RESEARCH ARTICLE

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Resveratrol-Induced Modulation of Key Genes and DNA Fragmentation in Chronic Myeloid Leukemia Cells

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Abstract

Objective: Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by the BCR-ABL1 fusion gene, which drives the uncontrolled proliferation of myeloid cells. Despite advancements in treatment, resistance to conventional therapies remains a significant challenge. Resveratrol, a natural polyphenol, has garnered attention for its potential therapeutic properties, including its ability to modulate key genes and induce apoptosis in cancer cells. This study investigated the effects of resveratrol on apoptosis, cell cycle regulation, and DNA fragmentation in CML cells. **Methods:** K562 CML cells were treated with resveratrol, and their effects were analyzed through CCK-8 assay for cell viability, TUNEL assay for DNA fragmentation, and real-time PCR for gene expression. Key apoptotic genes (BCL-2, AIF, BAX) were assessed alongside survival-related genes (*CASP3, PGC1α, Cyclin-D1, p53*) to evaluate resveratrol's anti-proliferative and pro-apoptotic potential. **Result:** Resveratrol exhibited a time-dependent reduction in K562 cell viability, with IC_{50} values decreasing from 282.2 μM at 24 hours to 107.1 μM and 102.4 μM at 48 and 72 hours, respectively. Apoptotic activity, assessed via the TUNEL assay, revealed significant DNA fragmentation in 55 ± 5% of treated cells, while control cells showed no fragmentation. Gene expression analysis demonstrated upregulation of pro-apoptotic genes, including BCL-2, AIF ($p < 0.05$), BAX ($p < 0.01$), and VDAC1 (4.5-fold, $p < 0.001$). Conversely, genes linked to cell survival and metabolism, such as *CASP3*, *PGC1α*, *NDUFA9, Cyclin-D1*, and p53, were slightly downregulated ($p < 0.05$), highlighting resveratrol's dual role in promoting apoptosis and inhibiting cell survival. **Conclusion:** These findings suggest that resveratrol exerts anti-proliferative and pro-apoptotic effects in CML cells by modulating key genes and induction of DNA fragmentation, highlighting its potential as a therapeutic agent for CML treatment.

Keywords: Resveratrol- Chronic Myeloid Leukemia (CML)- Apoptosis- DNA Fragmentation

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Introduction

Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by the overproduction of white blood cells due to the presence of the Philadelphia chromosome, which results from the fusion of the BCR and *ABL1* genes [1]. This genetic alteration leads to the production of an abnormal protein that drives uncontrolled myeloid cell growth. CML typically progresses through three phases: chronic, accelerated, and blast crisis, with most patients experiencing symptoms such as fatigue, weight loss, abdominal fullness, and splenomegaly. Although treatment has advanced significantly with the introduction of tyrosine kinase inhibitors (TKIs), resistance to these conventional therapies remains a significant challenge [2]. TKIs work by inhibiting the activity of the abnormal protein produced by the Philadelphia chromosome, thus improving patient outcomes and quality of life [3]. However, the development of drug resistance necessitates the exploration of alternative therapeutic options.

Resveratrol (C14H12O3), a natural polyphenol found in various plants such as grapes and berries, has garnered attention for its wide spectrum of pharmacological activities, including antioxidant and anti-inflammatory effects [4]. Recent studies have delved into its potential to regulate gene expression and maintain DNA integrity in the context of CML [4, 5]. This polyphenol may offer a promising approach to CML management by targeting key genes involved in cell proliferation, apoptosis, and differentiation. By modulating complex molecular pathways, resveratrol could potentially influence the

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progression of CML and serve as an adjunct or alternative to existing treatments.

This study focuses on exploring the effects of resveratrol on key genes associated with CML pathology. Specifically, the research aims to understand how resveratrol modulates gene expression and induces apoptosis in CML cells. Through advanced molecular techniques such as gene expression analysis and pathway mapping, this study seeks to uncover the mechanisms by which resveratrol exerts its therapeutic effects. The ultimate goal is to provide insights into novel treatment strategies for CML, emphasizing the need for further laboratory research and clinical trials to confirm the safety and efficacy of resveratrol-based therapies.

This research is significant as it establishes the molecular mechanisms underlying resveratrol's impact on CML cells, potentially paving the way for new therapeutic interventions. By investigating resveratrol's ability to induce apoptosis and modulate key genes related to cell survival and proliferation, this study contributes to the broader scientific and clinical efforts to develop advanced treatment strategies for CML and other hematological malignancies.

Materials and Methods

The study utilized various materials and kits. Resveratrol (purity 99.5%) was sourced from GLPBIO (USA). The Cell Counting Kit-8 (CCK-8) and One-Step TUNEL Apoptosis Assay Kit (Green Fluorescence) were obtained from Abbkine Scientific Co. Ltd (USA). Other key materials included phosphate-buffered saline (PBS, pH 7.4) from Euroclone (Italy), 4% paraformaldehyde from Sigma Aldrich (Sweden), Triton X-100 (0.3%) from Abbkine Scientific, and 4',6-diamidino-2-phenylindole (DAPI) from Abbkine Scientific. The key equipment included an Applied Biosystems QuantStudio 3 Real-Time PCR System (Fisher Scientific, USA), Bio Safety Cabinet level II (BioLab Scientific, Canada), centrifuge (Electra Medical, USA), CO_2 incubator (Thermo Fisher Scientific, USA), ELISA microplate reader (BioTek Synergy HTX, USA), fluorescence microscope (Canon, Japan), and UV/VIS Nano Spectrophotometer (Nabi, South Korea).

Cell Culture and IC_{50} Determination

K562 CML cells (ATCC-CRL-3343) were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Cells were maintained at 37°C in a humidified 5% CO_2 incubator and subcultured every 3-4 days. 3. For IC_{50} determination, K562 cells were seeded in 96-well plates (8×10^3 cells/well) and incubated for 24 hours. Resveratrol stock solution was prepared in DMSO and diluted to a range of concentrations (300 µM to lower dilutions) using RPMI 1640 media. Cells were treated with resveratrol for 24, 48, and 72 hours, followed by the addition of 10 µL of CCK-8 dye to each well. After an additional 3-4 hours of incubation, absorbance was measured at 450 nm using an ELISA microplate reader. IC_{50} values were calculated using GraphPad Prism software based on three independent experiments.

TUNEL Assay for DNA Fragmentation

Apoptosis was assessed using the One-Step TUNEL Apoptosis Assay Kit. K562 cells were treated with resveratrol at the IC_{50} concentration for 48 hours. Both treated and untreated cells were centrifuged, washed with PBS, and fixed with 4% paraformaldehyde. After permeabilization with 0.3% Triton X-100, cells were incubated with the TUNEL reaction mixture at 37°C for 2 hours. The cells were then counterstained with DAPI and analyzed using a fluorescence microscope. TUNEL-positive cells indicated apoptosis, with the proportion calculated to quantify apoptosis levels.

RNA Extraction and Quantitative Real-Time PCR (qRT-PCR)

Cells treated with resveratrol at the IC_{50} concentration for 48 hours underwent RNA extraction using the SV Total RNA Isolation System (Promega, USA). RNA concentration and purity were determined using the Nabi UV/VIS Nano Spectrophotometer. First-strand cDNA synthesis was performed using the Viva cDNA Synthesis Kit (Vivantis Technologies, South Korea). Quantitative Real-Time PCR was conducted using SYBR Green PCR Master Mix, with β-actin serving as the reference gene. Primer sequences for target genes (*BCL-2, BAX, CASP3, p53, AIF, VDAC1, NDUFA9, SDHA*, and *Cyclin-D1*) were sourced from the literature (Table 1). The qRT-PCR was carried out on an Applied Biosystems QuantStudio 3 Real-Time PCR System, using the ΔΔCt method to quantify gene expression changes.

Statistical analysis

All experiments were performed in triplicate, Kruskal–Wallis and Mann-Whitney tests were conducted for statistical analysis using GraphPad Prism 8.4.3 (San Diego, California, USA) and $P < 0.05$ was considered as significant.

Results

Anti-Proliferative Effects of Resveratrol on K562 Cells

The anti-proliferative effects of resveratrol on the K562 cell line were evaluated using the CCK-8 assay. IC_{50} values, indicating the concentration of resveratrol required to inhibit 50% of cell proliferation, were determined after 24, 48, and 72 hours of treatment. A clear time-dependent decrease in the IC_{50} values was observed (Figures 1,2).

As summarized in Table 2 and shown in Figures 3, 4, and 5, after 24 hours of treatment, the IC_{50} value was 282.2 µM. At 48 hours, the IC_{50} value significantly decreased to 107.1 µM, and by 72 hours, the IC_{50} further declined to 102.4 µM.

DNA fragmentation analysis by TUNEL assay

The TUNEL assay results demonstrated a significant increase in apoptotic activity in treated cells (Figure 5) compared to untreated (Figure 4). While the control group displayed uniform, dim fluorescence with no signs of DNA fragmentation, the treatment group showed prominent DNA fragmentation, indicated by bright fluorescent spots. Approximately 55 ± 5% of the treated cells exhibited DNA

Table 1. Primer Sequences

Gene	Primer name	Nucleotide sequence (5' - 3')	Reference
BAX	F	GGTTGTCGCCCTTTTCTACTTTGC	[6]
	R	ATGTCCAGCCCATGATGGTTCTG	
BCL-2	F	ATGTGTGTGGAGAGCGTCAAC	[6]
	R	AGCCAGGAGAAATCAAACAGAGG	
p53	F	GGACGGAACAGCTTTGAGGT	[7]
	R	CCCACGGATCTGAAGGGTGA	
Cyclin-D1	F	AGGAACAGAAGTGCGAGGAGG	[8]
	R	GGATGGAGTTGTCGGTGTAGATG	
β-actin	F	CCAACCGTGAAAAGATGACC	[9]
	R	ACCAGAGGCATACAGGGACA	
CASP3	F	ACATGGCGTGTCATAAAATACC	[10]
	R	CACAAAGCGACTGGATGAAC	
AIF	F	GATTGCAACAGGAGGTACTCCAAGA	[11]
	R	GATTTGACTTCCCGTGAAATCTTCTTC	
VDAC1	F	ACGTATGCCGATCTTGGCAAA	[12]
	R	TCAGGCCGTACTCAGTCCATC	
NDUFA9	F	CGACACTGGGAAACCAAAAAC	[13]
	R	GCATCCGCTCCACTTTATCC	
SDHA	F	AAACTCGCTCTTGGACCTGG	[14]
	R	TCTTCCCCAGCGTTTGGTTT	

fragmentation, confirming the treatment's effectiveness in inducing apoptosis. These findings highlight the marked increase in apoptotic activity caused by the treatment, as evidenced by the higher percentage of fragmented DNA in the treated cells compared to the control.

The gene expression in treated cells

The RNA concentration and purity from both control and resveratrol-treated K562 cell lines were assessed using the Nabi UV/VIS Nano Spectrophotometer. The control group had an RNA concentration of 442.1 ng/μL, with A260/A280 and A260/A230 ratios of 2.161 and 2.119, respectively, indicating high purity. In the treated group, the RNA concentration was slightly lower at 317.0 ng/μL, but the purity remained high, with A260/A280 and A260/A230 ratios of 2.162 and 2.202, respectively (Figure 6).

Gene expression analysis revealed that *VDAC1* was highly upregulated ($p < 0.001$) with a fold change of approximately 4.5 in the treated cells. *BCL-2*, AIF, and *BAX* were significantly upregulated, while *CASP3*, *PGCa1, NDUF, Cyclin D1*, and *P53* were slightly downregulated. SDHA showed a non-significant upregulation. These findings highlight the impact of resveratrol on gene

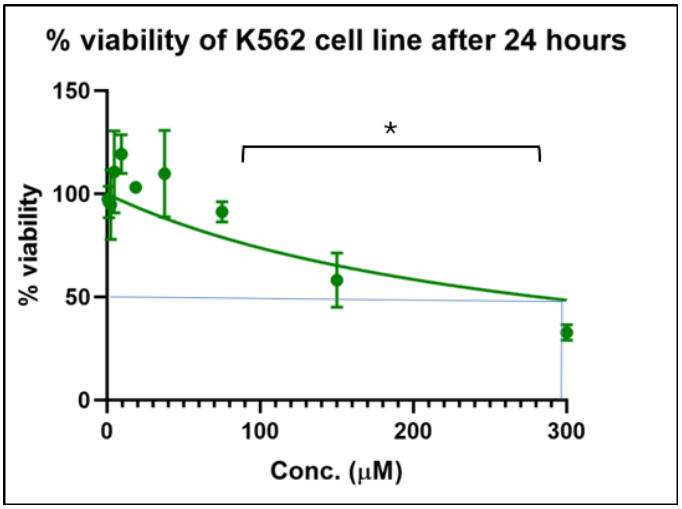

Figure 1. The Percentage Viability of *K562* Cells Following 24 hours of Treatment with Varying Concentrations of Resveratrol, as Measured by MTT Assay. The data shows a concentration-dependent decrease in cell viability, with an IC50 value calculated to be 282.2 μM. The values are presented as mean ± SEM, with experiments conducted at least three times. Statistical significance is indicated by *$p < 0.05$

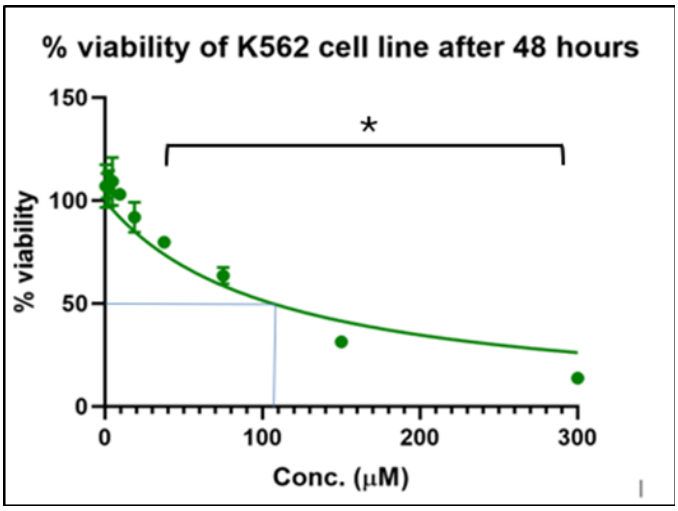

Figure 2. Percentage Viability of K562 Cells after 48 Hours of Treatment with Different Concentrations of Resveratrol, as Determined by the MTT Assay. The results show a concentration-dependent reduction in cell viability, with an IC50 value of 107.1 µM. Data are expressed as mean ± SEM from at least three independent experiments. Statistical significance is represented by *p < 0.05

Table 2. IC_{50} Values of Resveratrol Treatment after 24, 48, and 72 hours

Treatment duration	IC_{50}
24 hours	282.2 µM
48 hours	107.1 µM
72 hours	102.4 µM

expression and apoptotic regulation in K562 cells.

Discussion

The present study aimed to investigate the effects of resveratrol on the proliferation and apoptosis of CML cells, with a focus on their ability to modulate key apoptotic and regulatory pathways. Resveratrol, a natural polyphenolic compound, has been widely studied for its anti-cancer properties, particularly its role in inducing apoptosis and inhibiting cell proliferation across various cancer types [5]. However, the specific mechanisms by which resveratrol exerts its effects on CML cells remain to be fully elucidated. By examining its impact on cell viability, DNA fragmentation, and the expression of critical genes involved in apoptosis and cell cycle regulation, this study provides insights into the molecular underpinnings of resveratrol's anti-leukemic action.

This study demonstrates that resveratrol exerts a time-dependent, anti-proliferative effect on CML cells, with IC_{50} values significantly decreasing as exposure time increases. This enhanced activity aligns with previous reports, such as those by Wu et al and Kartal et al, which highlight the time-dependent inhibitory effects of resveratrol on cancer cell proliferation [4, 15].

Our TUNEL assay results further confirmed the apoptotic potential of resveratrol, with 55 ± 5% of treated cells showing DNA fragmentation, a hallmark of

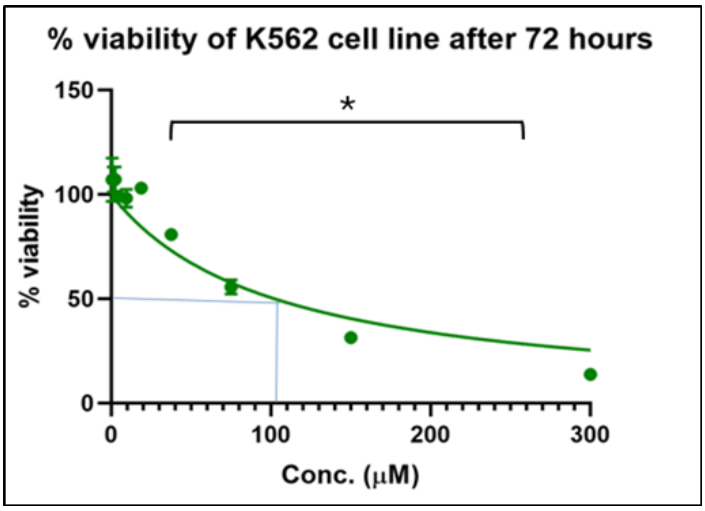

Figure 3. Percentage Viability of K562 Cells after 72 hours of Treatment with Varying Concentrations of Resveratrol, as Determined by MTT Assay. The data reveals a concentration-dependent decline in cell viability, with an IC50 value calculated at 102.4 µM. Values are expressed as mean ± SEM from at least three independent experiments. Statistical significance is denoted by *p < 0.05

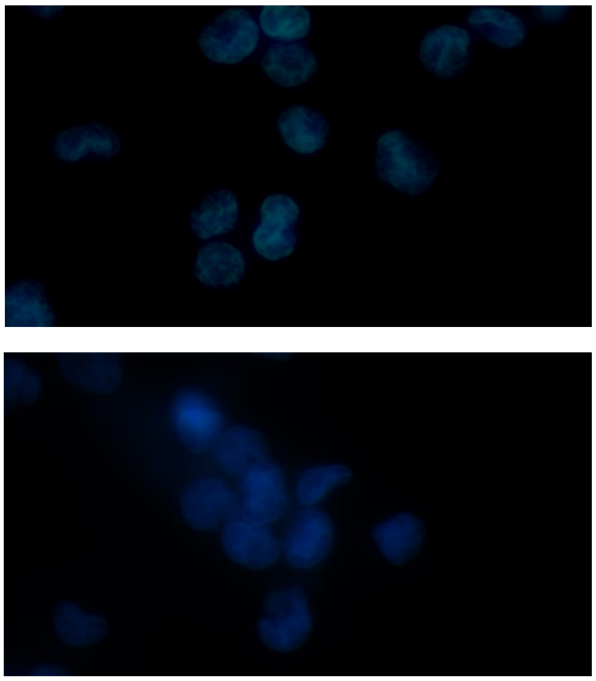

Figure 4. TUNEL Assay Images of the Control Group (Untreated K562 Cells) Showed No Signs of DNA Fragmentation. The cells exhibit uniform, dim fluorescence without any bright fluorescent spots, indicating the absence of apoptotic activity. These findings confirm that the untreated cells were not undergoing apoptosis under normal conditions.

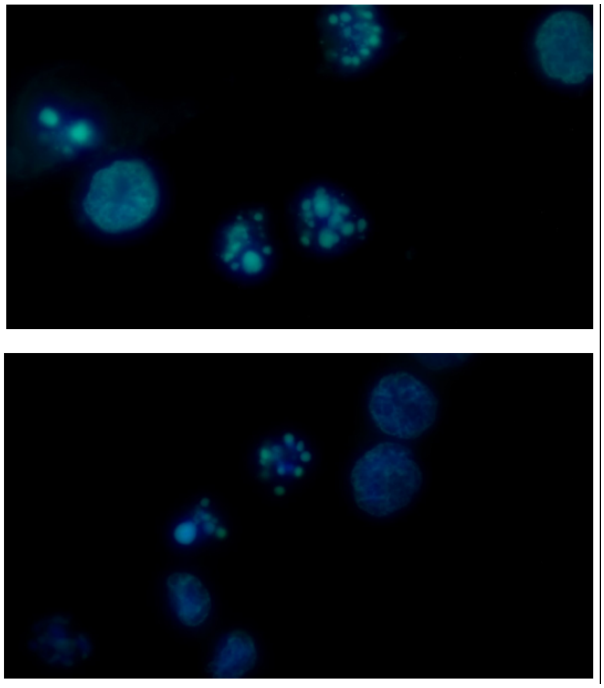

Figure 5. TUNEL Assay Images of the treatment group (resveratrol-treated K562 cells) showing clear signs of DNA fragmentation. The presence of bright fluorescent spots within the cells indicates apoptotic activity, a hallmark of DNA fragmentation. These results demonstrate the induction of apoptosis in the treatment group compared to the control group.

apoptosis. This observation is consistent with previous studies by Davoodvandi et al. [16] and Lin et al, which also reported that resveratrol induces DNA fragmentation, effectively triggering apoptosis in various cancer cell lines. This supports the potential use of resveratrol as a chemotherapeutic agent that promotes cell death via apoptosis [16, 17].

In gene expression analysis, the current results found that the pro-apoptotic gene *BAX* was significantly upregulated following resveratrol treatment, supporting its

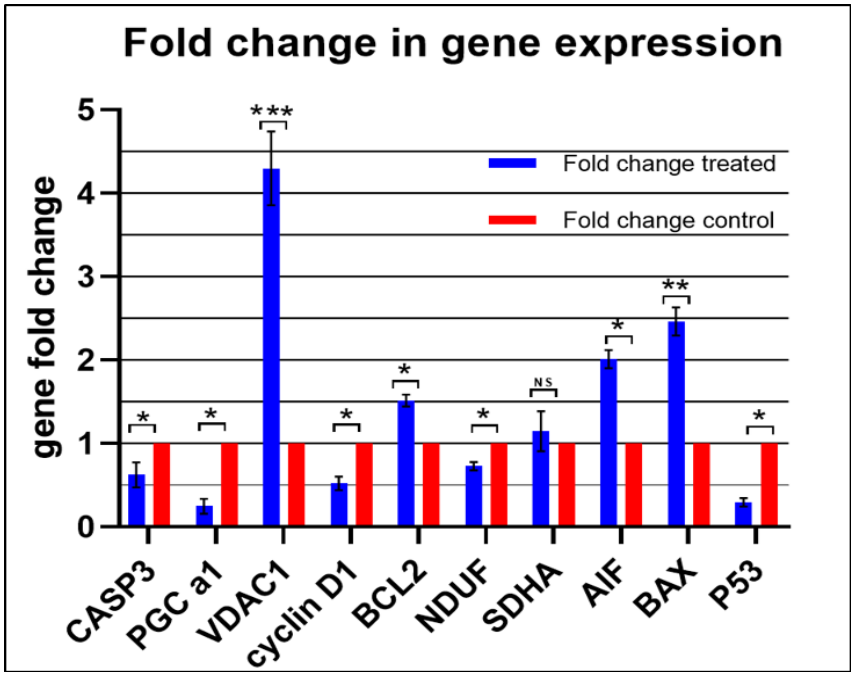

Figure 6. Fold Change in Gene Expression of Key Apoptotic and Regulatory Genes in *K562* Cells after Treatment with Resveratrol Compared to Control. The expression of *VDAC1, BAX, AIF,* and *BCL-2* was significantly upregulated, and other genes such as *CASP3, PGCa1*, and *Cyclin D1* showed significant downregulation changes in expression. SDHA exhibited non-significant changes, β-actin was used as the reference gene. Data represents the mean ± SEM of three independent experiments. (*$p < 0.05$), (**$p < 0.01$), (***$p < 0.001$).

role in facilitating apoptosis, particularly by counteracting anti-apoptotic factors like *BCL-2*. These findings align with previous studies, which demonstrated the pivotal role of *BAX* in resveratrol-induced apoptosis through both *p53*-dependent and p53-independent pathways, often involving mitochondrial dysfunction. Interestingly, Caspase-3, a central executioner of apoptosis, was downregulated in our study. This result contrasts with the expected role of Caspase-3 in apoptosis and raises the possibility of alternative regulatory mechanisms, such as *BAX*-mediated apoptosis bypassing Caspase-3 activation [18, 19]. This observation aligns with the findings by Seong et al, who also reported Caspase-3 downregulation in a resveratrol model. However, further investigation is needed to clarify these mechanisms [20].

The current study showed upregulation of *BCL-2*, an anti-apoptotic gene, which was unexpected given resveratrol's typical role in promoting apoptosis. This paradoxical result suggests a more complex interaction between resveratrol and apoptotic pathways, potentially involving a compensatory mechanism by which cells upregulate *BCL-2* in response to increased pro-apoptotic signals from *BAX*. This observation contrasts with a Li et al study, which showed opposing effects of resveratrol on *BCL-2* and *BAX* in different models [21].

In addition, resveratrol treatment downregulated Cyclin D1 and p53 in CML cells, both of which are key regulators of cell proliferation and apoptosis. This downregulation mirrors findings from Yung et al. [22] where resveratrol inhibited cell cycle progression through Cyclin D1 downregulation [22]. Also, Yu et al, [23] demonstrated resveratrol's modulation of *p53* expression via the MDM2/*p53* pathway . These results suggest that resveratrol's anti-proliferative effects in CML cells may be mediated, at least in part, through the inhibition of Cyclin D1 and *p53*.

VDAC1 was significantly upregulated following resveratrol treatment in current experiments, VDAC1 mediates mitochondrial dysfunction by regulating metabolite exchange and promoting apoptosis through increased mitochondrial membrane permeability [24, 25], suggesting the involvement of mitochondrial dysfunction in apoptosis induction. NDUF and SDHA genes are crucial for efficient ATP production and cellular energy metabolism [26]. The downregulation of these genes after resveratrol treatment typically involved in mitochondrial respiration, further supports the hypothesis that resveratrol induces cell death by impairing mitochondrial function. AIF, a key mediator of caspase-independent apoptosis, was also mildly upregulated, reinforcing the idea that resveratrol promotes apoptosis through multiple pathways.

In conclusion, this study highlights the complex regulatory landscape through which resveratrol induces apoptosis in CML cells. The simultaneous upregulation of pro-apoptotic genes (*BAX, VDAC1, AIF*) and anti-apoptotic genes (*BCL-2*), alongside the downregulation of Caspase-3, suggests that resveratrol's effects are mediated through a combination of traditional and novel apoptotic pathways. These findings point to resveratrol's potential as a therapeutic agent in CML treatment, especially in cases resistant to conventional therapies, warranting further research to optimize its clinical application. Future studies should focus on exploring the underlying mechanisms of resveratrol's action and evaluating its efficacy in combination with existing CML therapies to enhance treatment outcomes.

Author Contribution Statement

Belal Almajali contributed to the conception and design of the study. Laith Alhawamdeh conducted experimental work and data acquisition. Hamid Ali Nagi Al-Jamal Ali M. Atoom and Hanan Kamel M. Saad were responsible for data analysis and interpretation. All authors contributed to drafting the manuscript, critically revising it for intellectual content, and approving the final version for submission.

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General

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Scientific Approval

(IRB: AAU/1/3/2023-2024).

Ethical Declaration

The study received ethical approval from the Institutional Review Board (IRB) with approval number AAU/1/3/2023-2024.

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