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Research Paper

Combination of *Temu Kunci* Extract with *Sirsak* Leaf Extract Using Ultrasonic Maceration as a Candidate for Cervical Cancer (HeLa)

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ABSTRACT

Cervical cancer remains a leading cause of cancer-related mortality among women, primarily linked to Human Papillomavirus (HPV) types 16 and 18. Conventional treatments such as chemotherapy and radiotherapy are often limited by adverse effects and high costs, prompting the need for safer, natural-based alternatives. This study aimed to evaluate the anticancer potential of the combined ethanolic extracts of fingerroot (Boesenbergia pandurata Roxb.) and soursop leaves (Annona muricata L.) obtained through ultrasonic maceration as a candidate therapy for cervical cancer (HeLa). The study included plant determination, simplicia preparation, ultrasonic extraction using 96% ethanol, phytochemical screening, quantification of total flavonoid and phenolic contents, and cytotoxicity testing via MTT assay on HeLa cells. Data were analyzed by calculating IC_{50} and Combination Index (CI) values using SigmaPlot software. The results revealed that fingerroot and soursop extracts exhibited cytotoxic activity with IC_{50} values of 59.71 µg/mL fingerroot and 94.55 µg/mL soursop, respectively, while their combination showed synergistic effects (CI < 1). The conclusion of this study is that the ultrasonic maceration method shows that ginger and soursop leaf extracts have cytotoxic activity against cervical cancer cells (HeLa). The combination of the two extracts shows a strong synergistic effect against cervical cancer cells (HeLa) with a CI value of 0.365, making it a promising candidate for anticancer phytotherapy.

Keywords: Cervical Cancer, Boesenbergia Pandurata, Annona Muricata, Ultrasonic Maceration, Synergistic

INTRODUCTION

Cervical cancer is one of the most common types of cancer affecting women, especially those aged 30-39 years. Infection with Human Papillomavirus (HPV) types 16 and 18 is the main cause of this disease. Additionally, other risk factors such as smoking, having multiple sexual partners, and exposure to chemicals also contribute to an increased risk of cervical cancer (Novalia, 2023). In Indonesia, cervical cancer remains a serious public health problem, marked by high incidence and mortality rates. The main obstacle faced by the community is limited access to modern treatment due to high costs. Various therapeutic methods such as surgery, radiotherapy, chemotherapy, and molecular targeted therapy have been developed, but these treatments often cause side effects and are not affordable for all people (Romdhoni, 2017). Therefore, safer, more affordable treatments with minimal side effects are needed, one of which is through the use of natural ingredients as the basis for drug development.

Temu kunci contains various bioactive compounds such as flavonoids and essential oils that have antioxidant, antibacterial, and anticancer properties. A number of studies have reported that temu kunci is effective in helping to treat various diseases, including infections and inflammation (Mahmudah & Atun, 2017). Meanwhile, soursop is also known to have great potential as a natural medicine due to the acetogenin compounds found in its leaves, stems, and seeds. Acetogenin works by inhibiting energy production in cancer cells, thereby triggering cell death. Additionally, other compounds such as alkaloids, tannins, and flavonoids in soursop further enhance the anticancer effects through various mechanisms (Pertiwi et al., 2020).

According to Maritha & Handoko (2019), soursop leaf extract (*Annona muricata L.*), which contains acetogenin and flavonoid compounds, has been proven to have activity against HeLa cervical cancer cells with an IC50 value of 337 µg/µL. Meanwhile, ethanol extract of temu kunci rhizome (*Boesenbergia pandurata Roxb*.) containing Panduratin A showed cytotoxic activity with an IC50 value of 87 µg/mL, and the flavonoid content in it acted as an antioxidant that could enhance the cytotoxic effect (Handoko et al., 2011). The efficiency of extracting bioactive compounds such as flavonoids and acetogenins can be improved through the ultrasonic maceration method, which has been proven to be more effective than conventional methods (Q. Wang et al., 2016). However, most previous studies have only examined the single effects of each extract without assessing the potential of combining the two (Mahmudah & Atun, 2017; Pertiwi et al., 2020). The combination of herbal extracts with optimal extraction methods has the potential to produce stronger anticancer compounds with selective toxicity against cancer cells (Novalia, 2023; Proboningrat et al., 2019). Therefore, the novelty of this research lies in exploring the potential combination of ginger rhizome and soursop leaf extracts using ultrasonic maceration as a more effective candidate for cervical anticancer agents.

The stability and integrity of the chemical content of ginger and soursop leaves can be maintained using efficient and optimal extraction methods. Ultrasonic extraction was chosen as the most suitable method for processing ginger rhizomes and soursop leaves. As an initial stage of research, tests were conducted on extracts of both materials by analyzing their main bioactive compounds to assess their potential as anticancer candidates against HeLa cells (cervical cancer cells).

RESEARCH METHOD

This study used a laboratory experimental design to evaluate the anticancer activity of a combination of temu kunci rhizome extract (*Boesenbergia pandurate Roxb.*) and soursop leaves (*Annona muricata L.)* against cervical cancer cells (HeLa). The research was conducted over four months, from July 8 to October 1, 2025, at the Natural Materials Laboratory of the Faculty of Pharmacy, Buana Perjuangan University, Karawang, for the extraction and phytochemical analysis processes, and at the Cytogenetic Cell Culture Laboratory of the Faculty of Medicine, Padjadjaran University, for the cytotoxicity test.

The tools used in this research include an ultrasonic cleaner, glassware found in chemistry laboratories, a rotary evaporator, a UV-Vis spectrophotometer, a CO2 incubator, a Biosafety Cabinet (BSC), a centrifuge, an inverted microscope, and a 96-well plate. Materials used include temu kunci rhizomes and soursop leaves obtained from Klari subdistrict, Karawang city, West Java province, 96% ethanol, cervical cancer cell media (HeLa cells), Roswell Park Memorial Institute (RPMI)-1640 cell culture media, trypsin-EDTA, MTT reagent, dimethyl sulfoxide (DMSO), fetal bovine serum (FBS), PBS buffer, H2SO4, AlCl, Vitamin C, Quercetin, folin ceocalteu, gallic acid,

organic2,2-diphenyl-1-picrylhydrazil (DPPH),and distilled water.
The independent variables were several concentrations of temu kunci extract and soursop leaf extract in HeLa cell culture media testing with concentrations of 15.625; 31.25; 62.5; 125; 250; 500; 1000 ppm with a mixture of concentrations of 31.25 + 0; 31.25 + 15.625; 31.25 + 31.25; 31.25 + 62.5; 62.5 + 0; 62.5 + 15.625; 62.5 + 31.25; 62.5 + 62.5; 125 + 0; 125 + 15.625; 125 + 31.25; 125 + 62.5; 250 + 0; 250 + 15.625; 250 + 31.25; and 250 + 62.5 ppm. The dependent variable was the IC50 value obtained using an ELISA reader at a wavelength of 550-600 nm. The results of the combination values were in the form of a Combination Index (CI) processed using SigmaPlot software (Chao et al., 2019).

RESULTS AND DISCUSSION

Yield Results of Curcuma and Soursop Leaf Extracts Using Ultrasonic Maceration

The yield results show that from 447 grams of crude drug extracted using 10 liters of 96% ethanol through ultrasonic maceration, a yield of 5.77% was obtained for curcuma and 12.9% for soursop leaves. These values are comparable to the studies by Kautsari et al. (2021) and Amin et al. (2024), and support the findings of Momchev et al. (2020) that the ultrasonic method is more efficient than conventional maceration due to the cavitation effect that increases solvent penetration and extraction yield.

Phytochemical Screening Results / Qualitative Test

The results of the screening of ginger and soursop leaf extracts (see table below). These findings are consistent with the research by Promprom et al. (2024) and Y. Wang et al. (2025), which states that Boesenbergia rotunda rhizomes contain saponins, tannins, flavonoids, polyphenols, and alkaloids. In soursop leaves, these positive results are also in line with the research by Nsor et al. (2024) and Mutakin et al. (2022), which detected saponins, tannins, flavonoids, terpenoids/steroids, polyphenols, and alkaloids in the extract. The following is a table of phytochemical screening results from ginger and soursop leaf samples:

Table 1. Results of Phytochemical Screening/Qualitative Test

Test	Sampele	Pre-action	Result	+/-
Alkaloids	Temu Kunci	NH_3 + $CHCL_3$ + HCL + Dragendorf Reaction & Mayer Reaction	Brown sediment	+
	Sirsak Leaf		Cloudy sediment	+
Saponins	Temu Kunci	Water + HCL	Foam present	+
	Sirsak Leaf		Foam present	+
Tannins	Temu Kunci	1% Gelatin Solution	White sediment	+
	Sirsak Leaf		White sediment	+
Flavonoids	Temu Kunci	Magnesium + HCL	Yellow	+
	Sirsak Leaf		Yellow-orange	+
Triterpenoids / Steroids	Temu Kunci	Ether + Liberman Bouchard	Yellow	-
	Sirsak Leaf		Turns blue	+
Polyphenols/phenols	Temu Kunci	$FeCl_3$	Turns black	+
	Sirsak Leaf		Turns black	+

Phytochemical screening results showed that extracts of fingerroot rhizome (*Boesenbergia pandurata*) and soursop leaves (*Annona muricata*) contain saponins, tannins, flavonoids, terpenoids/steroids, polyphenols, and alkaloids, which play important roles in anticancer activity. Alkaloids together with acetogenins in soursop leaves are known to inhibit mitochondrial electron transport chain complex I, reduce ATP production, and selectively induce apoptosis in cancer cells (Mutakin et al., 2022). Saponins increase membrane permeability and activate caspases to support cytotoxic effects (Nsor et al., 2024), while tannins and polyphenols have high antioxidant activity capable of inhibiting cell proliferation by binding to proteins and suppressing enzyme activity (Widyananda et al., 2022). Flavonoids and terpenoids in fingerroot also play a role in inhibiting the cell cycle and inducing apoptosis. The combination of these active compounds is suspected to produce a synergistic effect between flavonoids, tannins from fingerroot, and alkaloids (*acetogenins*) from soursop leaves in enhancing cytotoxic activity against cervical cancer cells (Proboningrat et al., 2019).

Extract Standardization Results

The results of extract standardization in organoleptic testing can be seen in the table below:

Table 2. Extract Standardization Results of Organoleptic Test

Parameter	Temu kunci	Sirsak Leaf
identity		
Extract name	Fingerroot ethanol extract	Ethanol extract of soursop leaves
Other name	*Boesenbergia pandurata Roxb.*	*Annona muricata L.*
Parts of the Plant Used	Rhizome	Leaf
Name Indonesia	Temu kunci	Sirsak
Organoleptic		
Smell	Distinctly aromatic, slightly sharp	Aromatic with a slightly pungent scent
Taste	Bitter and harsh	Bitter
Color	Yellowish brown	Brownish green
Shape	Thick	Thick

In the organoleptic testing of the fingerroot extract, which is yellowish-brown in color, has a distinctive aromatic smell, tastes bitter-pungent, and has a thick consistency, the results are in line with the research by Girsang et al. (2019), which is due to the presence of flavonoid compounds and panduratin A. Meanwhile, in the organoleptic testing of soursop leaf extract, which is brownish-green in color, has a distinctive smell, tastes bitter, and has a thick consistency, the results are consistent with the research by Amin et al. (2024), caused by the presence of acetogenins and alkaloids. The thick consistency also indicates that the extract is rich in dissolved active compounds, and there are no signs of degradation such as a change in color to black or rancid odor, thus still meeting standard organoleptic parameters (FHI Edition II, 2022).

The following are the results of the standardization of the extract for moisture content, drying loss, and total ash content, which can be seen in the table below:

Table 3. Results of Extract Standardization for Moisture Content, Loss on Drying, and Total Ash Content

Test	Sampele	Examination Results	Requirements (FHI,2022)
Moisture Content Drying Loss	Temu Kunci	16,61%±6,60	≤ 10 %
	Sirsak Leaf	38,08%±16,25	
Total Ash Content Moisture Content	Temu Kunci	20,33%±0,39	≤ 10 %
	Sirsak Leaf	16,83%±0,15	
Drying Loss	Temu Kunci	2,67%±2,98	≤ 10,6 %
	Sirsak Leaf	6,66%±0,66	

The moisture content and drying loss of fingerroot and soursop leaf extracts that exceed herbal pharmacopoeia standards can be caused by suboptimal drying conditions such as excessively high temperatures, inappropriate drying times, and high air humidity that inhibits evaporation and allows the material to rehydrate (Amin et al., 2024). The particle size of the material also has an effect, where large cuts lead to uneven heat distribution, while overly fine particles easily reabsorb water vapor (Kim DongGyu et al., 2011). To achieve results according to the Indonesian Herbal Pharmacopoeia standards, it is recommended to use vacuum drying or freeze-drying methods, gradually adjusting the temperature and time, and controlling humidity and storing in closed containers to maintain the stability of active compounds and the physical quality of the extract (Nakra et al., 2025).

Quantitative Test Results

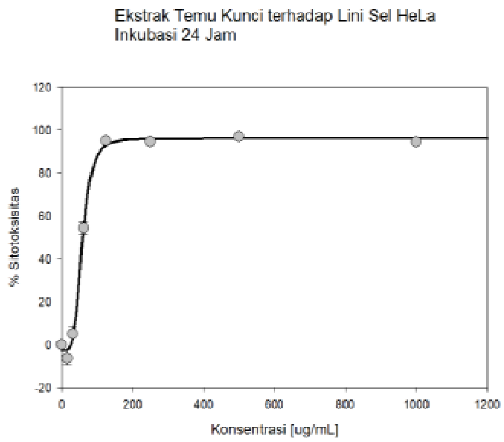
The results of the secondary metabolite content test showed that fingerroot extract contained a total of 6.196 mg QE/g of flavonoids and 159.71 mg GAE/g of total phenolics, while soursop leaf extract had 8.607 mg QE/g of flavonoids and 148.25 mg GAE/g of phenolics. The phenolic content of fingerroot was higher compared to the results of Widyananda et al. (2022), which was 25.04 mg GAE/g, while the flavonoid content of soursop leaves was lower than the 27.31 mg QE/g reported in the study by Nolasco-González et al. (2022). These differences in levels are influenced by the extraction method, type of solvent, and quality of the raw materials.

Testing of antioxidant activity using the DPPH method showed that soursop leaf extract has very strong free radical scavenging activity with an IC_{50} value of 6.24 µg/mL, while temu kunci extract showed strong activity with an IC_{50} value of 80.79 µg/mL. These results are in line with the study by Rikantara et al. (2022), which reported the high antioxidant potential of soursop leaves, and also indicate increased extraction effectiveness in temu kunci compared to the results of the study by Luthfi and Atun (2020). This antioxidant activity test was conducted to assess the extract's ability to neutralize free radicals, considering that oxidative stress plays an important role in the initiation and progression of cancer through DNA damage and disruption of cell apoptosis mechanisms.

High antioxidant activity indicates that the bioactive compounds in the extract, such as flavonoids and phenolics, can protect healthy cells from excessive oxidation and contribute to anticancer mechanisms by increasing selective oxidative stress in cancer cells (Mutakin et al., 2022; Nolasco-González et al., 2022). Thus, the results of antioxidant testing serve as an important basis for explaining how plant extracts work not only as direct cytotoxics but also through modulation of the cellular redox environment, which can enhance the effectiveness of extract combinations, affect compound bioavailability, or reduce cancer cell resistance to oxidation. Therefore, the antioxidant activity results obtained at this stage provide an initial indication that the tested extracts contain relevant bioactive components and support the continuation of cytotoxicity and synergistic testing (Mileo & Miccadei, 2016).

Single Cytotoxicity Test Results

The cytotoxicity test results indicated that the temu kunci extract had an IC50 value of 59.71 µg/mL and the soursop leaf extract had an IC50 value of 94.55 µg/mL, both of which are still considered active (<100 µg/mL) and can be identified as having potential as cervical cancer anticancer agents, although temu kunci is more potent than soursop leaves. However, these cytotoxicity test results are more potent compared to previous studies using the conventional maceration method, namely IC50 for soursop leaves was 337 µg/mL (Maritha & Handoko, 2019) and IC50 for temu kunci was 87 µg/mL (Handoko et al., 2011). This difference in potency proves that the ultrasonic extraction method is more effective in extracting bioactive compounds compared to the conventional method.



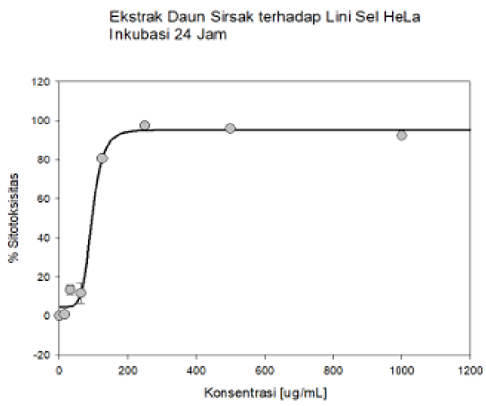


Figure 1. Cytotoxicity Test Results Curve of Both Extracts on HeLa Cells

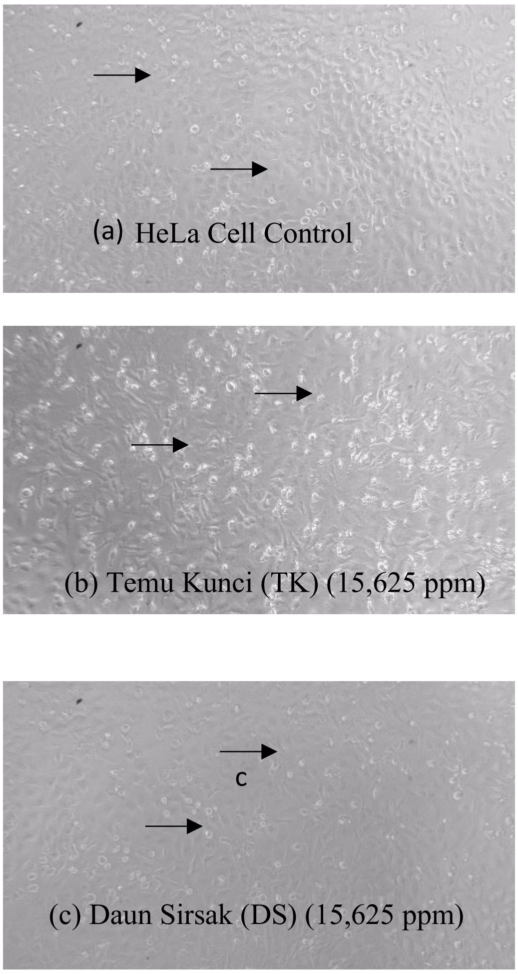


Figure 2. Comparison of cell growth inhibition results (anticancer activity) with single treatments using fingerroot extract (59.71 µg/mL) and soursop leaf extract (94.55 µg/mL) at a concentration of 15.625 ppm, which produced an active IC50 (<100 µg/mL), showing vacuolization/apoptosis with cell cultures grown in a 96-well plate and incubated at 37°C for 24 hours, followed by the addition of the MTT assay kit working reagent, and the absorbance was measured using a Multiskan EX ELISA reader. (a) HeLa cell control; (b) Fingerroot (15.625 ppm); (c) Soursop leaf (15.625 ppm).

Results of Cytotoxicity Test on Combination

Testing the combination of temu kunci extract and soursop leaf extract at various doses showed varied results. The Combination Index (CI) values at several doses were at CI<1, indicating a strong synergistic effect. For example, the combination of 125 ppm temu kunci + 62.5 ppm soursop leaf yielded a CI value of 0.32–0.42, while the combination of 250 ppm temu kunci + 31.25 ppm soursop leaf resulted in a CI value of 0.37–0.57. Combinations with CI values close to 1, such as at doses of 31.25 ppm temu kunci + 62.5 ppm soursop leaf (CI 0.97–1.06), indicate an additive effect, whereas CI values >1, such as 62.5 ppm temu kunci + 62.5 ppm soursop leaf (CI 1.07–1.15), indicate an antagonistic effect. The combination of the two extracts showed synergistic potential at certain doses, as reflected by CI values <1.

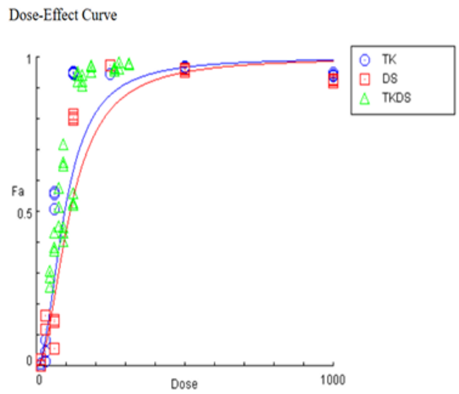


Figure 3. Cytotoxicity Test Curve of the Combination of Both Extracts Against HeLa Cells

This supports the hypothesis that the secondary metabolite interactions of both plants can complement each other's mechanisms, for example, acetogenins from soursop leaves, which are cytotoxic, combined with panduratin A from fingerroot, which is an antioxidant (Chahyadi et al., 2014). This synergistic effect has the potential to produce a combination extract with higher selective toxicity against cancer cells (Rikantara et al., 2022). Overall, these results confirm the novelty of the research, namely that the combination of fingerroot and soursop leaf extracts using an optimal extraction method can enhance anticancer effectiveness compared to single extracts, thus potentially being developed as a natural-based therapeutic candidate for cervical cancer. The following is an image of cancer cells (HeLa) with a combination of fingerroot and soursop leaf extract concentrations:

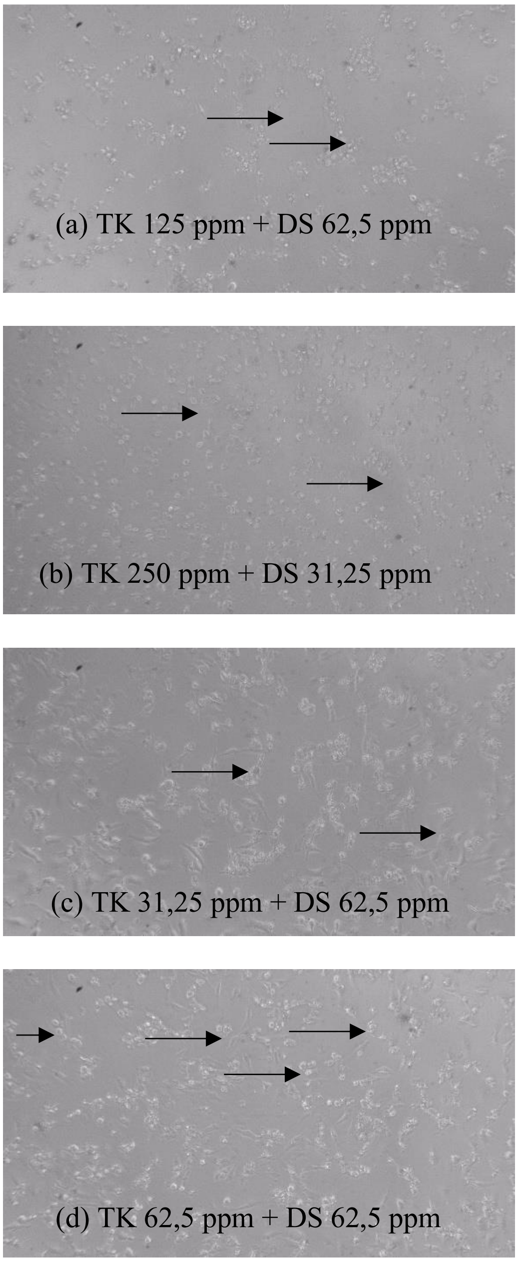


Figure 4. Comparison of cell growth inhibition results (anticancer activity) with the combination treatment of fingerroot (TK) extract + soursop leaves (DS). (a) TK 125 ppm + DS 62.5 ppm (synergistic/CI<1); (b) TK 250 ppm + DS 31.25 ppm (synergistic/CI<1); (c) TK 31.25 ppm + DS 62.5 ppm (additive/CI=1); (d) TK 62.5 ppm + DS 62.5 ppm (antagonistic/CI>1).

CONCLUSION

Based on the results of the study, it can be concluded that the ethanolic extracts of fingerroot rhizome (Boesenbergia pandurata Roxb.) and soursop leaves (Annona muricata L.) obtained through ultrasonic maceration exhibit significant anticancer activity against cervical cancer cells (HeLa). Ultrasonic maceration proved to be an effective extraction method, as indicated by higher extraction yields, rich phytochemical content, and stronger cytotoxic activity compared to conventional extraction methods. Phytochemical screening and quantitative analysis confirmed the presence of bioactive secondary metabolites, including flavonoids, phenolics, alkaloids, tannins, and saponins, which are known to contribute to anticancer mechanisms such as antioxidant activity, cell cycle inhibition, and apoptosis induction.

Single cytotoxicity testing demonstrated that fingerroot extract showed higher potency (IC_{50} 59.71 μg/mL) than soursop leaf extract (IC_{50} 94.55 μg/mL), both of which fall within the active cytotoxic category. Importantly, the combination of fingerroot and soursop leaf extracts produced a strong synergistic effect at specific concentration ratios, as indicated by Combination Index (CI) values <1, with the most notable synergism observed at CI values as low as 0.365. This synergistic interaction is likely due to complementary mechanisms of action between flavonoids and phenolic compounds from fingerroot and acetogenins from soursop leaves, enhancing selective cytotoxicity toward cancer cells.

Overall, the combination of fingerroot and soursop leaf extracts prepared by ultrasonic maceration shows promising potential as a natural-based anticancer phytotherapeutic candidate for cervical cancer. However, further studies are recommended, including mechanism-of-action analysis, selectivity testing on normal cells, and in vivo evaluation, to support its development into a safe and effective anticancer agent.

Declaration by Authors

Ethical Approval: Approved

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