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Research article

Antiproliferative Evaluation of *Dioscorea esculenta* Tuber Extracts on Breast Cancer Cell Lines

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Abstract: Breast cancer remains one of the most prevalent causes of cancer-related fatalities among women worldwide. Subtypes like MCF-7 and MDA-MB-231 provide formidable obstacles to treatment. There has been a recent uptick in research into the potential anticancer benefits of naturally occurring compounds derived from plants. One species of yam, *Dioscorea esculenta*, is very medicinally promising due to its abundance of bioactive chemicals. The phytochemical profile and antiproliferative activity of *D. esculenta* on MCF-7 and MDA-MB-231 breast cancer cell lines were evaluated. *D. esculenta* was extracted in both methanolic and aqueous forms using cold maceration. The extracts' antiproliferative effect on MDA-MB-231, MCF-7, and NIH-3T3 cell lines was evaluated using the MTT assay. The process of cell death in treated cancer cells was examined using flow cytometry. The results show that both extracts contain several phytochemicals, including tannins, phenols, alkaloids, flavonoids, terpenoids, and saponins. The antiproliferative effect on MDA-MB-231 was significantly highlighted by the *D. esculenta* methanolic extract (IC_{50} 5.50 µg/mL). Flow cytometry showed that *D. esculenta* methanolic extract induced programmed cell death in MDA-MB-231 cells, which indicates that the plant extract contains promising anti-infective compounds, which could be responsible for the observed antiproliferative effects. In sum, the results indicate that *D. esculenta* shows promise as a cancer treatment option due to its ability to selectively target aggressive breast cancer cells while avoiding normal cells.

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Introduction

As the leading cause of cancer-related mortality among women, breast cancer affects an estimated two million people every year [1, 2], making it a major public health concern around the world. Breast cancer affects a varied range of ethnic groups in Malaysia. For example, 1 in 30 Malay women, 1 in 23 Indian women, and 1 in 22 Chinese women will get the disease. The 5-year survival rate for women with breast cancer is 88% for stage I and 81% for stage II, depending on how quickly the disease is detected. The survival rate for malignancies detected at Stage III is 60%, which is much lower than Stage IV's 23% [3]. Due to their heterogeneity and resistance to standard chemotherapy, two kinds of breast cancers-hormone receptor-positive (MCF-7) and triple-negative (MDA-MB-231) present considerable treatment challenges [4, 5].

There has been a surge in interest in phytocompounds generated from plants as a potential new class of anticancer drugs due to their antiproliferative and pro-apoptotic effects on a variety of cancer types [6-8]. Of these, the yam-producing genus Dioscorea (D.) stands out. Saponins, terpenoids, alkaloids, phenolics, and diosgenin are only a few of the

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numerous active metabolites found in the plant esculenta that have attracted attention because of their potential anticancer effects [9, 10]. More recent studies have shown that this genus has cytotoxic and antiproliferative effects on breast cancer cells. The main bioactive compounds reported in *D. esculenta* are saponins, terpenoids, alkaloids, and phenolics; these compounds have shown modest cytotoxicity against MCF-7 cells [10]. Extracts from *D. esculenta* could be used as a cancer treatment since they showed strong antiproliferative effects in several kinds of cancerous cells [11]. Studies on the phytochemistry of *D. esculenta* documented many secondary metabolites with potential antioxidant, anti-inflammatory, antibacterial, antifungal, and strong antiproliferative properties[9, 12].

The antioxidant properties of the plant may improve its chemopreventive effects by mitigating oxidative stress, thereby aiding in the prevention of cellular damage and decreasing the risk of diseases such as cancer [9, 13, 14]. However, little is known about the underlying molecular mechanism of the antiproliferative effects of *D. esculenta*, and there is a lack of comparative studies on subtypes of breast cancer. Considering the worldwide impact of breast cancer and the limitations of existing chemotherapy treatments, the use of *D. esculenta* tuber extracts as possible cancer treatments is reasonable and justifiable. The antiproliferative properties and phytoconstituents of *D. esculenta* tuber extracts were the aim of this study.

Materials and Methods

Collection and Preparation of the Sample

The *D. esculenta* tubers were sourced from a market (Pasar Siti Khadijah), located in Kota Bharu, Kelantan, Malaysia. As part of the plant's authentication process, specialists from the Kulliyyah of Pharmacy at Malaysia's International Islamic University (IIUM) assigned an official voucher number PIIUM 0299 to the specimen. After the yam tubers were peeled and diced, they were dehydrated for 7 days at 60°C in an oven. A mechanical grinder was used to crush the dried tubers into a fine powder.

Method for extraction

One hundred milligrams of *D. esculanta* were macerated in 1 liter of methanol (w/v) in a ratio of 1:10 for three days. Following that, the cocktail was passed through a 0.2 µm filter before being concentrated at 45°C under reduced pressure. The aqueous extract was made by macerating 100 g of plant powder in 1 L of distilled water for 72 hours. An aqueous extract was obtained by removing the solvent using a rotary evaporator under reduced pressure at 45°C. The concentrated extracts were freeze-dried and stored at 4°C [15].

Phytochemical investigation

Both the water and methanol extracts of *D. esculenta* were tested for the content of tannins, phenols, alkaloids, flavonoids, terpenoids, and saponins, according to the procedure described by Mohan and Murugan [16].

Propagation and maintenance of cells

The cell lines used in this study were obtained from the American Type Culture Collection (ATCC®) in Manassas, VA. The cell lines were cultured in a medium that contained 10% heat-inactivated fetal bovine serum (FBS), 100 IU/mL penicillin, and 100 µg/mL streptomycin. The study also included the MDA-MB-231 and MCF-7 breast cancer cell lines, as well as the NIH 3T3 normal fibroblast cell line (HTB-26TM, HTB-22TM, CRL-1658TM in sequence) [17]. The cells were kept in a humidified atmosphere with 5% CO_2 at 37°C. Before starting the subculture, the flask was rinsed with 5 mL of phosphate-buffered saline (PBS) after removing the media. The flask was supplemented with 2 mL of 0.025% trypsin-EDTA to facilitate cell dissociation.

A carbon dioxide incubator was used to cultivate the virus for minutes before being examined under a microscope. To avoid cell denaturation caused by trypsin, 2 mL of media was added to the flask before the experiment began. To transfer the cell suspension, a new 15 mL centrifuge tube was utilized. Centrifuged at 1500 rpm (250 g) for 5 minutes at 24°C to extract any residual trypsin from the cell suspension. After discarding the supernatant, 2 mL of pre-warmed media was added to the cells to homogenize them. Before putting the cell suspension in the CO_2 incubator, it was moved to a fresh flask with 10 mL of media. Until the cells reached 80% confluence, they were passaged every two weeks, and the culture media was changed every two weeks [18, 19]. Evaluation of cell death using the MTT test

Extracts from *D. esculenta* were evaluated for their antiproliferative activities using the MTT assay [8, 10] . For the experiment, a 96-well plate was used, and the wells were filled with culture containers containing 90% confluent cells. Before treatment, cells were seeded onto 96-well plates and left to incubate for one day. 100 µL of medium was added to each well containing 5.0×10^4 cells. Using tamoxifen as a positive control, two-fold

serial dilutions were used to assess concentrations ranging from 0.04 mg/mL to 10 mg/mL. The cells used for the control group were cultured in 200 µL of fresh, pre-warmed media that contained 2 µL of 1% DMSO. For three days, the 96-well plate was kept at 37°C with 5% CO_2. The medium was drained after incubation, and 50 µL of a 2 mg/mL MTT solution was used to treat each well. The plate was maintained at 37°C in an incubator with 5% carbon dioxide for an additional four hours. After 4 hours of removing the MTT solution, 100 µL of DMSO was added to each well to dissolve the purple formazan crystals that had accumulated at the bottom. An orbital agitator was used to incubate the plate for 30 minutes. Using a spectrophotometric microplate reader, the absorbance at 570 nm was measured. We calculated the percentage of live cells using this formula:

$$\% \text{ cell viability} = \frac{(\text{absorbance of extracts})}{(\text{absorbance of control})} \times 100\%$$

The most potent extract against the cell lines was used for flow cytometry.

Detection of apoptosis via flow cytometry

The Annexin V Apoptosis Detection Kit (sc-4252 AK) was used to detect programmed cell death using a simple staining protocol. 1×10^4 cells were seeded overnight in a six-well plate. The media in the tubes post-therapy were collected and trypsinized. The harvested cells were centrifuged to sediment, and the supernatant was discarded. Thereafter, the cells were washed twice with Phosphate-Buffered Saline, centrifuged, and resuspended in 1 mL of 1X Assay Buffer to a total cell density of 1×10^6 cells/mL. Furthermore, the cells were placed in a flow cytometry tube containing 5 µL of PI and 5 µL of Annexin V-FITC. Shortly before the flow cytometry analysis, 400 µL of 1X Binding Buffer was pipetted into each tube [14, 20].

Data analysis

The data are presented as the mean ± standard error of the mean as obtained from triplicate experiments. The data's normality was evaluated using the Kolmogorov-Smirnov test. Statistical significance was assessed by conducting a one-way analysis of variance (ANOVA) on the results. GraphPad PRISM Version 10.6.1 was employed to conduct statistical analyses.

Results

Phytochemical contents

The phytochemical analyses revealed that saponins and terpenoids were the major compounds in both DEME and DEAE, as shown in Table I. However, DEME had the highest content of these bioactive metabolites.

Table 1. Detected phytochemical constituents in *D. esculenta* extracts.

Phytochemicals (units)	DEME	DEAE
Saponins (mg SE/g extract)	186.4 ± 0.04	185 ± 0.04
Tannins (mg TAE/g extract)	2.48 ± 0.45	2.18 ± 0.45
Phenols (mg GAE/g extract)	2.00 ± 0.41	1.82 ± 0.41
Terpenoids (%)	69	64
Alkaloids (%)	8	9
Flavonoids (mg QE/g extract)	0.17 ± 0.17	0.06 ± 0.17

The value was the average of three analyses ± standard error of the mean.

Cell proliferation - MTT assay

The antiproliferative effects of extracts from *D. esculenta* tubers on MDA-MB-231 and MCF-7 cell lines and NIH-3T3 (normal cell lines) were assessed after 72 hours of incubation. Treatment with DEME halts cell proliferation by 50% in MDA-MB-231 cells (IC_{50} 5.50 µg/mL). The DEAE recorded IC_{50} of 153.60 ± 1.29 µg/mL on MDA-MB-231 cells, while the IC_{50} on MCF-7 cells was 248.20 ± 1.05 µg/mL. On the other hand, tamoxifen demonstrated a pronounced inhibitory effect, with IC_{50} values of 3.55 ± 1.17 µg/mL against MDA-MB-231 cells and 0.81 ± 1.20 µg/mL on MCF-7 cells. The IC_{50} value of tamoxifen in NIH-3T3 cells was 3.05 ± 1.23 µg/mL (Table II). Tamoxifen demonstrated cytotoxicity toward both breast cancer and normal cells, as evidenced by its low IC_{50} values. The antiproliferative effects of extracts from *D. esculenta* tuber on the cell lines are depicted in Fig. 1, which depicts the dose-response curve against the control. The viability of cells decreased in a proportional manner as the concentrations of the extracts and the drug increased.

Table 2. The IC_{50} values of DEME, DEAE, and the control. Values are expressed as mean ± SE.

Cell lines	IC50 values (µg/mL)		
	DEME	DEAE	Tamoxifen
NIH-3T3	> 200	> 200	3.05±1.23
MCF-7	25.20 ± 1.48	> 200	0.81±1.20
MDA-MB-231	5.50 ± 1.17	153.60±1.29	3.55±1.17

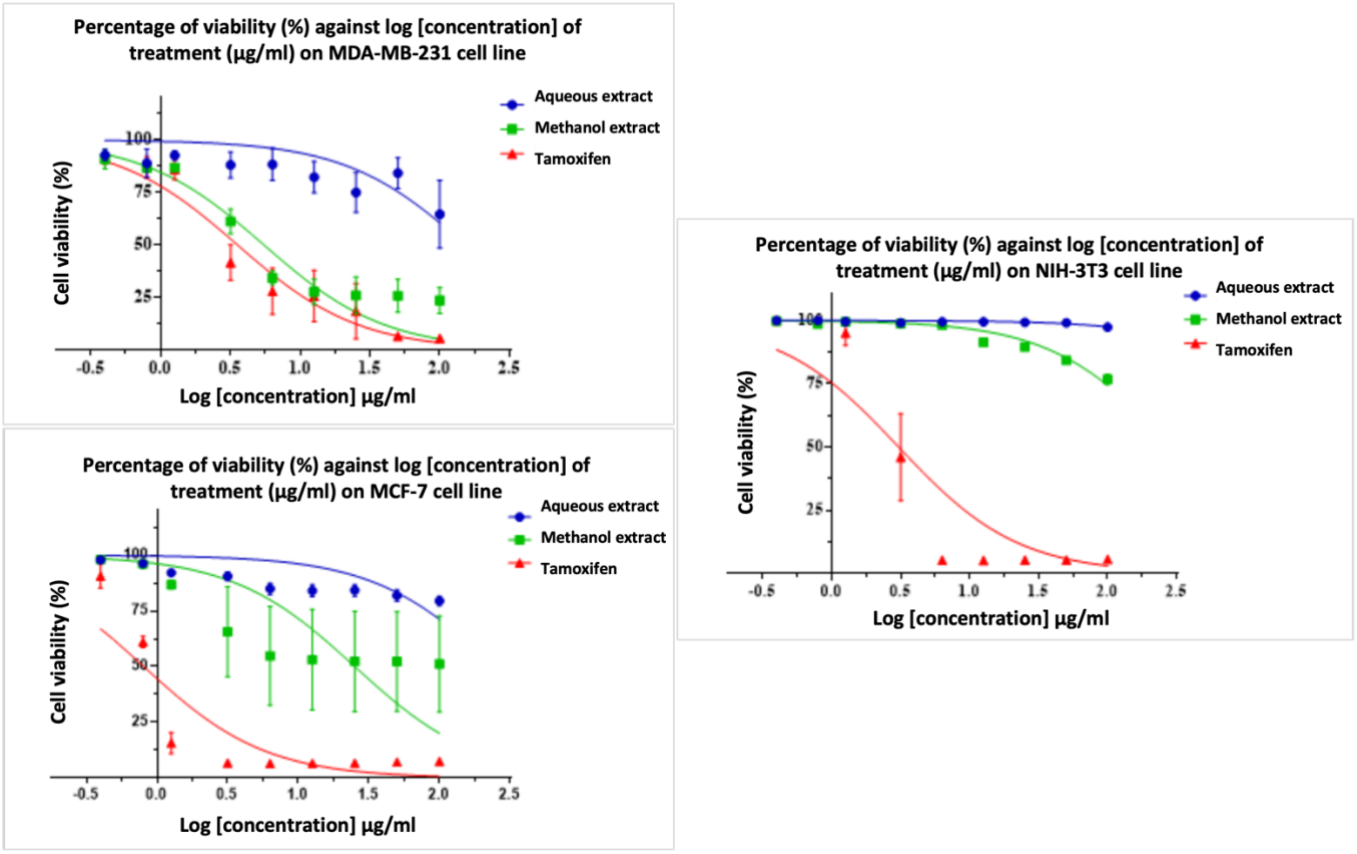

Figure 1. Dose-response curve illustrating the antiproliferative activity of DE extracts and the control (tamoxifen) on MDA-MB-231, MCF-7, and NIH-3T3 cell lines. Cell viability diminished with increasing concentrations of the extract and the drug.

Assessment of apoptosis through flow cytometry analysis

Apoptosis in MDA-MB-231 cells was assessed via flow cytometry utilizing propidium iodide (PI) and Annexin V. The total apoptosis of breast cancer (MDA-MB-231) treated with DEME is substantially different from that of untreated breast cancer, as demonstrated in **Figure 2**. A four-quadrant analysis was presented in scatter plots of MDA-MB-231 cells stained with PI/FITC-Annexin V following 72 hours of treatment. Q1 indicates necrosis, Q2 represents late apoptosis, Q3 signifies early apoptosis, and Q4 corresponds to viable cells **(Figure 3)**.

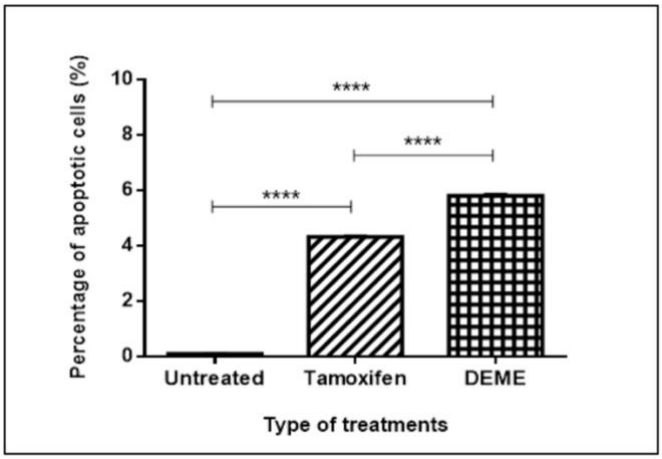

Figure 2. The percentage of apoptotic cells in quadrants Q2 and Q3 following the treatments against MDA-MB-231 cells. The **** indicates a $p<0.0001$, demonstrating a significant difference from the control group.

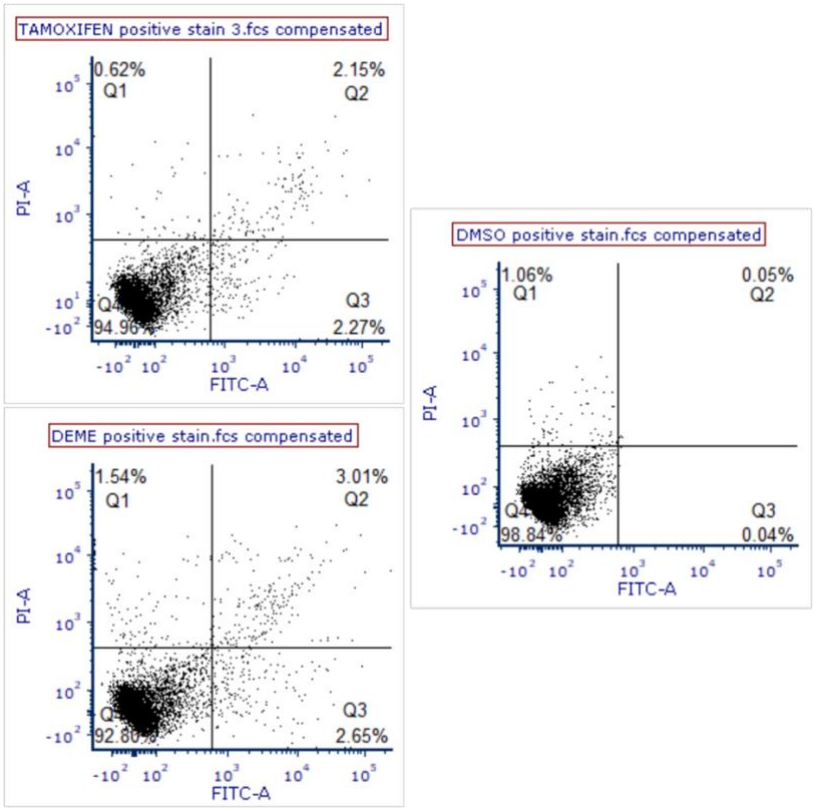

Figure 3. Scatter plots of MDA-MB-231 cells obtained using PI/FITC – Annexin V demonstrate a four-quadrant analysis.; Q1 = necrosis, Q2 = late apoptosis, Q3 = early apoptosis, Q4 = viable cells, after 72 hours of treatment. The cells were left untreated as the negative control, while tamoxifen served as the positive control. The same plot trends were observed in three independent experiments.

Discussion

Plants are instrumental in identifying novel anti-infectives and have garnered substantial interest due to their enormous phytoconstituent [21]. Among these, *D. esculenta* offers substantial pharmacological properties and could serve as an alternative remedy. Previous research by [10, 22] has demonstrated the plant's anticancer activity on MCF-7 and T47D cells.

However, there were limited studies on the anticancer potential of the plant tubers on MDA-MB-231 and MCF-7 cell lines. Therefore, this research represents a novel investigation into the antiproliferative effects of extracts from *D. esculenta* tuber on the MDA-MB-231 and MCF-7 cell lines. Qualitative phytoconstituent screening reveals that both *D. esculenta* extracts contain alkaloids, phenols, tannins, terpenoids, saponins, and flavonoids. Furthermore, the quantitative analysis of phytochemicals revealed high saponin content in both extracts. Notably, saponins have been shown to induce apoptosis in cancer cells, rendering them an alternative therapeutic option for cancer patients [6]. Additionally, the extracts contain other biologically active compounds, including phenols, terpenoids, and alkaloids, with antioxidant and anticancer activities that could cause apoptosis [12, 13, 22]. Thus, *D. esculenta* extract contains biologically active compounds that exhibit promising anticancer properties.

Antiproliferative activity is a characteristic of anticancer agents, as they can suppress the uncontrolled proliferation of malignant cells [18, 23]. The results of this study revealed that MDA-MB-231 cells were more sensitive to DEME treatment than MCF-7 cells. DEME remarkably suppressed the MDA-MB-231 and MCF-7 cell lines in a dose-dependent manner after 3 days of treatment. Nonetheless, MDA-MB-231 and MCF-7 showed less susceptibility to DEAE. It has been reported that most chemotherapeutic agents for cancer treatment induce numerous effects that deteriorate the patient's well-being [6]. Therefore, research on developing anticancer agents that selectively target malignant cells while minimizing effects on non-cancerous cells is of paramount importance [11]. Interestingly, both DEME and DEAE exhibited minimal antiproliferative activity against NIH-3T3 cells, with IC_{50} values exceeding 200 µg/mL.

The positive control demonstrated significant cytotoxicity against MDA-MB-231 and MCF-7 cells. However, it inhibited the proliferation of normal cell lines. This indicates that tamoxifen not only

suppressed cancer cell proliferation but also affected normal cells. In contrast to tamoxifen, DEME exhibited reduced cytotoxicity against non-cancerous cells, though it was less effective. The selective effects of DEME on cancer cells, without inducing adverse effects in non-cancerous cells, are worth noting [24]. In the same vein, [10] reported that the semi-polar fraction of *D. esculenta* demonstrated potent cytotoxicity against MCF7 breast cancer cells (IC_{50} of 632.42 µg/mL).

Apoptosis is a regulated cellular death process characterized by specific biochemical pathways that lead to morphological alterations and cell death [25]. The DEME demonstrated pronounced antiproliferative activity on MDA-MB-231 cells, and further analysis was performed to evaluate its apoptotic potential. Flow cytometry studies confirmed the antiproliferative effect, showing increased Annexin V binding in MDA-MB-231 cells exposed to DEME. Apoptotic cells can be identified by the exposure of phosphatidylserine on the cell membrane's outer surface [26]. These findings demonstrated that DEME induces apoptosis in MDA-MB-231 cells. Furthermore, the antiproliferative effect indicates that DEME suppresses the growth of various human breast cancer cell lines, including MCF-7 and MDA-MB-231 cells. DEME may therefore serve as an alternative cancer therapy in more aggressive forms of breast cancer by suppressing cell proliferation via the apoptosis pathway.

Conclusion

This study demonstrates that *D. esculenta* tuber extracts, particularly the DEME, exhibit significant antiproliferative effects against both breast cancer cell lines and induce considerable apoptosis. The observed antiproliferative effect could be attributed to numerous bioactive metabolites, including saponins, terpenoids, phenols, and alkaloids, detected in the *D. esculenta* extract. Notably, the methanol extract showed low cytotoxicity against normal NIH-3T3 cells, indicating selective toxicity toward cancer cells, a promising characteristic for therapeutic applications. These findings support the potential of *D. esculenta* as an effective and selective anticancer agent, particularly for aggressive breast cancer types. Further studies are therefore recommended to explore the in vivo efficacy and detailed molecular mechanisms underlying the anticancer effects of *D. esculenta*.

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