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Halotolerant *Bacillus licheniformis* Extract Induces Apoptosis in MCF-7 Cells via Modulation of *BAX*/*BCL-2* Expression

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ABSTRACT

Background and Aim: Breast cancer is one of the leading causes of cancer-related deaths among women worldwide. The resistance of advanced tumors to conventional treatments highlights the need for alternative therapies. Apoptosis, regulated by key proteins like *BAX* (pro-apoptotic) and *BCL-2* (anti-apoptotic), plays a crucial role in controlling cancer cell proliferation. This study aimed to investigate the effects of a halotolerant *Bacillus (B.) licheniformis* extract, isolated from Hoz-e Sultan Lake in Qom Province, on the expression of *BAX* and *BCL-2* genes in MCF-7 breast cancer cell line.

Materials and Methods: MCF-7 cells were treated with various concentrations of the bacterial extract and cell viability was assessed using MTT assay. Staurosporine was used as positive control. RNA extraction, cDNA synthesis, and Real-Time PCR were performed to evaluate target genes expression levels. Statistical analysis was conducted using an independent t-test and P-values less than 0.05 were considered significant.

Results: The extract significantly increased *BAX* expression ($P<0.05$) at 24, 48, and 72 hr, while *BCL-2* expression initially decreased but showed a slight increase at 48 hr. The IC_{50} values decreased over time, indicating time-dependent cytotoxicity.

Conclusion: The halotolerant *B. licheniformis* extract induced apoptosis in MCF-7 cells through *BAX*/*BCL-2* pathway modulation, suggesting its potential as an alternative therapeutic source. Further studies are needed to identify active compounds and validate efficacy *in vivo*.

Keywords: Apoptosis, *Bacillus licheniformis*, BAX, *BCL-2*, Breast Cancer, MCF-7

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1. Introduction

Breast cancer remains one of the most prevalent malignancies among women worldwide, accounting for a significant portion of cancer-related mortality **(1-3)**. Despite advancements in conventional treatments such as chemotherapy, radiotherapy, and hormone therapy, the emergence of drug resistance and recurrence underscores the urgent need for alternative therapeutic strategies **(4, 5)**. Apoptosis is a tightly regulated programmed cell death process that keeps up cellular homeostasis **(6, 7)**. Dysregulation of this pathway is a hallmark of cancer, allowing malignant cells to evade death **(8)**.

The *BCL-2* protein family plays a pivotal role in this balance, where *BAX* promotes apoptosis, while *BCL-2* acts as an anti-apoptotic regulator **(9)**. An increased *BCL-2*/*BAX* ratio has been frequently observed in breast cancer cells, contributing to their survival and resistance to therapy **(10, 11)**.

Halotolerant microorganisms from extreme environments have gained attention for their unique metabolic profiles and potential therapeutic applications **(12)**. Bacterial metabolites have recently gained attention for their anticancer potential, exhibiting cytotoxicity and immune modulation effects **(13, 14)**. Among them, *Bacillus (B.) licheniformis*, a spore-forming, Gram-positive bacterium commonly found in soil, has shown promising bioactive properties **(15, 16)**. The optimum growth temperature for *B. licheniformis* is approximately 50°C, though it can survive at much higher temperatures **(17)**. The ideal temperature for enzyme secretion is 37°C **(18)**. *B. licheniformis* can exist as resting spores, which can endure extreme environments and tolerate various nutritional conditions when favorable **(19)**.

However, its potential role in modulating apoptosis-related genes in breast cancer cells remains largely unexplored. This study aimed to evaluate the effects of a halotolerant *B. licheniformis* extract from the extreme environment of Hoz-e Sultan Lake on *BAX* and *BCL-2* expression at both at the transcriptional level in MCF-7 cells.

2. Materials and Methods

2.1 Bacterial Source and Extract Preparation

B. licheniformis strain LZBL-3 was isolated from Hoz-e Sultan Lake in Qom Province, Iran. Its extract was used on MCF-7 breast cancer cells. *B. licheniformis* strain *LZBL-3* was cultured in LB broth medium for 48 hr at 35°C. After multiplication, the culture was subjected to centrifugation at 1,500 × g for 10 min at 4°C. The liquid upper part was taken and passed through a 0.22 µm membrane filter (Millipore, USA) in order to get a cell-free extract.

2.2 Cell Culture

MCF-7 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at a temperature of 37°C in a 5% CO_2 incubator. Untreated cells were utilized as the control group.

2.3 Cytotoxicity and IC50 Determination

The cytotoxic effect of the bacterial extract was evaluated using MTT assay (Sigma-Aldrich, USA). Cells were seeded in 96-well plates (1×10^4 cells/well) and treated with various extract concentrations (0.5 to 5 mg/mL) for 24, 48, and 72 hr. The absorbance was measured at 570 nm using a BioTek microplate reader. The inhibitory concentrations 50% (IC_{50}) values were calculated using nonlinear regression in GraphPad Prism 9.0.

2.4 RNA Extraction, cDNA Synthesis, and Real-Time PCR

RNA was extracted using TRIzol reagent (Invitrogen, USA), and cDNA synthesis was performed with the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, USA) (20). Gene-specific primers (Table 1) were designed using NCBI Primer-BLAST. Real-Time PCR was conducted using SYBR Green Master Mix (Applied Biosystems, USA). GAPDH was used as the reference gene. Relative gene expression for *BAX* and *BCL-2* genes were calculated using the 2^−ΔΔCt method **(21)**.

2.5 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) and REST 2009 software. Data are presented as mean ± standard deviation (SD) from three independent biological replicates (n = 3). Multiple group comparisons were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. A P-value < 0.05 was considered statistically significant.

Table 1. Sequences of primers used for Real-Time PCR analysis of *BAX* and *BCL-2* genes in MCF-7 cells.

Accession Number	Genes	Forward Primer (5'→3')	Reverse Primer (5'→3')	Product Size (bp)	Reference
NM_001289746.2	*GAPDH*	GATGTTCTGGAGAGCCCC	GCCCAATACGACCAAATCC	93	Khoshandam et al **(21)**
NM_004324.4	*BAX*	CAGTTGAAGTTGCCGTCAG	AGTCTCACCCAACCACCC	150	
NM_000633.3	*BCL-2*	TGCATATTTGTTTGGGGCAG	CGTACAGTTCCACAAAGGCA	87	

3. Results

3.1 Cell Viability and IC_{50} Determination

The bacterial extract exhibited dose- and time-dependent cytotoxicity. The IC_{50} values decreased from 4.3 mg/mL at 24 hr to 2.1 mg/mL at 72 hr (Figure 1).

3.2 Gene Expression Analysis Results

The expression levels of *BAX* gene in the treatment group significantly increased over 24, 48, and 72 hr compared to the control group. In contrast, the expression level of *BCL-2* gene in the treatment group decreased after 24 hr compared to the control group. However, this decrease was not statistically significant. Additionally, the expression level of *BCL-2* gene in the treatment group increased compared to the control group over 48 and over 72 hours, and this increase was found to be significant (Figure 2).

3.3 Melting Curve

The melting curves obtained from the amplification of the studied genes are shown in Figure 3, which indicates the specific performance of the desired reaction.

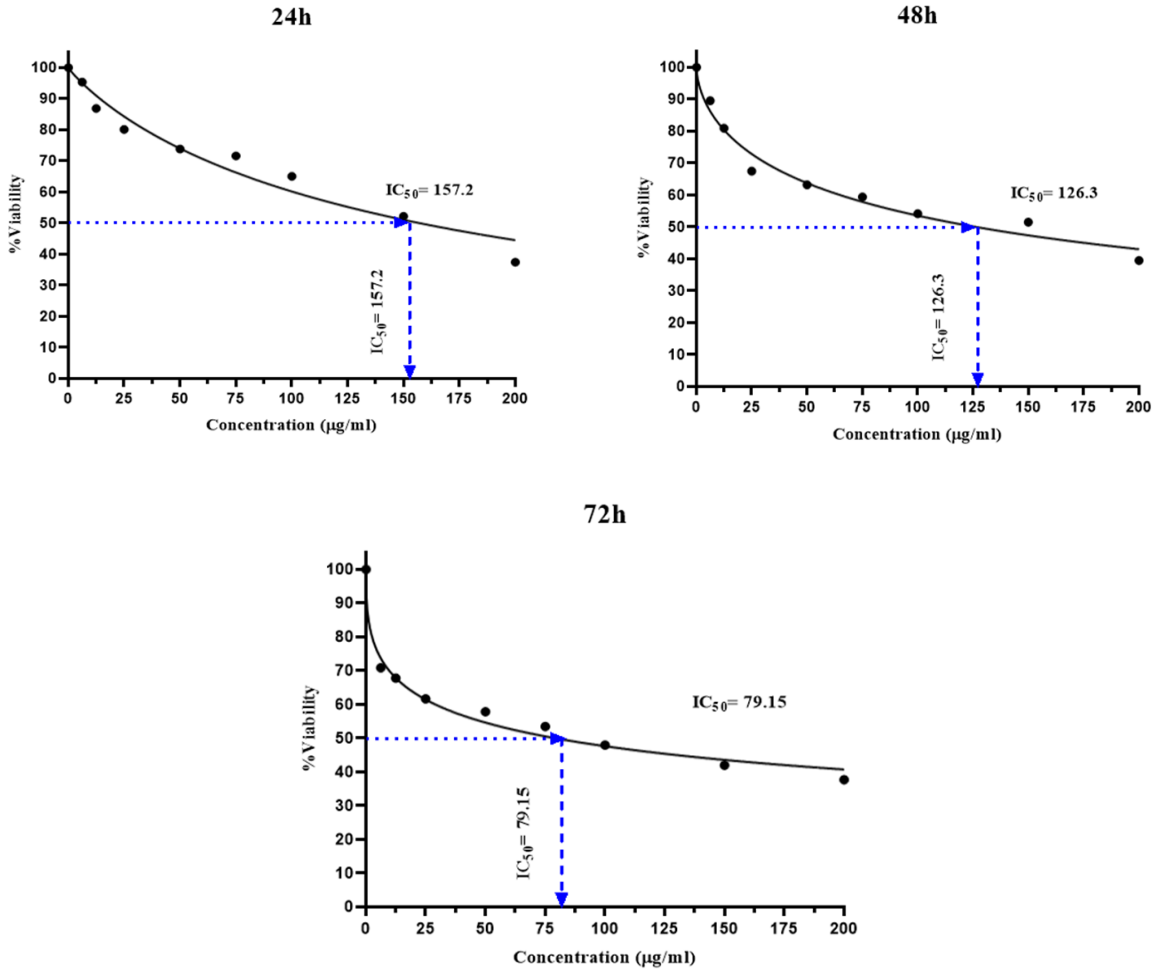


Figure 1. IC50 values of *Bacillus licheniformis* extract on MCF-7 cell viability at 24, 48, and 72 hours. IC50 values decreased over time, indicating time-dependent cytotoxicity. Error bars represent mean ± standard deviation (n=3 replicates). **(Prepared by Authors, 2025)**.

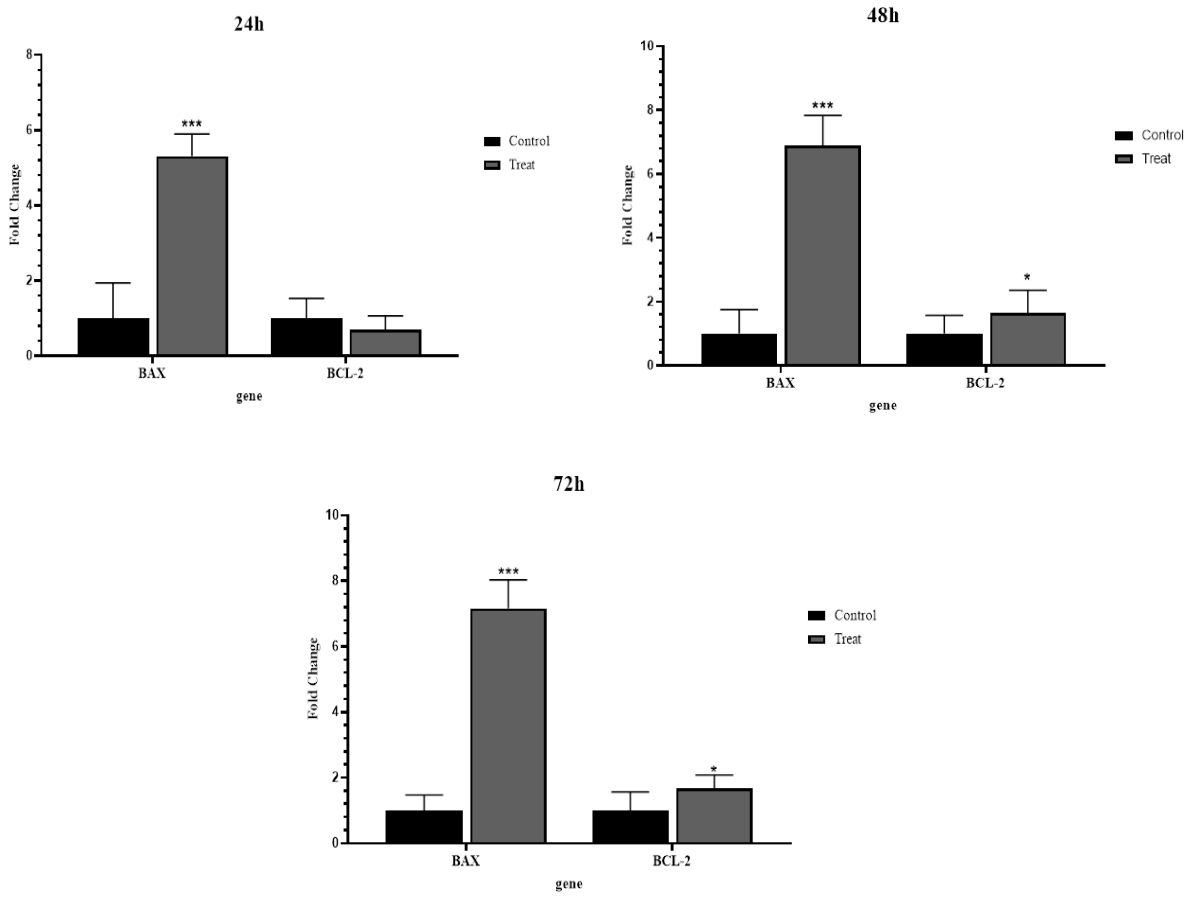


Figure 2. Relative expression levels of *BAX* and *BCL-2* genes in MCF-7 cells treated with *Bacillus licheniformis* extract at 24, 48, and 72 hours. *BAX* expression significantly increased at all time points (*P< 0.0001 at 24 h, P< 0.0001 at 48 h, P< 0.0001 at 72 h*), while *BCL-2* showed a non-significant decrease at 24 h (*P*=0.061), followed by a significant increase at 48 h (*P*=0.03) and 72 h (*P*=0.02). Error bars represent mean ± standard deviation (n=3 replicates) **(Prepared by Authors, 2025)**.

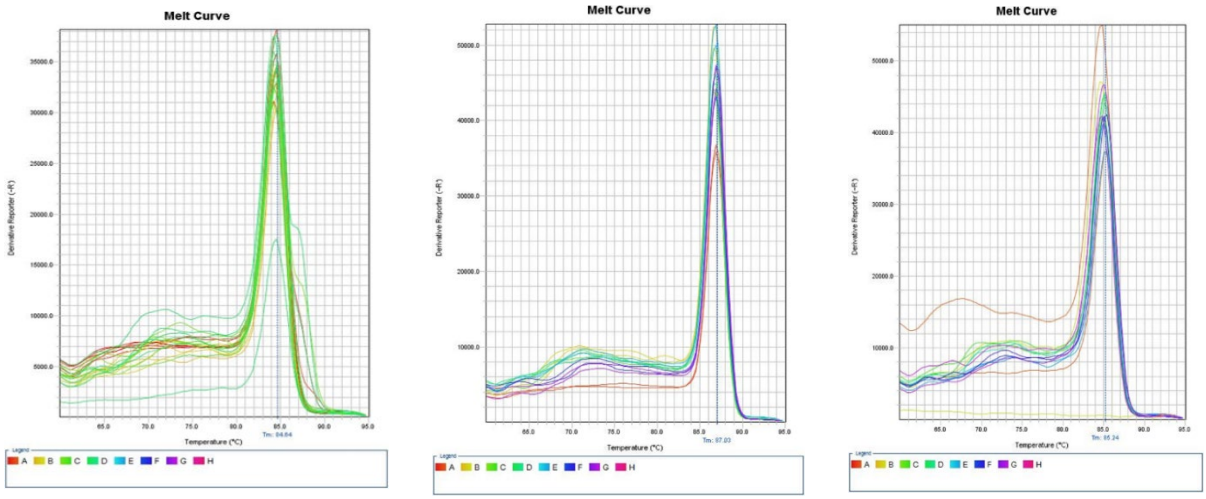


Figure 3. Melting curves from amplification of *GAPDH*, *BAX*, and *BCL-2* genes **(Prepared by Authors, 2025)**.

4. Discussion

Apoptosis is a type of genetically programmed cell death that has a vital function in various physiological and pathological conditions and acts like a double-edged sword **(2, 6)**. *BAX* protein serves as a key component in apoptosis, particularly in the intrinsic apoptotic pathway, while *BCL-2* protein exerts an anti-apoptotic effect in response to various apoptotic stimuli by preventing the release of cytochrome *C* from the mitochondria **(22)**. Both *BAX* and *BCL-2* are critical players in the mitochondrial pathway of apoptosis **(23)**.

In cancer cells, the balance between proliferation and apoptosis is often disrupted, necessitating the inhibition of apoptosis for excessive growth and proliferation **(24, 25)**. This disruption creates a direct link between the expression of these genes and the process of carcinogenesis **(26, 27)**. Therefore, investigating the effects of new drugs on the expression of these genes could enhance our understanding of therapeutic and diagnostic strategies in cancer research **(28, 29)**.

A study conducted in 2020 further suggested that *BCL-2* gene is integral to the progression of breast cancer **(30)**. It has been noted that *BCL-2* gene expression is increased in various cancer types, and the product of this gene plays a role in promoting growth and survival while inhibiting programmed cell death **(10, 31)**. In 2022, researchers examining the role of *BCL-2* family proteins in the regulation of apoptosis and cancer treatment concluded that these proteins are crucial regulators of apoptosis, significantly influencing tumorigenesis, development, and therapeutic responses **(9)**. Inhibition of apoptosis by members of the *BCL-2* family is often observed at elevated levels in human tumor tissues, which contributes to the prevention of apoptosis in tumor cells **(32)**. In this context, inhibition of *BCL-2* may re-enable apoptosis in these cells **(33)**. Consequently, effective and targeted antitumor drugs could be developed for the treatment of malignant tumors by either activating the expression of anti-apoptotic proteins or by promoting the expression of pro-apoptotic proteins **(34)**. Overall, these findings underscore the potential of *BCL-2* family proteins in cancer treatment **(23)**.

Our findings demonstrated that *Bacillus licheniformis* extract significantly upregulated *BAX* expression at all time points, promoting apoptotic pathways in MCF-7 cells. Conversely, *BCL-2* expression showed an initial decrease at 24 hr, followed by a surprising increase at 48 and 72 hr. This biphasic response suggests a dynamic interaction between pro-apoptotic and anti-apoptotic mechanisms. These results align with previous studies indicating that bacterial metabolites can induce apoptosis by targeting mitochondrial pathways **(35-37)**. The significant upregulation of *BAX* supports the hypothesis that *Bacillus licheniformis* triggers intrinsic apoptosis, consistent with findings from *Lactiplantibacillus plantarum* extracts, which similarly enhanced *BAX* expression while downregulating *BCL-2* in breast cancer models **(38)**. The observed resurgence of *BCL-2* expression at 48 and 72 hr may reflect an adaptive resistance mechanism. Studies have reported similar delayed *BCL-2* upregulation in response to apoptotic stress, potentially mediated by PI3K/AKT or NF-κB survival pathways **(39)**.

This highlights the need for combination therapies that simultaneously target pro-survival signaling to prevent late-stage resistance. The research outcomes serve as initial *in vitro* proof that *Bacillus licheniformis* extract is capable of altering the expression of genes linked to apoptosis in breast cancer cells. Nonetheless, more *in vivo* and clinical studies are necessary to confirm its therapeutic potential. Future research should focus on *in vivo* validation and proteomic analysis to uncover the secondary metabolites responsible for apoptosis induction. Additionally, the biphasic response of *BCL-2* expression highlights the importance of further studies to assess whether modulation of apoptotic pathways by bacterial extracts could affect cellular responses to other apoptosis-targeting interventions.

5. Conclusion

Our findings support the growing evidence that bacterial extracts, particularly *Bacillus licheniformis* represents a biologically active microbial source that modulates apoptosis-related gene expression in breast cancer cells under *in vitro* conditions. Further *in vivo* validation and mechanistic investigations are required to clarify the translational relevance of these findings. Moreover, combination strategies with *BCL-2* inhibitors may enhance the therapeutic efficacy and prevent late-stage cancer cell adaptation, a key challenge in breast cancer therapy.

6. Declarations

6.1 Acknowledgment

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6.2 Ethical Considerations

This study did not involve human participants or animals.

6.3 Authors' Contributions

All authors participated in the design, execution, and writing of the article equally. All participants agreed to be involved in this study. All authors read and approved the final version.

6.4 Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

6.5 Financial Support and Sponsorship

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6.6 Using Artificial Intelligence Tools (AI Tools)

ChatGPT was used only for grammar and syntax correction. The authors reviewed and approved the final manuscript and take full responsibility for its content.

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