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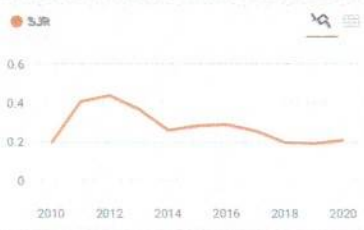

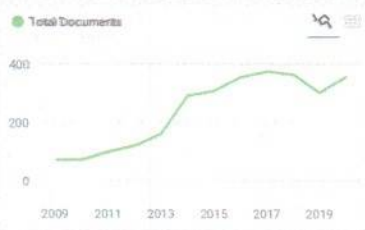

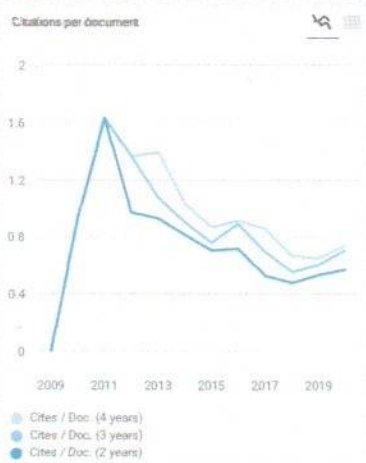

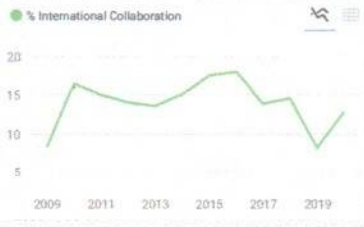

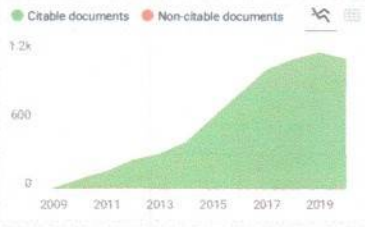

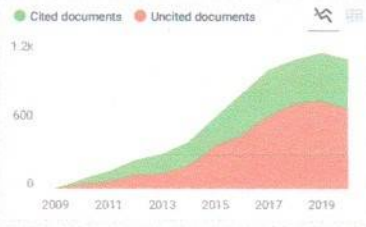

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Original Research Article

Apoptotic effect of *Physalis minima* Linn ethanol extract on breast cancer cells via p53 wild-type and Apaf-1 protein

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Abstract

Purpose: *To produce an anti-cancer agent from Physalis minima ethanol extract as well as prevent the growth of NMU-induced breast cancer and MCF-7 cell line.*
Methods: *This research used an animal model (Wistar-Furth rats), and cell line used in this study was normal breast-cell line MCF-7. The rats were administered with the ethanol extract of Physalis minima Linn (100, 250 and 400 mg/kg/day) by gavage, once a day for 4 weeks. Meanwhile, MCF-7 cell lines were cultured in medium and incubated in 100 µg/mL of ethanol extract of Physalis minima for 48 h. The samples were analyzed using histology and immunohistochemistry techniques for expression of p53 antibody DO-1 and APAF-1.*
Results: *The results of immunohistological analysis in the breast organ showed that Physalis minima Linn extract significantly ($p < 0.05$) increased the tumor suppressor protein p53 at doses of 100, 250 and 400 mg/kg/day. In addition, the extract also significantly ($p < 0.05$) increased APAF-1, which is a gene determining cell death, at doses of 100, 200 and 400 mg/day.*
Conclusion: *Ethanol extract of Physalis minima Linn inhibits the cytotoxic activity of NMU-induced breast cancer by increasing the tumor suppressor protein p53 and APAF-1. Thus, Physalis minima Linn extract can potentially be used as a complementary treatment for inhibiting the growth of breast cancer cells in patients.*

Keywords: *Apoptosis protease-activating factor-1, Breast cancer, MCF-7 cell line, Physalis minima, p53*

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INTRODUCTION

Breast cancer is one of the most common cancers in the world. It accounts for over 10.9% of all cancers, with reported incidence of about 1.38 million cases in 2008 [1]. Cancers are characterized by rapid and uncontrolled cellular growth, local tissue invasion and distant metastases [1]. Cancers happen due to the presence of carcinogens, including free radicals [2].

Scientists have studied the biological properties of several promising plants and herbs. Medicinal plants and herbs played important roles in the last half-century in treating cancer. Secondary metabolites and the derivatives have been applied towards cancer.

The anti-tumor agents that can kill or deactivate tumor cells without damaging normal tissue has been examined in HepA cells, HepG2 and MCF-7 cells [3]. Currently, plant-derived anti-cancer drugs are in regular clinical use for treating cancer. These anti-cancer drugs are vinblastine and vincristine, which is firstly extracted from *Catharanthus roseus* (Apocyanaceae) and then used in the treatment of various cancers, including testicular, breast, and lung cancers, and Kaposi's sarcoma [4,5]. An interesting anti-cancer plant selected for this study was *Physalis minima.* L. The decoction of this whole plant was given orally to treat cancer, while the leaves were used as a poultice for ulcer [6,7].

Studies have repeatedly stated the striking anti-cancer effect of *P. minima* against several cancer cell lines. The chloroform extract of *P. minima* produced a significant growth inhibition in human T-47D breast carcinoma cell death via p53, caspase3, and c-myc-dependent apoptotic pathways [7]. The aim of this research was to produce anti-cancer agents from *P. minima* ethanol extract, as well as prevent the growth of NMU-induced breast cancer and MCF-7 cell line.

EXPERIMENTAL

Animal model

Wistar-Furth Rats were purchased from The Pathology Anatomy Laboratory (Faculty of Medicine, Airlangga University, Surabaya, Indonesia). The rats were maintained under light/dark cycle for 12 h. The rats were fed with standard rodent diet and provided with water *ad libitum*. Rats were treated with N-nitrosometylurea of 50 mg/kg/bw for 5 weeks during maintenance. After 5 weeks of maintenance, ethanol extract of *Physalis minima* Linn of 100, 250 and 400 mg/kg/day were administrated to the rats by gavage once a day for 4 weeks. Placebo-treated rats were administered an equivalent volume of vehicle (0.5 % carboxymethyl cellulose sodium salt in water). All experimental procedures and protocols were approved by the Animal Care and Use Committee of the Airlangga University (ethical clearance no. 062-KE), and complied with the guidelines of `Guide for the Care and Use of Laboratory Animals` [8].

Cell culture

The cell lines used in this study were the normal breast-cell lines MCF-7 purchased from ATCC [7]. MCF-7 cells were grown in phenol red-free DME/F12 medium (Invitrogen Corp. and Life Technologies, Grand Island, NY) containing 10 % FBS and 1 % PenStrep to 80 - 90 % confluence. The MCF-7 cell lines were cultured in medium, and incubated in 100 µg/mL of ethanol extract of *Physalis minima* Linn for 48 h and then collected for further analysis.

Histological and immunohistochemical studies

At the end of treatment, the Wistar-Furth mice were euthanized with protocols consistent with previous research [9], and tumor tissue was removed, fixed overnight in 4 % paraformaldehyde solution, followed by paraffin infiltration and embedding step as described previously [8]. Immunohistochemical analysis was carried out for p53 antibody DO-1 (Santa Cruz, Inc., CA) and APAF-1 (Abcam).

Statistical analysis

The results are expressed as mean ± standard error of the mean (SEM). The different treatment groups were evaluated for statistical significance using Student`s t-test or one-way ANOVA. $P < 0.05$ was considered significant.

RESULTS

Effect of *Physalis minima* Linn ethanol extract on the expression of p53 in NMU-induced breast cancer cells

Figure 1 shows the expression of p53 in NMU-induced breast cancer. The *Physalis minima* Linn extract significantly ($p < 0.05$) increased the expression of p53. This result suggested that the administration of *Physalis minima* Linn extract was effective to suppress the cancer cell by p53.

Effect of *Physalis minima* Linn ethanol extract in increasing the expression of APAF-1 in NMU-induced breast cancer

Figure 2 shows that the administration of *Physalis minima* Linn extracts increased the expression of Apaf-1 in doses 100, 250 and 400 mg/kg/day with significant p<0,05 in NMU induced breast cancer. However, there is no significant difference in value between 250 and 400 mg/kg/day. The increasing Apaf-1 is well-known as the important component of the apoptotic pathway.

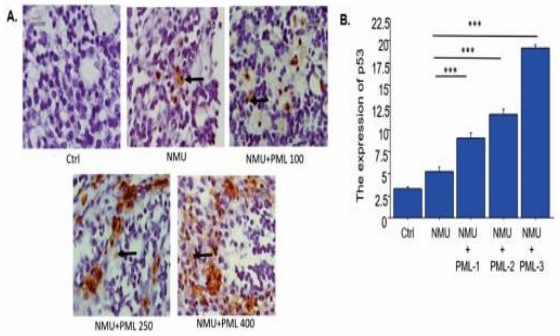

Figure 1: Effect of *Physalis minima* Linn ethanol extract to immunohistochemical profile (a) and the expression of p53 level (b) in NMU-induced breast cancer profile in *Rattus norvegicus*. Cntrl: control, NMU: *N-nitrosometylurea*, PML: *Physalis minima* Linn ethanol extract, NMU+PML-1: Low dose (100 mg/d), NMU+PML-2: Middle dose (250 mg/d), and NMU+PML-3: High dose (400 mg/d). *** represents $p < 0.01$ cs. Cntrl. All values were presented as mean ± SEM (n: 6).

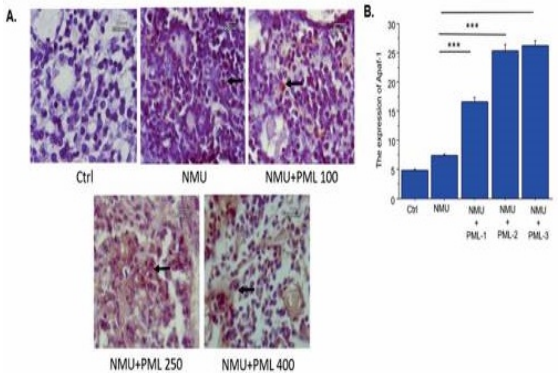

Figure 2: Effect of *Physalis minima* Linn ethanol extract to immunohistochemical profile (a) and the expression of Apaf-1 level (b) in NMU-induced breast cancer profile in *Rattus norvegicus*. Ctrl: control, NMU: *N-nitrosometylurea*, PML: *Physalis minima* Linn ethanol extract, NMU+PML-1: Low dose (100 mg/d), NMU+PML-2: Middle dose (250 mg/d), and NMU+PML-3: High dose (400 mg/d). *** represents $p < 0.01$ cs. Cntrl. All values were presented as mean ± SEM (n = 6)

Effect of *Physalis minima* Linn extract in MCF-7 cells

To gain insights into the mechanism by which physalis minima Linn extract potently reduced the apoptotic cells, the effects of physalis minima Linn extract mitosis and apoptosis was examined in MCF-7 cells. We incubated MCF-7 cells with PML- 12,5, 25, 50, 100 and 200 µg/ml for 48 hours. As we can see in figure.3 PML decreased the mitosis and increased the apoptosis cells MCF7.

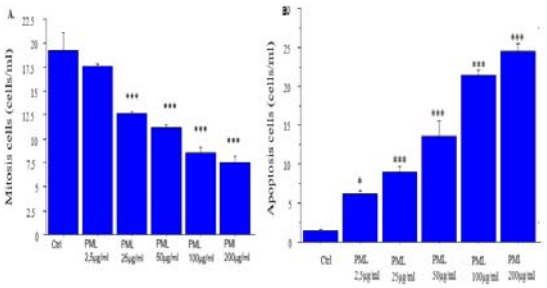

Figure 3: Effects of physalis minima Linn extract in MCF-7 cells (a) the effects of PML in mitosis cell of MCF-7 and (b) apoptosis cell in MCF-7. Ctrl: control, PML: Physalis minima Linn ethanol extract; *$p < 0.05$; $p < 0.001$ cs. Ctrl. All values were presented as mean ± SEM (n = 4)

DISCUSSION

Breast cancer is one of most awful diseases which is causes death among women. In the present study, there are evidences that indicate that *Physalis minima* Linn extract prevents the progression of cancer cells by increasing the expression of p53 and APAF1 in NMU-induced breast cancer in rats. Previous studies have demonstrated that *Physalis minima* Linn of *Physalis* genus is used in various biological and pharmacological activities including anti-inflammatory, quinone reductase induction, immunomodulatory, anti-tumor, antioxidant, anticarcinogenic, and hypoglycemic activities [9-11].

Breast cancer that is accompanied by the mutation of p53 allele will be retained in the wild-type of p53. Furthermore, the significance of detecting the wild-type p53 protein in the cytoplasm of cancer cells becomes clearer when it is appreciated that p53 protein excluded from the cell nucleus will no longer inhibit the proliferation of cells in culture [12].

It has been well established that p53-mediated apoptosis of most cells are induced through the activation of the death receptor (extrinsic) or the mitochondrial (intrinsic) pathway [12].

Overexpression of p53 can stimulate the extrinsic apoptotic pathway from the cell surface to intracellular signaling pathway [12,13]. However, in this study, the administration of *Physalis minima* Linn extracts significantly decreased the expression of wild-type p53. This result was correlated with the previous study that examined antioxidant activities of *Physalis peruviana*. It was found that the *Physalis minima* extract has the strongest superoxide anion scavenging and inhibitory effect on xanthine oxidase activities [14]. In addition, free radicals have been

regarded as the fundamental cause of a different kind of disease including breast cancer. The tissue injury caused by ROS are DNA damage, protein damage, and oxidation of enzymes. Alpha-tocopherol as an antioxidant is capable for mitigating free radical damage and scavenging ROS [14]. Apoptosis protease-activating factor (APAF-1) is an important tumor suppressor gene which plays a central function in DNA damage-induced apoptosis [14]. Besides, APAF-1 expression was defective in malignant melanoma or human leukemia cell lines, resulting in cancer development [14,15]. However, in this study, the extract of *Physalis minima* Linn significantly decreases apoptosis by the expression of APAF-1 in NMU-induced breast cancer. Recently, it has been reported that treatment using *P. minima* extracts were able to inhibit cell proliferation and induce apoptosis [16]. It is well established that cancer cells escape apoptosis through several mechanisms, including loss of function in tumor suppressor genes via mutations or epigenetic alterations [17]. As the core of the apoptosome complex, APAF-1 is crucial for programming the cell death, and its malfunction may lead to the progress of diverse human neoplasms [18-19].

In this study, the breast cancer cell lines of MCF-7 were used to examine the specific effects of *Physalis minima* Linn extract. The MCF-7 cells are estrogen-receptor (ER) positive and classified as log-grade and luminal type. Where a plant extract successfully acts as an anti-cancer drug, it should kill cancer cells without causing excessive damage to normal cells [9]. Recently, intensive studies have been conducted to examine the possible mechanism for the anti-cancer effects of plant-based drugs. Apoptosis is a specific model of cell death that can only target cancer cells with little or no damage to non-cancerous cells [10]. Information on the apoptotic effect elicited by the extracts and bioactive compounds of *Physalis* sp. are still limited to a few findings, such as the cell death signaling effects of physalins B and F on PANC-1 pancreatic cancer cells [19].

This present study showed that *Physalis minima* Linn decreased the number of mitosis and apoptosis of MCF-7 cell lines after 48 h treatment. Studies repeatedly pronounce the striking of anti-cancer effect of *P. minima* against several cancer cell lines. Chloroform extract of *P. minima* produced a significant growth inhibition in human T-47D breast carcinoma cell death via p53, caspase3, and c-myc-dependent apoptotic pathways97. An apoptotic and autophagic programmed cell death via cytotoxic effect also were found by *P. minima* chloroform extract against Caov-3 cells [20,21].

CONCLUSION

The extract of *Physalis minima* Linn inhibits the cytotoxic activity against NMU-induced breast cancer and breast cells line. The cytotoxic effect of extract inhibits cell growth and appears to induce apoptosis in MCF-7 cells. Thus, it can potentially be developed for the clinical management of breast cancer.

DECLARATIONS

Acknowledgement

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Conflict of interest

No conflict of interest is associated with this study.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Handayani designed the research, wrote the manuscript and analyzed the data, Retno Handajani wrote the manuscript and analyzed the data, Imam Susilo wrote the manuscript and analyzed the data, Achmad Basori wrote the manuscript and analyzed the data, and Hotimah Masdan Salim approved the revised manuscript and designed the research.

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