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# The Ethanol Extract of Red Banana Peel (*M.acuminata* Colla) Induce Cell Death and Inhibit Metastatic of Breast Cancer

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## Abstract

Breast cancer is the most common malignancy in women and the leading cause of cancer-related death. Death from cancer is caused by metastasis to distant organs. The metastatic process is a complex and continuous process, in which the ROS that causes oxidative stress plays a role in the metastatic cascade. While treatment with the chemotherapy agent Doxorubicin (DOX) also causes side effects on healthy organs. Extract ethanol Red Banana Peel (ERBP) *Musa acuminata* Colla contains phytochemical compounds in the form of flavonoid, tannin, saponin, triterpenoid, and alkaloid which are potential co-chemotherapy agents. This study aimed to determine the effect of ERBP on the metastatic ability of breast cancer cells MCF-7 and cell death in combination with DOX. MCF-7 Cell death was measured using the Trypan Blue Assay and metastatic ability was measured using the Scratching Wound Healing Assay. The anticancer activity from ERBP compounds showed that ERBP with or without DOX combination was effective in reducing viability and inhibiting metastasis of MCF-7 cell.

**Keywords:** antioxidant, cell viability, Red Banana Peel, metastatic, phytochemical

## 1. Introduction

Breast cancer is the most common malignancy in women and the leading cause of cancer-related death. It is reported that about 2.1 million new cases of breast cancer in women worldwide and the leading cause of cancer death in 135 countries [1]. More than 90% of patients die from metastasis, which is when cancer cells break out of the original tumor, spread systematically, and colonize distant organs [2,3].

Breast cancer cell metastasis is a complicated and sequential process [4,5]. Metastatic inhibition is challenging because it involves a cascade process, each of process has its own requirements [6]. ROS causes oxidative stress proven to play a role in the metastatic process, as a mediator of epithelial-mesenchymal transition (EMT), an increase in the Matrix Metaloproteinase (MMP) enzyme, induces angiogenesis through an increase in vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR), and hypoxic conditions that result in an increase in Hypoxia inducible factor-1α (HIF-1α) [7,8].

Chemotherapy is a common treatment for metastatic breast cancer in addition to surgery. The chemotherapy agent that is often used is Doxorubicin (DOX). Despite having anti-cancer

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activity, Doxorubicin causes an increase in ROS which accumulates in cardiomyocytes, causing cardiotoxicity in long-term use [9,10,11]. DOX treatment on MDA-MB 231 cells was shown to cause an increase in MnSOD which affects the EMT process.[7] Therefore, it is necessary to develop medicinal plants as co-chemotherapy agents with the aim of increasing the efficacy of chemotherapy drugs while reducing side effects [12].

The development of various types of cancer is associated with the consumption of flavonoids and other bioactive compounds contained in fruits and vegetables [13]. The peel of the fruit is a major by-product and several studies have shown that it is a good source of polyphenols, carotenoids and other bioactive compounds that have various beneficial effects on human health [14]. For example, the ethanol extract of apple peel containing flavonoids has been shown to inhibit cell migration and cell invasion of MDA-MBC 231 breast cancer cells and reduce the expression of MMP2 protein which plays a role in cell invasion [15]. This beneficial effect is due to the fact that some of the bioactive compounds in flavonoid-rich foods tend to act synergistically. A number of studies on phytochemical compounds as potential anti-cancer agents have found that these natural compounds influence many different signaling pathways involved in cancer development and progress [13]. Antioxidants prevent oxidative damage to various macromolecules such as nucleic acids, proteins, and lipids and scavenge free radicals resulting from biochemical reactions [8].

Red banana (*M. acuminata* Colla) is a wild banana originating from Southeast Asia [16], that peels are rich in phytochemical compounds, especially antioxidants such as phenolic compounds, gallocatechins, delphinidin anthocyanins, cyanidins and catecholamines [17]. Previous research reported that the ethanol extract of *M. acuminata* colla peels has the ability to kill HeLa cancer cells by 87%. Anti-proliferative activity on EACC cells caused cell death by 87%, which supports the potential of *M. acuminata* Colla's peel as an anticancer [18].

The purpose of this study was to prove the effect of the combination of the ethanol extract of red banana peel (*M.acuminata* Colla) (ERBP) with Doxorubicin on cell viability and inhibition of metastasis of MCF-7 breast cancer cells. Secondary metabolites, total flavonoids and antioxidant activity were measured before determining cell death by trypan blue assay and a scratching wound healing assay to measure the ability to inhibit metastasis breast cancer cell.

## 2. Methods and Material

### *2.1 Ethanolic extract of red banana peel (ERBP)*

Red banana peel (*M.acuminata* Colla) obtained from Tarakan, North Kalimantan, Indonesia. The simplicia of red banana peels was extracted by maceration and evaporation method with 90% ethanol solvent with a ratio of 1: 9. The concentrations of ERBP used were 25, 50, and 100µg/mL

The identification was authenticated at Laboratory of Ecology and Conservation of Tropical Forest Biodiversity, Faculty of Forestry, Universitas Mulawarman, Indonesia (No. 86/UN17.4.08/LL/2020).

### *2.2 Experimental Design*.

This experiment divide six groups: control (1), cells were treated with DOX 10 µg/ml alone (2), cells were treated with combination of 5 µg/ml DOX and ERBP 25, 50 or 100 µg/mL, respectively (3-5). Cells were treated with ERBP 100 µg/ml alone.

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*2.3 Phytochemical Test Ethanolic extract of red banana peel (ERBP)*

2.3.1. Identification of Flavonoid

Identification of flavonoids was carried out by dissolving 1g ERBP in hot methanol and added 0.1 g Mg and 5 drops of HCl.

2.3.2. Identification of Alkaloid

The identification of alkaloids was carried out using the Mayer, Wagner, and Dragendrof methods. 0.5 g ERBP were added with 2M HCl and 9 mL H2O, heated for 2 minutes, cooled and then filtered. The filtrate is divided into three parts; each part was added with Mayer, Wagner, and Dragendorf reagents.

2.3.3. Identification of Triterpenoid and Steroid

Triterpenoid and steroid identification were carried out by dissolving 0.5 g ERBP in 0.5 mL chloroform, then added 0.5 mL acetic anhydride and then dripped the solution with 2 ml $H_2SO_4$.

2.3.4. Identification of Tannin

Identification of tannin was carried out by dissolving 1 g ERBP in 10 mL H2O and then filtered. The filtrate was added with three drops of 1% $FeCl_3$.

2.3.5. Identification of Saponin

0.5 g ERBP was dissolved in 2 mL H2O, and then heated for 2-3 minutes, and cooled. A positive test of saponin was indicated when there was stable foam for 30 seconds.

*2.4 Determination of Total Flavonoid Content (TFC)*

Briefly, 20 mg ERBP was dissolved in 10 mL ethanol. Then, 300 µL ERBP solutions were mixed with 5% NaNO2 and 10% AlCl3. After 10 minutes incubation, 400 µL of 1 M sodium hydroxide and 480 µL H2O was added. The TFC was evaluated at 510 nm using a spectrophotometer. Quercetin was used as the reference compound to produce the standard curve; the results were expressed as mg Q/g.

*2.5 Diphenyl Picryl Hydrazyl (DPPH) Antioxidant capacity Assay*

The Antioxidant capacity of ERBP was examined using the 1,1-diphenyl1-2-picrylhdrazyl (DPPH) assay. DPPH solution was freshly prepared by dissolving 2 mg DPPH in 50 mL ethanol and incubated for 30 minutes in dark room. 10 mg ERBP was dissolved in 10 ml ethanol and incubation for 30 minutes in dark room. Concentration of the sample used is 250, 125, 62.5, 31.25µg/mL. DPPH solution was added with ERBP (1:1 ratio). The absorbance was measured at 515 nm using a spectrophotometer. Radical scavenging activity was calculated using the following formula:

$$\text{DPPH scavenging (\%)} = \left[\frac{Abs.Control - Abs.Sample}{Abs.Sample}\right] \text{X } 100$$

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$IC_{50}$ was calculated from the graph plotted of inhibition percentage against samples concentration and equals to sample concentration providing 50% inhibition.

*2.6 Cell culture*

MCF-7 cell line was obtained from the Biomedical Laboratory of Universitas Brawijaya, Indonesia. MCF-7 cells were cultured in RPMI-1640 supplemented with 10% FBS v/v, 1% Penicillin-Streptomycin at 37°C in 5% $C0_2$.

*2.7. Cell Viability Assay*

Cell viability was assessed by Trypan Blue dye assay, 6 x $10^4$ cells/ mL were transferred to 24 well plates then treated with single or combination of ERBP at 25, 50 or 100 µg/mL and then incubated 24 hours [19]. Cells were collected by centrifuge 800rpm, 5 minutes. 0.4% Trypan Blue was added into the cell suspension at a ratio (1: 1). The dilution of cells was applied to the Haemocytometer to calculate viability under a microscope. Viable cells will have a clear cytoplasm whereas a nonviable cell will have a blue cytoplasm.

The cells/ml was measured using the following formula: average cell count x dilution factor x $10^4$ cells/ml. The % cell viability was determined as [(no. of viable cells/ total no. of viable + non-viable cells) x 100. The percentage of growth inhibition was represented as {cell viability (control) – cell viability (with extract)}.

*2.8 Metastatic Inhibition With Scratching Wound Healing Assay*

MCF-7 cells were cultured in 24 well plates and allowed to reach 80% confluent. Cells were then treated with 10µg/mL DOX alone or combination with ERBP at 25, 50 and 100 µg/ml, respectively. A 200-µl pipette tip was used to make a straight scratch on the culture. Cells were reevaluated within 24 hours. The wound area was photographed under a microscope at 400 x. Metastatic ability was verified by measuring the number of cells that migrated to the wound area at 24 hours of observation with ImageJ software [6].

*2.9 Statistics Analysis*

Data are presented as the mean ± SD (standard deviation). The results were analyzed by the one-way ANOVA test, followed by Post Hoc Tukey test. Statistical analysis was performed with SPSS software version 23. (SPSS Inc., Chicago, IL, USA)

## 3. Results

### 3.1 Phytochemical Test

The result reveals that some of the phytochemicals constituents were present in the ERBP are flavonoid, alkaloid, tannin, triterpenoid and saponin, which shows a change in color according to the parameters, after adding some reagents. The phytochemical test as presented in Table 1.

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**Table 1. Phytochemical Test**

| Compound | Parameter | Result |
|---|---|---|
| Flavonoid | Orange | Positive (+) |
| Alkaloid | | |
| Meyer | White sediment | Negative (-) |
| Dragendrof | Orange sediment | Negative (-) |
| Bouchardat | Brown sediment | Positive (+) |
| Tannin | Dark brown | Positive (+) |
| Terpenoid | | |
| Steroid | Bluish Green | Negative (-) |
| Triterpenoid | Brownish orange | Positive (+) |
| Saponin | Permanent Foam | Positive (+) |

### 3.2 Determination of Total Flavonoid Content (TFC)

Total Flavonoid Content (TFC) of ERBP was determined by standard quercetin. Result were expressed as quercetin equivalents (mg Q/g) using the following equation Y= 0.0039X + 0.0044 at $R^2$ = 0.9866, and TFC of ERBP was 212.71 mg Q/g. The result of the TFC confirms that the extract was rich in flavonoids contents.

### 3.3. Determination of the Total Antioxidant Activity

The antioxidant capacity was measured using the 2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl (DPPH) Assay. The results show how much the ability of ERBP to inhibit radicals. Result shown that ERBP with percentage inhibition of 80.24% at concentration of 250µg/mL with $IC_{50}$ 6.12 µg/mL (Tab. 2 and Fig.1)

The radical scavenging activity of ERBP extracts against the DPPH radical was determined, the procedures were as follow: 3 mL of 0.1 mM DPPH radical solution was mixed with 3 mL of methanolic solutions of ERBP (concentration series of 75 – 175 µg/mL). After 30 min incubation at the dark room, absorbance decrease of the mixture was monitored at 515 nm (A sample). During reduction by the antioxidant, the solution color changed from violet to yellow pale. Blank samples with 3 mL of methanol and 3 mL of 0.1 mM DPPH radical solution were prepared and measured daily at same wavelength (A blank). Quercetin was used as positive control. The experiment was carried out in triplicate. Radical scavenging activity was calculated using the following formula.

**Table 2. Antioxidant capacity of ERBP**

| Concentration of ERBP (µg/ml) | % Inhibition | $IC_{50}$ (µg/ml) |
|---|---|---|
| 250 | 80.24 | 6.12 |
| 125 | 68.26 | |

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| | |
|---|---|
| 62.5 | 55.20 |

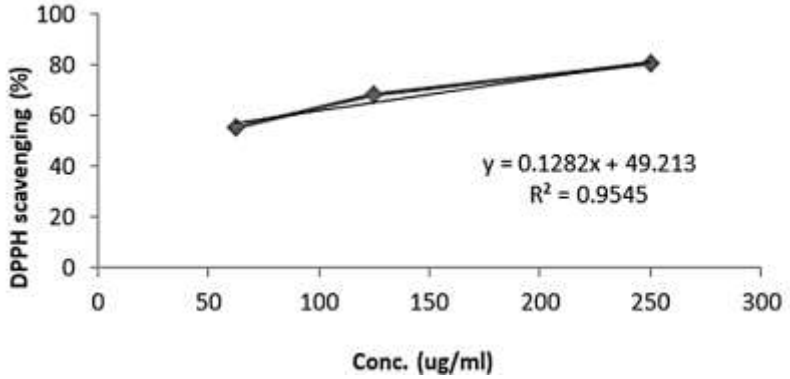


**Figure1.** The DPPH scavenging curve of ERBP shows an increase in the ability to inhibit radicals with increasing concentrations of ERBP. At a concentration of 250µg/ml inhibit 80.24% with a value of $IC_{50}$ 6.12 µg/ml.

### 3.3 Ethanol Extract of Red Banana Peel (ERBP) induce Cell Death

Trypan blue assay was used to assess the ability of the combination of ERBP and DOX in cell death by calculating cell viability. The results indicated that ERBP treatments could induce cell death, and the combination of 5 and 100µg/mL ERBP caused significantly increase cell death than either treatment DOX alone. In addition, single ERBP was also significantly increase cell death than treated DOX alone (Fig.2)

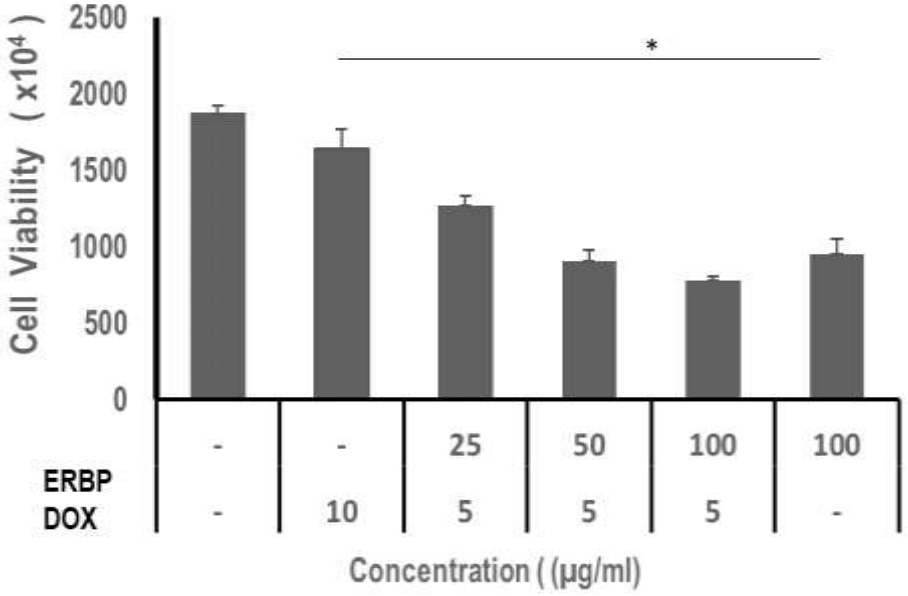


**Figure 2**. The Trypan Blue assay showed significantly decrease in the viability. The concentration of 5 and 100 µg/mL induced significantly increase cell death. Single treatment of

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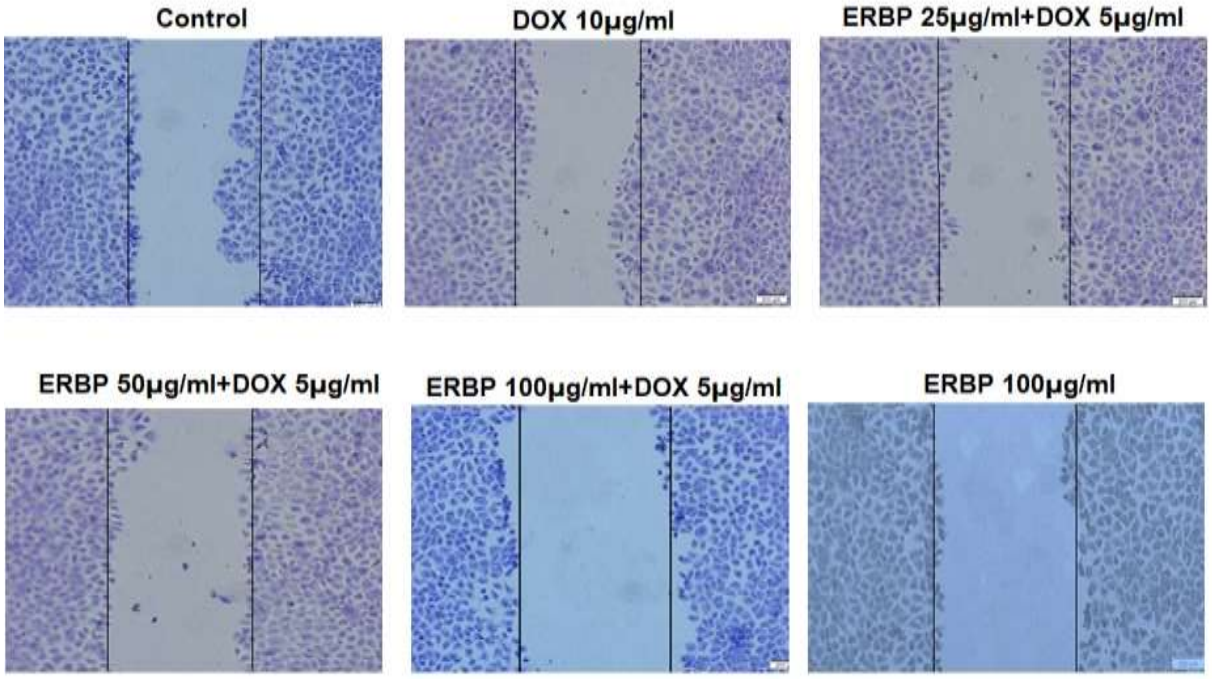
ERBP was also significantly increase cell death than DOX alone. Data were shown as mean ± SD, with n = 3 replicates in each group. *P < 0.05

### 3.4 Ethanol Extract of Red Banana Peel (ERBP) Inhibit Metastatic Ability of Breast Cancer Cell

The wound healing scratch assay was carried out to determine the effect of ERBP on metastatic cells. Metastatic ability was verified by measuring the number of cells that migrated to the wound area at 24 hours of observation (Fig. 3A). The combination of DOX and ERBP at 100 µg/ml and single dose of ERBP 100 µg/ml suppresses the number of migrated cells (Fig. 3B)




(A)

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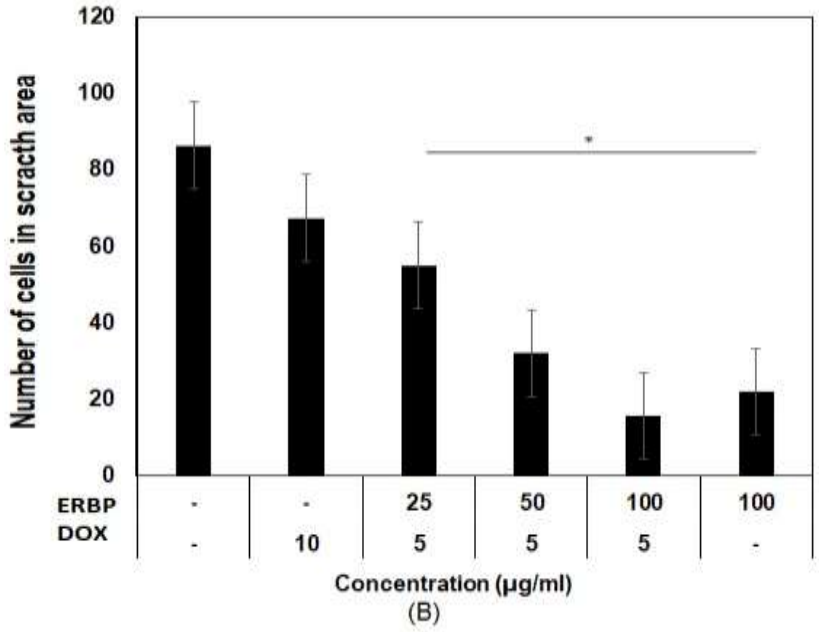


**Figure 3.** The migration effects of ERBP on MCF-7 cell metastatic ability. (A) The metastatic was inhibited after ERBP treatment determined by wound healing scratch assay. (B) ERBP inhibits metastatic cells based on the number of cells migrated to the wound area at 24 hours of observation. *P < 0.05 significantly different than treatment DOX alone with n = 3 replicates in each group.

## 4. Discussions

Plants are a major source of natural antioxidants because of their phytochemical content. The antioxidant properties are due to the hydroxyl groups in their structural formulas. Their main activity is to protect the defence system against oxidative stress by free radicals. Various antioxidant compounds can stabilize ROS such as hydroxyl anion radicals, superoxide ($O_2^-$), singlet oxygen ($O_2$*), and $H_2O_2$ [20].

The high value of antioxidant activity in ERBP is because it is proven to contain flavonoids. Flavonoids from plants act as antioxidants because their aromatic rings have free hydroxyl (OH). The ability of flavonoids to directly scavenge reactive oxygen species is the most important flavonoid antioxidant property. Flavonoids are able to chelate free radicals immediately by donating hydrogen atoms or by single electron [21,14]. The number of hydroxyl groups present in the aromatic ring is proportional to the antioxidant effectiveness of the substance [22, 23].

Our experiment proves that the combination of ERBP and Doxorubicin (DOX) increases cell death and decreases the survival of MCF-7 cancer cells. The combination of DOX and ERBP 100 µg/ml is more effective better than DOX alone. The mechanism of ERBP in causing cell death was not investigated in this study, but result is in line with Abou-elella and Mourad (2015) who reported that the ethanol extract of M. *acuminata* peel have potential antioxidant activity against various antioxidant system and anticancer due to the presence of various phyto-constituents which counteract the free radicals [18].

Oxidative stress has been shown to play a role in the metastatic process, the inhibition of metastasis by targeting reactive oxygen species (ROS) needs to be considered [4,8]. This study was shown the decreasing of cell number that migrated into the wound area. Inhibition of MCF-7 cell migration can predict the anti-metastatic potential of phytochemical compounds in ERBP. Various studies have also reported the role of flavonoids in influencing cancer-related pathways, one of which is reducing invasion and metastasis. Chemo-preventive flavonoids such as curcumin and broccoli show significant radical scavenging activity [13]. Flavonoid Baicalein and grape seeds suppresses the activity and expression of matrix metalloproteinase (MMP-2 and MMP-9) [24,25], *Vitis amurensis* grape inhibit breast tumor cell growth by suppressing the VEGF[25]. Catechins in green tea have been shown to transfer electrons or transfer hydrogen atoms to ROS-induced radical sites in DNA [24]. Curcumin suppresses the migration and invasion of pancreatic cancer cells [25,26]. In addition, flavonoids also act as intracellular antioxidants through inhibition of free radical-producing enzymes such as xanthine oxidase and NADPH oxidase which play a role in the angiogenesis process [27,28,29].

## 5. Conclusion

In conclusion, phytochemical compounds of Extract Ethanol Reb Banana Peel (ERBP) were effective in reducing cell viability and inhibiting MCF-7 cell metastasis with or without DOX combination. These results suggest that ERBP has potential as a co-chemotherapy agent in the treatment of breast cancer.

**Limitations and Future Studies:** This study did not identify the mechanism of ERBP in inhibiting metastasis and inducing cell death, and future studies are expected to examine inhibition pathways of metastasis and cell death activated by ERBP.

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**Ethical Approval:** All experiments were conducted according to the principles of Guide for the Care and Use of Laboratory in Indonesia and were approved by The Ethical Committee Universitas Brawijaya, Malang, Indonesia (09/EC/KEPK/01/2021).

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