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Original Article

In Vitro Cytotoxicity of Hibiscus sabdariffa *Linn* Extracts on A549 Lung Cancer Cell Line

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ABSTRACT

Background: Lung cancer is the one of the leading causes of cancer death. However, current treatments for lung cancer are expensive and show negative side effects. Therefore, the study concerning natural anticancer from plants has intensified. *Hibiscus sabdariffa Linn* are Indonesian herb plants which have been consumed as a drink, are known to have anticancer activity against several cancer cell lines. However, its potential cytotoxic activity on A549 lung cancer cell line is still unclear. **Objective:** This study aimed to identify cytotoxic activity of *Hibiscus sabdariffa Linn* extracts on A549 lung cancer cell line. **Materials and Method:** *Hibiscus sabdariffa Linn* flowers from Tangerang, province of Banten, Indonesia, were macerated in three different solvents: ethyl acetate, ethanol, and n-hexane. Afterwards, cytotoxic activity of *Hibiscus sabdariffa Linn* extracts on A549 lung cancer cell line were evaluated using MTT assay. There were eight variety of concentration of the extracts, the experiment has been done triplicate for each concentration. The anticancer activity is expressed by IC_{50} value. **Results:** *Hibiscus sabdariffa Linn* extracts in ethanol, ethyl acetate, and n-hexane showed IC_{50} value of 374.01 µg/mL, 719.28 µg/mL, and 906.57 µg/mL respectively, in which indicated weak cytotoxic activity on A549 lung cancer cell line. **Conclusion:** Ethanol, ethyl acetate, and n-hexane extracts of *Hibiscus sabdariffa Linn* are potential to be further developed as natural anticancer agents.

Key words: A549 Lung Cancer Cell Line, Cytotoxicity, *Hibiscus sabdariffa Linn.*

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INTRODUCTION

Lung cancer is a disease when the cells in the body, specifically in the lung, begin to proliferate out of control.[1] Lung cancer is the leading cause of cancer death globally. In Indonesia, based on WHO and GLOBOCAN data in 2018, lung cancer is a leading cause of cancer death, which has the highest mortality rate in male and the third highest mortality rate in female after breast and cervical cancer.[2,3] Primary cancer of the lung divided into two main types: Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). Non-Small Cell Lung Cancer is the most common type of lung cancer, accounting for 80-85% of total lung cancers. There are three subtypes of NSCLC, which are adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. A549 lung cancer cell line which is used in this study is collected from adenocarcinoma lung cancer patients.[4,5] Various factors can increase the risk of lung cancer, including smoking, industrial exposure, genetic polymorphism, overexpression of EGFR protein, and a family history of p53 mutation.[6] EGFR protein is related to the activation of Ras and PI3K that leads to cell proliferation.[7]

The treatment options for lung cancer such as surgery, chemotherapy, and radiotherapy, may produce undesired adverse effects including nausea, vomiting, hair loss, bleeding, skin problems, blood clotting, and required high cost.[8,9] Therefore, cancer patients may tend to choose alternative treatment that is considered cheaper and has no side effects, as stated in the study of Naja et al. Naja et al are also stated that the prevalence of alternative medicine users among lung cancer patients is 41%, with the most commonly used modality is dietary supplements, and herbal remedies.[10] In this regard, the study about potential anticancer from the herbs is widely conducted by many researchers.

In Indonesia, one of the herb plants that are known to have medicinal properties and widely consumed as tea, syrup, pudding, and cake, is *Hibiscus sabdariffa Linn.*[11] Study by Lin et al. reported that the phenolic compound of *Hibiscus sabdariffa Linn* could mediate activation of P38 MAPK/FASL cascade pathway and p53 signaling which can lead to apoptosis against human gastric carcinoma cells.[12] However, the study about cytotoxic activity of *Hibiscus sabdariffa Linn* on A549 lung cancer cell line is still unclear.

These facts inspired us to identify cytotoxic activity of *Hibiscus sabdariffa Linn* extract on A549 lung cancer cell line. This study is conducted using the experimental study design. We explore the cytotoxic activity of *Hibiscus sabdariffa Linn* collected from Tangerang, province of Banten, Indonesia. The first step is collecting *Hibiscus sabdariffa Linn* sample, drying, and grinding them become dry powder. Then, the powder were extracted and macerated in ethanol, ethyl acetate, and n-hexane, respectively. Furthermore, the cytotoxic activity of *Hibiscus*

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Figure 1: Morphology of *Hibiscus sabdariffa* Linn.[25]
Division : Magnoliophyta
Classis : Magnoliopsida
Ordo : Malvales
Familia : Malvaceae
Genus : Hibiscus
Species : Hibiscus sabdariffa

sabdariffa Linn extract on A549 lung cancer cell line was evaluated using the MTT assay method.

METHODS

Extraction and maceration of Hibiscus sabdariffa Linn samples

Hibiscus sabdariffa Linn flowers originated from a local market in Tangerang, Banten, Indonesia. About 100g of the flowers were dried, extracted, and macerated in a container with 500 ml of n-hexane, ethyl acetate, and ethanol, respectively. Those three different solvents are used to extract compounds based on the polarity of the solvent. The maceration process was done three time for 3 days for each solvent. Subsequently, the mixtures were filtered, the filtrate was collected, whereas the solid would be macerated again with the same solvent until three times. The collected filtrate was then concentrated with vacuum rotary evaporator to give a crude extract.[13]

MTT Assay

In this study, cytotoxic activity of *Hibiscus sabdariffa Linn* extracts on A549 lung cancer cell line is measured using MTT *assay.* Lung A549 cancer cell line is a culture collection of Bogor Agricultural Institute, Indonesia. At the beginning, the cancer cells will be counted using hemacytometre, planted and seeded according to the protocol. After that, the cancer cells will be cultured in DMEM, supplemented with 1% of penicillin-streptomycin and 10% of fetal bovine serum. Then, the cultured cells will be inputted into 2 plates, with each plate containing 96-microwell, and each well contained 10^4 cells. The plates will be incubated in the CO_2 incubator for 24 hours. Then, 10% of PBS will be added to wash the cell and removed the medium.[14]

Afterwards, 10 mg of the extract is diluted in 10 mL DMSO, and the solution will be diluted in stages to make 8 variety concentration of extract (1.5; 3.125; 6.25; 12.5; 25; 50; 100µg/mL) and placed triplicate in the wells. The plates will be incubated again for 24 hours. Later, the reagent of MTT *assay* was made by diluted 5 mg MTT in 10 mL PBS. 1 mL MTT reagent is diluted in 9 mL medium, then added 100 µl of the solution into the wells.[14]

The plates consisting of cancer cells, the extract, and the reagent of MTT were incubated for 4 hours. After that, it will be examined with the microscope, if the purple sediment of formazan has formed, in amount of 100 µl of DMSO is added to dissolve the purple sediment. The absorbance of the mixture is measured at 595 nm using an ELISA reader. Then, the calculation of percentage inhibition of cancer cells is carried out by the formula:[14]

$$\%\ \text{Inhibition} = \frac{(\text{absorbance of negative control} - \text{absorbance of treatment})}{\text{absorbance of negative control}} \times 100\%$$

The parameter which represented the concentration of the extract which can inhibit 50% of the growth of cancer cells is IC_{50} value. The calculation of IC_{50} value is obtained using the linear equation between log concentration of the extract and percentage inhibition of A549 lung cancer cell line, or using this formula below, with a is the gradient of the line, and b is a constanta.[14]

$IC_{50} = 10^{(50-b)/a}$

RESULTS

Cytotoxic activity of ethanol, ethyl acetate, and n-hexane extract hibiscus sabdariffa Linn

Figure 2 shows the relationship between the percentage inhibition of lung cancer cells with the concentration of ethanol extract *Hibiscus sabdariffa Linn.* As shown in Figure 2, none of the concentrations achieved a 50% inhibition of the cancer cell activity. The IC_{50} value of ethanol extract of *Hibiscus sabdariffa Linn* is calculated from the linear equation: y = 14.895x +7.4465 and the formula $IC_{50} = 10^{(50-b)/a)}$, with a = 7.4465 and b =14.895 to give IC_{50} value of ethanol extract *Hibiscus sabdariffa Linn* is 374.01 µg/mL.

Figure 3 shows the relationship between the percentage inhibition of lung cancer cells with the concentration of ethyl acetate extract *Hibiscus sabdariffa Linn.* Based on the graph, none of the concentrations achieved a 50% inhibition of the cancer cell activity. IC_{50} value of ethyl acetate extract of *Hibiscus sabdariffa Linn* is calculated from the linear equation y = 18.896x + 1.3827, or with formula $IC_{50} = 10^{(50-b)/a)}$, with a = 1.3827 and b = 18.896 to generate IC_{50} value of ethyl acetate extract of *Hibiscus sabdariffa Linn* is 719.28 µg/mL.

Figure 4 shows the relationship between the percentage inhibition of lung cancer cells with the concentration of n-hexane extract of *Hibiscus sabdariffa Linn.* The IC_{50} value of n-hexane extract of *Hibiscus sabdariffa Linn* is 906.57 µg/mL, which is calculated from the linear equation y = 16.071x + 2.4714 and the formula $IC_{50} = 10^{(50-b)/a)}$, with a = 2.4714 and b = 16.071.

IC_{50} value of ethanol, ethyl acetate, and n-hexane extracts of *Hibiscus sabdariffa Linn* is summarized in Table 1. Ethanol extract of *Hibiscus sabdariffa Linn* has the greatest cytotoxic activity on A549 lung cancer cell line among the others, as it has the lowest IC_{50}. Furthermore, cytotoxic activity of ethanol, ethyl acetate, and n-hexane extract of *Hibiscus sabdariffa Linn* are lower than the positive control, cisplatin (IC_{50} value of 3.60 µg/mL).

DISCUSSION

Extraction and Maceration of *Hibiscus sabdariffa Linn* Samples

The purpose of making three different extracts of *Hibiscus sabdariffa Linn* is to extract various secondary metabolites in different polarity because the secondary metabolites can be dissolved in the same polarity of the solvent. Therefore, different solvents with different polarity can affect the secondary metabolite containing in the extract. Based on a

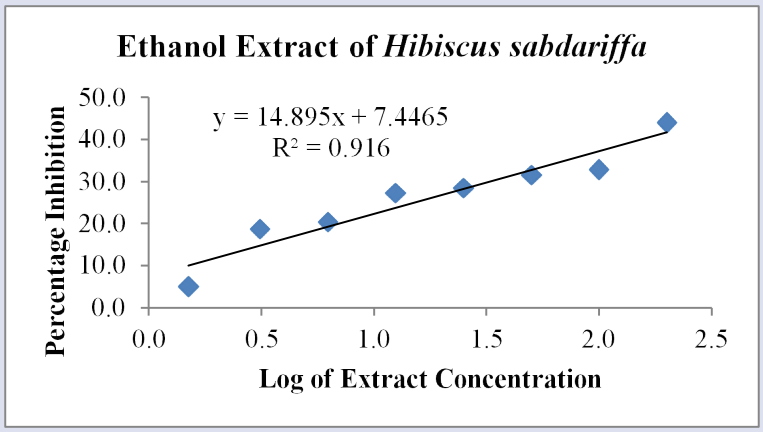

Figure 2: The relationship between ethanol extract of *Hibiscus sabdariffa Linn* and percentage inhibition of A549 lung cancer cell lines.

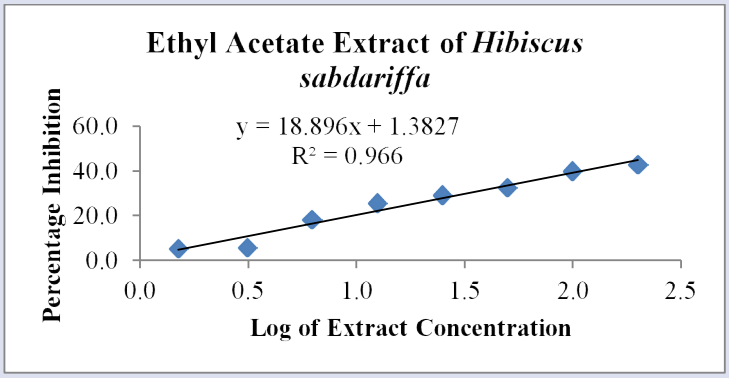

Figure 3: The relationship between ethyl acetate extract of *Hibiscus sabdariffa Linn* and percentage inhibition on A549 lung cancer cell lines.

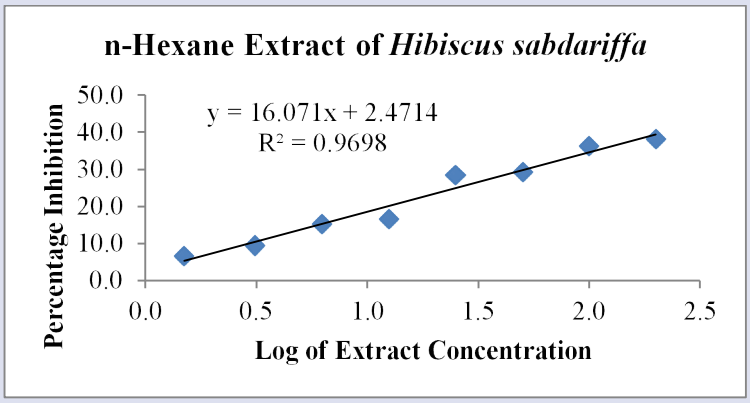

Figure 4: The relationship between n-hexane extract of *Hibiscus sabdariffa Linn* and percentage inhibition on A549 lung cancer cell lines.

Table 1: IC_{50} values of Ethanol, Ethyl Acetate, and n-Hexane Extract of *Hibiscus sabdariffa Linn* on A549 Lung Cancer Cell Line.

Hibiscus sabdariffa Linn Extracts	IC_{50} Values (µg / mL)*
Ethanol	374.01 ± 109.29
Ethyl Acetate	719.28 ± 55.19
n-Hexane	906.57 ± 130.61

*IC_{50} is the concentration of the extract which can inhibits 50% activity of cancer cells, expressed in mean value±SD. *SD: Standard deviation.

study by Widyawati *et al*., ethanol is a polar solvent that can effectively dissolve flavonoids, glycoside, alkaloid, saponin, terpenoid, sterol, phenol, tannin, and anthocyanin. Ethyl acetate is a semipolar solvent that can effectively dissolve flavonoid, alkaloid, and sterol. N-hexane is a nonpolar solvent that can effectively dissolve lignin, wax, sterol, terpenoid, and lipid.[15] The secondary metabolite containing in the extract is related to its anticancer activity. Rutin and quercetin as the derivate compound of flavonoid and triterpenoid are known to have anticancer activity to the lung cancer cells.[16,17] Alkaloid can induct apoptosis activity of the lung cancer cells.[18] Condurangogenin A, a derivate compound of glycoside, has cytotoxic activity to the lung cancer cells by increasing activation of p21, p53, and caspase-3 pathway; decreasing activation of the cyclin-dependent kinase, cyclin D1, and protein Bax expression; and arrest cell cycle in G0/G1 phase.[19] Steroid and triterpenoid in *Spathodea campanulata* have cytotoxic activity on lung cancer in the rat by inhibiting the malondialdehyde enzyme. Therefore, it can be determined at which polarity has the most active cytotoxic activity due to its secondary metabolite.[20]

Cytotoxic Activity of Ethanol, Ethyl Acetate, and n-Hexane *Extracts of Hibiscus sabdariffa Linn*

The MTT (*3-(4,5-dimethylthiazole-2-il)-2,5-diphenyltetrazolium bromide*) assay method was used to analyze cytotoxic activity of ethanol, ethyl acetate, and n-hexane extracts of *Hibiscus sabdariffa Linn*. This method has been commonly used to identify cytotoxic activity of the extract on different concentrations. The basic principle of the method is the mitochondrial activity in every living cells, so the greater the activity, the greater the amount of the living cells.[21] In mitochondria, there is a cellular reductase enzyme that can convert the tetrazolium compound in MTT reagent into the purple formazan crystal. The effect of cytotoxic activity of the extract is evident when the original yellow color of the tetrazolium compound is not changed to purple, indicates low mitochondrial activity. The lower the mitochondrial activity, the lower the amount of the living cells. The absorption of the sample is read using the ELISA reader in 595 nm.[22] The MTT assay uses IC_{50}- value as a parameter for the interpretation of cytotoxic activity. IC_{50} is the amount of extract concentration that can inhibit 50% activity of the cancer cells. The relationship between cytotoxic activity and the IC_{50} value is inversely proportional, therefore the lower the IC_{50} value indicates the higher cytotoxic activity.[14]

Figures 2-4 show the relationship between the percentage inhibition of lung cancer cells with the concentration of ethanol, ethyl acetate, and n-hexane extract *Hibiscus sabdariffa Linn*. The results indicate that the log concentration of the extracts is directly proportional to the percentage inhibition of the cancer cell activity. Therefore, we can conclude that the ability of the extract to inhibit the growth of lung cancer cell is concentration-dependent.

Based on the study from Atjanasuppat *et al,* the anticancer activity can be classified into four groups according to the IC_{50} value: IC_{50} ≤20 µg/mL is classified active; IC_{50} : 20–100 µg/mL is classified moderately active; IC_{50}: 100–1000 µg/mL is classified weakly active; and IC_{50} >1000 µg/mL is classified inactive.[23] As shown in Table 1, IC_{50} value of ethanol, ethyl acetate, and n-hexane extracts are included in 100-1000 µg/mL range, which means that all of *Hibiscus sabdariffa Linn* extracts are weakly active in inhibiting A549 lung cancer cells activity. Meanwhile, the positive control, cisplatin, is very active in inhibiting A549 lung cancer cell activity. The most active *Hibiscus sabdariffa Linn* extract is ethanol extract, as it has the lowest IC_{50} among the three extracts. Therefore, *Hibiscus sabdariffa Linn* extracts is potential to be further developed as a natural anticancer agent.

According to previous research, the study about cytotoxic activity of *Hibiscus sabdariffa Linn* extract on lung cancer is still limited. But, the studies on anticancer activity of *Hibiscus sabdariffa Linn* against other cancer cells has conducted by many researchers. A study by Amran et al. reported that anticancer activity of methanol extract of *Hibiscus sabdariffa Linn* on breast cancer cell MCF-7 is weakly active, with IC_{50} value of 112.1 µg/mL.[24] Furthermore, a study by Chin et al which evaluated anticancer activity of *Hibiscus sabdariffa Linn* on prostate cancer cells using western blot discovered that *Hibiscus sabdariffa Linn* extract inhibits PI3K expression which involved in migration pathway and metastasis of prostate cancer cells. PI3K is known to be involved in the pathogenesis of lung cancer.[25] Another study by Cheng et al reported that the acetone extract of another species of *Hibiscus, Hibiscus syriaca,* has an active anticancer activity to A549 lung cancer cells with IC_{50} value of 9.4 µg/mL, by modulation of p53 pathway and apoptosis induced factor.[26]

CONCLUSION

The ethanol, ethyl acetate, and n-hexane *Hibiscus sabdariffa Linn* extracts showed anticancer activity which can be further developed as a source of natural anti-lung cancer from plants. Further studies are needed to evaluate the specific anticancer mechanism of *Hibiscus sabdariffa Linn* extracts on A549 lung cancer cell line.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this study.

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ABBREVIATIONS

g: gram; mL: millimeter; nm: nanometer; CO_2: Carbon dioxide; FKUI: Fakultas Kedokteran Universitas Indonesia; IC_{50}: Inhibition Concentration 50%; MTT:(3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide); NSCLC: Non-Small Cell Lung Cancer; PBS: Phosphate- Buffered Saline; PI3K: Phosphoinositide 3-kinase; %: Percentage; µg: microgram; µl: microliter; µg/mL: microgram/milliliter.

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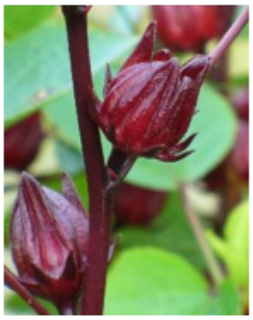
GRAPHICAL ABSTRACT



Hibiscus sabdariffa

In vitro cytotoxicity analysis of *Hibiscus sabdariffa* extracts on A549 lung cancer cell line

IC_{50} value of ethanol, ethyl acetate, and n-hexane extract of *Hibiscus sabdariffa* on A549 lung cancer cell line

Extract	IC_{50} value (µg / mL)
Ethanol	374,01 ± 109,29
Ethyl Acetate	719,28 ± 55,19
n-Hexane	906,57 ± 130,61

SUMMARY

Hibiscus sabdariffa Linn originated from Tangerang, Banten, Indonesia, showed cytotoxic activity on A549lung cancer cell line with IC_{50} of 374.01 µg/mL, 719.28 µg/mL, and 906.57 µg/mL.

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