ORIGINAL ARTICLE

Increased Hela Cell Death Using Cytotoxic Test Of Hexane N Fraction, Ethanol And Purple Leaf Ethyl Acetate (*Graptophyllum Pictum* L) In Cervical Cancer

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ABSTRACT

Introduction: Cervical cancer can be treated with one or a combination of surgery, irradiation (radiotherapy), chemotherapy drugs, immune system enhancement, and hormones. This study aims to determine whether there is an increase in HeLa cell death using the N fraction of hexane, ethanol, and ethyl acetate *Graptophyllum pictum* L in cervical cancer. **Methods:** This research is an experimental study. Data analysis with One-way ANOVA followed by the Mann-Whitney Test to determine the real difference between treatment concentrations. Then the IC50 value of the extract using probit analysis. **Results:** It was found that the ethanol fraction of *Graptophyllum Pictum* L increased the greatest mortality against HeLa cells of cervical cancer. Statistical tests with One Way ANOVA. Therefore there are significant differences between treatment groups. Then, the statistical test continued with the Mann-Whitney test p-value of > 0.05 each. The morphology of untreated HeLa cells appeared polygonal, and many fusions and cytoplasm were visible. While the treated HeLa cells appeared few, separated from each other, and showed shrinkage due to treatment, the cells became round and disconnected and showed cell shrinkage. This cell shrinkage can occur because the cells lack fluid. Cells that lack fluid will cause cell death due to the cytotoxic effect of *Graptophyllum Pictum* L. **Conclusion:** The occurrence of increased HeLa cell death by administration of N Hexane, ethanol, and Ethyl Acetate fractions *Graptophyllum Pictum* L in cervical cancer with the most considerable cell death caused by ethanol fractions.
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Keywords: HeLa Cell, Cytotoxic, *Graptophyllum Pictum* L, Cervical Cancer, IC50

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INTRODUCTION

Graptophyllum pictum L is a plant that has a role in health as a medicine. The efficacy of *Graptophyllum pictum* L includes analgesics and anti-inflammatory, has phagocytosis properties, and supports the formation of immunoglobulins (1). Triterpenes, flavonoids, steroids, tannins, and saponins are phytochemicals found in *Graptophyllum pictum* L (2). According to Kusumawati et al. (3), the content of *Graptophyllum pictum* L is even more, including tannins, alkaloids, steroids and glycosides, phenols (including flavonoids, anthraquinones), saponins, coumarins, and sugars.

Many women already know about the dangers of cervical cancer, but few carry out early screening, so many cases are found to be at an advanced stage (4). Cervical cancer is a disease that can be treated with chemotherapy drugs, radiation, and surgery. Today, the primary treatments for metastatic tumors are radiotherapy and chemotherapy (chemical drugs). Chemotherapy in cervical cancer patients has not been specific (5), So the treatment of cervical cancer still has side effects that make sufferers feel uncomfortable (6).

Cervical cancer can be identified using HeLa cells. Cell cycle regulation that loses its function causes cells to multiply abnormally so that the process of cell apoptosis does not run properly, it can cause cancer (7). Natural ingredients derived from nature can be used to be researched as drugs that can increase cell death without causing side effects (8). All cervical cancer patients cannot obtain the use of cervical cancer drugs because it requires high costs. Currently, cancer management is progressing, and along with these advances, the costs

incurred for cancer treatment are also higher (9). Various ways are done to reduce cancer incidence even though it has cost a lot of money (10).

Chemotherapy treatment still has terrible side effects. The onset of other diseases caused by cancer is caused by a poor quality of life (5). *Graptophyllum pictum* L is clinically efficacious as an anti-inflammatory (1), contains antioxidants, flavonoid compounds, tannins, alkaloids, sitosterol, glycosides and saponins, and can also clinically suppress the growth of WiDr cells and MCF-7 cells (5). There is no clinical evidence regarding the cytotoxic effect of *Graptophyllum pictum* L on HeLa cells. With the intervention of cervical cancer control using traditional *Graptophyllum pictum* L treatment, it is hoped that cases of cervical cancer can decrease (11). Cervical cancer is a disease in women that dominates second only to breast cancer caused by abnormal cells (12). Cervical cancer requires expensive treatment and has terrible side effects. Many plants with medicinal potential have been clinically studied to reduce the side effects of chemotherapy treatment (13). Lousy response to chemotherapy is also obtained by breast cancer patients (14). In colorectal cancer, patients who get treatment with chemotherapy also have harmful effects, one of which is the presence of nerve disorders (15).

Graptophyllum pictum L fraction with specific doses can exert cytotoxic effects on HeLa cells. This study aims to determine whether there is an increase in HeLa cell death using the N fraction of hexane, ethanol, and ethyl acetate *Graptophyllum pictum* L in cervical cancer.

MATERIALS AND METHODS

This research used 3 treatment groups with fractionation using the nonpolar solvent N-hexane, the semipolar solvent Ethyl Acetate, and the polar solvent Ethanol (16) Doxorubicin is a positive control. It has been clinically proven to treat cervical cancer because it contains nano particulates (17). The cell line used is HeLa cells derived from epithelial cells of cervical cancer (18). RPMI 1640 dan M199 (GIBCO), Fetal Bovine Serum/ FBS (Sigma), dimetil sulfosida/ DMSO, akuabides, alkohol 70%, Yellow MTT.

Cells 1.0 x 10^4 / well were inserted into plate 96 wells and then incubated at 37°C using a CO^2 incubator (5%) for 24 hours. The treated cells were reincubated using a CO^2 incubator (5%) for 24 hours at 37oC. Cells were washed with Phosphate Buffer Saline (PBS), then added with 0.5 mg/mL MTT (3-(4,5-dimetylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), re-incubated 4 hours at 37°C. After that, add regent stopper sodium dodecyl sulfate ((SDS) (10%) in HCl 0.01 M) to the cells, incubating again overnight at 28°C (19,20).

HeLa cell culture is performed with complete media in pumpkin culture. HeLa cell maintenance is carried out in a 5% CO2 incubator at 37°C. HeLa cell retrieval is carried out when the cells are 80% confluent, that is, cells evenly distributed as monolayer cells to cover the tissue disk. Cells were washed using RPMI three times and then given trypsin as much as 0.5 mL per flask (21). A hemocytometer is a device used to see if cells appear solid. After that, the cell is inserted into a 96-well plate at 100 µL / well. The cells to be used are then incubated overnight and then treated (22).

Cytotoxicity effect is assessed to see a compound able to increase cancer cell death measured using IC_{50}. HeLa cells were inserted in plates of 96 wells with a density of $1X10^4$ cells / mL 100 and divided into cell control treatment groups, media control, positive control, and N fractions of Hexane, Ethanol, and Ethyl Acetate with a concentration of 11,72; 23,44; 46,87; 93,75; 187,5; 375, and 750 µg / l). Then, incubate for 24 hours. Next, MTT reagents are added to each plate and set at 37°C for 4 hours. Each well is added 100 µl DMSO so the resulting formazan crystals can be lost. The final microplate is read at a wavelength of 540 nm (10,22,23).

Data analysis with One Way ANOVA followed by Mann Whitney Test to determine the difference between treatment concentrations. Then, the IC_{50} value of the extract using probit analysis. The Ethics Commission was obtained from the Health Polytechnic of the Ministry of Health Tanjungkarang (Bandar Lampung, License No. 153/KEPK-TJK/II/2023).

RESULTS

Morphological picture of HeLa cell changes before and after treatment with *Graptophyllum pictum* L

HeLa cells are cell lines that are easy to culture. Within 24 hours, HeLa cells will grow to 2 times the amount planted at the time of culture. The description of HeLa cells that are considered confluent after incubation for 24 hours and meet the criteria for use is shown in Figure 1.

Cytotoxic activity of the N fraction of Hexane *Graptophyllum pictum* L

In Figure 2, it can be seen that an increase in the concentration of the Hexan N fraction of *Graptophyllum pictum* L above the concentration of 23.44 µg/ml given to HeLa cells will further decrease the viability of HeLa cells. From the percentage of cell viability, inhibitory concentration (IC50) can be calculated using probit regression analysis, and IC50 fraction N Hexan *Graptophyllum pictum* L against HeLa cells is 249 µg / ml.

Cytotoxic activity of Ethanol fraction *Graptophyllum pictum* L

In Figure 3, it can be seen that an increase in the concentration of *Graptophyllum pictum* L Ethanol fraction above the concentration of 23.44 µg/ml

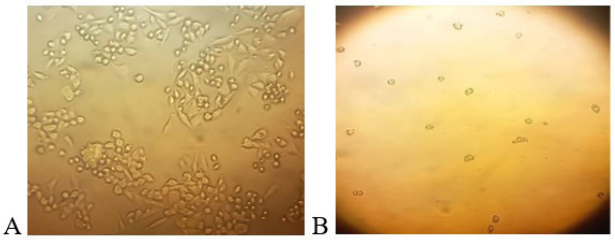

Figure 1: HeLa cell morphology after 24-hour incubation (viewed with 400x magnification inverted microscope) a. Cell morphology before treatment, b. Cell morphology after treatment

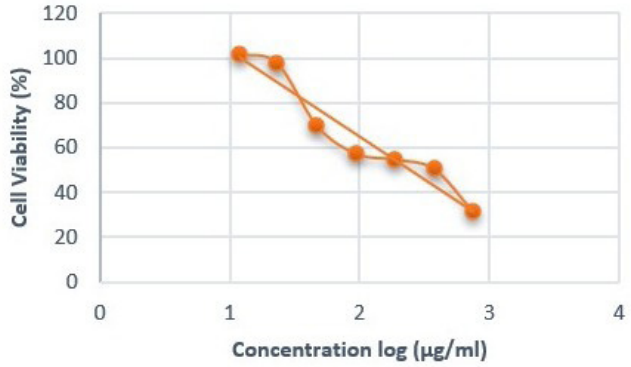

Figure 2: Cytotoxic activity of the N fraction of Hexane *Graptophyllum pictum* L

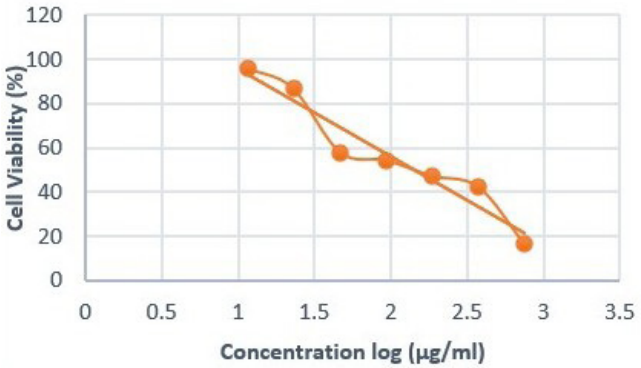

Figure 3: Cytotoxic activity of Ethanol fraction *Graptophyllum pictum* L

given to HeLa cells will further decrease the viability of HeLa cells. From the percentage of cell viability, inhibitory concentration (IC50) can be calculated using probit regression analysis, and the IC50 fraction of *Graptophyllum pictum* L Ethanol fraction against HeLa cells is 143 µg / ml

Cytotoxic activity of Ethyl Acetate fraction *Graptophyllum pictum* L

In Figure 4, an increase in the Ethyl Acetate fraction *Graptophyllum pictum* L above the concentration of 23.44 µg/ml given to HeLa cells will further decrease the viability of HeLa cells. From the percentage of cell viability, inhibitory concentration (IC50) can be calculated using probit regression analysis, and the

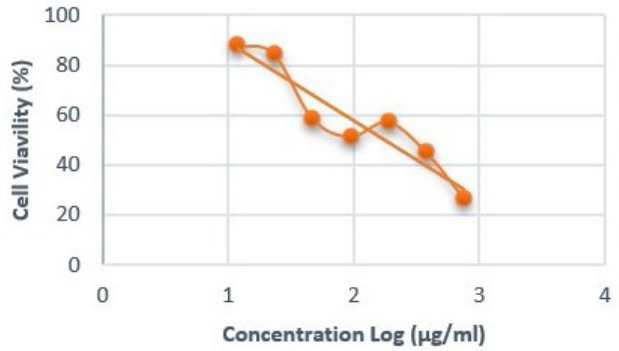

Figure 4: Cytotoxic activity of Ethyl Acetate fraction *Graptophyllum pictum* L

IC50 fraction of Ethyl Acetate *Graptophyllum pictum* L against HeLa cells is 177 µg / ml.

Cytotoxic activity of Doxorubicin as a positive control

In Figure 5, it can be seen that an increase in Doxorubicin concentration above the concentration of 23.44 µg/ml given to HeLa cells will further decrease the viability of HeLa cells. From the percentage of cell viability, inhibitory concentration (IC50) can be calculated using probit regression analysis, and IC50 Doxorubisin against HeLa cells is 203 µg / ml.

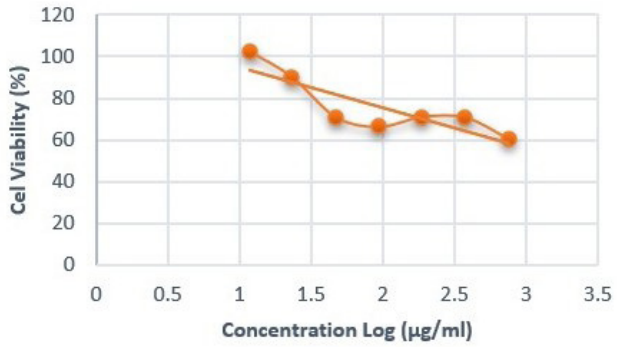

Figure 5: Cytotoxic activity of Doxorubicin as a positive control

Statistical analysis

The average percentage of HeLa cells that died in each group was tested for normality using the Saphiro-Wilk test. Each group obtained p>0.05, meaning the data is usually distributed. Furthermore, in the homogeneity test, the p variant > 0.05 means homogeneous data. Thus, this data meets the requirements of the One Way ANOVA statistical test. Statistical tests with One-way ANOVA obtained a p-value of > 0.05. Therefore there are significant differences between treatment groups. Then, the statistical test continued with the Mann-Whitney test and got a p-value of > 0.05.

DISCUSSION

The morphological changes observed in treated HeLa cells may indicate cytotoxic effects associated with cell

injury and loss of viability. Cell shrinkage may occur when cells experience fluid imbalance, which can eventually contribute to cell death (8,24). Increased cell death may also involve intracellular energy disruption and DNA fragmentation, both of which are commonly associated with apoptotic processes (24).

Graptophyllum pictum L. may exert its biological effects by inhibiting the formation and activity of reactive oxygen species, which can damage cellular components such as DNA, lipids, carbohydrates, and proteins. Antioxidants prevent free radical activity by donating electrons, thereby reducing further free radical formation (25). The quinolone compounds found in *Graptophyllum pictum* L. may also contribute to anti-inflammatory activity through more stable chemical interactions that inhibit pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8 proteins (26).

The antioxidant potential of purple leaf extract is associated with its flavonoid content. Higher flavonoid levels are linked to stronger free radical-scavenging ability. This activity is influenced not only by the number of hydroxyl groups in phenolic compounds, but also by the position of the hydroxyl group and the presence of a 4-oxo group in the basic structure. Phenolic compounds and flavonoids in *Graptophyllum pictum* L. can donate hydrogen atoms to DPPH radicals, resulting in the formation of stable DPPH-H compounds, also known as picrylhydrazine molecules (5).

The cytotoxic activity of *Graptophyllum pictum* L. fractions may be explained by their ability to reduce HeLa cell viability and increase cell death. Based on IC50 activity classification, compounds with IC50 values of ≤20 µg/mL are considered very active, 21–200 µg/mL moderately active, 201–500 µg/mL weakly active, and >500 µg/mL inactive (27). Therefore, the cytotoxic potential of each fraction can be interpreted according to this classification.

The ethyl acetate fraction may show cytotoxic effects because it can extract semi-polar compounds from *Graptophyllum pictum* L. However, as a semi-polar solvent, ethyl acetate may not extract all active substances present in the plant. In addition, HeLa cells possess estrogen receptors, which may influence their response to treatment (28,29). This could make HeLa cells more resistant to induction by semi-polar fractions. Recent studies also indicate that mitochondria play an important role in cancer chemotherapy, particularly through intrinsic and extrinsic apoptotic pathways involved in programmed cell death (30,31).

The relatively weaker cytotoxic effect of the hexane fraction may be related to the type of compounds extracted by non-polar solvents. To enhance the cytotoxic potential of *Graptophyllum pictum* L., combination with other medicinal plants may be considered. Such combinations may produce synergistic effects against HeLa cells while potentially reducing adverse effects associated with chemical anticancer drugs (32). For example, binahong leaves (Anredera cordifolia [Tenore] Steen) have been reported to demonstrate cytotoxic activity against HeLa cells (32).

Previous studies have also reported estrogenic effects of *Graptophyllum pictum* L. hexane leaf extract in Sprague-Dawley rats with orally induced diabetes, including increased uterine diameter, mucosal layer thickness, lumen epithelial cell height, and glandular epithelial cell height (33). These findings suggest that *Graptophyllum pictum* L. may contain bioactive compounds capable of influencing hormone-responsive tissues.

Doxorubicin is commonly used as a positive control in anticancer studies (22). As a positive control, doxorubicin is generally expected to produce stronger cytotoxic activity than plant fractions. However, reduced sensitivity of HeLa cells to doxorubicin may occur due to increased activity of antioxidant defense enzymes, such as superoxide dismutase and catalase, which can lower doxorubicin toxicity (35). Drug resistance is also an important factor that may reduce the effectiveness of anticancer agents (36). This issue is not limited to anticancer drugs, as resistance is also a major concern in antimicrobial therapy (37).

CONCLUSION

Increased HeLa cell death by administration of N Hexane, ethanol, and Ethyl Acetate fractions *Graptophyllum pictum* L in cervical cancer with a potential IC50 value is quite active. IC50 values ≤ 20 µg/ml = classified as very active, IC50 21-200 µg/ml = moderately active, IC50 201-500 µg/ml = weakly active, and IC50 > 500 µg/ml = inactive. The ethanol fraction of *Graptophyllum pictum* has the greatest cytotoxic effect because it dissolves in polar solvents to maximize the absorption of substances that have the potential to become cancer drugs. *Graptophyllum pictum* can be an alternative to traditional medicine for cervical cancer.

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