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Boric Acid-Induced Apoptosis in Breast Cancer Subtypes: Comparative Gene Expression and Machine Learning Study

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Abstract

Aim: Breast cancer is a diverse illness that arises from the interplay of outside factors and genetic predisposition. Recently, artificial intelligence approaches have enabled the systematic analysis of potential anticancer agents such as boric acid by modeling the functions of apoptotic regulators. This study proposes an artificial intelligence-based analytical approach to evaluate how boric acid (B) affects cell survival and cell death through apoptosis pathway modulation.

Method: Viability of cells was determined by applying boric acid at various concentrations of 0.1, 1, 10, 50, 100, and 1000 ng/mL to cells at 24 h and 72 h using the cell viability test. Lastly, total RNA was isolated at 24 and 72 hours, and messenger RNA (mRNA) expression levels of specific genes were established by quantitative PCR (qPCR). An analysis was carried out using artificial intelligence based upon the Extreme Gradient Boosting (XGBoost) solution, a technique that enables the development of a pair of predictive models for cell viability and relative mRNA expression.

Results: After 24- and 72-hour treatments, boric acid reduced cell viability in MCF-7 and MDA-MB-231 cells in a rate- and time-sensitive manner in relation to the unaffected category. The triple-negative breast cancer phenotype was shown to be more susceptible to apoptosis at both time periods, as evidenced by the increased lethal consequences of boric acid in MDA-MB-231 cells compared to MCF-7 cells. However, boric acid was found to induce both intrinsic and extrinsic apoptosis in both breast cancer cell lines. Specifically for internal apoptosis signaling, ENDOG, BAX, Caspase-9, and Caspase-3 mRNA expression increased, while BCL-2 mRNA expression decreased, and the BAX/BCL-2 ratio was determined to shift towards apoptosis. Furthermore, apoptotic effects were detected in MCF-7 cells at 24 and 72 hours into the experiment, with this effect being particularly higher in MDA-MB-231 cells at 24 hours. The results obtained showed that boric acid induced the extrinsic apoptosis pathway by increasing mRNA FAS, FASLG, and CASP8 mRNA expression levels at 72 hours in MCF-7 cells and at 24 hours in MDA-MB-231 cells. However, boric acid increased MYC expression in MDA-MB-231 cells at 24 hours, while this effect was observed in MCF-7 cells at 72 hours of the experiment. The optimized XGBoost models were insufficient and showed highly non-homogeneous Margin of Deviation (MoD) values, with cell viability in the range of ±100% and mRNA expression spanning -4000% to +2000%.

Conclusions: The results obtained indicate that boric acid regulates cellular survival and death in breast cancer subtypes through MYC-dependent mechanisms and that this effect exhibits a more pronounced

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antitumor effect in MDA-MB-231 cells. So, it is concluded that boric acid may be a promising therapeutic agent for breast cancer if supported by additional research. Moreover, the inability of the current AI models also accentuates the complexity and non-linearity of the cellular response and suggests that the quantitative biological outcome can be better predicted with a broader multi-feature set.

Keywords: Boric acid, MCF-7, MDA-MB-231, XGBoost.

Meme Kanseri Alt Tiplerinde Borik Asit ile İndüklenen Apoptoz: Karşılaştırmalı Gen Ekspresyonu ve Makine Öğrenmesi Çalışması

Öz

Amaç: Meme kanseri, dış faktörlerin ve genetik yatkınlığın etkileşimi sonucu ortaya çıkan çok yönlü bir hastalıktır. Son zamanlarda yapay zeka yaklaşımları, apoptotik düzenleyicilerin işlevlerini modelleyerek borik asit gibi potansiyel antikanser ajanlarının sistematik analizini mümkün kılmaktadır. Bu çalışma, borik asit (B)'in apoptoz yolak modülasyonu üzerinden hücre sağkalımı ve hücre ölümünü nasıl etkilediğini değerlendirmek amacıyla yapay zeka tabanlı analitik bir yaklaşım önermektedir.

Yöntem: Hücre canlılığı, MCF-7 ve MDA-MB-231 meme kanseri hücre hatlarında 0.1, 1, 10, 50, 100 ve 1000 ng/mL konsantrasyonlarında borik asit uygulamasından 24 ve 72 saat sonra hücre canlılığı testi ile değerlendirildi. Son olarak, 24 ve 72 saatte toplam RNA izole edildi ve belirli genlerin mRNA ekspresyon seviyeleri kantitatif PCR (qPCR) ile belirlendi. Deneysel kantifikasyon için yapay zeka tabanlı bir analitik yaklaşım kullanıldı. Sonrasında hücre canlılığı ve mRNA ekspresyonunun iki bağımsız tahmin modelini oluşturmak için Extreme Gradient Boosting (XGBoost) çerçevesi kullanıldı.

Bulgular: Deneyin 24 ve 72. saatlerinde, borik asit, kontrol grubuna kıyasla, doz ve zamana bağlı olarak MCF-7 ve MDA-MB-231 hücre canlılığında azalmaya yol açtı. Borik asidin sitotoksik etkileri, MDA-MB-231 hücrelerinde MCF-7 hücrelerine göre daha güçlü gözlemlendi, bu da her iki zaman noktasında da üçlü negatif meme kanseri fenotipinde apoptoza karşı daha yüksek bir duyarlılığa işaret etmektedir. Bununla birlikte borik asit, her iki meme kanseri hücresinin iç ve dış apoptozunu indüklediği tespit edilmiştir. Özellikle iç apoptoz sinyallemesi için, ENDOG, BAX, Caspase-9 ve Caspase-3 mRNA ekspresyonu artarken, BCL-2 mRNA ekspresyonu ise azaldı ve BAX/BCL-2 oranının apoptoza doğru yön değiştirdiği belirlendi. Ayrıca apoptotik etkiler, deneyin 24. ve 72. Saatlerinde MCF-7 hücrelerinde belirlenirken özellikle bu etkinin deneyin 24. saatinde MDA-MB-231 hücrelerinde daha yüksek olduğu ortaya çıktı. Elde edilen sonuçlar, borik asitin MCF-7 hücrelerinde 72. saatte ve MDA-MB-231 hücrelerinde ise 24. saatte mRNA FAS, FASLG ve CASP8 mRNA ekspresyon seviyelerinin artarak dış apoptoz yolunu indüklediğini gösterdi. Bununla birlikte borik asit, MDA-MB-231 hucrelerinde 24. saatte MYC ekspresyonunu artırırken bu etki MCF-7 hücrelerinde deneyin 72. saatinde belirlendi. Çalışma, optimize edilmiş XGBoost modellerinin tahmin doğruluğunun yetersiz olduğunu, hem hücre canlılığı (±%100'e kadar) hem de mRNA ifadesi (-%4000'den +%2000'e kadar değişen) için son derece tutarsız sapma marjı değerlerine sahip olduğunu ortaya koydu.

Sonuç: Elde edilen sonuçlar, borik asidin meme kanseri alt tiplerinde hücresel sağkalım ve ölümü MYC-bağımlı mekanizmalar üzerinden düzenlediğini ve bu etkinin MDA-MB-231 hücrelerinde daha belirgin antitümoral etki ortaya koyduğunu göstermektedir. Bu nedenle, daha ileri gelişmiş deneylerle desteklenen borik asit, meme kanserini tedavi etmek için kullanılabilecek potansiyel bir terapötik ajandır. Ayrıca, mevcut yapay zeka modellerinin başarısızlığı, hücresel yanıtın son derece karmaşık ve son derece doğrusal olmayan bir yapıya sahip olduğunu göstermekte, bu da nicel biyolojik sonuç tahminlerini mümkün kılan daha geniş, çok özellikli bir setin önemli bir gereklilik olduğunu ortaya koymaktadır.

Anahtar Sözcükler: Borik asit, MCF-7, MDA-MB-231, XGBoost.

Introduction

Breast cancer subtypes include hormone receptor-positive, HER2-enriched, and triple-negative breast cancer, each with distinct genetic signatures. LncRNAs like MIR200CHG promote tumors by binding regulatory proteins[1]. Treatment resistance develops through gene mutations, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and sphingolipid signaling[2,3]. Sphingosine kinase activity correlates with chemoresistance, while Sphk2 inhibition may induce apoptosis. Cancer cells resist apoptosis through protein overproduction or mitochondrial dysfunction. NF-κB enables drug-resistant cell survival[4,5]. ADAM12 enhances death in the tumor microenvironment. Preclinical studies show promise in targeting apoptotic programs. Apoptosis induction through mitochondrial, FS-7-associated surface antigen (Fas) and Fas Ligand (FasL); FasL/Fas, phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and mitogen-activated protein kinases (MAP kinase) pathways advances therapy[6-8]. Breast cancer's heterogeneity affects treatment efficacy, while resistance stems from gene expression variations. Identifying cell survival drivers is crucial for reducing resistance. Artificial intelligence (AI) advances cancer research by analyzing multi-omics data to identify pathways where traditional analyses fail[9,10]. AI enables patient risk stratification through clinical metrics analysis, supporting personalized medicine[11]. For drug selection, AI speeds development using computer assisted engineering to find promising drugs[12,13]. AI technology with three-dimensional models improves prediction of drug effects, enhancing preclinical screening[14]. AI recognizes biomarkers, processes data, and elevates image analysis for improved diagnostics[15,16]. AI models have reduced time-to-hypothesis and integrated heterogeneous data into clinical decisions, offering precision in oncology[9]. AI in cancer research applies to molecular regulator discovery, drug efficacy evaluation, and biomedical data handling.

Boric acid is a naturally occurring, water-soluble form of boron—a trace element that is not synthesized endogenously but is obtained through dietary intake and rapidly absorbed from the gastrointestinal tract, entering the bloodstream predominantly as boric acid (98.4%) with only 1.6% as borate anion, with a recommended upper intake level of 20 mg/day in humans[17,18]. Chemically, boric acid (H_3BO_3) functions as a Lewis acid with a pKa of approximately 9.24; at physiological pH 7.4, it exists predominantly in its undissociated monomeric form rather than as borate anion[18]. At the molecular level, boric acid modulates intracellular Ca^{2+} signaling and activates the Nrf2 antioxidant pathway, thereby regulating transcription factors involved in anti-inflammatory gene induction[19,20]. Boric acid has well-documented antiseptic, anti-inflammatory, and antimicrobial properties; specifically, it inhibits lipopolysaccharide-induced TNF-α formation, suppresses pro-inflammatory cytokines, and enhances anti-inflammatory cytokine expression under conditions of inflammatory and oxidative stress[17,20]. In mineralized tissues, physiological concentrations of boric acid upregulate key osteogenic markers including RunX2, BSP, OCN, OPN, COL-I, and BMP-4/-6/-7, and induce tuftelin — a differentiation factor critical for the initial stages of bone and tooth formation and mineralization[18,19]. Literature has explored its therapeutic potential in cancer treatment, including its biocompatibility and bioavailability[21]. Studies show boric acid

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inhibits cancer cell growth, with research demonstrating dose-dependent suppression of breast cancer cell proliferation. While calcium fructoborate induced apoptosis through caspase-3 activity, boric acid inhibited growth without clear apoptosis induction, suggesting different mechanisms requiring further study[21]. In prostate cancer cells, boric acid induced senescence-like changes, reduced cell cycle proteins, and metastatic potential, demonstrating chemopreventive properties[22]. The focus on boric acid in breast cancer treatment stems from its proven growth-inhibiting effects, low toxicity, and potential synergy with other therapies. Studies show beneficial effects when combining boric acid with agents like paclitaxel in polymeric delivery systems[23]. Given breast cancer's heterogeneity, new drugs targeting multiple cellular pathways are needed. While boric acid shows promise, further research is needed to understand its role in breast cancer regulation[21,23]. This study used mRNA profiling and AI-based interpretation to investigate boric acid's effects on MYC-driven transcription and caspase-dependent apoptosis in breast cancer cells.

Materials and Methods

Cell culture

MCF-7 cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) with 1 g/L D-Glucose, 4 mM L-Glutamine, and 1 mM Pyruvate (Gibco, USA), supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. MDA-MB-231 cells were cultured in DMEM/F-12 with 2.5 mM L-Glutamine and 15 mM HEPES (Gibco, USA), supplemented with 10% FBS and 1% penicillin-streptomycin

Assessment for the survival of cells

The cell viability test was used to assess the impacts of various concentrations of B at 0.1, 1, 10, 50, 100, and 1000 ng/mL on cells after 24 and 72 hours. Here 5×10^3 cells of the twentieth passage were treated. MCF-7 and MDA-MB-231 cells were treated with B at the indicated concentrations for 24 h and 72 h independently. At each time point, cells were treated continuously from the time of seeding until the designated endpoint (24 h or 72 h). Untreated cells served as the control group. At the end of each incubation period, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reagent was added to each well and incubated for an additional 2 hours.

mRNA Expressions

Total RNA was isolated from MCF-7 and MDA-MB-231 cells at 24 and 72 hours using a monophasic solution of phenol and guanidine isothiocyanate (TRIzol Reagent; Invitrogen, Camarillo, CA, USA) according to the manufacturer's instructions. Complementary DNA (cDNA) synthesis was performed using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, Waltham, MA, USA) according to the manufacturer's protocol. The mRNA expression levels of ENDOG, Caspase-3, Caspase-8, Caspase-9, BAX, BCL-2, FAS, FASLG, MYC, and GAPDH were quantified by quantitative real-time PCR (qPCR) using Maxima SYBR Green qPCR Master Mix (2X)

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(Thermo Scientific, Waltham, MA, USA). Gene-specific primer sequences are listed in Table 1. Reactions were performed in a total volume of 20 µL. The thermal cycling conditions were as follows: initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s. All reactions were performed using a BIORAD-CFX real-time PCR system (USA). Relative mRNA expression levels were calculated using the 2−ΔΔCt method, with GAPDH serving as the reference gene for normalization. All samples were run in triplicate.

Table 1. Human-origin and apoptosis-related gene primer sequences, 5'-3'

Primers	**Forward (5'-3')**	**Reverse (3'-5')**
ENDOG	GCATGCCTGGAACAACCTTGAGAA	TGCCTCCAGGATCAACACCTTGAA
Caspase3	TTAATAAAGGTATCCTCGGGGT	CATGGAGAACACTCCCAGCCT
Caspase8	TCTGGAGCATCTGCTGTCTG	CCTGCCTGGTGTCTGAAGTT
Caspase9	GGCTGTCTAC GGCAC AGATG GA	CTGGCTCGGGGTTACTGCCAG
BAX	AGTGGCAGCTGACATGTTTT	GGAGGAAGTCCAATGTCCAG
BCL-2	CCGGGAGATCGTGATGAAGT	ATCCCAGCCTCCGTTATCCT
FAS	GCCAATTCTGCCA! TAAGC	TTGGCTTCATTGACACCACTCGGGGT
FASLG	GGATTGGGCCTGGGGATGTTTCA	TTGTGGCTCAGGGGCAGGTTGTTG
MYC	TGA GGA GAC ACC GCCCAC	CAACATCGATTTCTTCCTCATCTT C3
GAPDH	CAAGGTCATCCATGACAACTTTG	GTCCACCACCCTGTTGCTGTAG

Ethical Statement

The experiments used established human breast cancer cell lines (MCF-7 and MDA-MB-231). With no primary tissues, patient data, or animal models used, the study does not require ethics committee approval.

Statistical Analysis

Tukey's honestly significant difference (HSD) test and Dunnett's test were employed in a one-way analysis of variance (ANOVA) to investigate the RT-PCR and cell viability results.

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Extreme Gradient Boosting (XGBoost) Model Development

To systematically evaluate the non-linear impacts of boric acid (B) on cellular dynamics, two independent machine learning frameworks were established using the Extreme Gradient Boosting (XGBoost) regressor algorithm. XGBoost is a scalable tree-boosting system that implements gradient-descent optimization architectures optimized for multi-dimensional biological datasets. XGBoost Model 1 (Cell Viability Predictor) was developed to map experimental exposure parameters directly to cell viability percentages. XGBoost Model 2 (mRNA Expression Predictor) was designed to predict the relative transcription fold-changes of core apoptotic regulatory pathways. The models' parameters are shown in Table 2.

Table 2. Input and output limitations of developed XGBoost Models

	Inputs				**Output**
XGBoost Model 1	Time	Cell Types	Concentrations		Cell Viability
XGBoost Model 2	Time	Cell Types	Gene	Concentrations	mRNA Expression

The experimental input domains and targeting profiles for both models were explicitly formalized to map architectural parameters into quantitative target outcomes. Feature Set for Model 1 includes Time (24 h and 72 h; continuous numerical representation), B (0.1, 1, 10, 50, 100, and 1000 ng/mL; numerical scaling), and Cell Type (MCF-7 and MDA-MB-231). Feature Set for Model 2 includes Time (24 h and 72 h), B (1, 10, 50, and 100 ng/mL), Cell Type, and Gene Name (categorical spectrum encompassing ENDOG, caspase3, caspase8, caspase9, BAX, BCL-2, FAS, FASLG, and MYC). To facilitate optimal multi-variant algorithmic parsing, categorical features (Cell Type and Gene Name) were mapped into numerical vector spaces using one-hot encoding frameworks prior to model deployment. This avoids imposing artificial ordinal constraints on biological classes.

To prevent programmatic overfitting while maximizing generalized testing performance on non-homogeneous profiles, the collective experimental data matrix was partitioned into an 80% training repository and a 20% independent validation testing partition. Hyperparameter optimization was executed through an exhaustive grid-search pipeline integrated with internal k-fold cross-validation (k=5) on the training cohort. The optimized hyperparameter optimization matrix encompassed the following operational variations:

- Learning Rate: Explored within the bounds of [0.01, 0.05, 0.1, 0.2] to systematically scale step-size shrinkage.
- Maximum Tree Depth (max_depth): Varied from 3 to 8 to effectively regulate tree architectural complexity and mitigate model variance.

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- Number of Estimators (n_estimators): Investigated from 50 to 500 steps to track structural boosting stabilization points.

Subsample weights and column sampling metrics were closely controlled to ensure tree construction steps were regularized against data-density imbalances. To quantify the contribution of each variable, feature importance was calculated, identifying Boric Acid Concentration (0.53163) as the primary driver of model predictions, followed by Cell Type (0.235684) and Time (0.232685). The performance of the models derived by both approaches has largely been evaluated with the Margin of Deviation (MoD) which determines the percentage difference between the predicted values (result from the creation of the XGBoost models) based on actual target values obtained in the experiment. It expresses Equation 1, the key to the MoD calculation:

$$MoD\ (\%) = \left[\frac{X_{targ} - X_{pred}}{X_{targ}}\right] x\ 100 \quad (1)$$

Here, X_{targ} represents the actual target value obtained from the experimental measurements (cell viability or mRNA expression), and X_{pred} represents the corresponding value predicted by the developed XGBoost model. The MoD is helpful in determining the predictive reliability and error characteristics of the AI models compared to biological changes.

Results

Boric acid diminished the survival rate of breast cancer cells.

Boric acid reduced MCF-7 and MDA-MB-231 breast cancer cell viability at 24 h and 72 h. MCF-7 viability decreased dose-dependently up to 1000 ng/mL at 24 h ($p<0.01$) and at 72 h with 0.1-100 ng/mL, peaking at 100 ng/mL ($p<0.01$). MDA-MB-231 viability decreased with 0.1-100 ng/mL at both times ($p<0.01$), strongest at 50-100 ng/mL. MDA-MB-231 cells were more sensitive, indicating greater triple-negative phenotype susceptibility.

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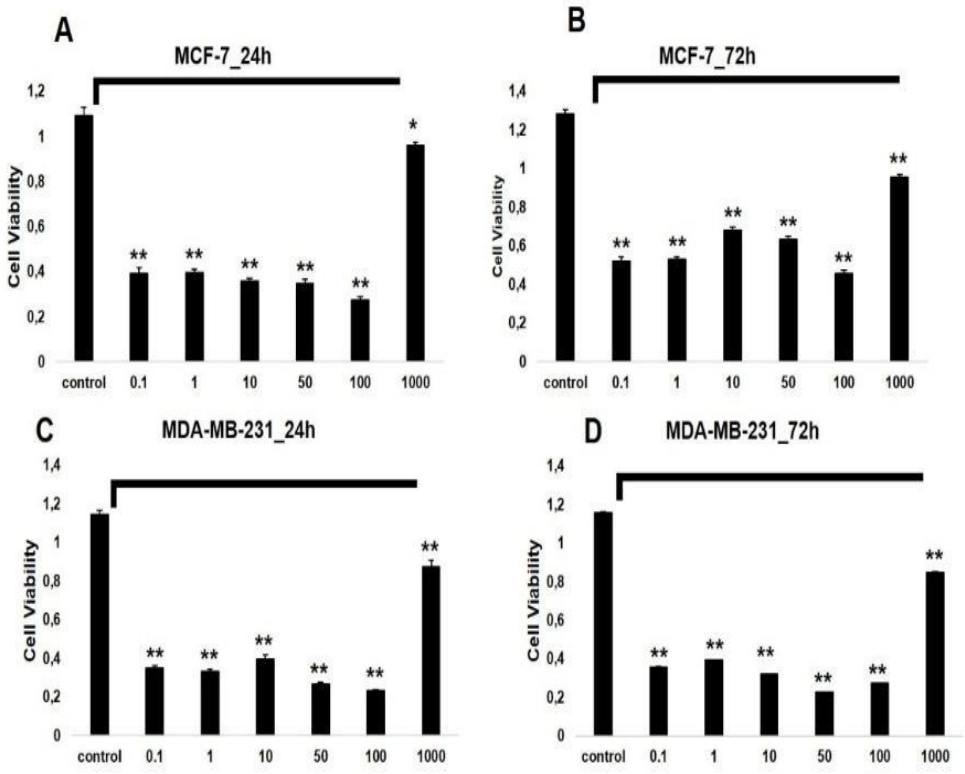
Figure 1. Boric acid effects on MCF-7 and MDA-MB-231 breast cancer viability. MCF-7 cells were treated with boric acid (0.1-1000 ng/mL) for 24 h and 72 h (**A**-**B**); ***p < 0.001 vs control. MDA-MB-231 cells received equivalent treatments at 24 h and 72 h (**C**-**D**) ; ***p < 0.001 vs control.



mRNA Expression Results

Boric acid's impacts on apoptosis were investigated via intrinsic and extrinsic markers in breast cancer cells. Both lines showed increased ENDOG expression after treatment, with MCF-7 increases at 72h (100 ng/mL) and MDA-MB-231 increases at 72h (50-100 ng/mL) ($p<0.01$) (Figure 2A-D). Caspase genes increased in both lines (Figure 3-5). MCF-7 showed increased caspase-3 at 72 h with 100 ng/mL and at 50-100 ng/mL at 24 h (Figure 3A, 3B), while M($p < 0.01$)DA-MB-231 peaked at 50 ng/mL after 24 h (Figure 3C, 3D). Caspase-8 and -9 increased dose-dependently ($p<0.01$) (Figure 4, 5). Pro-apoptotic BAX increased dose-dependently ($p<0.01$) (Figure 6A-D), while Bcl-2 decreased in both lines (Figure 7A-D). FAS/FASLG increased significantly ($p<0.01$) (Figure 8A-D, 9A-D). MYC expression increased in both lines ($p<0.01$) (Figure 10A-D). Boric acid activated both extrinsic and intrinsic apoptotic pathways.

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Figure 2. Effect of B on ENDOG gene mRNA expression in MCF-7 at 24h (**A**), 72h (**B**), and MDA-MB-231 at 24h (**C**), 72h (**D**). B concentrations (1, 10, 50, 100 ng/mL) were tested using quantitative reverse transcription-polymerase chain reaction (RT-PCR). Bars show mean with 95% confidence interval. *p<0.05, **p<0.01 indicate significant differences versus control.

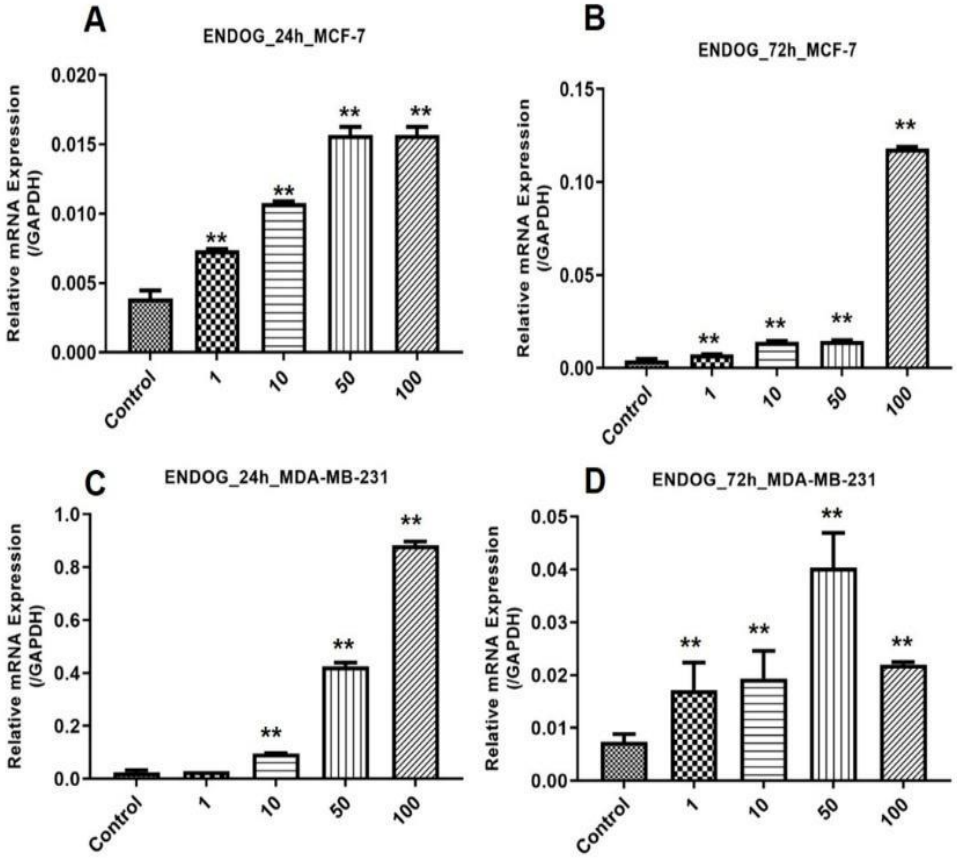

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Figure 3. The effect of B on caspase-3 expression in MCF-7 at 24h (**A**), 72h (**B**) and MDA-MB-231 at 24h (**C**), 72h (**D**). B concentrations (1, 10, 50, 100 ng/mL) were tested on caspase-3 mRNA expression in MCF-7 and MDA-MB-231 using RT-PCR at 24h and 72h. Bars show mean with 95% CI. *p<0.05, **p<0.01 vs control.

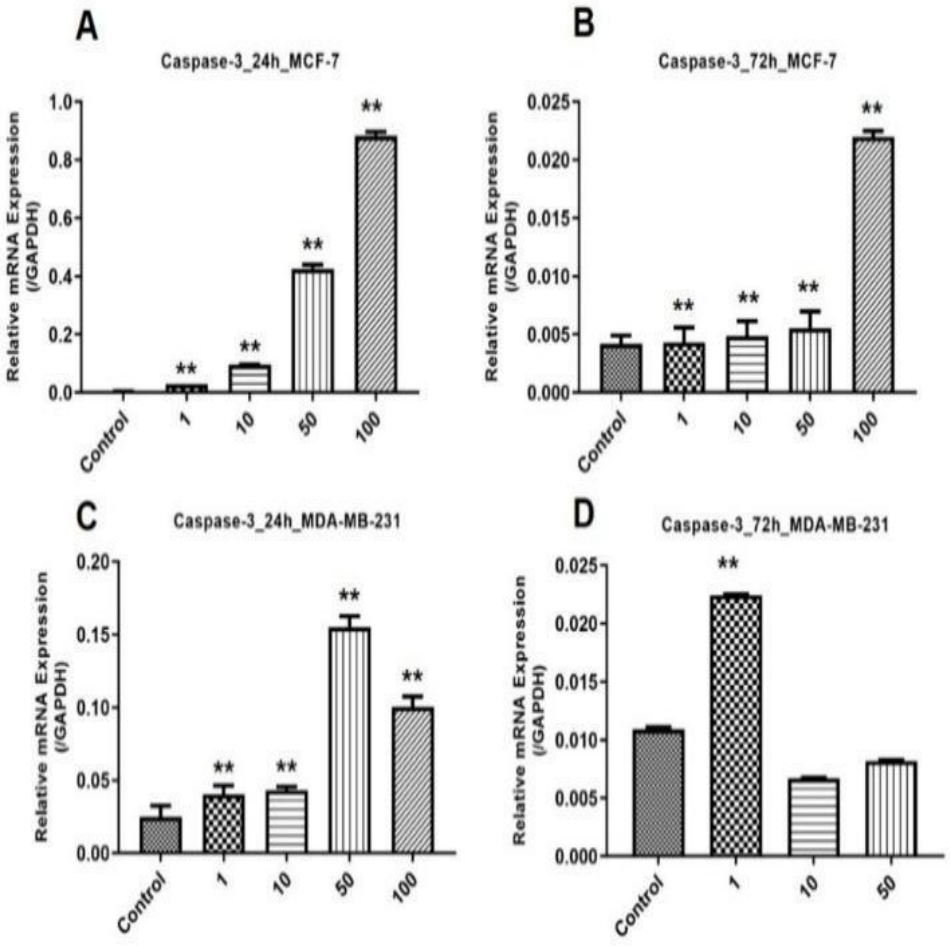

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Figure 4. Effect of B on caspase-8 expression in MCF-7 at 24 h (**A**), 72h (**B**) and MDA-MB-231 at 24 h(**C**), 72h (**D**). B concentrations (1, 10, 50, 100 ng/mL) were tested on caspase-8 mRNA expression in MCF-7 and MDA-MB-231 using RT-PCR at 24 h and 72 h. Bars show mean with 95% confidence interval. *p<0.05, **p<0.01 vs control.

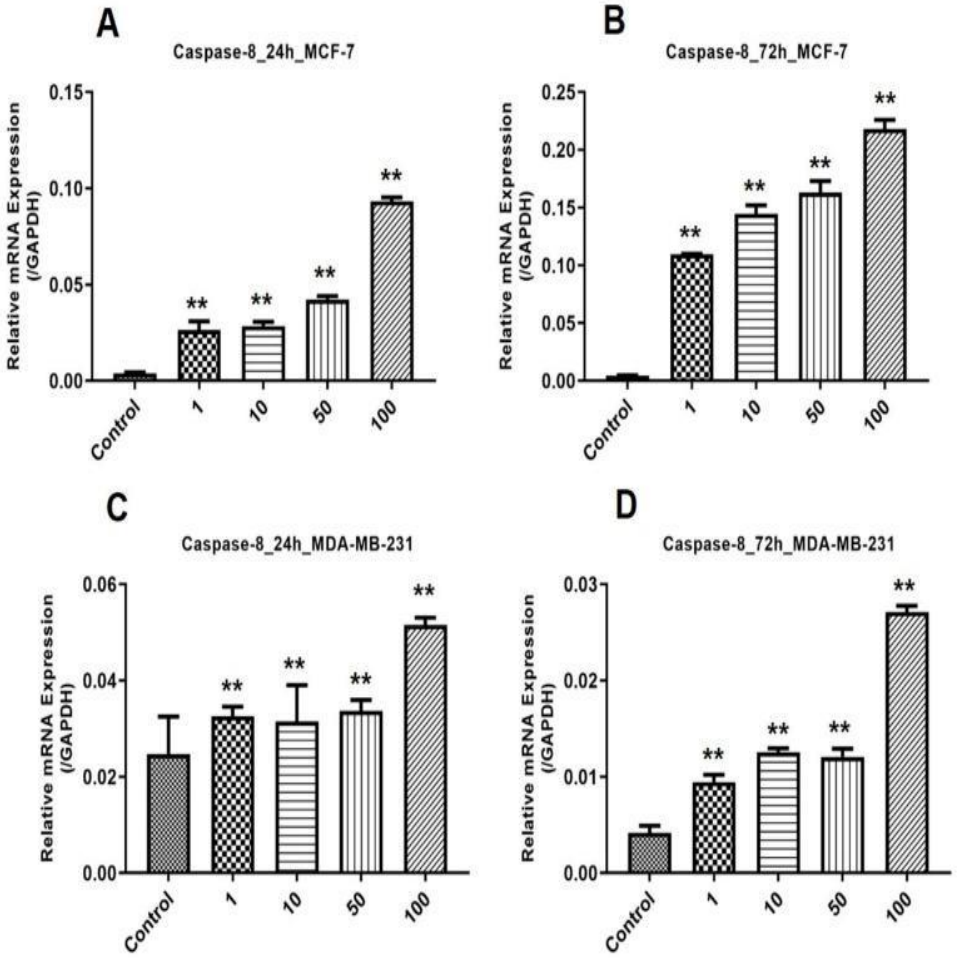

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Figure 5. B affecting caspase-9 expression in MCF-7 at 24 h (**A**), 72h (**B**), and MDA-MB-231 at 24 h (**C**), 72 h (**D**). Effect of B concentrations (1, 10, 50, 100 ng/mL) on Caspase-9 gene mRNA expression in MCF-7 and MDA-MB-231 using RT-PCR at 24 h and 72 h, with bars showing mean at 95% confidence interval. *p<0.05, **p < 0.01 versus control.

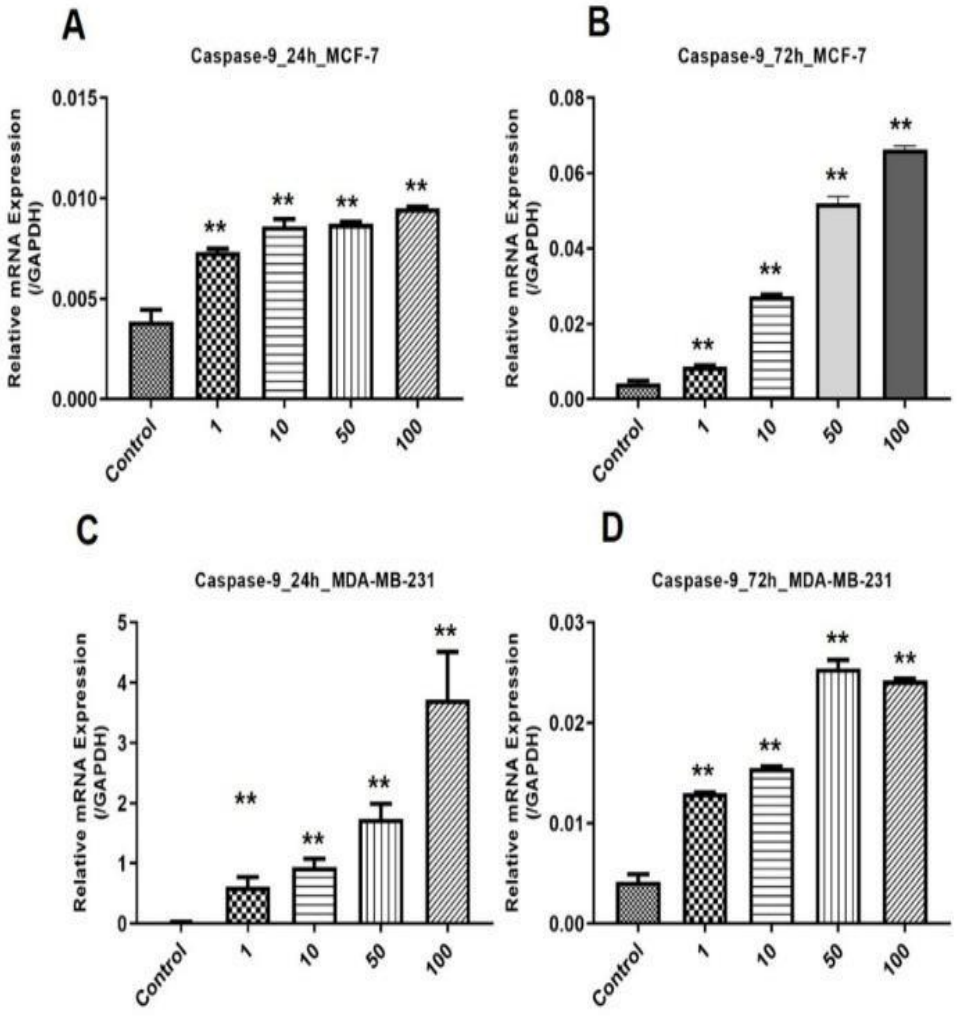

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Figure 6. Effects of B on BAX expression in MCF-7 at 24h (**A**), 72h (**B**) and MDA-MB-231 at 24 h(**C**), 72h (**D**). B concentrations (1, 10, 50, 100 ng/mL) effects on BAX gene mRNA expression in MCF-7 and MDA-MB-231 using RT-PCR at 24 h and 72 h. Bars show mean with 95% confidence interval. *p<0.05, **p<0.01 vs control.

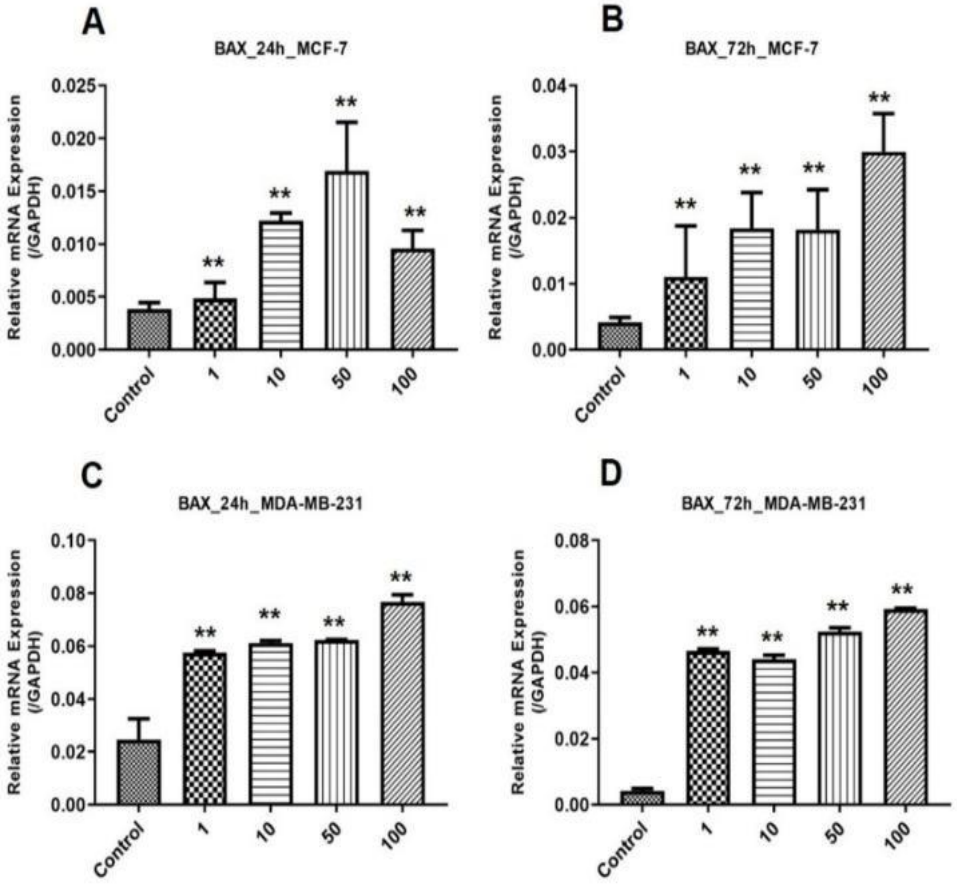

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Figure 7. Influence of B on Bcl-2 expression in MCF-7 at 24 h (**A**), 72h (**B**) and MDA-MB-231 at 24 h (**C**), 72 h (**D**). Effect of B concentrations (1, 10, 50, 100 ng/mL) on Bcl-2 mRNA expression in MCF-7 and MDA-MB-231 using RT-PCR at 24 h and 72 h; bars show mean with 95% confidence interval. *p<0.05, **p<0.01 vs control.

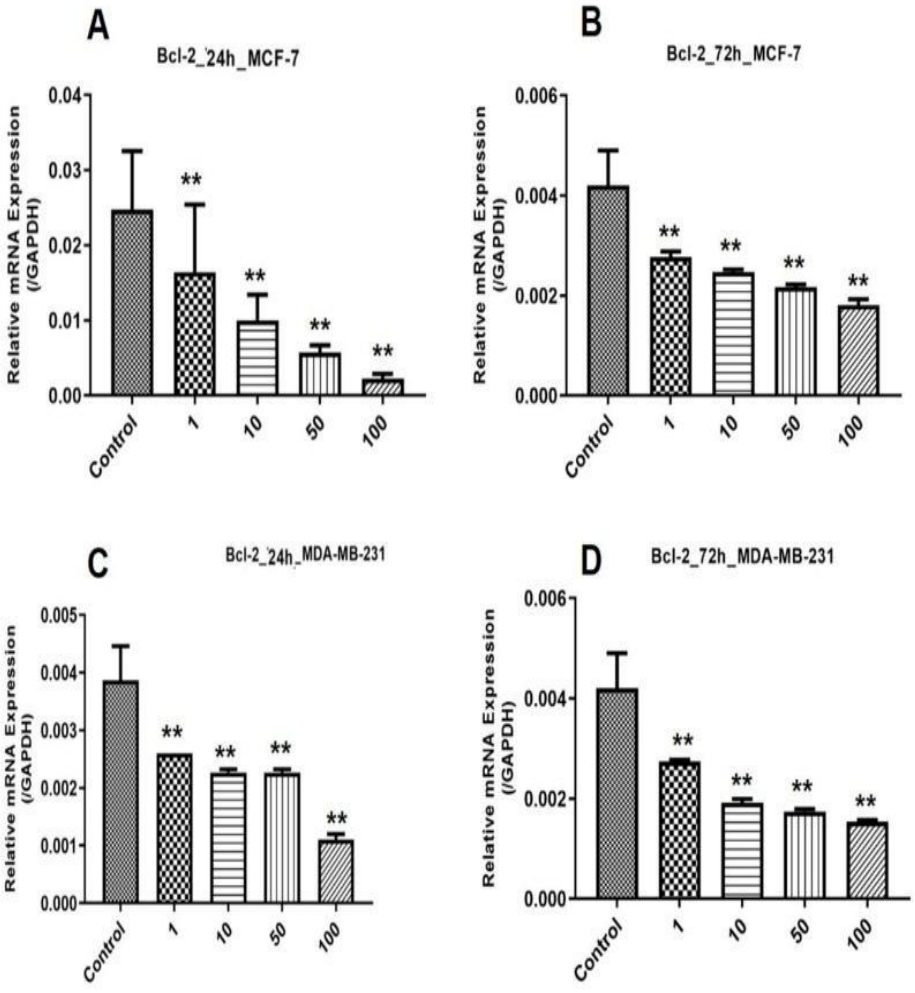

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Figure 8. Effect of B on FAS expression in MCF-7 at 24 h (**A**), 72h (**B**) and MDA-MB-231 at 24 h (**C**), 72h (**D**). B concentrations (1, 10, 50, 100 ng/mL) were tested on FAS gene mRNA expression in MCF-7 and MDA-MB-231 using RT-PCR at 24 h and 72 h. Bars show mean with 95% confidence interval. *p<0.05, **p<0.01 vs control.

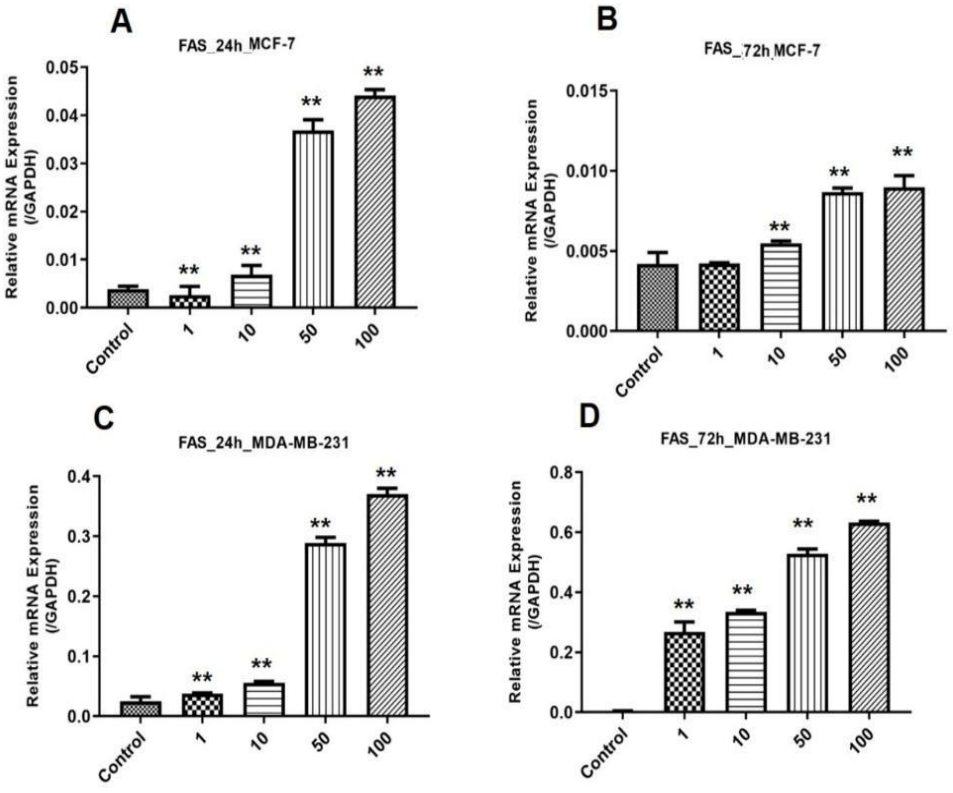

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Figure 9. Effect of B on FASLG expression in MCF-7 at 24 h (**A**), 72h (**B**) and MDA-MB-231 at 24 h(**C**), 72h (**D**). B concentrations (1, 10, 50, 100 ng/mL) were tested on FASLG gene expression in MCF-7 and MDA-MB-231 using RT-PCR at 24 h and 72 h. Bars show mean with 95% confidence interval. *p<0.05, **p<0.01 vs control.

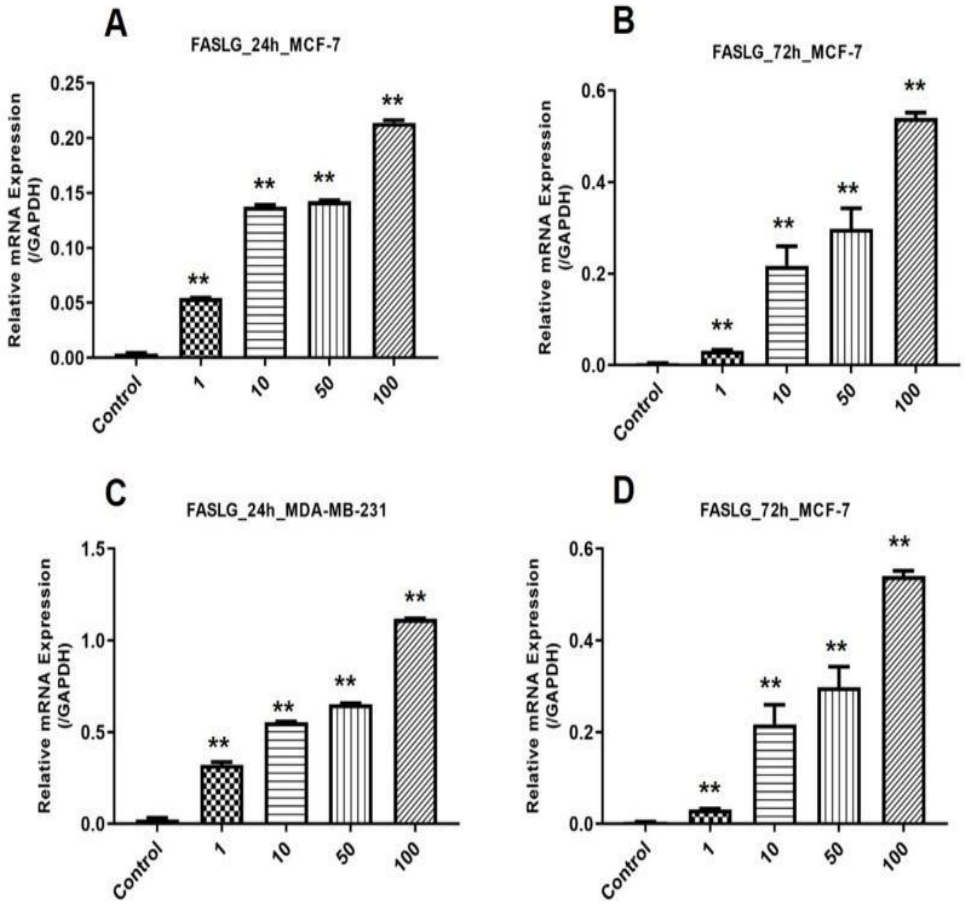

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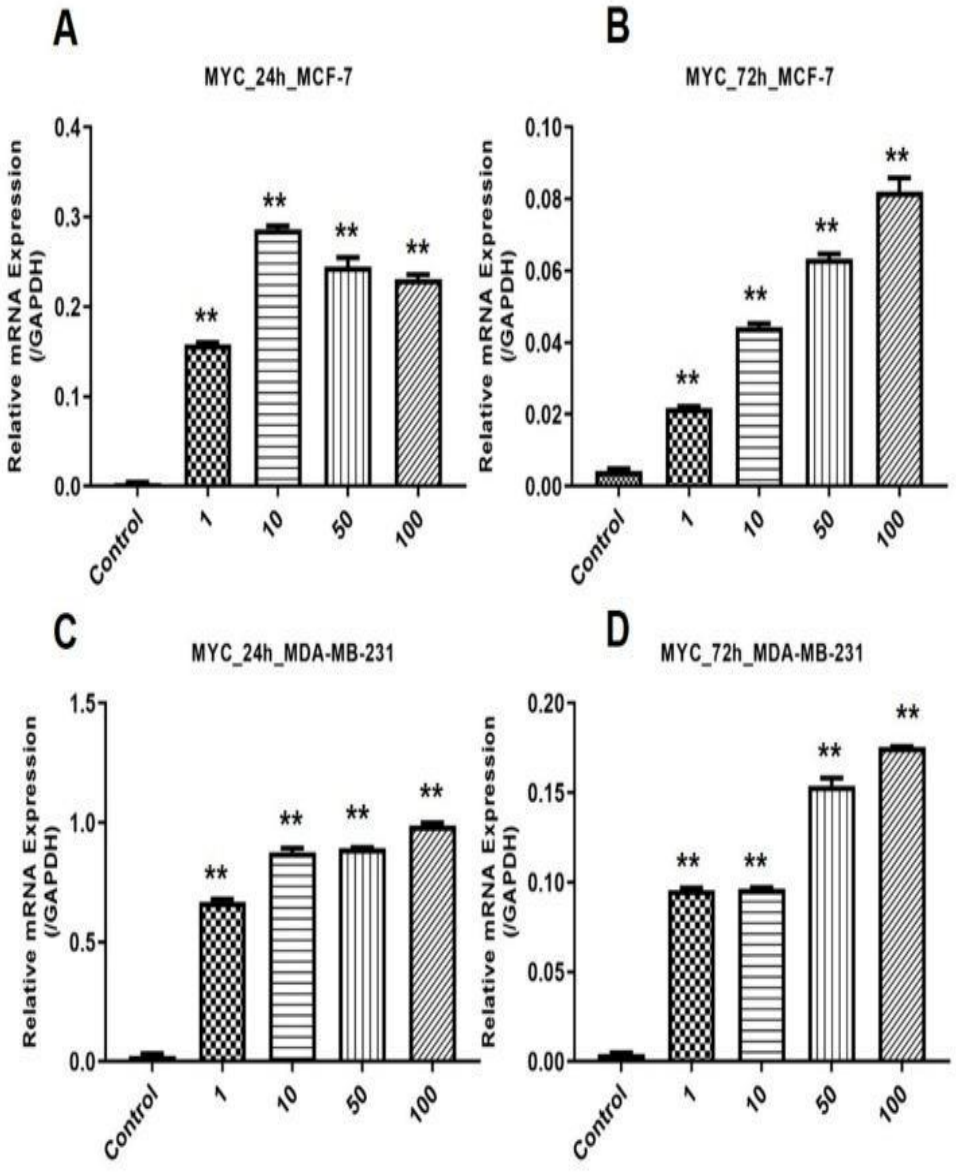
Figure 10. B effect on MYC expression in MCF-7 at 24 h (**A**), 72 h (**B**) and MDA-MB-231 at 24 h (**C**), 72 h (**D**). B concentrations (1, 10, 50, 100 ng/mL) affected MYC gene mRNA expression in MCF-7 and MDA-MB-231 cells at 24 h and 72 h by RT-PCR. Bars show mean with 95% confidence interval. *p<0.05, **p<0.01 vs control.



XGBoost Model Results

There are significant limitations in mapping boric acid to two optimized XGBoost models specifically designed to predict breast cancer cell viability (Model 1) and apoptosis mRNA expression (Model 2).

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XGBoost Model 1: Cell Viability Prediction

Two optimized XGBoost models were used to predict boric acid's effect on breast cancer cell viability (Model 1) and apoptosis mRNA expression (Model 2). Data showed the model based on in vitro results was inadequate for revealing boric acid's effect. Figure 11A compares experimental and predicted cell viability for XGBoost Model 1. While values show a linear trend, indicating a general match, prediction accuracy varies significantly. Boric acid-induced cytotoxicity is undetectable from the total mass using Model 1 due to high MoD in Equation 1, with prediction errors reaching ±100%. Similarly, comparative analysis of Cell Viability (Figure 13A) shows the absolute error between actual and predicted values.e predicted) suggests the model consistently diverges by ±0.2 units (bad for prediction performance).

XGBoost Model 2: mRNA Expression Prediction

XGBoost Model 2's performance in predicting mRNA expression of apoptosis genes showed poor stability. PCR results were compared to XGBoost predictions (Figure 11B), with Figure 12B showing high variability in prediction accuracy. MoD values for mRNA Expression (Equation 1) ranged from -4000% to +2000%, indicating substantial deviations from experimental values. Due to this large error distribution, the model failed to accurately predict molecular stress response and gene expression changes from boric acid treatment. Both XGBoost models, despite optimization, could not predict cell viability and mRNA expression in MCF-7 and MDA-MB-231 cell lines.

Figure 11. Experimental target values were compared with XGBoost model predictions: cell viability with Model 1 predictions (**A**), and target mRNA expression with Model 2 predictions (**B**).

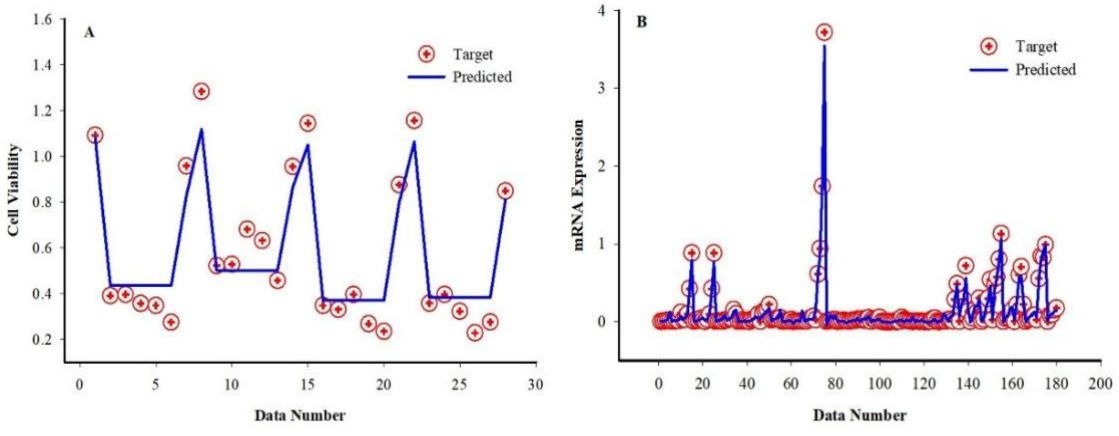

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Figure 12. Ministry of Defence examination of the anticipated values for the XGBoost models. MoD distribution for Model 1 (cell viability prediction) (**A**). Distribution of MoD for Model 2 (mRNA Expression Prediction) (**B**).

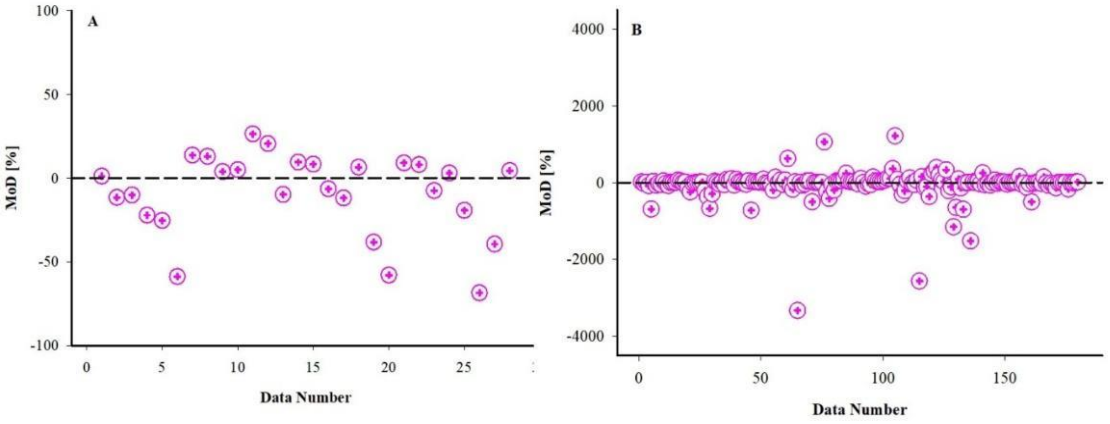
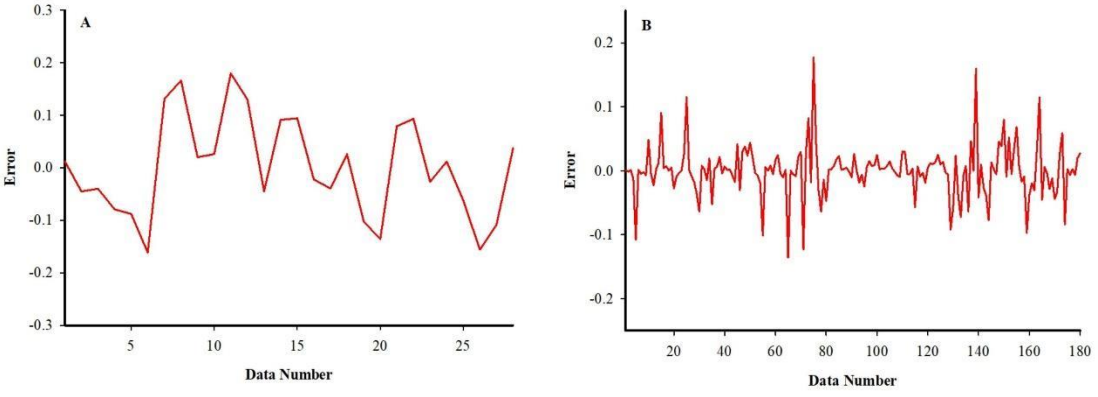


Figure 13. Comparison of expected values from XGBoost with experimental target values. Error distribution of cell viability prediction using XGBoost: Model 1 (**A**). Error distribution of mRNA expression prediction using XGBoost: Model2 (**B**).



Discussion

In the present study, B reduced cell viability in both MCF-7 and MDA-MB-231 cells in a concentration- and time-dependent manner. Notably, MDA-MB-231 cells exhibited markedly greater sensitivity to B at both 24 and 72 hours compared to MCF-7 cells, suggesting that the triple-negative phenotype—characterized by the absence of estrogen receptor, progesterone receptor, and HER2—confers heightened susceptibility to boric

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acid-induced cytotoxicity. This differential response is consistent with the greater aggressiveness and distinct metabolic profile of TNBC cells[24,25].

Research shows B has varying cytotoxic and apoptotic effects by cell type. HeLa cells show higher sensitivity than normal HUF cells, with lower IC50 value and G1 arrest, nuclear abnormalities, and autophagy-related gene changes linked to endoplasmic reticulum (ER) stress[24]. Studies of human breast tumor cell lines showed gene expression differences drive pro-apoptotic drug development[25]. Boric acid modulates both apoptosis pathway genes and genes essential for apoptosis. The upregulation of GRP78, p-IRE1α, p-PERK, CHOP stress pathways, and cleaved caspase-3 indicates ER stress links to programmed cell death. Cellular death pathways including p53, MAPK, TNF, PI3K/AKT, and NF-κB are modulated through defined factors[26]. Quercetin modifies apoptosis-associated gene expression by upregulating pro-apoptotic genes and downregulating anti-apoptotic genes, impacting death receptor signaling[27]. Artificial intelligence can analyze gene expression to understand interactions from boric acid exposure, identifying key regulators and forecasting cell responses to boric acid-activated stress in cancer cells. AI targets factors like caspase activation and unfolded protein response (UPR) that trigger apoptotic response[24]. Different cellular lineages demonstrate biological heterogeneity, with analyses showing boric acid targets various apoptotic pathways. The protective effect against apoptosis in mouse granulosa cells during heat stress indicates boron compounds modulate ER stress signals selectively[28]. While boric acid induces apoptosis in DU-145 prostate cancer cells[29], effects vary across cancers. It slows human breast cancer cells without consistently inducing apoptosis, while calcium fructoborate causes apoptosis. Different boron compounds function through varied approaches, with effectiveness depending on cell type. This research advances knowledge through studying endoplasmic reticulum-stress response and autophagy-related gene expression. Boric acid shows promise in breast cancer management, with studies showing both boric acid and calcium fructoborate inhibit proliferation in MDA-MB-231 cells dose-dependently.

Calcium fructoborate significantly induced apoptosis by reducing p53 and Bcl-2 protein levels and activating caspase-3[21]. A central finding of this study is the coordinated upregulation of BAX, ENDOG, Caspase-9, and Caspase-3 mRNA alongside downregulation of BCL-2, resulting in a pro-apoptotic shift in the BAX/BCL-2 ratio in both cell lines. This pattern is mechanistically consistent with mitochondria-mediated intrinsic apoptosis[26]. Notably, the upregulation of ENDOG—an endonuclease released from mitochondria during apoptosis—in both cell lines represents a finding not previously documented for boric acid in breast cancer cells, supporting caspase-independent nuclear DNA fragmentation as a concurrent mechanism.

The present data also demonstrate activation of the extrinsic apoptotic pathway, evidenced by elevated FAS, FASLG, and CASP8 mRNA levels. Importantly, this activation displayed a cell-type-specific temporal pattern: extrinsic pathway induction occurred at 72 hours in MCF-7 cells but as early as 24 hours in MDA-MB-231 cells. This earlier engagement of the death receptor pathway in MDA-MB-231 cells may partly

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explain their greater overall apoptotic susceptibility and suggests that the two pathways are not activated simultaneously but rather follow a cell-phenotype-dependent sequence.

Perhaps the most mechanistically distinctive finding of this study is the upregulation of MYC expression under B treatment in both cell lines, albeit with an opposing temporal pattern: MYC was induced at 24 hours in MDA-MB-231 cells and at 72 hours in MCF-7 cells. This is paradoxical given MYC's canonical role as an oncogene promoting proliferation; however, sustained or aberrant MYC overexpression in the context of concurrent pro-apoptotic signaling is well-recognized as a trigger for apoptosis—a phenomenon termed 'MYC-induced apoptosis' first demonstrated in fibroblasts[30,31] and subsequently linked to the CD95/FAS pathway when BCL-2 survival signals are suppressed [32]— particularly when survival signals such as BCL-2 are simultaneously suppressed, as observed here. This MYC-driven, caspase-dependent apoptotic axis may represent a novel mechanism of boric acid action in breast cancer.

While earlier studies suggested boric acid might inhibit breast cancer through pathways other than apoptosis[21], the present findings demonstrate unequivocally that boric acid induces both intrinsic and extrinsic apoptotic programs in MCF-7 and MDA-MB-231 cells. Beyond the molecular mechanisms identified here, the translational potential of B in breast cancer management has been further explored through nanomedicine-based delivery strategies.

Nanomedicine shows promise for delivering boric acid to breast cancer. Boric acid and paclitaxel in polymeric nanocarriers showed higher drug uptake and potentially more potent effects. Nanoparticle systems with boric acid present a novel strategy for treating breast cancer, addressing drug resistance and side effects[33]. Understanding molecular aspects of breast cancer stages is crucial for personalizing therapy. Metabolomics and nanoparticle-assisted therapy improve cancer detection[34,35]. LAT1 shows upregulated expression associated with boron-containing compounds[36], which accumulate more in aggressive breast cancers[37]. This enables targeted boron injection for neutron capture therapy[38]. Boric acid-based therapies within personalized regimens offer promising solutions[21], particularly when combined with other treatments based on tumor biology and patient genetics[22]. The failure of the XGBoost models to predict mRNA expression outcomes is itself a biologically informative finding: it quantitatively demonstrates that the regulatory network activated by boric acid—encompassing MYC-driven transcription, dual-pathway apoptosis, and cell-type-specific timing—cannot be captured by a feature set limited to time, concentration, and cell identity alone. This reinforces the conclusion that boric acid's mechanism is inherently multi-dimensional. The AI study aimed to develop models interpreting complex datasets to predict biological outcomes. While XGBoost Model 1 showed good universal fit, it produced large prediction errors upon detailed analysis. Specifically, in detail in Figure 12A the MoD for cell viability can often be seen as high percentages, showing that the model was unable to accurately predict the exact magnitude of cytotoxicity across different cell lines and at different concentrations. The failure was particularly pronounced for the XGBoost Model 2 (mRNA Expression) as the MoD (Figure 12B) shows pronounced variances, ranging

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from approximately -4000% to +2000%. The large deviation rates in other variables are also demonstrated with strong error distributions in Figures 13A and B in the above plot, suggesting that the models fail to adequately capture the quantitative properties of the biological response. That the optimized XGBoost models do not provide a good prediction of these results indicates that the settings available (e.g., temporal range, cell type, concentration, and gene names) were insufficient for capturing the complexity behind the biological responses due only to boric acid. The experimental results showed that boric acid induces elaborate biological processes: the stimulation of intrinsic and extrinsic apoptotic pathways occurs concurrently; it triggers phenotype-specific reaction in MDA-MB-231 cells, and delayed or late-phase activation in MCF-7 cells followed by high dosage and time dependence. Relative mRNA expression, as measured by the 2-ΔΔCt approach, is the product of deep cross-talk within a vast number of signaling networks, including MYC-regulated transcription and caspase cascades, a dynamic cellular condition. Thus, the fall from grace of the evolved XGBoost models demonstrate one of the difficulties introduced by the reliance on typical experimental parameters (time, concentration, cell type) to model the high-dimensional dynamic regulatory systems of biological systems. Although AI has a considerable advantage in combining multiple types of data used for diagnosis and targeted therapies, accurate prediction of complex biological results, such as mRNA expression, requires a denser and wider feature set in addition to potentially multiomics data types (e.g., proteomics or epigenetics) that move beyond the scope of the main variables used in training the model.

Conclusion

Results show boric acid modulates mRNA expression for cell viability and apoptosis in breast cancer. AI enables pathway analysis and improves diagnosis through imaging and biomarkers. AI models predict outcomes and accelerate drug development. This study advances therapeutics while showing AI's role in cancer biology. However, XGBoost models showed ±100% errors in Cell Viability and -4000% to +2000% instability in mRNA expression, requiring more data.

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