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Original Research Article

Poncirin Inhibits Cell Viability and Induces Caspase-mediated Apoptosis in Cervical Cancer Cells

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Abstract

Background: Cervical cancer continues to pose a considerable global health concern, disproportionately impacting women in low- and middle-income nations due to various barriers. Although mostly preventable with immunization and screening, it ranks as the fourth most widespread cancer among women worldwide.
Objectives: The present study examines the capacity of poncirin to suppress viability and promote apoptosis in cervical cancer HeLa cells.
Materials and Methods: In this work, a 3-(4,5)-dimethylthiahiazo(-z-y1)-3,5-di-phenytetrazoliumromide (MTT) test was utilized to study the effect of poncirin (5–160 μM) on the growth of HeLa cells. Apoptosis in the experimental HeLa cells was examined using a dual staining technique. The activities of caspase enzymes in the cells were evaluated using kits.
Results: The MTT assay findings indicated a substantial decrease in HeLa cell growth after treatment with poncirin. The findings of the dual staining test confirmed the initiation of apoptosis in the poncirin-treated HeLa cells. Moreover, the poncirin treatment significantly elevated caspase enzyme activities in the HeLa cells, thereby facilitating apoptotic induction.
Conclusion: The present findings indicate that poncirin treatment significantly inhibits growth and enhances caspase-mediated apoptotic cell death in HeLa cells. Consequently, it can serve as an anti-tumor candidate for the treatment of cervical cancer.

Keywords

HeLa cell line, poncirin, apoptosis, caspases, cervical cancer

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Introduction

Cervical cancer, a significant contributor to female cancer-related mortality globally, is defined as a malignant neoplasm developing from the cells of the cervix uteri, the region connecting the uterus and vagina. Cervical cancer predominantly affects women worldwide, ranking as the fourth most prevalent cancer among women, followed by breast, colorectal, and lung cancers. In 2020, there were about 604,127 new incidences of cervical cancer identified, and 341,831 mortalities attributed to the disease worldwide, highlighting its devastating impact on global health (Singh et al., 2023). Notably, a disproportionate burden of cervical cancer falls upon low- and middle-income nations, where nearly 90% of cervical cancer-associated mortalities occur. Despite advancements in cervical cancer screening and prevention strategies, the disease remains a formidable challenge, especially in developing nations where access to healthcare resources is limited (Bray et al., 2024). The common etiological agent that participates in the onset of cervical cancer is chronic infection with high-risk human papillomavirus (HPV) genotypes, especially HPV 16 and 18, which account for nearly 70% of all cervical cancer incidences. HPV is responsible for the vast majority of cervical cancer diagnoses (Hochmann et al., 2020). It is estimated that roughly 75% of women will contract an HPV infection at

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some point in their lives, but only a small percentage of these infections will persist and potentially result in cell abnormalities that could develop into carcinoma. Beyond HPV infection, other causes of cervical cancer include smoking, immunosuppression (e.g., HIV infection), multiple sexual partners, early age at first sexual intercourse, long-term use of oral contraceptives, and a history of other sexually transmitted infections (Vallejo-Ruiz et al., 2024).

The pathogenesis of cervical cancer is a complex and multistep process involving the interplay of viral oncogenes, host cellular factors, and environmental influences. Infection with high-risk HPV types initiates a cascade of cellular events characterized by the incorporation of viral DNA into the host genome, resulting in the overexpression of viral oncogenes E6 and E7 (Kurnia et al., 2022). The overexpression of E6 and E7 disrupts normal cellular processes, resulting in genetic mutations and epigenetic changes that lead to the conversion of normal cervical cells into precancerous and cancerous cells. Cervical cancer initiates in the transformation region, the junction between the ectocervix's squamous epithelium and the endocervix's columnar epithelium, characterized by ongoing metaplastic alterations (Ojha et al., 2022). Current treatment modalities for cervical cancer encompass surgery, radiotherapy, chemotherapy, and targeted therapies, tailored to the stage and extent of the disease. However, despite these advances, significant challenges remain in the effective treatment of cervical cancer, particularly in developed stages (Dicu-Andreescu et al., 2023). Chemotherapy regimens, typically consisting of platinum-based agents, are commonly used in combination with radiation therapy for locally developed cervical cancer or as palliative treatment for metastatic disease, but are often associated with significant toxicities, including myelosuppression, nausea, vomiting, and peripheral neuropathy (Boitano et al., 2023).

The limitations of current therapies for cervical cancer underscore the need for the advancement of novel and more potent therapeutic strategies that can increase patient outcomes and reduce treatment-related toxicities. Alternative therapies that can enhance patient outcomes and decrease treatment-associated toxicities are urgently needed (Burmeister et al., 2022). Poncirin is a bioactive flavanone glycoside compound found extensively in several citrus species, including *Citrus trifoliata* (syn. *Poncirus trifoliata*). It has already been reported that poncirin demonstrated neuroprotective (Yang et al., 2020), hepatoprotective (Ullah et al., 2020), and anti-diabetic (Yousof Ali et al., 2020) properties. Furthermore, poncirin induced apoptosis in gastric cancer AGS cells (Saralamma et al., 2015). Poncirin also inhibited cell growth, metastasis, and tumor growth in a breast cancer model (Yun et al., 2024). Zhao et al. (2021) reported that poncirin decreased cisplatin resistance in cisplatin-resistant osteosarcoma cells. However, there are no reports on the anti-tumor effects of poncirin against the cervical cancer model. Therefore, this study examines the capacity of poncirin to suppress viability and promote apoptosis in cervical cancer cells.

Materials and Methods

Chemicals

Poncirin (purity: ≥95.0% high-performance liquid chromatography [HPLC]), Dulbecco's Modified Eagle Medium (DMEM) medium, 3-(4,5)-dimethylthiahiazo(-z-y1)-3,5-di-phenytetrazoliumromide (MTT) reagent, and others were purchased from Sigma-Aldrich, USA. The assay kits to estimate caspase activities were obtained from Elabscience, USA.

Cell Culture Maintenance

The human cervical cancer HeLa cells were acquired from ATCC, USA, and further cultivated in DMEM medium enriched with 10% fetal bovine serum (FBS) and 1% antimycotic mixture in a 5% CO_2 incubator. The mature cells were harvested when they reached 80% confluency and used for further treatment and tests.

MTT Assay

The growth of control and treated cervical cancer HeLa cells was assessed with the MTT assay. HeLa cells were cultivated for 24 h in a 96-well plate and then exposed to poncirin at diverse dosages (5, 10, 20, 40, 80, and 160 μM) for another 24, 48, and 72 h. Subsequent to the treatment, a mixture of 20 μL MTT and 100 μL DMEM was added to the wells for a duration of 4 h. After dissolving the formazan crystals with dimethyl sulfoxide (DMSO) (100 μL), the absorbance was measured at 570 nm.

Acridine Orange/Ethidium Bromide (AO/EB) Staining Assay

The dual staining technique was conducted on the experimental HeLa cells to examine the apoptotic level. The HeLa cells were cultured for 24 h and subsequently treated with 40 μM of poncirin for an additional 24 h. A mixture of AO/EB (100 μg/mL) was thereafter added to the wells and incubated for 5 min in a shady place. The apoptotic level was evaluated in HeLa cells utilizing a fluorescent microscope.

Analysis of Caspase Activities

The experimental HeLa cells were collected, lysed with cell lysis buffer, and the suspension was processed to evaluate caspase activities. The activities of caspase-3, -8, and -9 were quantified in control and poncirin-treated HeLa cells. The tests were conducted with test kits (Elabscience, USA) according to the methods outlined by the manufacturer.

Statistical Analysis

The statistical tests were conducted using GraphPad Prism software, and the data are portrayed as mean ± standard deviation (SD) of triplicates ($n = 3$). The results were evaluated using one-way analysis of variance (ANOVA) and Tukey's *post hoc* tests, with a significance fixed at $p < .05$.

Results

Effect of Poncirin on Cervical Cancer HeLa Cell Viability

Figure 1 illustrates the results of the MTT test, demonstrating the effect of poncirin on the proliferation of HeLa cells. Poncirin treatment markedly diminished the proliferation of HeLa cells across a range of doses (5–160 μM) at 24, 48, and 72 h. The elevated levels of poncirin demonstrated increased inhibitory activity on the proliferation of HeLa cells (Figure 1). The IC_{50} concentration of poncirin was determined to be 40 μM against HeLa cells, and this dose was used for the following investigations.

Effect of Poncirin on the Apoptotic Level in HeLa Cells

The dual staining approach was employed to investigate the level of apoptosis in the experimental HeLa cells, with results presented in Figure 2. Following treatment with 40 μM of poncirin, the HeLa cells exhibited elevated amounts of red fluorescent cells, indicating the onset of apoptotic cell death, suggesting the apoptotic activity of poncirin against HeLa cells.

Effect of Poncirin on Caspase Activities in the HeLa Cells

The activities of caspase-3, -8, and -9 in normal and poncirin-exposed HeLa cells were analyzed, with results depicted in Figure 3. The untreated control cells illustrated moderate caspase activities. However, the treatment of 40 μM poncirin to HeLa cells considerably elevated the caspase-3, -8, and -9 activities.

Discussion

Cervical cancer continues to pose a considerable global health concern, disproportionately impacting women in low- and middle-income nations because of various hurdles. Although mostly preventable with immunization and screening, it ranks as the fourth common cancer among women worldwide (Sung et al., 2021). Factors contributing to this disparity include limited access to healthcare services, lack of awareness about prevention strategies, and inadequate screening programs. The high mortality rates highlight the critical need for improved access to early detection and therapy. The onset of cervical cancer is a multistep mechanism, typically progressing from

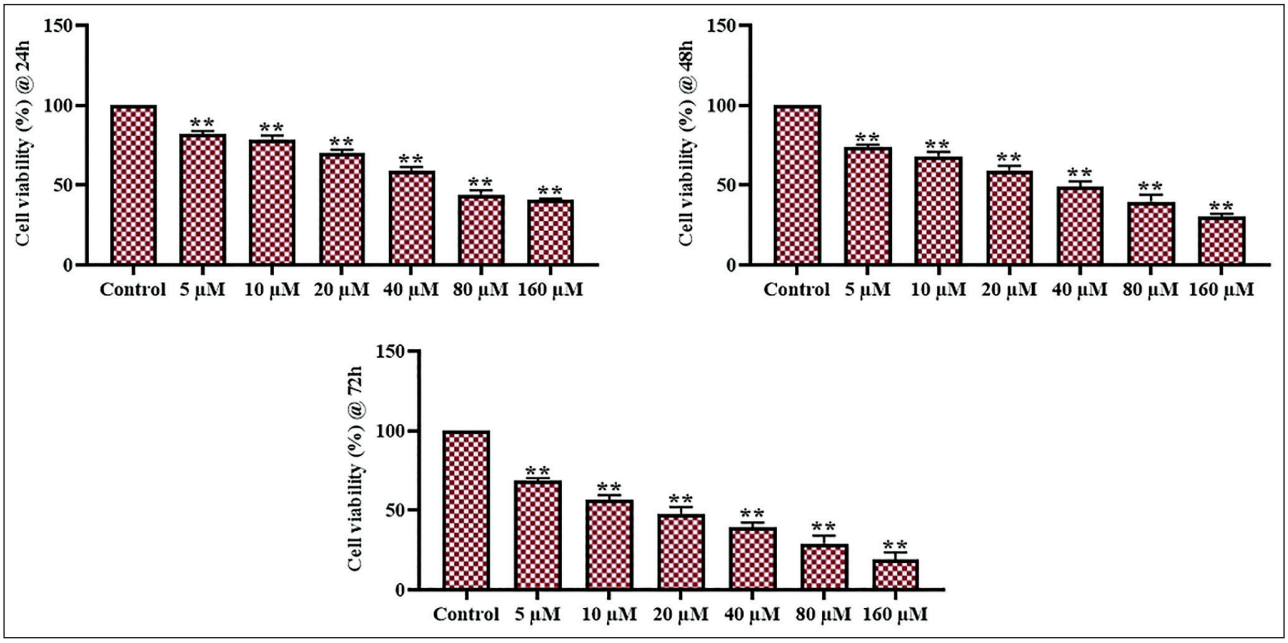


Figure 1. Effect of Poncirin on the Cervical Cancer HeLa Cell Viability. Poncirin Treatment at Several Dosages (5–160 μM) Reduced HeLa Cell Viability in a Dose-dependent Manner. The Data are Shown as the Mean ± Standard Deviation (SD) of Triplicates. The Values Underwent One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Analyses by GraphPad Prism Software. The Symbol "**" Indicates Statistical Significance at a $p < .05$ in Comparison to the Control Group.

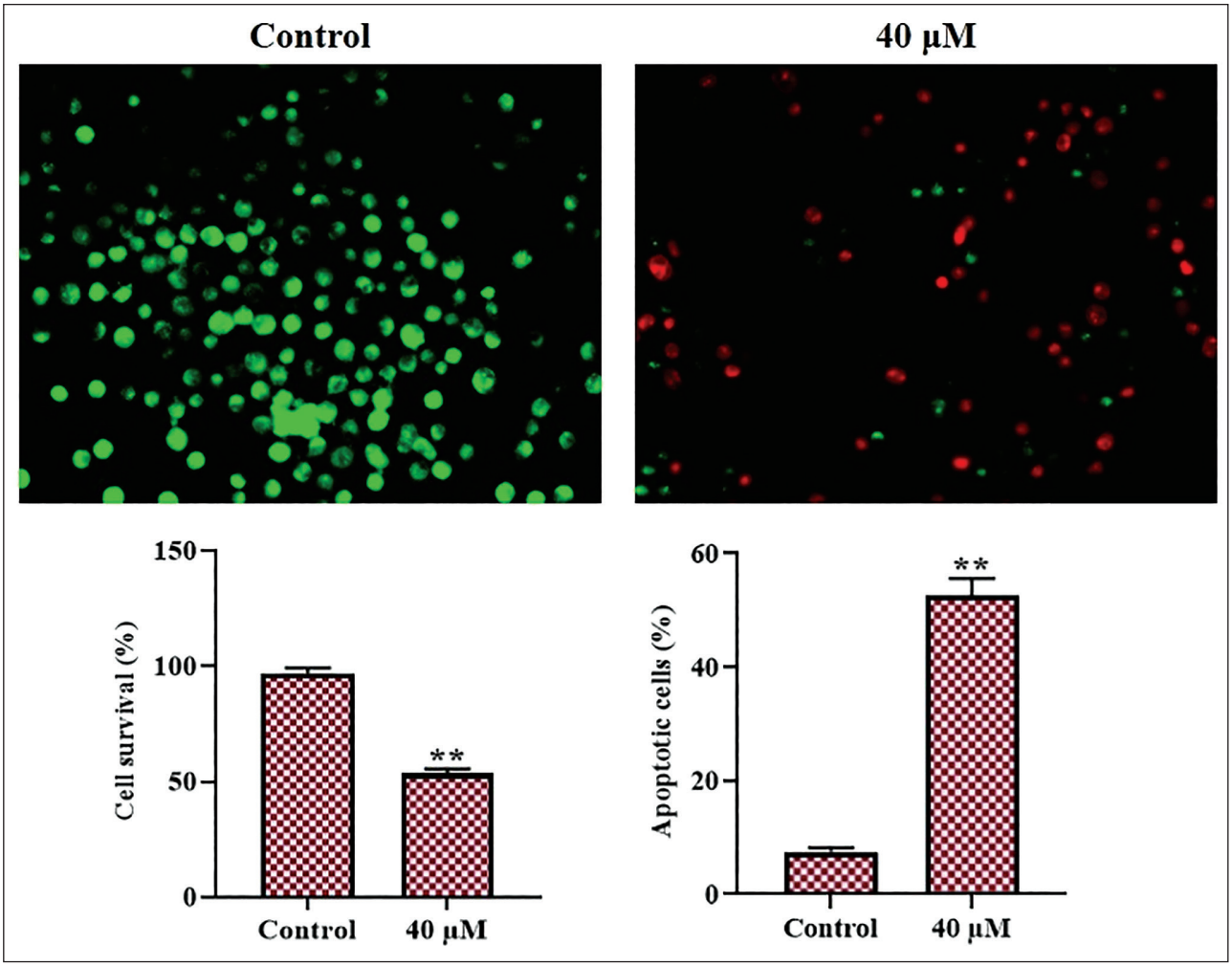


Figure 2. Effect of Poncirin on the Apoptosis in HeLa Cells. Following Treatment with 40 μM of Poncirin, the Cervical Cancer HeLa Cells Displayed Pronounced Red Fluorescence, Validating the Presence of Apoptosis in Cells. The Data are Shown as the Mean ± Standard Deviation (SD) of Triplicates. The Values Underwent One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Analyses by GraphPad Prism Software. The Symbol "**" Indicates Statistical Significance at a $p < .05$ in Comparison to the Control Group.

precancerous lesions, such as cervical intraepithelial neoplasia, to invasive cancer over a period of several years (Li et al., 2025). This protracted timeline offers a window of opportunity for early detection and intervention through regular screening. However, factors such as co-infection with HIV, smoking, and long-term utilization of oral contraceptives can accelerate disease progression. It is imperative to understand the underlying molecular mechanisms of carcinogenesis to develop targeted therapies and preventative strategies (Taghizadeh et al., 2019). Current treatment modalities for cervical cancer include surgery, radiation therapy, and chemotherapy, often utilized in combination based on the stage and extent of the disease. While these approaches can be effective, they are frequently associated with significant adverse effects that can affect a patient's quality of life. These adverse effects highlight the imperative need for safe and effective therapeutic interventions that minimize harm to healthy tissues while effectively eradicating cancerous cells. Furthermore, the development of resistance to conventional chemotherapeutic agents displays a substantial challenge in the management of advanced cervical cancer (Bhattacharjee et al., 2022).

Apoptosis, a meticulously regulated and evolutionarily preserved mechanism of programmed cell death, is important for sustaining tissue homeostasis, removing damaged or superfluous cells, and sculpting the developing body. This intricate cellular self-destruction mechanism is characterized by a distinct set of morphological and biochemical hallmarks, such as shrinkage of cells, chromatin condensation, fragmentation of DNA, and the development of apoptotic bodies (Morana et al., 2022). The execution of apoptosis involves a cascade of molecular events, primarily regulated by caspases, which act as both initiators and executioners of the apoptotic program (Mishra et al., 2023). Deregulation of apoptosis is involved in the onset of a wide spectrum of human diseases,

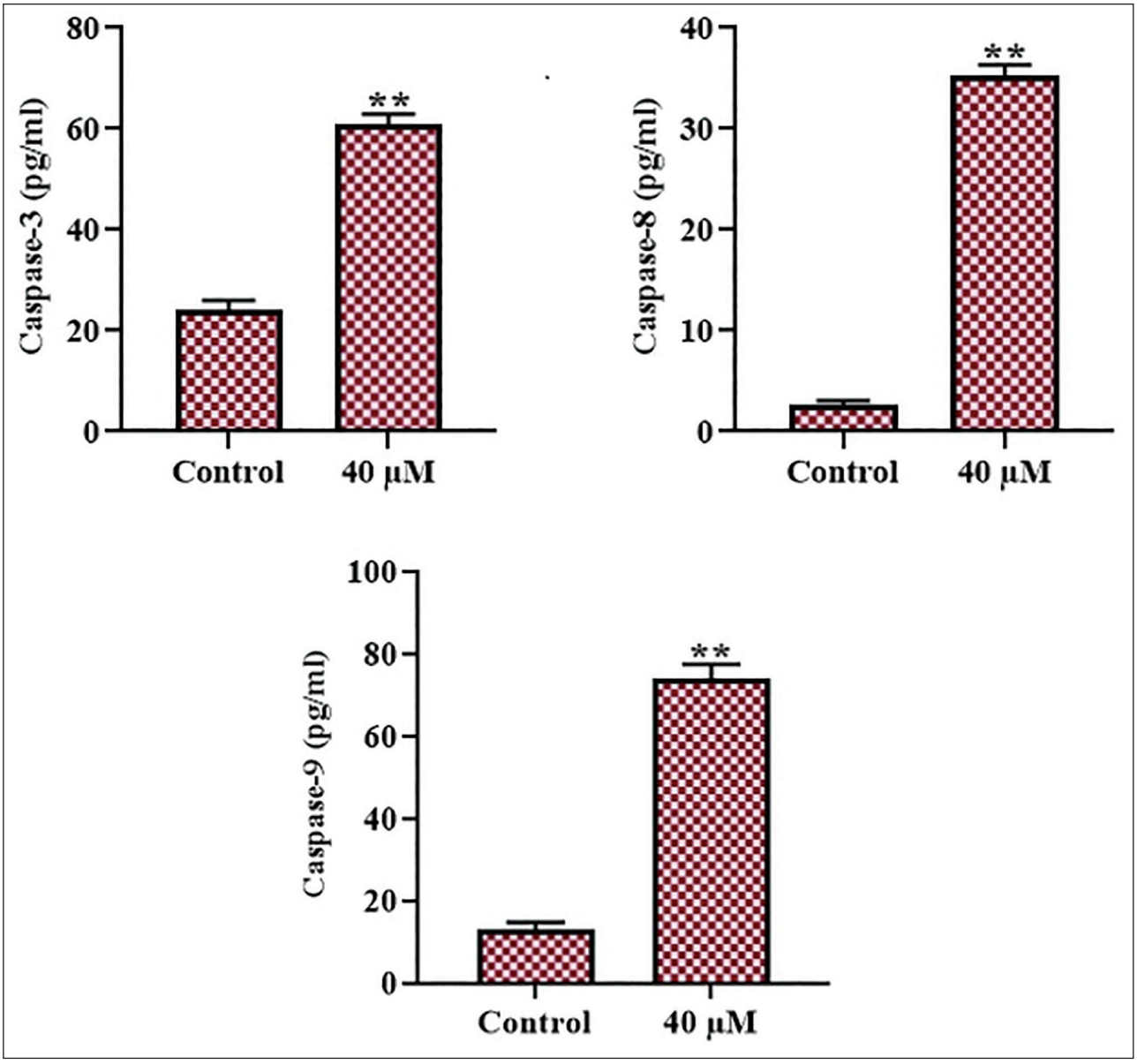


Figure 3. Effect of Poncirin on the Caspase Activities in the HeLa Cells. The Data are Shown as the Mean ± Standard Deviation (SD) of Triplicates. The Values Underwent One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Analyses Utilizing GraphPad Prism Software. The Symbol "**" Indicates Statistical Significance at a $p < .05$ in Comparison to the Control Group.

most notably cancer, where it can contribute to uncontrolled cell proliferation, cancer advancement, and resistance to treatments. Understanding the complexities of the apoptotic mechanism and how cancer cells evolve to evade apoptosis has driven research toward developing novel techniques designed to trigger apoptosis selectively in tumor cells (Carneiro & El-Deiry, 2020). The importance of apoptosis in cancer is underscored by the observation that many cancer cells exhibit defects in their apoptotic pathways, rendering them resistant to normal cell death signals (Mishra et al., 2023). This resistance to apoptosis can arise from a variety of mechanisms, such as overexpression of anti-apoptotic genes, downregulation of pro-apoptotic genes, mutations in key apoptotic genes, and alterations in signaling pathways that regulate apoptosis. For instance, the escape of apoptosis is a major characteristic of residual tumor cells that persist after therapy (Vogler et al., 2025).

The imbalance between cell growth and apoptosis is an essential factor in tumorigenesis, as it allows pre-cancerous and cancerous cells to escape elimination and accumulate genetic and epigenetic alterations that promote their survival and proliferation. Furthermore, the tumor microenvironment can also influence the sensitivity of cancer cells to apoptosis, with factors such as growth factors and cytokines providing

survival signals that guard tumor cells from undergoing apoptosis (Thumpati et al., 2025). The therapeutic effect of modulating apoptosis in cancer therapy is immense, as the capacity to selectively trigger apoptosis in tumor cells can lead to tumor regression and improved patient outcomes. Standard cancer treatments often rely on their ability to trigger apoptosis in cancer cells, but their efficacy can be restricted by the development of drug resistance and the potential for off-target effects on normal tissues (Farzaneh Behelgardi et al., 2022). Consequently, there is considerable interest in developing new therapeutic strategies that particularly target the apoptotic machinery in tumor cells, either by stimulating pro-apoptotic pathways or by inhibiting anti-apoptotic pathways. Targeting apoptosis signaling pathways has developed as a useful method for anti-cancer treatment (Mishra et al., 2023). In this work, the findings of the dual staining assay indicated that the poncirin treatment considerably increased the apoptotic level in the HeLa cells. Therefore, it was evident that poncirin can induce and enhance apoptosis in cervical cancer cells.

Caspases, a family of cysteine-aspartic proteases, are essential executors of apoptosis, which is pivotal for sustaining tissue homeostasis and removing unnecessary cells. Apoptotic dysregulation is a major hallmark of tumor, where malignant cells escape programmed cell death, participating in uncontrolled proliferation and resistance to therapy. Understanding the intricate involvement of caspases, particularly caspase-3, -, and -9, in the apoptotic pathways is crucial for developing targeted cancer therapeutics aimed at reinstating proper apoptotic function in cancerous cells (Zhao et al., 2018). The apoptotic machinery is mainly orchestrated through two principal pathways: the death receptor and the mitochondrial pathways. Both pathways ultimately converge on the stimulation of effector caspases, like caspase-3, which dismantle the cell by cleaving a multitude of cellular substrates (Riedl & Shi, 2004). Caspase-3, a central executioner caspase, is activated by both the extrinsic and intrinsic apoptotic pathways, serving as a critical convergence point in the apoptotic cascade. Once activated, caspase-3 degrades several cell components, including structural proteins, DNA repair enzymes, and signaling molecules, dismantling the cell from within (Huang et al., 2011). The cleavage of these substrates leads to the characteristic morphological alterations connected with apoptosis. Caspase-3 activation leads to DNA fragmentation, contributing to irreversible DNA damage and cellular demise (Zhou et al., 2018).

Caspase-8 plays an imperative role in initiating apoptosis in response to death receptor signaling. Upon activation, caspase-8 directly stimulates downstream effector caspases, triggering apoptosis. Caspase-8 also degrades Bid protein, generating tBid, which translocates to mitochondria and enhances mitochondrial outer membrane permeabilization, linking the intrinsic and extrinsic apoptotic pathways. This link enhances the apoptotic signal and facilitates effective cell death (Newton et al., 2019). Caspase-9 is activated within the apoptosome in response to mitochondrial outer membrane permeabilization and release of cytochrome c. Once activated, caspase-9 directly stimulates downstream effector caspases, triggering apoptosis (Avrutsky & Troy, 2021). The discharge of cytochrome c is a critical step in the intrinsic pathway, as it triggers the development of the apoptosome and the subsequent stimulation of caspase-9 (de Vasconcelos et al., 2020). Disruptions in apoptotic pathways are a hallmark of cancer, which results in uncontrolled cell growth, resistance to therapy, and cancer progression. Tumor cells often escape apoptosis via several mechanisms, including the upregulation of anti-apoptotic genes, downregulation of pro-apoptotic proteins, inactivation of caspases, and mutations in apoptosis-related genes (Qian et al., 2022). Aberrations in apoptotic pathways are commonly linked to resistance against anti-cancer treatments. Targeting these apoptotic defects represents a promising strategy for cancer therapy (D'Amico & De Amicis, 2024). The present findings witnessed that the poncirin treatment considerably elevated the caspase-3, -8, and -9 activities in the cervical cancer HeLa cells. These results highlight that poncirin treatment can induce and enhance the caspase-mediated apoptosis in cervical cancer cells.

In addition to these findings, the present study has several limitations. Our *in vitro* findings need validation in *in vivo* models to assess poncirin's efficacy and safety. Future studies should investigate poncirin's effects in xenograft models to evaluate its translational value. Additionally, the pharmacokinetic and safety profiles of poncirin require thorough investigation. The clinical relevance of poncirin's anti-tumor effects remains to be determined. Further research is needed to bridge the gap between our *in vitro* findings and potential clinical applications. Moreover, the study's reliance on a single cell line (HeLa) warrants investigation in other gynecologic cancer models. Future studies should also explore poncirin's effects on normal cells and tissues to assess potential toxicity.

Conclusion

The present findings indicate that poncirin treatment significantly inhibits growth and triggers apoptosis in cervical cancer HeLa cells. Poncirin treatment induced apoptosis by elevating caspase enzyme activities in HeLa cells. Consequently, it possesses the capacity to be an effective anti-tumor candidate to treat cervical cancer. Further research is required to elucidate the precise molecular pathways behind poncirin-induced apoptosis in HeLa cells.

Abbreviations

ANOVA: Analysis of variance; AO/EB: Acridine orange/ethidium bromide; DMEM: Dulbecco's Modified Eagle Medium; DMSO: Dimethyl sulfoxide; FBS: Fetal bovine serum; MTT: 3-(4,5)-Dimethylthiahiazo(-z-y1)-3,5-di-phenytetrazoliumromide; SD: Standard deviation.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

Not applicable.

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