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Metabolomic and Cytotoxicity Profiles of Ethanol Extract of *Peronema canescens* Jack on Human Non-small Lung Cancer Cell A549

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ABSTRACT: Cancer has a high prevalence and mortality in the world. Cancer treatment is still hampered by high levels of side effects, drug resistance and the lack of affordable prices for anticancer drugs. It is necessary to develop new anticancer drugs to help overcome this problem. One of the plants that has the potential to be developed as an anticancer drug is Sungkai (*Peronema canescens* Jack). This study aims to determine the cytotoxic activity of sungkai leaf and identify its metabolomic profile. The sungkai leaves were macerated for 24 hours with 96% ethanol. Metabolomic profiles were analyzed with Ultra High-Performance Liquid Chromatography-High Resolution Mass Spectrometry (UHPLC-HRMS). Chemical structure identification was performed by MS-DIAL and MS-FINDER platforms. The ethanol extract of sungkai leaves was analyzed for its cytotoxic activity using the MTT test on A549 lung cancer cells and its selectivity on normal HDFa fibroblast cells. The ethanol extract of sungkai showed IC_{50} 105,21 µg/mL on A549 cells and no cytotoxic activity against normal HDFa cells. Based on the metabolomic analysis, 7 furano terpenoid compounds were detected in the ethanol extract, namely peronemin A_2; A_3; B_1; B_2; B_3: C_1; and D_1 along with other compounds. In conclusion, the ethanol extract of *P. canescens* leaves has cytotoxic and selective activity against A549 lung cancer cells, and potential to be further developed as an anticancer drug candidate. Peronemins and other substances like flavonoids and polyphenols may be linked to the cytotoxic properties of sungkai leaves.

Keywords: ***Peronema canescens* Jack; anticancer; UHPLC-HRMS;metabolomics; peronemins.**

Introduction

Cancer prevalence in Indonesia and around the world is still very high. In 2024, there were 20 million cancer cases with a death rate of 9.7 million. Lung cancer has the highest mortality rate at 12.4%, followed by breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%) [1]. Cancer-related deaths are expected to increase to more than 13.1 million by 2030 [2].

Cancer treatment options include surgery, radiation, chemotherapy, hormonal treatment, and biological therapy. However, conventional therapies have potential side effects, the risk of disease recurrence, and high drug resistance [3]. The use of natural products has emerged as an alternative for cancer prevention and treatment. One promising plant for anticancer development is *Peronema canescens* Jack (Sungkai). *P. canescens* has been reported to have antioxidant, antibacterial, anti-inflammatory, anticancer, and uric acid-lowering activities [4–6].

Previous studies have shown that chloroform extracts from *P. canescens* exhibited cytotoxic effects on colon cancer (HT-29) and cervical cancer (HeLa) cells, with IC_{50} values of 103.5 µg/mL and 389.1 µg/mL, respectively. The ethyl acetate extracts also showed cytotoxic effects on these cells with IC_{50} values of 486.4 and 281.9 µg/mL, respectively. Meanwhile, the ethanol extract exhibited cytotoxic effects on HT-29 cells with an IC_{50} value of 420.17 µg/mL and weaker cytotoxic effects on HeLa cells with an IC_{50} of 253.19 µg/mL [7].

While the cytotoxic activity of *P. canescens* extracts seems limited, as indicated by IC_{50} values exceeding 100 µg/mL, it remains scientifically valid to conduct further analysis with various cancer

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cell lines. The variation in cytotoxic effects across different cell types can be attributed to their distinct molecular characteristics, and the extracts might exhibit enhanced activity or selectivity in alternative models. Furthermore, crude extracts might include active compounds at low concentrations that could be separated through additional fractionation, possibly uncovering more potent constituents. The extracts may also demonstrate synergistic effects when used alongside standard treatments or show additional pharmacological properties, including anti-inflammatory or immunomodulatory activities pertinent to cancer therapy. This study utilizes A549 non-small cell lung cancer (NSCLC) cells as the target model, chosen based on a mechanism-guided rationale. Previous *in silico* investigations have highlighted various furano-terpenoids found in *P. canescens*, such as peronemin A2, A3, B1–B3, C1, and D1, as potential inhibitors of dihydrofolate reductase (DHFR) and voltage-gated potassium channels (Kv1.3). These targets are known to play significant roles in the proliferation and survival of cancer cells [4]. The expression of DHFR [8] and Kv1.3 channels [9] in A549 cells establishes them as a pertinent model for evaluating compounds that interact with these specific targets.

Despite the great potential of *P. canescens* as an anticancer agent, research on this plant remains constrained. No studies have yet examined the chemical content of sungkai leaves using a metabolomics approach. Therefore, this research aims to test the cytotoxic activity of *P. canescens* ethanol extract on A549 lung cancer cells and study its metabolomic profile.

Methods

Materials

The materials used for the preparation of the ethanol extract and metabolomics test include–sungkai leaves (*P. canescens*), 96% ethanol, methanol *p.a* (J.T. Baker), *n*-hexane *p.a.* (J.T. Baker), ethyl acetate *p.a.* (J.T. Baker), distilled water, Eppendorf tubes, anhydrous Na_2SO_4 (Supelco Merck Germany), and formic acid. The materials for the anticancer test include sodium hypochlorite (NaOCl 1%), A549 cells (ATCC), DMSO (Sigma Aldrich Merck Germany), glycerol (Merck Germany), 96-well clear polystyrene plates, Fetal Bovine Serum (Sigma), Trypsin-EDTA (Sigma), DMEM (Gibco), 1% Penicillin and Streptomycin (Meiji Indonesia), MTT (Sigma), 10% sodium dodecyl sulfate (Merck), cell culture flasks, and blue and yellow tips.

Equipment

The equipment used includes maceration tools, Biosafety Cabinet Level 2 (Thermo Scientific), CO_2 incubator (Esco), liquid nitrogen tank (U.S. Solid Cryogenics), refrigerator (Sharp), oven (Memmert), autoclave, rotary evaporator (Heidolph L400), SpeedVac (Thermo), Multimode reader (Biotek Synergy H1), centrifuge (Beckman), and UHPLC-HRMS (Thermo).

Plant Determination

Determination of *P. canescens* was carried out at the Pharmacy Biology Laboratory, Gadjah Mada University, Yogyakarta (determination letter no. 0462/S.Tb/X/2023), and the specimen was stored at the Natural Drug Development Laboratory, Department of Pharmacy, Islamic University of Indonesia, with voucher number 01/X/L.POBA/2023.

Preparation of Ethanol Extract of *P. canescens*

The *P. canescens* plant used in this study was sourced from Kiram Park, Banjar Regency, South Kalimantan. The fresh leaves, which were not damaged or infected by pests, were used. The preparation of the simplicia (dried plant material) was carried out at the Pharmacy Biology Laboratory of STIKES ISFI Banjarmasin. The sungkai leaves were dried in an oven at 40°C until a constant dry weight was achieved.

A total of 240 g of powdered *P. canescens* leaf simplicia was extracted with 96% ethanol in a 1:5 ratio, in triplicate, for 24 hours. The filtrate was concentrated using a rotary evaporator to obtain a thick extract, and the yield was calculated using the following formula:

$$\%\ Yield = \frac{Weight\ of\ extract}{Weight\ of\ powder\ (simplisia)} x\ 100\%$$

Cytotoxic Activity Test on A549 Lung Cancer Cells

A549 Cell Culture

The cells were taken out from -80°C storage and thawed using a 37°C water bath. The thawed cancer cells were transferred (1 mL) to a flask containing 65 mL of complete DMEM medium and incubated for 2–3 hours in a 5% CO_2 incubator at 37°C. A new flask was prepared with 5-6 mL of 20% complete medium, and the cells were incubated again in a 5% CO_2 incubator at 37°C. The media was changed every 2–3 days as needed.

Harvesting Cancer Cells

The cells to be harvested are those that reach ~80% confluence when observed under a microscope. The cancer cells were washed with DMEM and 1 mL of 0.25% trypsin-EDTA was added to detach the matrix adhering

to the flask. The cells were then incubated for 5 minutes in a 5% CO_2 incubator at 37°C. Next, the cells were transferred to a conical tube containing 3 mL of medium and centrifuged at 5000 rpm for 15 minutes. The pellet was resuspended in 10% complete medium, and a suspension of 10^4 cells/well was prepared in a 96-well microplate.

Preparation of Sample Dilution Series

The extract was prepared in a series of 5 dilutions using DMSO solvent. The stock solution of *P. canescens* leaf extract was made at a concentration of 200,000 µg/mL and homogenized using a vortex. The concentration series ranged from 125 to 5000 µg/mL, specifically: 125, 250, 500, 1250, and 5000 µg/mL.

Cytotoxicity Test

Five mg of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) was dissolved in 1 mL of PBS solvent and added to 9 mL of empty RPMI media in a conical tube. A 100 µL of the MTT reagent was added to each well containing cells, including the cell control and media control. The microplate was wrapped in aluminum foil and incubated for 4 hours in a 5% CO_2 incubator at 37°C to form formazan crystals. The absorbance analysis was conducted using a Multimode reader at 595 nm. The percentage of cell viability was calculated by comparing it to the cell control group. The IC_{50} value (the concentration where 50% cell growth inhibition occurs) was determined from the dose-response curve using the IC_{50} calculator (AAT Bioquest). To assess the selectivity of the *P. canescens* ethanol extract as an anticancer agent, human fibroblast cells (HDFa) were used as a normal cell control.

Metabolomics Analysis Using UHPLC-HRMS

The ethanol extract of *P. canescens* was analyzed using liquid chromatography (Thermo Scientific™ Vanquish™ UHPLC Binary Pump) and high-resolution mass spectrometry (Thermo Scientific™ Q Exactive™ Hybrid Quadrupole Orbitrap™ High-Resolution Mass Spectrometer) as per previous methods [10] with modifications. Analytical liquid chromatography was performed using a Thermo Scientific™ Accucore™ Phenyl-Hexyl column (100 mm length, 2.1 mm internal diameter, 2.6 µm particle size). The mobile phase consisted of MS-grade water with 0.1% formic acid (A) and MS-grade methanol with 0.1% formic acid (B). A gradient method was used at a flow rate of 0.3 mL/min. The mobile phase B was initially set at 5% and gradually increased to 90% over 16 minutes. The mixture was maintained at 90% for 4 minutes before returning to the initial condition (5% B) at 25 minutes. The column temperature was maintained at 40°C, and the injection volume was 2 µL. Full MS/dd-MS2 acquisition was performed in positive ion mode. The scan range was set from 67–1000 m/z with a resolution of 70,000 for full MS and 17,500 for dd-MS2, operating in positive ion mode.

Raw UHPLC/HRMS data were analyzed using MS-DIAL version 4.92 [11]. Automatic feature identification was conducted from 0.3 to 20.0 minutes to capture mass signals ranging from 100 to 1500 Da in positive mode. Peak detection was set to an amplitude of minimum peak height 10^6 to remove the baseline. MS1 and MS2 tolerances were set at 0.01 and 0.04 Da, respectively, in centroid mode. Peak lists were then transferred to Microsoft Excel. The molecular formulas and structural features were determined using MS-FINDER-RIKEN PRIMe version 3.60 [12,13], utilizing databases like UNDP, KNApSAcK, NANPDB, DrugBank, FooDB, and PlantCyc.

Statistical Analysis

All measurements were performed in triplicate. Statistical analysis was carried out using one-way analysis of variance (ANOVA) with Graph-Pad Prism ver 9 software. The UHPLC-HRMS data were analyzed descriptively, and putative structures were matched with the database from the Thermo database and SciFinder.

Result and Discussion

The ethanol extract of *P. canescens* was obtained as a thick, dark brown liquid with a yield of 15.84%. The ethanol solvent used in this study has semi-polar properties and aims to extract both polar and non-polar compounds from the *P. canescens* plant. This study selected 95% ethanol instead of 70% ethanol to enhance the extraction of semi-polar and less polar bioactive chemicals from P. canescens, which are expected to encompass cytotoxic elements such as alkaloids, flavonoids, and terpenoids. Although 70% ethanol is more effective for extracting highly polar chemicals, it may simultaneously co-extract undesirable substances such as sugars or tannins. The reduced water content in 95% ethanol enhances the efficiency of concentration and drying of the extract, rendering it more appropriates for subsequent biological testing, including cytotoxicity studies [14].

The viability test results shown in Table 1 illustrate the cytotoxic effects of the ethanol extract on A549 lung cancer cells and HDFa (normal human dermal fibroblast) cells across a concentration range of 12.5 to 500 ppm. The extract demonstrated a significant cytotoxic

Table 1. Viability of A549 and HDFa cells.

Concentration (ppm)	A549 cells		HDFa cells	
	% Cell viability	% Inhibition	% Cell viability	% Inhibition
500	2.15±1.47	97.85±1.47	86.96±1.51	13.04±1.51
250	15.14±1.67	84.86±1.67	95.94±1.41	4.06±1.41
125	32.46±1.70	67.54±1.70	95.98±1.63	4.02±1.63
50	87.84±0.33	13.03±1.26	99.65±2.59	0.35±2.59
25	89.28±1.18	11.02±0.73	99.94±0.07	0.06±0.07
12.5	90.82±1.64	9.18±1.64	99.94±0.03	0.06±0.03

effect on A549 cells in a dose-dependent manner. At the highest concentration of 500 ppm, the viability of A549 cells decreased significantly to 2.15±1.47%, indicating a substantial inhibition rate of 97.85±1.47%. As the concentration decreased, cell viability increased while inhibition decreased, resulting in 90.82±1.64% viability and only 9.18±1.64% inhibition observed at 12.5 ppm (Table 1).

The extract demonstrated minimal cytotoxic effects on HDFa normal cells across all tested concentrations (Table 2). At 500 ppm, cell viability was relatively high at 86.96±1.51%, showing only 13.04±1.51% inhibition. At concentrations of 125 ppm and lower, cell viability remained above 95%, with inhibition values under 5%, demonstrating exceptional cell tolerance. The results indicate that the extract selectively inhibits the growth of A549 cancer cells while showing minimal toxicity to normal HDFa cells, highlighting its potential as a selective anticancer agent.

MTT test showed *P. canescens* had an IC_{50} of 105.21 µg/mL (low toxicity) against A549 lung cancer cells (Table 2). Meanwhile, doxorubicin, a positive control, had an IC_{50} of 76.2 µg/mL. The cytotoxic activity observed in this study differs from previous studies on the anticancer activity of the ethanol extract against colon cancer cells (HT-29) and cervical cancer cells (HeLa) [15]. This difference is due to the variation in cancer cell types and the source of plant material used [16].

In addition to cytotoxic activity, the selectivity of the ethanol extract on cancer cells is crucial, as measured by the selectivity index (SI). Samples with an SI ≥ 2 indicate high selectivity against cancer cells without toxicity to normal cells, making them potential candidates for further development. Doxorubicin had an SI of 0.11 on HDFa fibroblast cells, indicating a high level of toxicity. Previous studies reported the cardiotoxicity of doxorubicin due to its impact on fibroblast cells, resulting in cardiomyopathy [17,18]. The ethanol extract of *P. canescens* showed negligible cytotoxic activity against normal HDFa fibroblast cells, making it a promising candidate for further development as a lung cancer drug.

UHPLC-HRMS analysis was performed at the Advanced Characterization Laboratory–BRIN, Gunung Kidul, Yogyakarta. The UHPLC-HRMS positive ion mode analysis of the *P. canescens* ethanol extract detected 426 peaks. In an LC-MS chromatogram, a single peak is typically assumed to correspond to one compound, especially when the peak is sharp, symmetrical, and accompanied by a prominent m/z signal in the mass spectrum. Nevertheless, this assumption is not consistently correct, particularly when baseline separation has not been attained. In this study, mass spectral analysis of each peak can effectively distinguish overlapping compounds by examining their unique m/z values. Using

Table 2. Cytotoxic activity ad Selectivity Index (SI) of ethanol extract of *P. canescens*.

Sample	Parameter	IC_{50} (µg/mL)	
		Sel A549	Sel HDFa
Ethanol extract	IC_{50} (µg/mL)	105.22	2.43×10^{36}
	SI	≥2	-
Doxorubicin	IC_{50} (µg/mL)	76.20	8.05
	SI	0.11	-

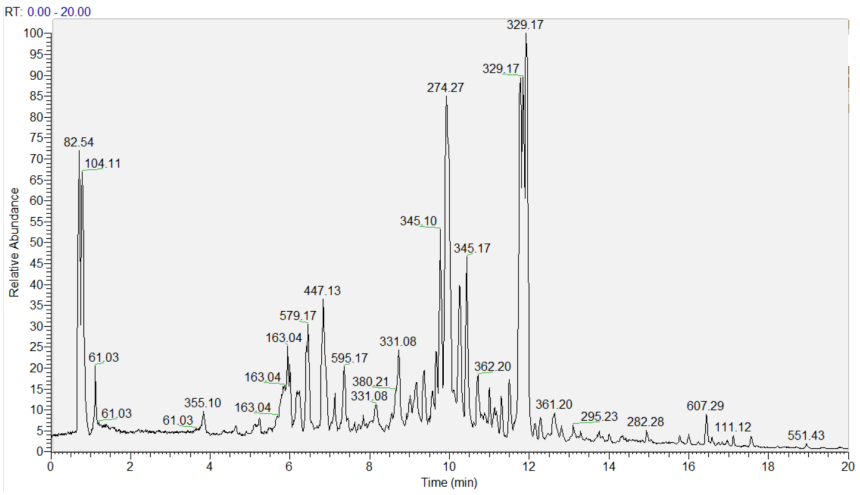

Figure 1. Chromatogram UHPLC-HRMS (positive ionization) of ethanol extract of *P. canescens* displays a diverse chemical profile with peaks eluting between 0–20 minutes and molecular weight range between 100−1500 Da. The x-axis represents retention time (RT) in minutes, while the y-axis shows the relative abundance of ion signals, indicating the intensity of detected compounds. The number in each peak of chromatogram shows mass to charge ratio (m/z) of the dominants compounds.

a high-resolution mass spectrometry, peak deconvolution and enhanced chromatographic techniques with MS-DIAL helped precise identification. The large number of compounds detected reflects the chemical diversity of *P. canescens*, which holds potential for further exploration. The base peak chromatogram of the UHPLC-HRMS analysis is shown in Figure 1.

Among the 426 peaks, fifteen dominant compounds were identified in this study (Table 3), some of which were reported in previous studies [4,19,20]. The identified compounds were further analyzed by comparing the obtained data with the SciFinder database, looking for similarities in m/z values for each marker compound. Seven major furano terpenoid compounds were detected in the ethanol extract, namely peronemin A2, A3, B1, B2, B3, C1, and D1 (Figure 2). Peronemin B1, B3, and A3 had observed m/z values of 329.1747 and a Δ mass error of 0.103289 ppm. Additionally, peronemin B2, A2, C1, and

Table 3. Metabolomic profiles of *P. canescens* ethanol extract.

Compound	Formula	RT (mnt)	Observed m/z	Theoretical m/z	A mass error (ppm)
4-hydroxycoumarin	$C_9H_6O_3$	6.134	163.0391	163.0389	0.85
Caffeic acid	$C_9H_8O_4$	5.994	181.0496	181.0495	0.63
D-(-)-Quinic acid	$C_7H_{12}O_6$	0.824	193.0713	193.0706	3.28
Apigenin	$C_{15}H_{10}O_5$	8.502	271.0605	271.0601	1.77
Physicon	$C_{16}H_{12}O_5$	6.812	285.0758	285.0757	0.21
Chrysoeriol	$C_{16}H_{12}O_5$	7.356	301.0705	301.0706	0.45
Quercetin	$C_{15}H_{10}O_7$	5.747	303.0500	303.0499	0.30
Isorhamnetin	$C_{16}H_{12}O_7$	7.118	317.0656	317.0655	0.09
Peronemin A_1; Peronemin B_1; Peronemin B_2	$C_{20}H_{12}O_6$	11.706	329.1747	329.1747	0.10
Quercetin dimethyl ether	$C_{17}H_{14}O_7$	8.728	331.0809	331.0812	0.81
NP-003294	$C_{18}H_{16}O_7$	9.761	345.0968	345.0968	0.22
Peronemin B_3; Peronemin C_1; Peronemin D_1	$C_{20}H_{24}O_5$	10.435 11.76	345.1696	345.1696	0.08

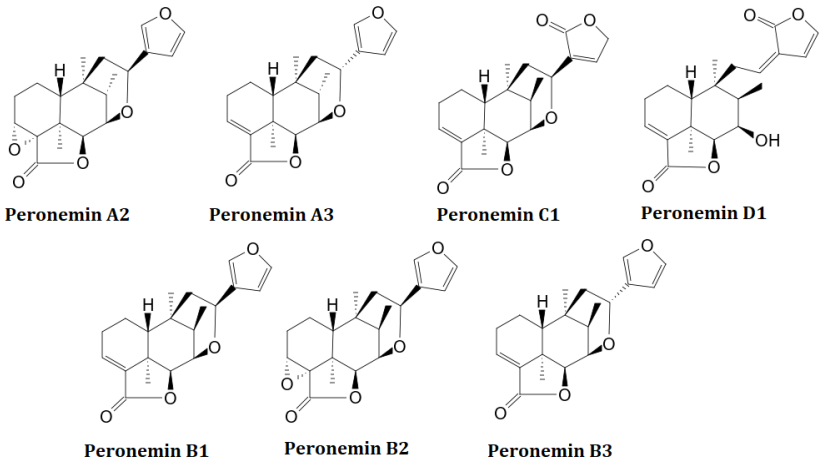

Figure 2. Chemical structures of Peronemins from *P. canescens* (Scifinder).

D1 were detected with observed m/z values of 345.1696 and a Δ mass error of 0.086914 ppm. These findings achieved small Δ mass error values, indicating a minimal difference between observed and theoretical m/z values [13,21].

Peronemin compounds have been reported as anticancer agents through *in silico* modeling, with a dihydrofolate reductase inhibitor (DHFR inhibitor) approach [4]. Peronemin A2, A3, B1, B2, and B3 exhibit anticancer activity by targeting the voltage-gated K channel subunit proteins, while Peronemin C1 and D1 target the dihydrofolate reductase protein.

The voltage-gated K (Kv1.3) channel is an integral membrane protein that is selectively permeable to potassium ions and is expressed in the nuclei of cancer cells, such as A549 lung cancer cells. The Kv1.3 channel is also expressed in various human cells, including B and T cells, fibroblasts, macrophages, osteoclasts, lungs, thymus, lymph nodes, and testes [9]. Kv1.3 activity plays an important role in cell proliferation and apoptosis. Meanwhile, DHFR catalyzes the reduction of dihydrofolate to tetrahydrofolate using NADPH and is involved in synthesizing raw materials for cell proliferation in both prokaryotic and eukaryotic cells [8].

The presence of peronemins in the ethanol extract likely contributes to its anticancer activity in A549 lung cancer cells. Other detected compounds, such as caffeic acid, apigenin, and quercetin, are well-studied compounds known to possess antioxidant and anticancer activities [22–25]. These compounds may act synergistically with peronemins in exerting anticancer effects on A549 lung cancer cells.

Conclusion

The ethanol extract of *P. canescens* leaves exhibited cytotoxic activity against A549 lung cancer cells with negligible toxicity on normal HDFa fibroblast cells. This cytotoxic activity is likely due to the presence of furano terpenoid compounds, including peronemins B2, A2, A3, B1, B2, B3, C1, and D1, along with other compounds like caffeic acid, apigenin, and quercetin, which are known antioxidants. Further research is needed to isolate the active compounds from *P. canescens* and test them on lung cancer cells to validate their potential as new anticancer agents.

Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article.

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