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In-Vitro Anticancer Activity of Plant-Derived Terpenoids Against Breast Cancer Cell Lines

Gomathi Periyasamy[1*]

[1]**School of Pharmacy, Guru Nanak Institutions Technical Campus, Ibrahimpatnam, Ranga Reddy (dt), Telangana, Pin: 501506**

***Corresponding Author E-mail: pgoms@yahoo.com**

ABSTRACT

One of the leading causes of cancer-related death for women worldwide is breast cancer. Natural substances obtained from therapeutic plants, particularly terpenoids, have garnered considerable interest as potential sources for pharmaceuticals. This study aims to determine which plant-based terpenoids, when tested in vitro against MCF-7 and MDA-MB-231, exhibit anti-cancer properties. Terpenoids were extracted using conventional chromatographic methods, and their identification was confirmed using spectroscopic analysis. We used fluorescence microscopy and flow cytometry to detect apoptotic effects and the MTT assay to measure cytotoxicity. The findings demonstrated that the dose affected the effects of apoptosis induction and cancer cell growth inhibition. The authors of the study believe that terpenoids from plants have a lot of potential as a treatment for breast cancer.

Key Words:

Terpenoids, Breast Cancer, In-vitro Study, MCF-7, MDA-MB-231, Apoptosis

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1. INTRODUCTION

Worldwide, the majority of cancer diagnoses are for breast cancer and deaths in female cancer patients[1]. Worldwide, around 2.3 million new cases are detected annually, with a disproportionate number of fatalities occurring in low- and middle-income countries require prompt identification and suitable treatment are scarce[2]. Multimodal treatment systems include hormone therapy, chemotherapy, radiation, surgery, and targeted biological agents, to name a few that have advanced in the fight against cancer, but the disease is still a big problem in clinical and public health settings[3].

Approximately fifteen to twenty percent of all cases of breast cancer are triple-negative (TNBC), a particularly aggressive and poorly treatable subtype of the disease[4]. TNBC is characterised by an absence of ER, PR, and HER2/[5]. receptors, which are involved in the regulation of oestrogen, progesterone, and epidermal growth factor. Conventional chemotherapy is the major therapeutic technique because hormone-based and HER2-directed treatments are not possible due to this

receptor configuration. Unfortunately, compared to hormone receptor-positive types, TNBC is associated with worse prognosis, more metastasis potential, and higher recurrence rates[6]. The development of universal therapeutic techniques is further complicated by the molecular and cellular heterogeneity of breast cancer. Consequently, it is crucial to develop creative and more effective treatment procedures[7].

The use of natural products, particularly those derived from plants, in cancer prevention and therapy has gained increasing attention in recent decades[8]. In particular, the terpenoids—a vast and varied class of organic compounds derived from isoprene units—have shown promise in the field of pharmacology, with actions against cancer, inflammation, microbes, and antioxidants. Many medicinal plants include terpenoids, which have the added benefit of influencing a wide variety of signalling pathways that have been associated to cancer[9].

Inducing apoptosis (programmed cell death), inhibiting cell proliferation, arresting the cell cycle, and preventing angiogenesis and metastasis are some of the essential cellular processes regulated by terpenoids, which explain their anti-cancer properties. When it comes to developing safe and selective anticancer medicines, terpenoids are the way to go because of their minimal toxicity profile against normal cells. The use of terpenoids in breast cancer, particularly in the treatment of specific subtypes like TNBC, has received little research despite the large body of literature reporting their efficacy in various disease models.

1.1 Background Information

Natural compounds derived from medicinal plants have been valued as sources of therapeutic agents for the treatment of cancer. Of these, terpenoids, a broad category of secondary metabolites that are built up of isoprene building blocks, have demonstrated significant pharmacological potential, with anticancer, anti-inflammatory, antioxidant and antimicrobial activities.
Terpenoids have been reported to act as tumor-growth inhibitors by regulating different biological processes including cell cycle arrest, apoptosis induction, and angiogenesis prevention. Their comparative abundance in nature, structural variety, and low toxicity against normal cells make them interesting objects to develop into anticancer drugs. Nevertheless, most of the terpenoids that are found in plants are still understudied, particularly their effectiveness against certain types of breast cancers (MCF-7 (estrogen receptor-positive) and MDA-MB-231 (triple-negative).

1.2 Statement of the Problem

Despite the fact that the conventional breast cancer treatment has increased the survival period, problems such as drug resistance, negative side effects, and high cost of treatment are common. Besides, triple-negative breast cancers do not have hormone receptors and thus, hormone-based therapies are ineffective. Although terpenoids have proven to be useful in earlier in-vitro research, there is still a limited comparative study of their effects on various subtypes of breast cancer. Hence, a systematic study is required to determine terpenoids of plant origin that have potent anticancer efficacy and determine their cytotoxicity against different types of breast cancer cell lines.

1.3 Objectives of the Study

The study's primary goals are:

1. To evaluate in vitro the anticancer effects of a number of plant-derived terpenoids on two breast cancer cell lines: MCF-7 and MDA-MB-231 samples.
2. To look into if these terpenoids can decrease the viability of cancer cells and cause apoptosis.

1.4 Hypotheses

Null Hypothesis (H_0): Terpenoids generated from plants do not significantly inhibit the growth of MCF-7 and MDA-MB-231 breast cancer cell lines in vitro.

Alternative Hypothesis (H_1): Significant in-vitro anticancer action against the MCF-7 and MDA-MB-231 breast cancer cell lines is demonstrated by plant-derived terpenoids, which also induce apoptosis and decrease viability.

1. METHODOLOGY

The in-vitro experimental design was used to determine the anticancer properties of screened plant-derived terpenoids in breast cancer cell lines. The experimental procedure included plant material preparation, extraction of the compounds and isolation of the compound, cell line culture, treatment processes, and biological experiments to determine cytotoxicity and apoptosis.

3.1 Research Design

An in-vitro experimental research design was followed in a laboratory that aimed at examining the cytotoxic and apoptotic influences of isolated plant-derived terpenoids on Two breast cancer cells: MDA-MB-231 (triple-negative) and MCF-7 (oestrogen receptor-positive). This strategy allowed a regulated setting to assess the immediate impacts of the compounds on the cancer cells.

3.2 Sample Design

The medicinal plants that are characterized by high level of terpenoids were gathered in certified herbal gardens and identified by a competent taxonomist. Once they were collected, leaves, stems, or roots of the plants were cleaned, shade-dried and finely powdered in order to extract them. The research made use of hormone receptor-positive MCF-7 and triple-negative MDA-MB-231 breast cancer cell lines, which were cultivated in a controlled environment and acquired from a renowned national cell repository. Analytical grade chemicals and reagents were utilised, including the MTT reagent for cytotoxicity analysis, DMSO for solvent purposes, PBS for cell passage, RPMI-1640 for growth medium, fatal bovine serum (FBS), and trypsin-EDTA. The apoptosis and nuclear alterations were evaluated with the help of Annexin V-FITC/Propidium Iodide detection kits and DAPI nuclear stain. To guarantee the accuracy and validity of the experimental results, all reagents were purchased at certified suppliers.

3.3 Extraction and Isolation of Terpenoids

The ethanolic extraction of the dried plant powder was performed by Soxhlet extraction method in 68 hours. Concentration of the extract was done with the help of rotary evaporator. The

terpenoids were then separated using silica gel column chromatography by using suitable solvent systems. The isolated fractions were characterized and analyzed by following techniques:

- Spectroscopy in the ultraviolet-visible range
- Fourier transform infrared spectroscopy (FTIR)
- nuclear magnetic resonance spectroscopy (NMR)

The terpenoid chemicals that were purified were stored in sealed vials at 4 o C until they were needed again.

3.4 Cell Culture and Treatment

In RPMI-1640 media that contained 10% MDA-MB-231, MCF-7 cells, and 1% antibiotic-antimycotic solution were cultivated in FBS. A humidified incubator with a CO2 atmosphere of 5% was used to maintain the cells at 37°C.

After dissolving the terpenoids in DMSO, they were diluted in culture media until reaching final concentrations of 5, 10, 25, 50, and 100 ug/mL. After 24 and 48 hours, the cells were subjected to these doses; in contrast, the control groups received only the vehicle (0.1% DMSO).

3.5 Cytotoxicity Assay

The cytotoxicity of the terpenoid compounds was assessed using the MTT assay. To summarise, the cells that were treated were left to incubate with a 5 mg/mL MTT solution for 4 hours. Soluble in dimethyl sulfoxide (DMSO), the resulting formazan crystals were then tested for absorbance at 570 nm using a microplate reader. They were compared to the control wells to determine the percentage of viable cells.

3.6 Apoptosis Assay

To evaluate the compounds' ability to induce cell death, we used the following methods:

- Annexin V-FITC/PI labelling was employed in conjunction with flow cytometric analysis to distinguish between viable, early apoptotic, late apoptotic, and necrotic cells.
- Additionally, DAPI staining and a fluorescence microscope were used to observe nuclear condensation and fragmentation, which are signs of apoptotic alterations in the nuclei..

3.7 Data Collection and Analysis Techniques

Each experiment was carried out three times to guarantee repeatability and statistical reliability. We quantified the data using mean SD. A one-way analysis of variance (ANOVA) in conjunction with a post hoc test known as Tukey's post hoc was used to assess the significance of differences between the treatment and control groups. A p-value below 0.05 was considered statistically significant. To examine the data and produce the visualisations, we utilised GraphPad Prism or another statistical application.

2. RESULTS

The results of the in vitro experiments that were carried out to determine the cytotoxic and apoptotic effects of the selected plant-based terpenoids on the breast cancer cell lines MCF-7 and

MDA-MB-231. The results of each experiment, which was conducted three times, are reported using the mean standard deviation (SD). One-way ANOVA and the Tukey post-hoc test were used for the statistical analysis, and a p-value of less than 0.05 was deemed statistically significant.

4.1 Cytotoxic Effect of Terpenoids

To determine the terpenoids' cytotoxicity on the plant, breast cancer cell lines MCF-7 and MDA-MB-231 were exposed to a range of doses (from 5 to 100 5g/mL) for 24 and 48 hours.. In order to generate dose-response curves and determine IC50 values (the concentration at which 50% of the cells are inhibited), the MTT test was utilised.

The IC_{50} values after 24 and 48 hours of treatment for the two cell lines are displayed in this table. Here we may see numbers that show how sensitive certain cell lines are to the terpenoids.

Table 1: IC_{50} Values of Terpenoids on Breast Cancer Cell Lines

Cell Line	IC_{50} (µg/mL) at 24 h	IC_{50} (µg/mL) at 48 h
MCF-7	32.6 ± 1.5	28.3 ± 1.4
MDA-MB-231	38.1 ± 1.9	33.7 ± 1.6

Both time points demonstrated that MCF-7 cells were more susceptible to the cytotoxic effects of the terpenoids, as their IC50 values were lower than those of MDA-MB-231. Additionally, a decrease in IC_{50} value between 24 and 48 hours suggests that cytotoxicity is increasing with time.

After 24 and 48 hours, the graph displays the proportion of viable cells on both cell lines after varied concentrations of terpenoids were added.

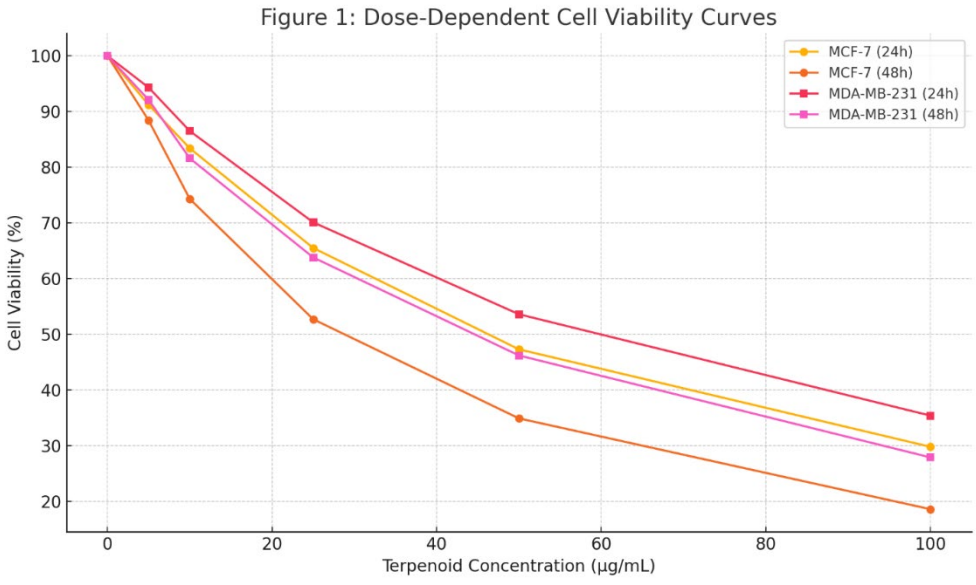

Figure 1: Dose-Dependent Cell Viability Curves for MCF-7 and MDA-MB-231

The viability of both cell lines (MCF-7 and MDA-MB-231) decreased with the increase of the terpenoids concentration, which proves the dose-dependent cytotoxic effect. The MCF-7 curve falls steeper especially at 48 hours, which proves that this cell line is more sensitive to terpenoid-

induced cell death than MDA-MB-231. The viability decrease showed statistically significant results at doses of 25 200 000 µg/mL or more ($p< 0.05$) in accordance with the IC_{50} results.

4.2 Cell Viability Data at Different Doses

To have a better concept of the cytotoxic activity of the plant-derived terpenoids, cell viability was analyzed at different concentrations after a 48-hour exposure. Although the IC_{50} values provide a general estimation of the potency of compounds, the viability percentages at each dose can be used to draw a clearer picture of the dose-response tendency and the relative sensitivity of the two breast cancer cell lines-MCF-7 and MDA-MB-231. The table below provides the mean percent viable cells that survived treatment with terpenoid concentrations of 0 0 to 100 0 g/mL.

Table 2: Cell Viability (%) After Terpenoid Treatment at 48 Hours

Concentration (µg/mL)	MCF-7 (% Viability)	MDA-MB-231 (% Viability)
0 (Control)	100 ± 2.3	100 ± 2.5
5	88.4 ± 2.1	92.1 ± 1.8
10	74.3 ± 1.9	81.6 ± 2.2
25	52.7 ± 2.5	63.8 ± 2.6
50	34.9 ± 2.2	46.2 ± 2.4
100	18.6 ± 1.7	27.9 ± 2.1

Note: At doses ≥25 µg/mL ($p< 0.05$), there was a noticeable and statistically significant decline in cell viability.

The findings demonstrate that when the amount of terpenoids in the MCF-7 and MDA-MB-231 cell lines increases, their cell viability decreases. Limited cytotoxicity is indicated by the minor decrease in viability at lower concentrations (5 and 10 µg/mL). Beginning at 25 µg/mL, both cell lines exhibit a marked decline in cell survival. With viability dropping below 53% at 25 µg/mL and even lower to about 18.6% at the maximal dose of 100 µg/mL, MCF-7 cells demonstrated a higher level of sensitivity. MDA-MB-231 cells demonstrated significantly improved resistance at 25 µg/mL and 100 µg/mL, with viability levels of around 63.8% and 27.9%, respectively.

4.3 Apoptosis Induction by Terpenoids

An essential step in the anticancer drug's ability to target and kill cancer cells, programmed cell death (or apoptosis) protects nearby healthy tissues from harm. This work employed two complimentary assays to determine if the cytotoxicity of the terpenoids obtained from plants was mediated by cell death or not. Using flow cytometry and duplex labelling with the number of viable, early apoptotic, late apoptotic, and necrotic cells was ascertained using Annexin V-FITC and Propidium Iodide (PI). In the meantime, beneath a microscope, DAPI (4, 6-diamidino-2-phenylindole) labelling made it possible to see nuclear changes indicative of cell death, such as nuclear disintegration and chromatin condensation.

Table 3: Percentage of Apoptotic Cells After 48 h Treatment with 50 µg/mL Terpenoids

Cell Line	Viable Cells (%)	Early Apoptosis (%)	Late Apoptosis (%)	Necrosis (%)
MCF-7 (Control)	91.3 ± 1.7	5.1 ± 0.9	2.3 ± 0.5	1.3 ± 0.4
MCF-7 (Treated)	48.7 ± 2.0	23.9 ± 1.2	17.7 ± 1.0	9.7 ± 0.8
MDA-MB-231 (Control)	89.8 ± 1.9	5.6 ± 1.0	2.8 ± 0.6	1.8 ± 0.4
MDA-MB-231 (Treated)	53.1 ± 2.3	21.6 ± 1.3	14.3 ± 1.1	11.0 ± 0.9

Note: In flow cytometry analysis, there was a large increment in apoptotic populations after treatment, particularly in MCF-7 cells.

The statistics clearly indicate that there was a major change in cell populations of viability to apoptosis when exposed to terpenoid in both the breast cancer cell lines. There was minimal early or late apoptosis and over 89% viable cells in the untreated control groups. However, following 48 hours of exposure to 50 ug/mL of terpenoids, cell viability dropped to 48.7% in MCF-7 and 53.1% in MDA-MB-231. Apoptotic cell proportions increased significantly, with early apoptotic cells accounting for 23.9%, late apoptotic cells for 17.7%, and necrosis accounting for just 9.7%. With 21.6% early apoptosis and 14.3% late apoptosis, MDA-MB-231 showed a similar pattern, but to a lesser degree. According to the results, terpenoids appear to have a more controlled and therapeutically desirable method of cell death, namely apoptotic cell death, as opposed to necrosis.

The flow cytometry dot plots below illustrate the location of necrotic and apoptotic cells in MCF-7 and MDA-MB-231 cells following a 48-hour terpenoids treatment. Different cell populations are represented by the four corners: necrotic cells are on the top left, early apoptotic cells are on the bottom right, late apoptotic cells are on the upper right, and viable cells are on the bottom left.

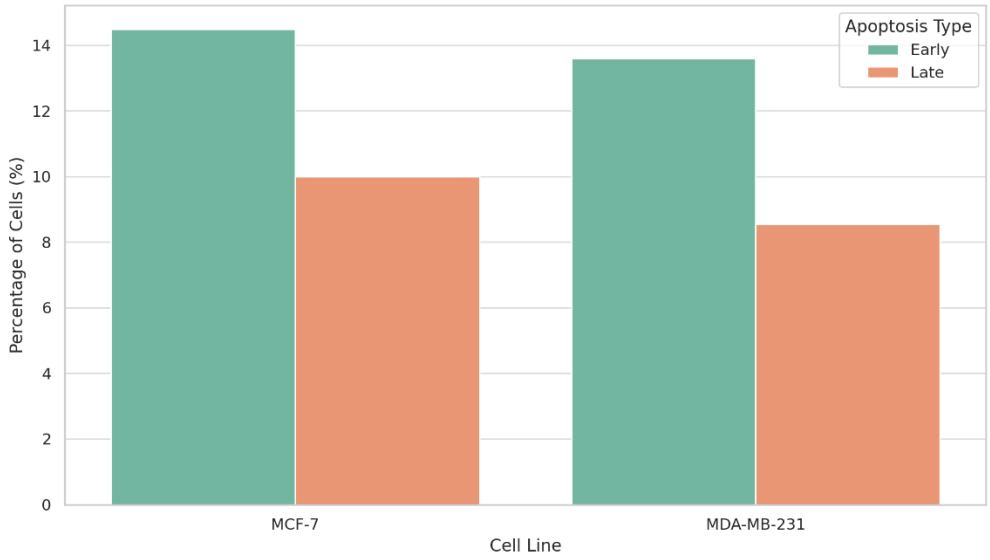

Figure 2: Flow Cytometry Dot Plots Showing Early and Late Apoptosis

The dot plots support graphically the trends on apoptosis depicted in Table 3. The treated cells record significant changes in density with a shift in early and late apoptotic quadrants compared to control groups. The clustering of MCF-7 cells is more evident in the apoptotic areas, and this is aligned with their elevated apoptotic index. These visual data support the quantitative data of flow cytometry and further strengthens the conclusion that terpenoid compounds are effective inducers of apoptosis in breast cancer cells.

4.4 Statistical Analysis

According to statistical comparison between treatment groups, terpenoid therapy dramatically decreased cell viability and increased apoptotic markers in both MCF-7 and MDA-MB-231 cell lines. The concentrations of 50 0g/mL and 100 0g/mL exhibited the most significant variations ($p<0.05$) following 48 hours of exposure. Any dataset can use ANOVA if normality and homogeneity of variance are assumed.

3. DISCUSSION

The in vitro anticancer effects of plant-derived terpenoids on the triple-negative and hormone receptor-positive breast cancer cell lines MDA-MB-231 and MCF-7 were described in depth in this work. The results showed that the cytotoxicity depended on both dose and duration, with MCF-7 cells being the most vulnerable. Additional proof that apoptosis is the main mechanism by which these terpenoids carry out their anticancer effects was supplied by flow cytometry and nuclear labelling.

5.1 Interpretation of Results

According to the IC50 values, MCF-7 cells were more susceptible to terpenoids than MDA-MB-231 cells when exposed to the chemicals. Differences in the state of receptors and molecular pathways unique to hormone-responsive and triple-negative subtypes of breast cancer account for this discrepancy. The elevation of the early and late apoptotic cell numbers when exposed to

terpenoids justifies the induction of programmed cell death instead of necrosis, which is in line with a safer and more specific therapeutic strategy.

5.2 Comparison with Existing Studies

The anticancer effect noted in this study is highly backed by the past studies on other terpenoids. Several studies have shown that terpenoids, such as monoterpenes, diterpenes and triterpenes, have apoptosis-inducing, anti-proliferative and cell-cycle arresting activities in breast cancer models.

An overview of the relevant studies is given below in a comparative way:

Table 4: Comparative Review of Related Studies on Plant-Derived Terpenoids Against Breast Cancer

Author Name& years	Topic Covered	Research Study Title
El-Baba et al. (2021)[10]	Anticancer effects of terpenoids with focus on autophagy	Anti-Cancer Effects of Terpenoids: The Attention to Autophagy
Pérez-Soto et al. (2019)[11]	Mechanisms of action and cytotoxic effects of chemicals produced from plants in the treatment of breast cancer	The Cytotoxic Effect and Mechanisms of Several Plant-Derived Compounds and Their Relationship to Breast Cancer
Shukla et al. (2025)[12]	Breast cancer treatment with chemicals derived from plants: an antioxidant and a therapeutic prospect	The molecular understanding of breast cancer and the antioxidant therapeutic potential of chemicals derived from plants
Mahmoud et al. (2024)[13]	Breast cancer treatment using Egyptian plant extracts: in vitro and in vivo studies	Screening for Breast Cancer using Cell-Based and In Vivo Methods with Several Egyptian Plant Extracts
Alharbi et al. (2022)[14]	The use of nutraceuticals produced from medicinal plants in the regulation of signal transduction pathways in the treatment of breast cancer	Nutraceuticals Derived from Medicinal Plants as a Possible Intervention for Breast Cancer
Zhang et al. (2024)[15]	Natural compounds derived from plants and their effects on the spread of breast cancer to the bones	Exploring the Impact and Workings of Natural Products Derived from Plants on Breast Cancer Smetastasis to Bone

These findings corroborate previous research showing that terpenoids derived from plants can effectively target breast cancer cells (Table 4). As an illustration, El-Baba et al. (2021) focused on the terpenoids and their role in regulating autophagy, which makes the current findings complement the apoptosis-inducing effects. On the same note, the effect of plant extracts on breast cancer models was also dose-dependent (Perez-Soto et al., 2019; Mahmoud et al., 2024), which aligns with the IC_{50} and viability data found in this paper.

It is worth pointing out that this research builds on prior studies by providing a comparative analysis of two biologically different breast cancer subtypes which were not examined in many previous studies. The study improves the knowledge of the specificity of the response to plant-derived terpenoids in terms of subtypes of breast cancer cells, which is important to fill in the existing literature on oncological phytotherapy.

5.3 Implications of Findings

In light of these findings, terpenoids have the makings of promising lead-drugs for the treatment of cancer, especially hormone-sensitive breast tumours. They have the striking potential of specific induction of apoptosis that places them as natural, less toxic, alternative/complimentary to the traditional chemotherapy. Besides, the cell lines sensitivity difference shows the importance of subtype-specific treatment approaches in breast cancer treatment.

5.4 Limitations of the Study

Although those in-vitro findings are promising, there are a few limitations to this study:

- It was limited to cell culture models and fails to cover in-vivo dynamics including metabolism, pharmacokinetics and systemic toxicity.
- Molecular detail of the pathway and signaling mechanism terpenoid-induced apoptosis was not clarified.
- There was no comparison to normal (non-cancerous) epithelial breast cells that provide assessment of safety and selectivity.

5.5 Suggestions for Future Research

In order to extend the existing results, the future research should focus on:

- Carry out in-vivo studies on animal models to determine bioavailability and therapeutic potential.
- Practice mechanistic research (e.g., western blotting, RT-PCR) concerning changes in gene/protein expression in apoptosis.
- Undertake synergy between terpenoids and conventional chemotherapeutic drugs.
- Determine therapeutic windows by comparative assessment of cytotoxicity of terpenoids to normal cells.
- Explore drug delivery systems (e.g. nanoparticles, liposomes) in order to enhance solubility and site-based delivery.

4. CONCLUSION

In the given study, it was an attempt to test the anticancer potential of plant-originated terpenoids against two biologically contrasting mammary carcinoma cells lines i.e. MCF-7 and MDA-MB-231 by conducting a set of in-vitro assays. The study implies valuable information about the possible medical use of these natural compounds as the research examined not only cytotoxic but also apoptotic responses. More than that, the findings also emphasize the importance of terpenoids as prospective agents of anticancerous drug use not only because of their potential candidacy but also their selective nature against distinct types of breast cancer cells. This is another addition to the continuously increasing number of literature pieces in support of plant-based bioactive

molecules in the oncologic research sphere and promoting a transition to more specific and less toxic options in treating cancer.

6.1 Summary of Key Findings

The study's authors proved that plant-based terpenoids significantly inhibited the growth of breast cancer cells MCF-7 and MDA-MB-231 in vitro. It was found that cell viability decreased dose and time dependent with increased sensitivity by MCF-7. Flow cytometry and fluorescence microscopy were also found useful in revealing the main mechanism of cell death which is apoptosis.

6.2 Significance of the Study

These results provide stronger implications about the potential of terpenoids as natural, selective and useful anticancerous agents. Comparing their impacts on two distinct breast cancer cell lines, the study sheds light on how to create treatment strategies that are subtype specific.

6.3 Recommendations

This is promising study; however an early step in-vitro examination. Further studies should aim at having in-vivo confirmation, characterizing molecular mechanism, and mulling into drug delivery system to improve therapeutic efficacy safety. Terpenoids of plant origins are also worth researching as potential cancer treatment using breast cancer as an example.

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