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In vitro assessment of the anticancer activity of quinaldic acid against human breast cancer cells (MCF-7)

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ABSTRACT

Breast carcinoma represents one of the most frequently diagnosed types of cancer among women throughout the world. The drawbacks of current chemotherapy drugs include adverse side effects, development of drug resistance and lack of selectivity for cancer cells. This highlights the need to develop novel, highly active antitumor compounds with improved therapeutic efficacy and safety. Quinaldic acid (QA) is a biologically active compound that has shown antiproliferative activity in some cancer models, but its anticancer activity against breast carcinoma has not been sufficiently investigated. The present research aims to study the anticancer activity of QA in MCF-7 cells (human breast adenocarcinoma cells). Antiproliferative activity was determined with the MTT assay, with cisplatin used as the standard drug. The generation of reactive oxygen species (ROS), polarization of mitochondrial membrane and nuclear morphology were studied to evaluate the possible mechanisms of action of QA. The apoptosis inducing potential and quantitative estimation of apoptotic cells were identified with AO/EtBr staining and flow cytometry respectively. QA showed dose-dependent antiproliferative activity against MCF-7 cells along with considerably lower cytotoxicity in normal L929 cells, which indicates its higher cytotoxicity against carcinoma cells. The QA treatment resulted in a significant increase in ROS production and depolarization of the mitochondrial membrane, which highlights the effective role of the intrinsic apoptosis pathway. DAPI and AO/EtBr staining revealed prominent apoptotic features and a higher percentage of apoptotic cells. Flow cytometry viable cell count reduction and an increase in early and late apoptotic cell counts. QA showed greatest and selective anticancer activity against MCF-7 by inducing ROS-mediated mitochondrial dysfunction and apoptosis, while exhibiting comparatively low cytotoxicity toward normal fibroblast cells.

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INTRODUCTION

Cancer continues to be a leading cause of morbidity and mortality in the world, posing a significant public health challenge despite numerous advancements achieved in the diagnosis and treatment. According to Globocan 2022, over 20 million new cancer cases and around 10 million cancer deaths are documented each year, with the burden of cancer expected to increase significantly in the decades ahead owing to the increased population, increase in aging population and changes in lifestyle behaviours (Bray *et al.*, 2024; Balch *et al.*, 2026). While advancements in early diagnosis and therapeutic approaches resulted in increased survival rates in developed nations, death rates remain continuously high in low and middle-income nations due to late diagnosis and lack of proper health care facilities and treatments (Moten *et al.*, 2014; Dos Anjos *et al.*, 2025).

Breast cancer is among the most frequently reported malignancies in women and is a common cause of cancer mortality globally. The current estimates show that the number of women diagnosed with breast cancer exceeds 2.3 million per year, accounting for almost 25% of all cancers in women and about 670,000 deaths per year (Arnold *et al.*, 2022; Kim *et al.*, 2025). The prevalence of breast cancer is rising, especially in those countries that undergo rapid social and economic development and shifts in reproductive behaviour, urbanization, obesity and changes in sedentary lifestyles (Wilkinson and Gathani, 2021). Global projections suggest that the number of cases of breast cancer annually could exceed 3 million in the year of 2040 to 2050 (Freihat *et al.*, 2025).

There are several molecular subtypes of breast carcinoma, each having distinct characteristics in their biological properties, treatment responsiveness and prognosis. Risk factors for breast carcinoma include increased age, familial history, genetic mutations in BRCA1 and BRCA2, long-term exposure to estrogen, obesity, alcohol consumption, lack of exercise and various reproductive factors (Abdulkareem, 2013). Further, dysregulation in cell signaling pathways involved in oxidative stress, cell proliferation, apoptosis, angiogenesis and metastasis plays an important role in the development and progression of tumors (Ryspayeva *et al.*, 2025; Dong *et al.*, 2025).

The current treatment regimen for breast carcinoma, including surgery as well as other treatments such as chemotherapy, radiation, hormonal and immunotherapy, has been responsible for considerable improvements in the survival rates of patients. However, these approaches still suffer from various limitations, which include drug resistance, tumor recurrence, systemic toxicity and severe side effects such as cardiotoxicity, neurotoxicity, osteoporosis, cognitive dysfunction and fatigue, leading to poor quality of life (Burguin *et al.*, 2021). Moreover, drug resistance to conventional chemotherapy drugs is also another major challenge for successful treatment (Wang *et al.*, 2019), which makes it necessary to identify new compounds that would selectively kill cancer cells without harming healthy tissues. Consequently, naturally occurring and small bioactive molecules with multitargeted mechanisms of action (Asma *et al.*, 2022) have gained attention as potential candidates for the development of new anticancer therapies.

Studies demonstrated that the redox imbalance and dysfunctions of mitochondria play an important role in cancer cells survival and apoptosis. Increased levels of oxidative stress may cause the dysfunction of mitochondrial membrane potential, activation of the intrinsic apoptosis pathway, condensation of chromatin and DNA fragmentation. Therefore, compounds that can regulate oxidative stress and mitochondrial signaling have become promising targets for the development of new therapeutic approaches in cancer treatment (Liu *et al.*, 2025; Aghamir *et al.*, 2026).

Quinaldic acid (quinoline-2-carboxylic acid) is a biologically active quinoline derivative. It is an endogenous metabolite of the kynurenine pathway of tryptophan metabolism. QA has also been isolated from natural sources such as *Ephedra pachyclada*.

Previous studies have demonstrated diverse pharmacological activities of QA and its derivatives, such as antimicrobial, antiinflammatory and antiproliferative properties. Notably, QA has been reported to suppress the proliferative activity of human colon carcinoma cells while exhibiting minimal toxicity toward normal epithelial cells (Tamilarasi *et al.* 2026) Mechanistic studies have shown that QA modulated key signaling pathways involving ERK1/2, p38 MAPK, CREB and Akt that regulate cell proliferation and apoptosis (Langner *et al.*, 2015). However, its anticancer activity and underlying mechanisms in breast cancer cells remains to be explored. In this context, the current study examined the anticancer potential of QA against human MCF-7 cancer cells.

MATERIALS AND METHODS

Cell culture conditions

The Human MCF-7 and Murine L929 fibroblast cells were procured from an established cell culture repository. The cells were grown in Dulbecco's Modified Eagle Medium (DMEM) and 10% Fetal Bovine Serum (FBS) and 1% penicillin-streptomycin. Cells were cultured at 37°C under humidity with 5% carbon dioxide.

MTT cell viability assay

The cytotoxicity efficacy of QA and standard drug cisplatin was determined using the MTT assay. MCF-7 and L929 cells were seeded in a 96-well plate and left overnight for proper cell adhesion under normal culture conditions. MCF-7 cells were treated with cisplatin (10-100 µg/mL) and QA (0.2-100 µg/mL), while L929 cells were treated with QA (0.2-100 µg/mL) for 24 hours. After treatment, MTT solution (0.5 mg/mL) was added and kept for 4 hours of incubation. Formazan crystals were dissolved using DMSO and absorbance was taken at 570 nm.

DAPI fluorescence staining

Apoptosis-associated nuclear morphological changes were examined using DAPI fluorescence staining. MCF-7 cells were seeded in 24-well plates at a density of 4×10^3 cells/well and incubated for 24 h to allow attachment. The cells were then exposed to QA (3, 6 and 11 µg/mL) for 24 h. After treatment, the cells were washed with PBS and stained with DAPI (10 µL in 500 µL PBS) for 10-15 min in the dark. After removing excess stain, nuclear morphology was examined using a fluorescence microscope (Olympus CKX-53, Japan). Apoptotic cells were identified by chromatin condensation and nuclear fragmentation and their percentage was determined from at least three randomly selected fields.

AO-EtBr dual fluorescence staining

The MCF-7 cells were treated with QA (3, 6 and 11 µg/mL) for 24 h and stained with AO/EB (100 µg/mL each), followed by observation under a fluorescence microscope. The cells were categorized into viable, early apoptosis, late apoptosis and necrosis depending on fluorescence and nuclear structure. The apoptotic cells were counted in at least three random fields and presented as percentages.

Carboxy-H2DCFDA staining

Intracellular reactive oxygen species production in MCF-7 cells was assessed by Carboxy-H2DCFDA fluorescent probe method. Cells were treated with QA (3, 6 and 11 µg/mL) for 24 hours and then stained with 10 µM Carboxy-H2DCFDA for 30 minutes at 37°C in the dark conditions. The fluorescence of the probe was determined by a microplate reader at 485/535 nm and representative images were taken by an Olympus CKX-53 fluorescence microscope.

Mitochondrial membrane potential (ΔΨm) assessment folds

The effect of QA on the ΔΨm of MCF-7 cells was determined by JC-1 staining. In this experiment, after treating the MCF-7 cells with QA (3, 6 and 11 µg/mL) for 24 h, the cells were stained with JC-1 (2-10 µM) dye for 20-30 min at 37°C in the dark. The fluorescence was examined under an Olympus CKX-53 fluorescence microscope.

Annexin V-FITC/PI apoptosis assay

Quantification of apoptosis induced by QA on MCF-7 cells was determined through Annexin V-FITC/PI assay. Cells were treated with 11.37 µg/mL of QA for 24 hours

and stained using Annexin V-FITC and PI and were then analyzed using SYSMEX flow cytometry. Cells were categorized as live, early apoptosis, late apoptosis, or necrosis using FlowJo software.

Statistical analysis

The data were expressed as the mean ± SD. Statistical differences between the groups were analyzed by one-way ANOVA followed by post hoc tests. Statistical significance was set at $p < 0.05$.

RESULTS

Effect of QA on MCF-7 cells viability

Microscopic observation of MCF-7 cells following 24 h treatment with quinaldic acid (QA) revealed distinct morphological alterations compared with untreated control cells. QA treatment resulted in a reduction in cell density, loss of normal adherent morphology, cellular rounding and shrinkage, increased intercellular spaces, and increased numbers of detached and rounded cells.

At higher QA concentrations, these alterations became more pronounced, with increased cellular debris and loss of viable adherent cells. The concentration-dependent morphological alterations observed in the cells were in line with the decrease in cell viability in the 24 hour MTT assay, indicating the cytotoxicity effect of QA against MCF-7 cells (Fig. 1).

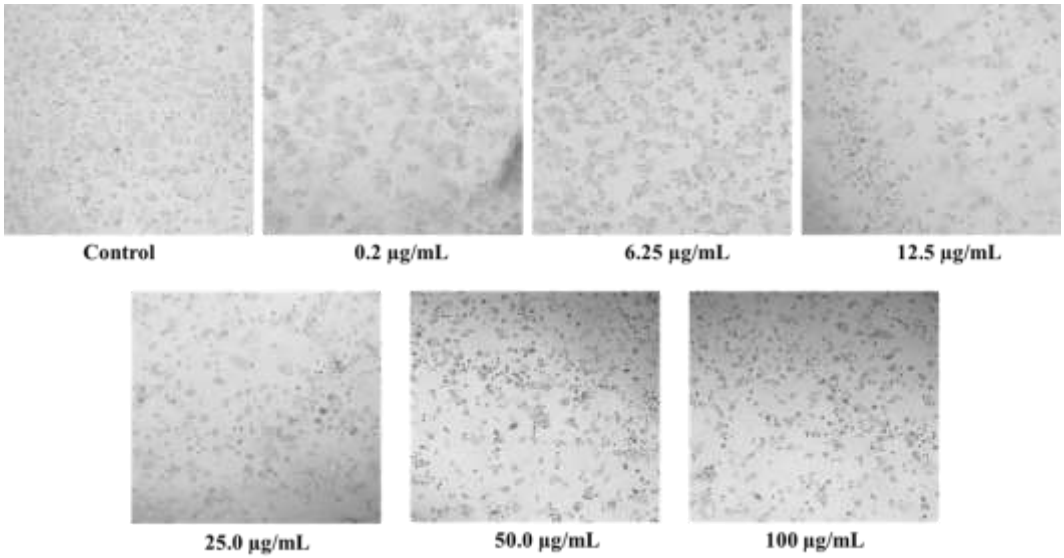

Fig. 1. Effect of quinaldic acid on the morphology of MCF-7 breast cancer cells after 24 h treatment

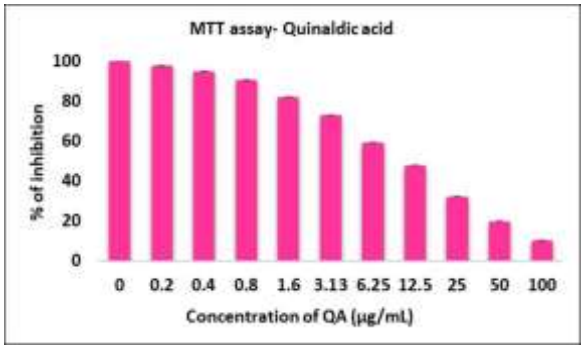

Fig. 2. Cytotoxic effect of quinaldic acid on MCF-7 cells determined by the MTT assay

Data represent the mean ± SD of three independent experiments performed in triplicate.

QA exhibited concentration-dependent cytotoxicity against breast carcinoma MCF-7 cells after treatment for 24 h. Cell viability remained relatively unaffected at lower concentrations (0.2-0.8 µg/mL) but declined progressively at concentrations ≥1.6 µg/mL. A pronounced decrease in cell viability was noted between 6.25 and 50 µg/mL, with minimal viable cells detected at 100 µg/mL, demonstrating a dose-dependent cytotoxic effect. The IC50 was found at 11.37 µg/mL (Fig. 2).

Cytotoxic effect of QA on L929 cells

QA induced dose dependent cell viability reduction and cell viability remained above 90% at

concentrations up to 0.8 µg/mL and gradually reduced to 83.92, 78.26, 73.31, 68.92, 60.21, 55.09 and 44.39 at 1.6, 3.13, 6.25, 12.5, 25, 50 and 100 µg/mL, respectively. The IC_{50} value was 73.78 µg/mL, indicating comparatively lower cytotoxicity toward L929 cells (Fig. 3).

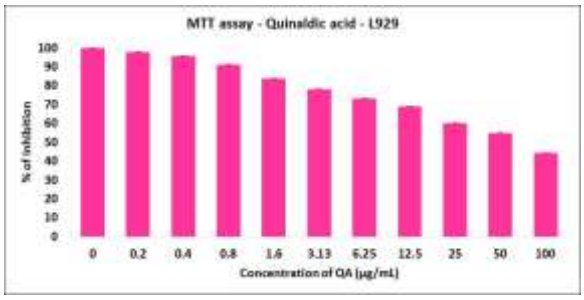

Fig. 3. Cytotoxic effect of quinaldic acid on L929 cells determined by the MTT assay
Data represent the mean ± SD of three independent experiments performed in triplicate.

Cytotoxic effect of cisplatin on MCF-7 cells

Cisplatin produced a dose response reduction in cell viability, which declined from 81% at 10 µg/mL to 63%, 35% and 14% at 20, 30 and 40 µg/mL, respectively. Nearly complete loss of viability was observed at concentrations of 50 µg/mL and above. The IC_{50} value of cisplatin was found at 24.53 µg/mL confirming its potent antiproliferative effect against MCF-7 cells (Fig. 4).

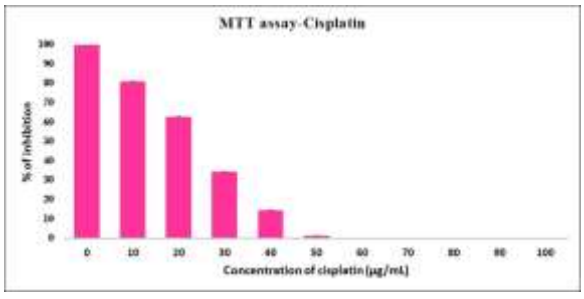

Fig. 4. Cytotoxic effect of cisplatin on MCF-7 cells determined by the MTT assay
Data represent the mean ± SD of three independent experiments performed in triplicate.

QA induces nuclear morphological alterations in MCF-7 cells (DAPI staining)

Cells that were not treated with QA showed uniformly stained nuclei with normal morphology, while cells exposed to 3, 6 and 11 µg/mL concentrations of the QA exhibited increased condensation of chromatin and irregularities in the nuclei. The most pronounced effects were observed at 6 and 11 µg/mL (Fig. 5).

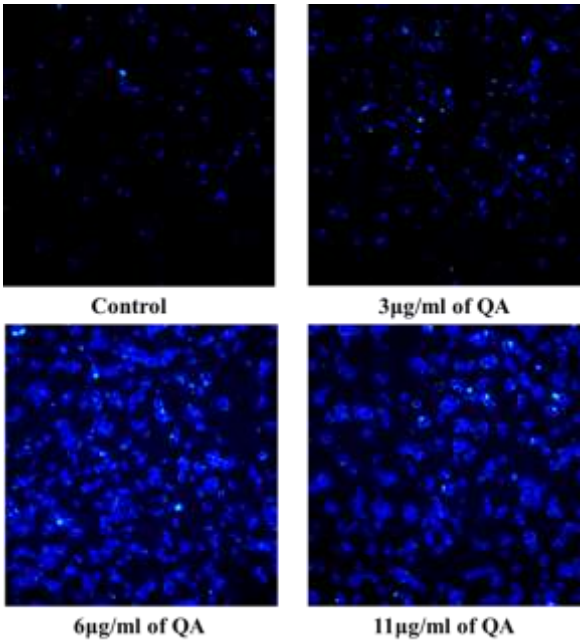

Fig. 5. DAPI fluorescence staining of MCF-7 cells following quinaldic acid treatment

QA promotes apoptosis in MCF-7 cells (AO-EtBr dual fluorescence staining)

In the control group, most of the cells exhibited green fluorescent staining, which was indicative of cell viability. On the other hand, in cells treated with 3, 6 and 11 µg/mL concentrations of QA, there was an increasing number of red/orange fluorescent cells and a decreasing number of viable cells. This observation was more prominent in 6 and 11 µg/mL concentrations, suggesting a concentration-dependent induction of apoptotic cell death (Fig. 6).

QA increases intracellular ROS levels (carboxy-H2DCFDA staining)

Treatment of MCF-7 cells with QA resulted in a dose-dependent increase in intracellular ROS generation, as detected by carboxy-H2DCFDA staining. As compared to the low levels of fluorescence in non-treated cells, increasing amounts of green fluorescence were observed in following exposure to 3, 6 and 11 µg/mL of the QA, with the highest level seen at 11 µg/mL, indicating enhanced ROS accumulation (Fig. 7).

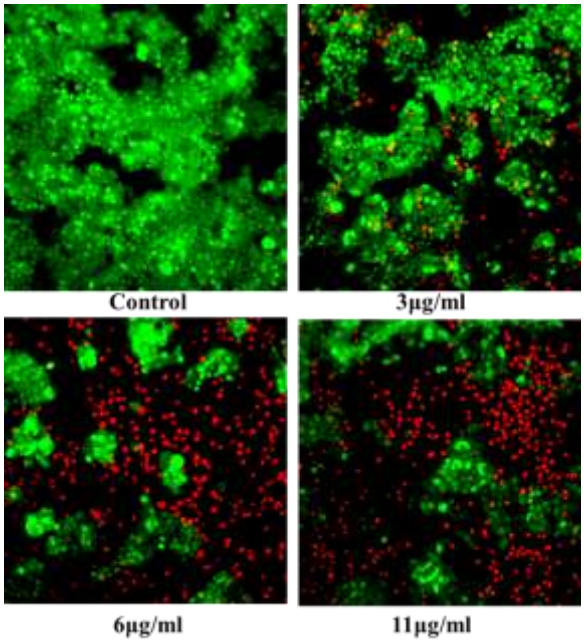

Fig. 6. AO–EtBr dual fluorescence staining of MCF-7 cells following quinaldic acid treatment

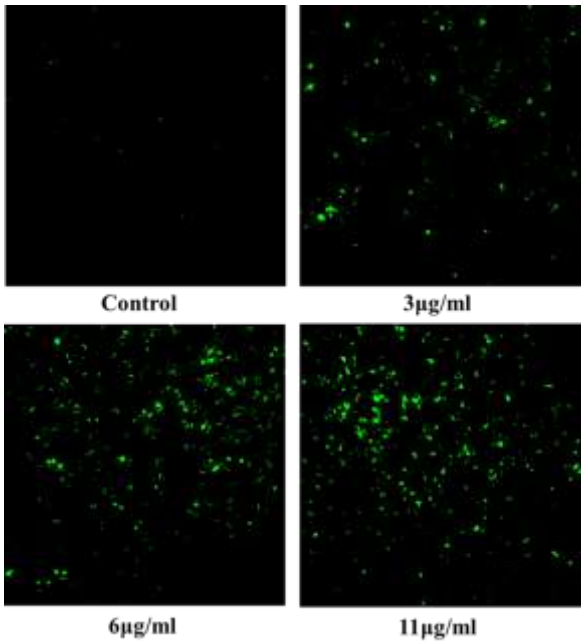

Fig. 7. Effect of quinaldic acid on intracellular ROS generation in MCF-7 cells

QA induces mitochondrial membrane depolarization (JC-1 staining)

A dose-dependent disruption in mitochondrial membrane potential was evident in MCF-7 cells stained with JC-1 after exposure to QA. Untreated cells were observed predominantly red/orange fluorescent, indicating polarization of the mitochondria. When cells were treated with 3, 6 and 11 µg/mL QA, there was a reduction in red/orange fluorescence and an increase in green fluorescence, with more pronounced depolarization occurred at doses of 6 and 11 µg/mL (Fig. 8).

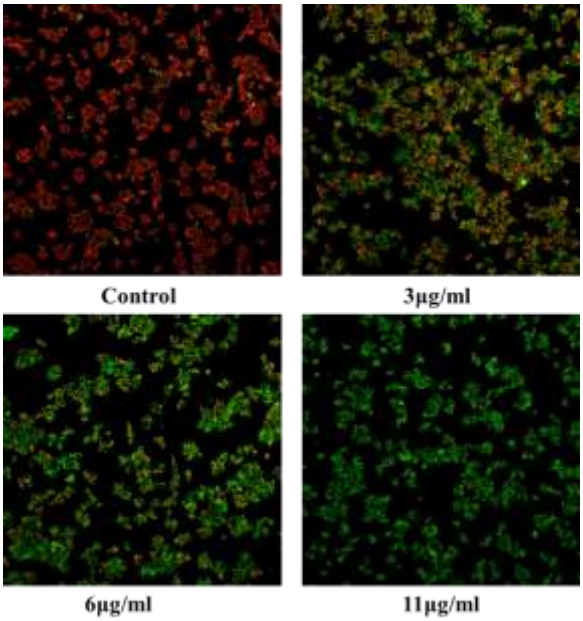

Fig. 8. Effect of quinaldic acid on mitochondrial membrane potential in MCF-7 cells

QA induces apoptosis in MCF-7 cells (Annexin V-FITC/PI flow cytometry analysis)

Annexin V-FITC/PI flow cytometric analysis confirmed the pro-apoptotic effect of QA. In untreated cells, 94.29% of the population remained viable, while early apoptosis, late apoptosis and necrosis accounted for 0.73%, 1.48% and 3.50%, respectively. MCF-7 cells were treated with QA at the IC_{50} level (11.37 µg/mL) for 24 h and stained with Annexin V-FITC and propidium iodide (PI).24 markedly decreased the viable cell population to 10.81% and increased early and late apoptotic cell count to 51.14% and 35.60%, respectively. The necrotic population remained low at 2.45%, indicating that QA primarily triggers apoptotic rather than necrotic cell death in MCF-7 cells (Fig. 9).

Representative flow cytometry dot plots illustrated the distribution of living (Annexin V^-/PI^-), early apoptotic (Annexin V^+/PI^-), late apoptotic (Annexin V^+/PI^+) and necrotic (Annexin V^-/PI^+)

cells between the control group and the QA treated group. The bar graph shows the percentage of viable, early apoptotic, late apoptotic and necrotic cells. There is a significant reduction in living cells, while significant increase in early and late apoptotic cells was noted in the QA group. Data are presented as the mean ± SD of three independent experiments.

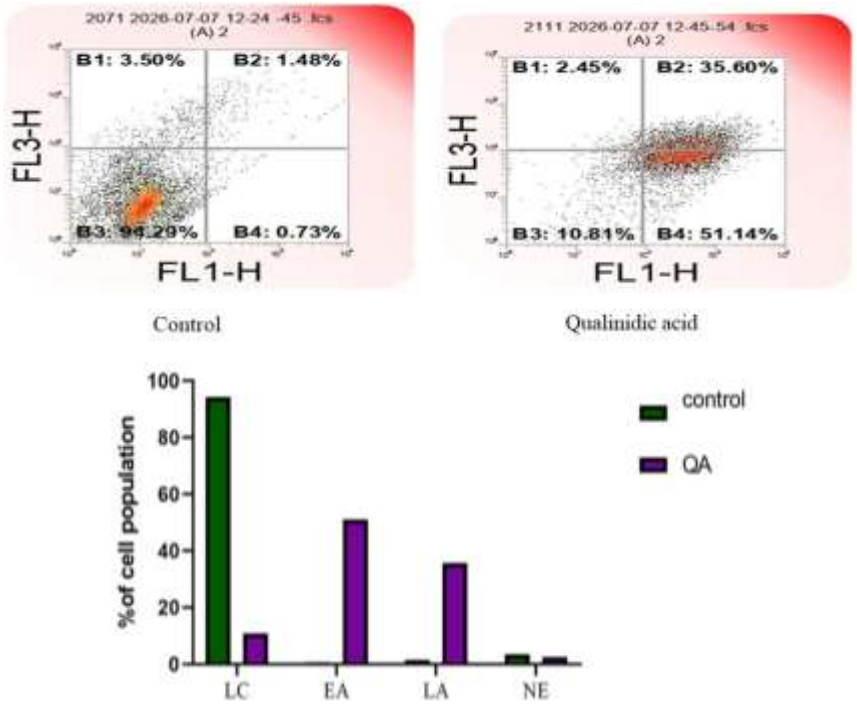

Fig. 9. Quinaldic acid induces apoptosis in MCF-7 cells as determined by Annexin V-FITC/PI flow cytometry analysis

DISCUSSION

Breast cancer remains a significant global health burden despite substantial advances in its diagnosis and therapeutic management (Łukasiewicz *et al.*, 2021). While chemotherapy, endocrine therapy, targeted therapy and radiotherapy have improved clinical outcomes, their efficacy may be compromised by treatment related toxicities (Chaudhari *et al.*, 2024; Wu *et al.*, 2026). This has increased the interest in identifying new anticancer agents that preferentially act against cancer cells with reduced side effects on healthy tissues. In the present study, QA showed a prominent antiproliferative activity against MCF-7 in dose dependent manner, while its effect on normal L929 fibroblasts was comparatively weaker. The findings suggest that, QA produced redox imbalance, mitochondrial dysfunction and induction of apoptosis in MCF-7 cells, contribute to the cytotoxic activity of QA.

The MTT analysis showed that QA reduced the viability of MCF-7 cells in a dose responsive manner. At lower concentrations (0.2-0.8 µg/mL), most cells remained viable, whereas a progressive reduction in viability was observed from 1.6 µg/mL onward. The reduction became more pronounced between 12.5 and 50 µg/mL, with very low viability at 100 µg/mL. The IC_{50} calculated for the QA compound was 11.37 µg/mL, demonstrating high sensitivity of MCF-7 cells to QA. Cisplatin, which served as the standard drug, induced a dose-dependent reduction in the viability of MCF-7 cells and the IC_{50} was found at 24.53 µg/mL. Thus, under the experimental conditions, QA had a lower IC_{50} compared to cisplatin. However, this result must be understood as an *in vitro* test of cytotoxic potential and must not be considered a validation to the superiority of efficacy clinically.

One of the notable observations from this experiment was the sensitivity of the normal L929 fibroblast cells

to QA. Cell viability was above 90% at 0.8 µg/mL and progressively reduced with an increase in concentration to reach 44% at 100 µg/mL. The IC_{50} value of 73.78 µg/mL was significantly higher compared to those determined in MCF-7 cells. This highlights the sensitivity of MCF-7 cells to QA compared to L929 cells under the experimental conditions applied. The selective activity is favorable when assessing anti-cancer effect, as the selective effect would target cancerous cells only. Similarly, Langner *et al.* (2015) demonstrated that QA inhibited the growth of HT-29 colon cancer cells with low levels of cytotoxicity towards normal epithelial cells.

As evidenced by subsequent experiments, oxidative stress may be involved in the induction of cytotoxicity. Due to metabolic changes, cancer cells usually possess relatively high levels of basal ROS. Therefore, cancer cells are more sensitive to oxidative stress than normal cells (Akter *et al.*, 2026; Nikiforova, 2026). The present study observed bright green fluorescence in control MCF-7 cells when stained with Carboxy-H_2DCFDA, while QA exposure at 3, 6 and 11 µg/mL caused increasingly red/orange fluorescent and decreased the green fluorescent. The increased red/orange fluorescence was detected at 6 and 11µg/mL which suggested the increased generation of ROS within the cell. The results obtained demonstrated that QA disrupted the redox homeostasis of MCF-7 cells. Overproduction of ROS, exceeding the antioxidant capacity of the cell, may damage cell components and activate signal pathways leading to cause cell death (Akter *et al.*, 2026; Nikiforova, 2026).

The increased ROS production was accompanied by disruption of mitochondrial membrane potential, which was demonstrated using JC-1 staining. Untreated cells were predominantly stained red-orange, indicating mitochondrial polarization. However, with an increasing concentration of QA, red-orange fluorescence decreased, while green fluorescence increased, especially at 6 and 11 µg/mL. The loss of mitochondrial membrane potential is a significant characteristic of mitochondrial dysfunction and is directly linked to intrinsic apoptosis (Ly *et al.*, 2003). The simultaneous increase in ROS and depolarization of mitochondria reported in the current study demonstrates the link between oxidative stress and mitochondrial dysfunction and cell death induced by QA. However, as both phenomena were not directly assessed in this study, more detailed studies are required in order to identify the sequence of events.

Morphological changes in the nuclear architecture provided further confirmation of apoptosis.

The nuclei of the control cells showed relatively normal and equally stained structures, while those of the QA-exposed cells showed increasing nuclear irregularity and condensation, especially at a dose of 6 and 11 µg/mL QA confirmed by DAPI staining. These features are indicative of apoptosis and show that the decrease in cell viability occurred with changes in the nuclear architecture. Therefore, QA produced dose-dependent efficacy against MCF-7 cells.

The current Annexin V-FITC/PI flow cytometry analysis showed that QA-induced cytotoxicity in MCF-7 cells is primarily due to apoptosis rather than necrosis. The IC_{50} of QA (11.37 µg/mL) caused a predominant reduction of viable cells from 94.29% to 10.81%, whereas early and late apoptotic cells increased significantly to 51.14% and 35.60%, respectively. On the other hand, there were only 2.45% necrotic cells. The pronounced increase in both early and late apoptotic populations suggests that QA treatment promoted progression of MCF-7 cells through different stages of programmed cell death. The predominance of early apoptotic cells implies initiation of apoptosis, while the substantial increase in late apoptotic cells implies further progression of apoptosis. These results are in agreement with the decreased cell viability determined by the MTT test and the results of DAPI and AO-EtBr staining strongly confirm apoptosis as a primary mode of QA-induced cytotoxicity in MCF-7 cells.

The results indicate that there is a probable chain of events, whereby QA causes an increase in ROS within the cell, depolarization of the mitochondrial membrane and apoptosis. The later changes observed in the nucleus and increases in Annexin V-positive population confirm this hypothesis. Even though apoptosis associated genes or proteins such as Bax, Bcl-2, cytochrome c, caspases and PARP were not analyzed in the present study; mitochondrial dysfunction may have contributed to QA-induced apoptotic signaling through modulation of these apoptotic markers.

Furthermore, the comparatively lower toxicity shown in the L929 cell line than in MCF-7 cells deserves attention. This observation is especially important in considering the side effects of traditional breast cancer treatments. Thus, the effectiveness of the compound on cancerous cells in comparison to normal cells would make it a lead compound for developing an anticancer drug.

CONCLUSION

QA showed strong and selective cytotoxic activity towards MCF-7 breast cancer cells with comparetively lower cytotoxic activity towards normal L929 fibroblasts. The findings suggested that QA-induced cytotoxicity is linked to ROS production, mitochondrial membrane depolarization and apoptosis. Overall, QA can be used as a promising lead compound for further study as an anticancer drug.

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