</sub> O <sub>2</sub>	270.5
5	n-Hexadecanoic acid	21.324	1.67	C <sub>16</sub> H <sub>32</sub> O <sub>2</sub>	256.4241
		21.736	10.91		
6	2,3,4-Trihydroxybenzaldehyde	21.564	0.60	C <sub>7</sub> H <sub>6</sub> O <sub>4</sub>	154.12
7	Hexadecanoic acid, ethyl ester	21.931	0.72	C <sub>18</sub> H <sub>36</sub> O <sub>2</sub>	284.4772
8	Tetradecanoic acid	22.314	0.15	C <sub>14</sub> H <sub>28</sub> O <sub>2</sub>	228.3709
9	Heptadecanoic acid	22.383	0.63	C <sub>17</sub> H <sub>34</sub> O <sub>2</sub>	270.4507
10	9,12-Octadecadienoic acid, methyl	22.892	0.20	C <sub>19</sub> H <sub>34</sub> O <sub>2</sub>	294.4721
		23.458	63.35		
		23.968	4.18		
11	9,12-Octadecadienoic acid (Z,Z)-	23.968	4.18	C <sub>18</sub> H <sub>32</sub> O <sub>2</sub>	280.4455
		25.078	0.26		
		25.272	0.17		
12	Octadecanoic acid	23.624	8.91	C <sub>18</sub> H <sub>36</sub> O <sub>2</sub>	284.4772
13	3-Chrysenamine	24.225	1.67	C <sub>18</sub> H <sub>13</sub> N	243.3025
14	Linoleic acid ethyl ester	25.186	0.33	C <sub>20</sub> H <sub>36</sub> O <sub>2</sub>	308.4986
15	Bicyclo[3.2.0]heptan-2-one, 6-hydroxy-5-(ethoxycarbonylmethyl)-6-vinyl	25.364	0.28	C <sub>13</sub> H <sub>20</sub> O <sub>4</sub>	240.29
16	4-Cyanobenzoic acid, tridecyl este	26.136	0.20	C <sub>21</sub> H <sub>31</sub> NO <sub>2</sub>	329.4763
17	1,2-Bis(trimethylsilyl)benzene	28.179	0.07	C <sub>12</sub> H <sub>22</sub> Si <sub>2</sub>	222.47
18	2-Ethylacridine	28.454	0.27	C <sub>15</sub> H <sub>13</sub> N	207.27
19	Silicic acid, diethyl bis(trimethylsilyl) ester	28.734	0.40	C <sub>10</sub> H <sub>28</sub> O <sub>4</sub> Si <sub>3</sub>	296.58
20	Cholest-20-ene-3,6-diol, 5.alpha.,6.alpha.)-	29.678	0.37	C <sub>27</sub> H <sub>46</sub> O <sub>2</sub>	402.7
21	delta.-Tocopherol, O-methyl-	30.388	0.79	C <sub>28</sub> H <sub>48</sub> O <sub>2</sub>	416.6795
22	1,4-Bis(trimethylsilyl)benzene	30.571	0.20	C <sub>12</sub> H <sub>22</sub> Si <sub>2</sub>	222.47
23	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	33.083	0.17	C <sub>14</sub> H <sub>22</sub> O <sub>2</sub>	222.3233

CDKN1B, and CDKN1C functioning as proliferative inhibitors (Ale-Agha *et al.*, 2018). Among them, CDKN1B (p27), a CDK inhibitor of the Kip protein family, involves in the G1/S phase checkpoint. It is demonstrated that the considerable upregulation of *CDKN1B* could be associated with the growth inhibition of non-small-cell lung cancer cells at the G1/S phase (Leem *et al.*, 2018; Li *et al.*, 2018; Wang *et al.*, 2021). In previous reports on *Streptomyces* sp., the upregulation of *CDKN1B* (p27) contributing to anticancer activity was also observed (Cho *et al.*, 2015). Therefore, the SS162-cultured medium also affected A549 cells' proliferation via the upregulation of the *CDKN1B* gene besides the decrease in the *TPX2* level mentioned above.

The investigation of the SS162-EA extract's cytotoxicity showed that the IC<sub>50</sub> value was 407.38 µg/ml toward the A549 cell line. Regarding previous works evaluating the anticancer activity of *Streptomyces* sp., the IC<sub>50</sub> values of crude extracts were approximately 200–400 µg/ml, to which the value of SS162-EA extract is comparable (Rajivgandhi *et al.*, 2020; Tan *et al.*, 2019, 2015). In addition, importantly, similar to SS162-cultured medium, SS162-EA extract also exhibited a lower toxicity to BJ-5ta human normal fibroblasts than A549 cells, in which calculated selectivity index (SI) (the ratio of IC<sub>50</sub> on normal cell line to IC<sub>50</sub> on cancer cell line) is greater than 2.5. Compared to other studies,



this SI value is higher, implying the potential of *Streptomyces* sp. SS162's secondary metabolites presenting in the extract (Fahmy and Abdel-Tawab, 2021; Tan *et al.*, 2015). The GC-MS analysis of SS162-EA extract revealed 23 chemical constituents in SS162-EA extract belonging to saturated fatty acids, unsaturated fatty acids, fatty acid esters, steroids, and phenolic compounds. n-Hexadecanoic acid (12.58%), 9,12-octadecadienoic acid (Z,Z)- (67.96%), octadecanoic acid (8.91%), and 3-chrysenamine (1.67%) present as major compounds in the extract, among which hexadecanoic acid and octadecadienoic acid are familiar constituents which *Streptomyces* spp. produce when compared with other reports (Al-Dhabi *et al.*, 2020; Mothana *et al.*, 2022; Qi *et al.*, 2019). However, the percentage amount of 9,12-octadecadienoic acid (Z,Z)- in SS162-EA extract was much higher. Regarding the anticancer activity of these compounds, n-hexadecanoic acid was reported on cytotoxicity against HCT-116 and HT-29 colorectal cancer cell lines with IC<sub>50</sub> values of 0.8 and 36.04 µg/ml, respectively (Bharath *et al.*, 2021; Ravi and Krishnan, 2017), while 9,12-octadecadienoic acid and 3-chrysenamine have not been investigated yet.

It is also hypothesized that besides the constituents concentrated in the EA fraction, there were other constituents in the SS162-cultured medium contributing to the anticancer activity of *Streptomyces* sp. SS162. The morphological results supported this hypothesis since SS162-EA extract did not cause a nonadherent round feature on A549 cells which the SS162-cultured medium could induce. In fact, *Streptomyces* spp. could produce a variety of chemical structures, including peptides, alkaloids, macrolides, lactones, indoles, terpenes, and quinones upon which varied solvents have been used, such as EA, methanol, and hexane, aiming to improve extraction efficiency (Ser *et al.*, 2017; Sivalingam *et al.*, 2019). For that reason, seeking bioactive agents in an SS162-cultured medium could also be continued using other extraction approaches.

## CONCLUSION

The genus *Streptomyces* from the marine environment presents as a promising source of bioactive secondary metabolites. In this research study, it is demonstrated that *Streptomyces* sp. SS162, derived from marine corals, possesses significant cytotoxic activity against the A549 lung carcinoma cell line while being less toxic to normal cells. More particularly, the SS162-cultured medium could effectively inhibit the proliferation of A549 cells via the upregulation of *CDKN1B* and the downregulation of *TPX2* expression levels. The EA crude extract of SS162-cultured medium also owns antiproliferative capacity on cancer cells with high selectivity (SI >2.5). Therefore, bioactive compounds from *Streptomyces* sp. SS162 contributing to anticancer activity against lung carcinoma cells need to be identified and isolated in further studies.

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## AUTHORS' CONTRIBUTIONS

THN and TTBN contributed equally to designing experiments, collect data, performing statistical analysis, and writing the manuscript. LTYN carried out experiments and analyzed the database. NHC supervised experiments and reviewed the manuscript. DTPT designed experiments, supervised experiments, and reviewed the manuscript. All authors reviewed and approved the final manuscript for publication.

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## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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