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AL-KAUNIYAH JOURNAL TEMPLATE

# EFIKASI EKSTRAK BIJI SALAK DAN KULIT JERUK PAMELO TERHADAP APOPTOSIS DAN PROLIFERASI SEL HeLa

## EFFIFACY OF SALAK SEED AND POMELO PEEL EXTRACTS ON HeLa CELL APOPTOSIS AND PROLIFERATION

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**Abstract**

Pengembangan terapi adjuvan bertujuan untuk mengurangi kekambuhan kanker dan meminimalkan efek samping obat. Biji salak dan kulit jeruk bali mengandung senyawa bioaktif seperti terpenoid, flavonoid, likopen, dan polifenol, sehingga berpotensi menjadi kandidat terapi adjuvan. Penelitian ini mengevaluasi efek ekstrak biji salak pondoh dan kulit jeruk bali, baik secara tunggal maupun kombinasi, terhadap sel kanker serviks (HeLa). Ekstrak diuji dengan perbandingan 1:3 (1S3J), 1:1 (1S1J), dan 3:1 (3S1J). Analisis in silico menunjukkan afinitas ikatan yang kuat terhadap COX-2 (antiinflamasi), Caspase-3 (apoptosis), dan PI3K (proliferasi). Uji in vitro memperlihatkan bahwa semua perlakuan mampu menurunkan viabilitas sel HeLa. Kombinasi 1S1J menunjukkan efek antiinflamasi yang lebih baik, menghambat migrasi dan proliferasi sel, mengurangi nekrosis, serta meningkatkan apoptosis dibandingkan perlakuan lainnya. Temuan ini menunjukkan bahwa kombinasi ekstrak, khususnya dengan perbandingan 1:1, lebih efektif dibandingkan ekstrak tunggal karena adanya kerja sinergis senyawa bioaktif, menjadikan kombinasi 1S1J sebagai kandidat yang menjanjikan untuk terapi adjuvan kanker serviks.

**Kata kunci**: Antiinflamasi; Antiproliferasi; Biji salak pondoh; Induksi apoptosis; Kulit jeruk pamelo

***Abstract***

*The development of adjuvant therapies aims to reduce cancer recurrence and minimize drug side effects. Salak seeds and pomelo peel contain bioactive compounds such as terpenoids, flavonoids, lycopene, and polyphenols, making them potential candidates for such therapies. This study examines the effects of Salak pondoh seed and pomelo peel extracts, individually and in combination, on cervical cancer (HeLa) cells. Extracts were tested in ratios of 1:3 (1S3J), 1:1 (1S1J), and 3:1 (3S1J). In silico analysis revealed strong binding affinities to COX-2 (anti-inflammatory), Caspase-3 (apoptosis), and PI3K (proliferation). In vitro tests showed all treatments reduced HeLa cell viability. The 1S1J combination showed superior anti-inflammatory effects, inhibited cell migration and proliferation, reduced necrosis, and increased apoptosis compared to other treatments. These findings suggest that the combination extracts, especially the 1:1 ratio, perform better than single extracts due to the synergistic action of bioactive compounds, making the 1S1J combination a promising candidate for adjuvant therapy in cervical cancer.*

***Keywords**: Anti-inflammation; Antiproliferation; Apoptosis induction; Salacca zalacca seeds; Pomelo peel*

## INTRODUCTION

Cervical cancer is a serious disease requiring special attention in Indonesia. It is the second most common cancer and ranks third in cancer-related mortality in Indonesia (Khairunnisa *et al*., 2022). Currently, surgery is the primary treatment for cervical cancer, but it has limitations. Recurrence has been reported in 40% of patients following surgery. Adjuvant therapies can help reduce recurrence rates, one example being doxorubicin. However, high doses of doxorubicin cause systemic toxicity, while low doses risk inducing cancer cell resistance. Therefore, developing more effective adjuvant therapies is essential to minimize side effects, eliminate residual cancer cells, and reduce the risk of recurrence after primary treatment.

The exploration of natural products as adjuvant agents in cancer therapy is increasingly recognized. Natural compounds are known to contain bioactive substances with cytotoxic properties that typically exhibit fewer side effects compared to conventional pharmaceuticals (Yanto & Sulistianingsih, 2017). Salak Pondoh (*Salacca zalacca* (Gaertn.) Voss) seeds and Pomelo (*Citrus maxima* (Burm.) Merr.) peel show considerable potential as natural therapeutic agents against cervical cancer. Research conducted by Purwanto *et al*. (2015) identified that Salak Pondoh seeds are rich in polyphenols, alkaloids, and terpenoids, which are associated with antioxidant and cytotoxic activities. Similarly, Pomelo peel contains flavonoids and lycopene, which have been shown to induce apoptosis in cancer cells (Suryanita *et al*., 2019). Consequently, Salak Pondoh seeds may function as antioxidants and anti-inflammatory agents, while Pomelo peel demonstrates cytotoxic effects against cervical cancer cells. This evidence supports the potential application of these natural products as effective adjuvants in cervical cancer treatment, providing a promising alternative with reduced side effects compared to standard chemotherapy regimens.

The utilization of salak seeds and pomelo peels as research materials for sustainable practices is particularly relevant, given the significant annual increase in the production and consumption of these fruits globally (Tantrayana & Zubaidah, 2015; Aji *et al*., 2017). As consumption rises, organic waste, including salak seeds and pomelo peels, becomes a pressing issue, with a large portion of the pomelo fruit discarded and salak seeds often treated as waste. Their utilization supports global zero waste initiatives aimed at reducing organic waste. Moreover, this research is novel, as no studies have investigated the synergistic effects of salak seed extract and pomelo peel extract on enhancing anti-cancer efficacy. By examining mechanisms such as anti-inflammatory effects, cytotoxicity, apoptosis induction, and cancer cell antiproliferation, this study could significantly contribute to developing more effective and environmentally friendly therapies for cervical cancer.

## MATERIALS AND METHODS

### Location and Time

The study was conducted from April 1 to July 31, 2024, at the Biochemistry Laboratory of the Faculty of Biology, Universitas Gadjah Mada (UGM) for the extraction of pomelo peel and salak seeds. In vitro assays (MTT assay, anti-inflammatory tests, apoptosis tests, and migration proliferation tests) were performed at the Parasitology Laboratory of the Faculty of Medicine, Public Health, and Nursing. Gas chromatography-mass spectrometry (GC-MS) analysis was conducted at the Integrated Research and Testing Laboratory (LPPT) of UGM.

### Equipment

The equipment used included a maceration chamber, rotary evaporator, mill, maceration vessel, a complete set of glassware, oven, magnetic stirrer, pH meter, centrifuge, mortar, pestle, dropper pipette, GC-MS instrument, 5% CO2 incubator, ImageJ software, microplate reader, BD FACSCalibur™ flow cytometer (California, USA), 96-well plates, micropipettes (10, 100, and 1000 µL), blue tips, red tips, yellow tips, UV/Vis spectrophotometer, and light microscope.

### Materials

The materials used included salak seeds and pomelo peel, 70% ethanol, 96% ethanol, albumin, sodium diclofenac, phosphate-buffered saline (PBS), HeLa cells, Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), streptomycin, dimethyl sulfoxide (DMSO), MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), 10% SDS, FITC

Annexin V Apoptosis Detection Kit with PI (Biolegend, USA), 4% paraformaldehyde, Tris-buffered saline, concentrated HCl, magnesium ribbon (Mg), and Mayer's hematoxylin.

**Collection, Plant Determination, and Sample Preparation of *Salak Pondoh* Seeds and Pomelo Peel**

The *Salak pondoh* seed samples were obtained from small businesses (UMKM) in Sleman Regency, Yogyakarta Special Region, while the pomelo peel samples were collected from UMKM in Sukoharjo Regency, Central Java Province. The seeds and peels were selected from ripe fruits, with dark brown *Salak* seeds and greenish-yellow pomelo peels. Plant species determination was conducted by a botanist at the Plant Systematics Laboratory, Faculty of Biology, Universitas Gadjah Mada (UGM), to confirm the species used in the research. Sample preparation began with the weighing and thorough washing of *Salak* seeds and pomelo peels, followed by cutting them into smaller pieces. The samples were then dried and ground into a fine powder.

**The Extraction of Salak pondoh seed**

The extraction of *Salak pondoh* seeds was performed using the maceration method according to Nurihardiyanti et al. (2015). A total of 300 g of seed powder was soaked in 96% ethanol. The mixture was periodically stirred over two days, followed by remaceration with 96% ethanol. After combining the resulting macerates, the solvent was evaporated to obtain a concentrated extract, and the yield was calculated.

**The Extraction of Pomelo peel**

The extraction of pomelo peel was carried out using the maceration method according to Wenas *et al*. (2021). A total of 250 g of pomelo peel powder was macerated with 70% ethanol. The sample was periodically stirred over two days, followed by remaceration with 70% ethanol. The ethanol extract was then evaporated using a rotary evaporator to obtain a concentrated extract, and the yield was calculated.

**Preparation of Combined Extracts of *Salak Pondoh* Seeds and Pomelo Peel**

The ratios of the combined extracts of *Salak pondoh* seeds and pomelo peel in this study were S=4:0, J=0:4, 1S3J=1:3, 1S1J=1:1, and 3S1J=3. The extracts were prepared at a concentration of 1000 ppm using DMSO as the solvent, according to the respective combination ratios. The mixtures were then stirred and homogenized using a centrifuge. The method for preparing the combined extracts was based on the protocol established by Noviardi *et al*. (2019).

**Analysis of Phytochemical Profiles and In Silico Testing**

Qualitative detection of flavonoids was performed using the Wilstatter test, while the phytochemical profile was analyzed using Gas Chromatography-Mass Spectrometry (GC-MS). Subsequently, the detected compounds were tested in silico using molecular docking methods against target proteins (Handoyo *et al*., 2022).

**Anti-inflammatory Test**

The anti-inflammatory effects were assessed using the denaturation method of BSA (bovine serum albumin). Albumin was mixed with TBS (tris-buffered saline) and the sample extract. Diclofenac sodium was used as a positive control. Absorbance readings were taken at a wavelength of 660 nm using a UV/Vis spectrophotometer. The data obtained were calculated using the percentage inhibition formula for protein denaturation as an indicator of effectiveness (Madhuranga & Samarakoon, 2023).

**Preparation and Culture of HeLa Cells**

HeLa cell stocks were placed in a dish containing DMEM medium supplemented with 10% FBS (fetal bovine serum) and streptomycin. The cell culture was incubated at 37°C with 5% $CO_2$ humidity. Once the cells entered the logarithmic phase, they were harvested and transferred to a 96-well plate at a density of $2 \times 10^3$ cells per well (Bai et al., 2021). The cells were divided into seven treatment groups: a control group with 0.1% DMSO medium, a positive control with doxorubicin, and five treatment groups with sample extracts S, J, 1S3J, 1S1J, and 3S1J, each diluted to concentrations of 500, 250, 125, 62.5, and 31.25 $\mu$g/mL, respectively. Each treatment group was incubated for 48 hours.

**Cytotoxicity Test**

Cytotoxicity and antiproliferation were assessed using the MTT assay. After post-treatment incubation, the test solution was discarded, and the wells were rinsed with PBS (phosphate-buffered saline). Culture medium and 10 $\mu$L of 5 mg/mL MTT solution were added to each well, followed by incubation for an additional 4 hours. Living cells would be observed as purple. Subsequently, 10% SDS (sodium dodecyl sulfate) was added. Absorbance was measured using a microplate reader at a wavelength of 595 nm to obtain cell viability data and IC50 values (Wijayanti *et al*., 2015).

**HeLa Cell Proliferation Inhibition Test**

The inhibition of proliferation was assessed using the scratch wound healing assay method. After 24 hours of cell incubation, a scratch was made on the bottom of the wells. Cells were treated and observed at 0, 12, 24, and 36 hours. The area of the scratch was measured and documented. Scratch area analysis was performed using ImageJ software, and the percentage closure was calculated using an appropriate formula (Bai *et al*., 2021).

**Apoptosis Test**

The apoptosis test was conducted using flow cytometry analysis with the FITC Annexin V Apoptosis Detection Kit with PI, following the kit's procedures. The stained cells were analyzed using a BD FACScalibur™ flow cytometer, allowing for the determination of the percentage of apoptotic cells as an indicator of effectiveness (Bai *et al*., 2021).

**Data Analysis Method**

Qualitative data analysis was performed descriptively. Quantitative data analysis was conducted using ANOVA and Principal Component Analysis (PCA) with Minitab software, applying multivariate data analysis techniques.

## RESULTS (12 pt)

**Extraction of Salak Pondoh Seeds and Pomelo Peel**

The powder from the salak seeds that underwent maceration and evaporation yielded 5.15 g of concentrated extract, resulting in a yield of 1.1%. Meanwhile, the pomelo peel powder, after maceration and evaporation, produced 15.68 g of concentrated extract, corresponding to a yield of 3.2%.

**Phytochemical Compounds in Salak Pondoh Seed and Pomelo Peel Extracts**

**Table 1.** Detection of flavonoids in the extracts

| Sample | Color | Flavonoid |
|---|---|---|
| Salak Pondoh Seed | Yellowish clear | - |
| Pomelo Peel | Dark red | + |

Table 1 shows that the pomelo peel extract contains flavonoid compounds, indicated by a color change to dark red. In contrast, the salak pondoh seed extract does not contain flavonoid compounds, as no color change was observed.

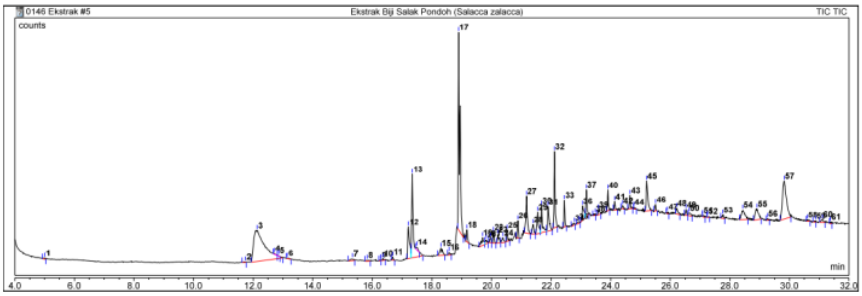


**Figure 1.** Total ion chromatogram (TIC) of salak pondoh seed extract

In Figure 1, there are 61 peaks representing 15 compounds in the salak pondoh seed extract.

**Table 2.** Phytochemical compounds in salak pondoh seed extract

| *Peak* | *Retention Time* | *% Peak Area* | **Compound name** |
|---|---|---|---|
| 1 | 5.01 | 0.07 | *9-Octadecenoic acid, (2-phenyl-1,3-dioxolan-4-yl) methyl ester* |
| 31 | 21.90 | 2.18 | *Ethyl iso-allocholate* |
| 3 | 12.13 | 20.17 | *Lactose* |
| 6 | 13.15 | 0.11 | *2-Myristynoyl pantetheine* |
| 11 | 16.69 | 0.19 | *Cyclopropanebutanoic acid, 2-[[2-[[2-[(2-pentylcyclopropyl)methyl]cyclopropyl]methyl]cyclopropyl]methyl]-, methyl ester* |
| 12 | 17.21 | 3.36 | *n-Hexadecanoic acid* |
| 19 | 19.70 | 1.05 | *Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester* |
| 13 | 17.34 | 8.14 | *Hexadecanoic acid, ethyl ester* |
| 30 | 21.68 | 2.18 | *7-Methyl-Z-tetradecen-1-ol acetate* |
| 17 | 18.90 | 17.05 | *9,12-Octadecadienoic acid, ethyl ester* |
| 18 | 19.17 | 0.77 | *Eicosanoic acid* |
| 20 | 19.82 | 0.38 | *Cinnamic acid, 4-hydroxy-3-methoxy-, (5-hydroxy-2-hydroxymethyl-6-[2-(4-hydroxy-3-methoxyphenyl)ethoxy]-4-(6-methyl-3,4,5-trihydroxytetrahydropyran-2-yloxy)tetrahydropyran-3-yl) ester* |
| 57 | 29.82 | 8.83 | *Sitosterol* |
| 27 | 21.18 | 3.27 | *9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester* |
| 32 | 22.11 | 4.53 | *Diisooctyl pthalate* |

Based on the results presented in Table 2, the peak area with the highest percentage is lactose (20.07%), followed by 9,12-Octadecadienoic acid, ethyl ester (17.05%), and hexadecanoic acid, ethyl ester (8.14%). Additionally, compounds such as 9-octadecenoic acid, methyl ester, sitosterol, and cinnamic acid were also identified, which possess antioxidant and anti-inflammatory properties.

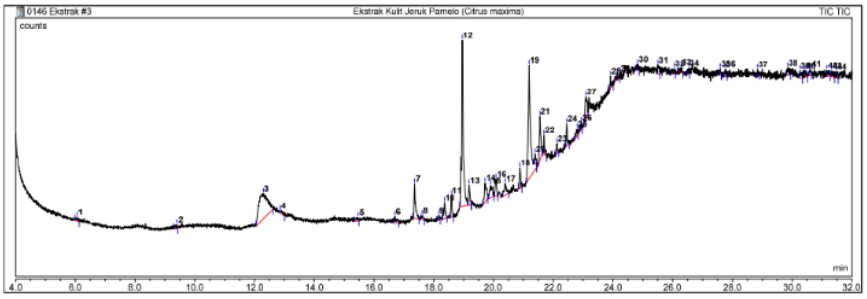


**Figure 2. Total ion chromatogram (TIC) of pomelo peel extract**

Figure 2 shows 44 peaks representing 15 compounds in the pomelo peel extract.

**Table 3.** Phytochemical compounds in pomelo peel extract

| *Peak* | *Retention Time* | *% Peak Area* | **Compound name** |
|---|---|---|---|
| 1 | 6.05 | 0.49 | *[1,1'-Bicyclopropyl]-2-octanoic acid, 2'-hexyl-, methyl ester* |
| 2 | 9.40 | 0.51 | *2-Myristynoyl pantetheine* |
| 3 | 12.29 | 15.84 | *Melezitose* |
| 27 | 23.09 | 3.27 | *Ethyl iso-allocholate* |
| 7 | 17.36 | 3.55 | *Hexadecanoic acid, ethyl ester* |
| 10 | 18.36 | 1.68 | *11-Octadecenoic acid, methyl ester* |
| 11 | 18.59 | 1.64 | *Cyclopropanebutanoic acid, 2-[[2-[[2-[(2-pentylcyclopropyl)methyl] cyclopropyl]methyl]cyclopropyl]methyl], methyl ester* |
| 12 | 18.96 | 18.89 | *(E)-9-Octadecenoic acid ethyl ester* |
| 14 | 19.72 | 2.75 | *Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester* |
| 15 | 19.90 | 2.23 | *Propanoic acid, 2-methyl-, (dodecahydro-6a-hydroxy-9a-methyl* |
| 18 | 20.89 | 1.49 | *7-Methyl-Z-tetradecen-1-ol acetate* |
| 19 | 21.19 | 17.82 | *9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester* |
| 21 | 21.55 | 4.17 | *Glycidyl oleate* |
| 34 | 26.55 | 0.49 | *Hexadecanoic acid, 1a,2,5,5a,6,9,10,10a-octahydro-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1H-2,6a-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl ester* |
| 38 | 29.85 | 1.19 | *3-Pyridinecarboxylic acid, 2,7,10-tris(acetyloxy)-1,1a,2,3,4,6,7,10,11,11a-decahydro-1,1,3,6,9-pentamethyl-4-oxo-4a,7a-epoxy-5H-cyclopenta[a]cyclopropa[f]cycloundecen-11-yl ester* |

According to Table 3, the most dominant compound in the pomelo peel extract is (E)-9-octadecenoic acid ethyl ester (18.89%), followed by 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester (17.82%), and melezitose (15.84%). Additionally, the pomelo peel extract contains propanoic acid, methyl ester, and ethyl iso-allocholate, which have potential as anticancer agents.

**Molecular Docking Assay**

**Table 4.** Results of molecular docking for salak pondoh seed extract

| Compound (Ligan) | Group of compound | Target protein | Native Ligan | Binding Affinity (kcal/mol) | | Amino-acid residues |
|---|---|---|---|---|---|---|
| | | | | Native Ligan | Ligan | |
| *cinnamic acid* | Asam Lemak | 5KIR (COX-2) | COH | -9,5 | -9,4 | SER 146, GLU 140, LEU 238, ASN 144, ARG 242 |
| Sitosterol | Fitosterol | 5KIR (COX-2) | COH | -9,5 | -8,4 | ARG 61, ARG 44, THR 62, LYS 546, ASP 125, HIS 122, PRO 542, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | ALA 543 |
| | | 3GJQ (Caspase-3) | *Peptide Inhibitor* | -6,5 | -7,2 | LYS 137, GLY 125, GLU 124, ARG 164, PRO 201, TYR 197 |
| | | 5ITD (PI3K) | 6CY | -7,3 | -6,7 | SER 774, MET 772, SER 919, ILE 932, THR 856, MET 922, GLN 859, TRP 780 |
| *9-octadecenoic acid, methyl ester* | Asam Lemak | 5KIR (COX-2) | COH | -9,5 | -8,1 | SER 353, LEU 531, TRY 355, LEU 359, VAL 349 |
| | | 3GJQ (Caspase-3) | *Peptide Inhibitor* | -6,5 | -6,4 | VAL 266, PRO 201, TYR 197 |
| | | 5ITD (PI3K) | 6CY | -7,3 | -6,7 | ILE 800, TRP 780, MET 772 |

The extract of Salak Pondoh seeds shows potential anti-inflammatory effects and the ability to induce apoptosis. The anti-inflammatory effect on the target protein COX-2 is indicated by the compound cinnamic acid, which exhibits a ligand binding affinity comparable to that of the native ligand for COX-2. Meanwhile, the induction of apoptosis in caspase-3 is demonstrated by the compounds sitosterol and 9-octadecenoic acid, methyl ester, which have binding affinities that are below or close to that of their native ligands.

**Table 5.** Results of molecular docking for pomelo peel extract

| Compound (Ligan) | Group of compound | Target protein | Native Ligan | Binding Affinity (kcal/mol) | | Amino-acid residues |
|---|---|---|---|---|---|---|
| | | | | *Native Ligan* | Ligan | |
| *Ethyl iso-allocholate* | Steroid | 5KIR (COX-2) | COH | -9,5 | -7,0 | PRO542, HIS 122, SER 126, TYR 373, GLN 372, GLN 370, PHE 367, ARG 61 |
| | | 3GJQ (Caspase-3) | *Peptide Inhibitor* | -6,5 | -8,6 | VAL 266, MET 268, LYS 137, TYR 195, LEU 136, THR 140, TYR 197, GLY 125, PRO 201, GLU 124, ARG 164 |
| | | 5ITD (PI3K) | 6CY | -7,3 | -7,0 | ASP 933, ILE 932, THR 856, MET 922, TRP 780, MET 772, ILE 800 |
| *Propanoic acid, methyl ester* | Asam Lemak | 5KIR (COX-2) | COH | -9,5 | -7,2 | SER 143, LEU 224, LEU 145, SER 146, ASN 144, GLU 236, LEU 238, THR 237 |
| | | 3GJQ (Caspase-3) | *Peptide Inhibitor* | -6,5 | -8,1 | VAL 266, TYR 197, GLY 125, PRO 201, GLU 124, ARG 164, CYS 264 |
| | | 5ITD (PI3K) | 6CY | -7,3 | -7,8 | MET 772, LYS 802, ASP 933,PHE 934, ASP 810, LEU 807, ILE 932, TYR 836, ILE 800, ILE 932 |
| Hesperidin | Flavonoid | 3GJQ (Caspase-3) | *Peptide Inhibitor* | -6,5 | -9,4 | Pro201, Arg164, Val266, Arg164, Tyr197, Glu124 |

The extract of pomelo peel is capable of inducing apoptosis and exhibiting antiproliferative effects. The ability to induce apoptosis in caspase-3 is demonstrated by the compounds ethyl iso-allocholate and hesperidin, which show a better binding affinity compared to their native ligands.

Additionally, the compound propanoic acid, methyl ester can induce apoptosis and has antiproliferative effects on PI3K.

**Antiinflammation test**

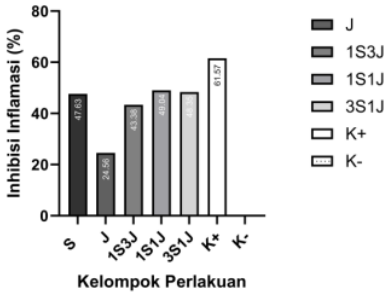


**Figure 3.** Percentage of inhibition of inflammation

*Note: S = salak pondoh seed extract, J = pomelo peel extract, 1S1J = 1:1 combination, 3S1J = 3:1 combination, K+ = positive control, K- = negative control.*

The highest percentage of inflammation inhibition is demonstrated by the positive control (doxorubicin) at 61.57%, followed by the 1S1J combination extract (49.04%) and the single salak pondoh seed extract (47.63%). The lowest percentage is observed in the single pomelo peel extract (24.56%).

**Viability test**

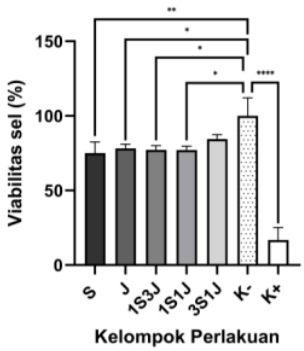


**Figure 4.** Cell viability percentage

*Note: S = salak pondoh seed extract, J = pomelo peel extract, 1S1J = 1:1 combination, 3S1J = 3:1 combination, K+ = positive control, K- = negative control.*

The IC50 value for the positive control (doxorubicin) is 6.063 µg/mL, while the IC50 value for the negative control (medium only) is 1505.65 µg/mL. The IC50 values for the extracts are as follows: 762.47 µg/mL for S, 1015.42 µg/mL for J, 864.59 µg/mL for 1S1J, and 922.68 µg/mL for 1S3J. Based on these IC50 values, the treatments S, 1S3J, and 1S1J are classified as having moderate cytotoxicity.

**Apoptosis test**

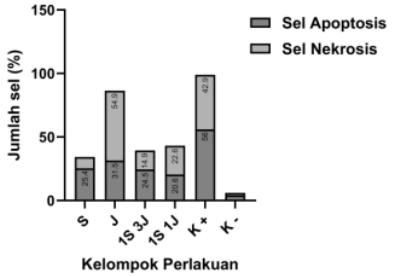


**Figure 5.** Percentage of cells undergoing apoptosis and necrosis
*Note: S = salak pondoh seed extract, J = pomelo peel extract, 1S1J = 1:1 combination, 3S1J = 3:1 combination, K+ = positive control, K- = negative control.*

Figure 5 illustrates that each treatment successfully induced apoptosis. The treatment with pomelo peel extract exhibited the highest percentage of cell death due to apoptosis and necrosis, at 31.5% and 54.9%, respectively. Additionally, the combination extracts demonstrated a decrease in the percentage of necrosis while still inducing apoptosis.

**Proliferation test**

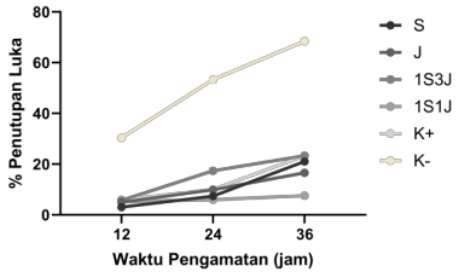


**Figure 6.** Percentage of wound closure in hela cell culture medium
*Note: S = salak pondoh seed extract, J = pomelo peel extract, 1S1J = 1:1 combination, 3S1J = 3:1 combination, K+ = positive control, K- = negative control.*

According to Figure 6, each treatment group was able to inhibit wound closure. Overall, the combination of salak pondoh seed extract and pomelo peel extract was more effective in hindering wound closure compared to the positive control (doxorubicin), although the difference was not statistically significant. This wound closure capability reflects the rate of cell proliferation; thus, a slower wound closure indicates that the treatment effectively inhibits cancer cell proliferation. The 1S1J treatment represents the optimal combination and shows potential as an antiproliferative agent for HeLa cells.

***Principal Componet Analiysis* (PCA)**

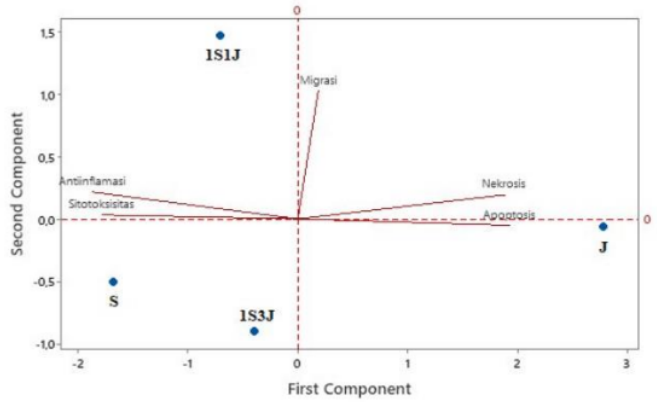


**Figure 7.** The Principle component (PC) in PCA analysis

The PCA results indicate that the 1S1J treatment is the most effective, showing the closest alignment with the evaluated indicators, especially in the anti-inflammatory, cytotoxicity, and migration assays.

## DISCUSSION

### Phytochemical Composition of Salak Pondoh Seed Extract and Pamelo Peel.

In this study, it was found that pomelo peel extract contains flavonoids, whereas no flavonoids were detected in *Salak pondoh* seed extract. Flavonoids are known to have anticancer properties. This is supported by Priani *et al*. (2021), who reported that pomelo peel contains the flavonoid hesperidin. Hesperidin is a bioactive compound believed to have potential as an anticancer agent, as it can induce cell death through apoptosis and autophagy in cancer cells. In this study, GC-MS analysis of *Salak pondoh* seed extract revealed the presence of 9-octadecenoic acid, methyl ester, sitosterol, and cinnamic acid (Table 2), all of which have antioxidant and anti-inflammatory properties (Maharani & Fernandes, 2021). In contrast, pomelo peel extract contains propanoic acid, methyl ester, and ethyl iso-allocholate. Thakur & Ahirwar (2019) reported that these compounds have anticancer potential by inducing apoptosis.

### In Silico Testing with Molecular Docking

Cinnamic acid in the salak pondoh seed extract exhibits anti-inflammatory effects, while sitosterol and 9-octadecenoic acid methyl ester can induce apoptosis. This is supported by Endrini *et al*. (2014), who reported that sitosterol from *Strobilanthes crispus* has the ability to induce apoptosis in the HepG2 cell line and Caco-2 cells. The apoptosis-inducing activity of 9-octadecenoic acid methyl ester was also documented by Ahmad *et al*. (2018), who found that its presence in *Callistemon lanceolatus* can induce apoptosis in HepG2 cells. The anti-inflammatory activity of cinnamic acid derived from *Cinnamomum verum* against Caco-2 cells was highlighted by Pagliari *et al*. (2023).

The extract from pamelo peel demonstrates apoptosis-inducing and antiproliferative activities. Compounds such as ethyl iso-allocholate, propanoic acid methyl ester, and hesperidin exhibit apoptosis-inducing activity. These findings are consistent with previous research indicating that ethyl iso-allocholate in *Trigonella foenum-graecum* shows the capacity to induce apoptosis in A549 lung cancer cells (Thakur & Ahirwar, 2019). Additionally, the apoptosis-inducing activity of hesperidin found in tea and *Citrus maxima* has been shown to affect HepG2 and Bel7402 cells via the PI3K/AKT/mTOR pathway (Wen *et al*., 2012). Moreover, Dian *et al*. (2012) reported that 100 mg/kg of cinnamic acid from incense exhibits anti-inflammatory activity in Wistar strain rats.

### Anti-Inflammatory Activity and Viability Testing

The anti-inflammatory activity of the single extract from salak pondoh seeds exhibited a higher inflammation inhibition value compared to the single extract from pamelo peel. However, the combination of both extracts, specifically in the 1S1J treatment group, demonstrated superior inflammation inhibition compared to all other treatment groups (Figure 3). This indicates that the combination of salak pondoh seed extract and pamelo peel extract enhances the anti-inflammatory effects, as assessed by the albumin denaturation assay.

In the cytotoxicity testing, both the single extract of salak pondoh seeds and the combination extracts significantly reduced cell viability compared to the untreated control (Figure 5). The treatments S, 1S3J, and 1S1J exhibited cytotoxic effects and fell within the category of moderate cytotoxicity. Thus, these three treatments have potential as adjunct therapies for cervical cancer.

**Apoptosis and Inhibition of HeLa Cell Proliferation Testing**

Cancer cell death can occur through apoptosis or necrosis. However, apoptosis is a preferable mechanism for cancer cell death compared to necrosis. The single extract from pamelo peel exhibited the highest rate of cell death via apoptosis (Figure 5). In addition to inducing apoptosis, the single extract from pamelo peel also caused necrotic cell death, which was even greater than that induced by doxorubicin. Nevertheless, the combination of pamelo peel extract with salak pondoh seed extract significantly reduced the percentage of necrotic cell death. The optimal combinations were found to be 1S1J and 1S3J.

Thus, the bioactive compounds in the extracts of salak pondoh seeds and pamelo peel demonstrated synergistic effects, as the combined extracts were able to suppress necrotic cell death while promoting apoptosis. The HeLa cell proliferation assay showed that all treatment groups effectively inhibited wound closure. In general, the combination of salak pondoh seed extract and pamelo peel extract was more effective at inhibiting wound closure compared to the positive control, doxorubicin, although this difference was not statistically significant (Figure 6). The inhibition of wound closure indicates a reduction in proliferation among HeLa cells. The 1S1J combination emerged as the most optimal and potential antiproliferative agent against HeLa cells. This finding is consistent with the in silico results, where the bioactive compounds in both extracts were shown to inhibit proliferation through the suppression of the PI3K pathway.

**Principal Component Analysis (PCA)**

The combination of salak pondoh seed extract and pomelo peel extract at a 1:1 ratio exhibits the highest anti-inflammatory activity compared to other treatments. Furthermore, this combination shows moderate toxicity towards cervical cancer cells (HeLa). The 1S1J treatment also demonstrates the ability to induce apoptosis, reduce cell death due to necrosis, and inhibit the migration and proliferation of HeLa cells. These effects are influenced by the different types of phytochemical compounds synthesized and their biomedical activities. Salak pondoh seed extract has anti-inflammatory activity, while pomelo peel extract exhibits antiproliferative properties. Both extracts also possess the ability to induce apoptosis. Therefore, the combination of these two extracts is necessary to maximize anti-inflammatory and antiproliferative effects, as well as apoptosis induction. This is supported by Belhouala *et al*. (2024), who reported that the combination of extracts from Bryonia dioca, Aristolochia longa, Telephium imperiati, and Evernia prunastri exhibited higher anticancer activity against HT-29, PC-3, and A-549 cell lines compared to individual extracts. This combination indicates a synergistic mechanism among the phytochemical constituents that enhances anticancer and antiangiogenic activities while reducing toxicity.

The mechanism of action of the combination of salak pondoh seed extract and pomelo peel extract as an anticancer adjuvant includes the inhibition of the PI3K protein produced by cancer cells. PI3K is an enzyme that plays a crucial role in promoting the proliferation and migration of cancer cells while inhibiting their apoptotic capabilities. Therefore, the inhibition of PI3K leads to a reduction in both proliferation and migration activities of cancer cells, while simultaneously inducing apoptotic activity. Additionally, the combination of extracts also demonstrates the ability

to inhibit the COX-2 enzyme, resulting in a reduction of inflammatory activity (Song *et al*., 2020; Tan *et al*., 2023).

## CONCLUSION AND SUGGESTION

The extracts of salacca seed (Salacca zalacca) and pomelo peel (Citrus maxima) exhibit potential as adjunctive agents in cervical cancer therapy. Their combinationin a 1:1 ratio,demonstrates higher efficacy compared to their individual extracts, especially in inhibiting inflammation, proliferation, and metabolism of HeLa cells.


## ACKNOWLEDMENTS

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