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Effects of Trichostatin A on the Histone Deacetylases (HDACs), Intrinsic Apoptotic Pathway, p21/Waf1/Cip1, and p53 in Human Neuroblastoma, Glioblastoma, Hepatocellular Carcinoma, and Colon Cancer Cell Lines

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Abstract

Background: The aberrant and altered patterns of gene expression play an important role in the biology of cancer and tumorigenesis. DNA methylation and histone deacetylation are the most studied epigenetic mechanisms. Histone deacetylase inhibitors (HDACIs) such as valproic acid (VPA) and trichostatin A (TSA) are a group of anticancer compounds for the treatment of solid and hematological cancers. Previously, we reported the effect of two HDACIs, valproic acid (VPA) and TSA, on colon cancer and hepatocellular carcinoma (HCC), respectively. The aim of the current in vitro study is to investigate the effects of TSA on the intrinsic apoptotic pathway, p21/Waf1/Cip1 (p21), p53, and histone deacetylases (HDACs) 1, 2 and 3 in human neuroblastoma LAN-1, glioblastoma GBM-29, HCC SMMC7721, and colon cancer COLO 201 cell lines.

Materials and methods: In this lab-trial study, all three cell lines were seeded at the density of 3 × 105 cells per well and incubated for 24 hours. Then, the cells were treated with TSA based on IC50 values for 24 hours except in the control groups; the control cells were treated with the equal amounts of the DMSO solvent. Subsequently, cell viability, cell apoptosis and gene expression were determined by three techniques including MTT assay, flow cytometry assay, and qRT-PCR.

Results: The result of qRT-PCR indicated that TSA could increase the expression levels of Bid, BimEL, Noxa, p21, and p53 genes and decrease those of Bcl-xL, RIP, Mcl-1, XIAP, HDACs 1, 2 and 3 significantly ($P < 0.0001$) by which it inhibited cell growth and induced significant cell apoptosis in LAN-1, GBM-29, SMMC7721, and COLO 201 cell lines (p value<0.001).

Conclusion: TSA can affect cell apoptotic via the intrinsic apoptotic pathway in LAN-1, GBM-29, SMMC7721, and COLO 201 cell lines.

Keywords: Apoptosis, Histone deacetylase, Mitochondrial, Trichostatin A

Introduction

The aberrant and altered patterns of gene expression play a significant role in the biology of cancer and tumorigenesis. Gene alterations often occur at the epigenetic level that is not accompanied by changes in DNA structure. Epigenetic gene silencing is very important in cell differentiation, development, and imprinting. However, it can result in the development of numerous human cancers (1). Generally, epigenetic modifications result in the heritable silencing of genes without a change in the DNA sequence. These modifications, i.e., DNA methylation and histone deacetylation, are the most studied epigenetic mechanisms. Histone acetylation and deacetylation are controlled by histone acetyltransferases (HATs) and HDACs, respectively. As gene expression regulators, HDACs remove an acetyl group from the N-terminal tails of histone proteins, resulting in chromatin compaction and gene silencing (2). To date, 18 different HDACs have been identified in mammalian cells (3). Even though DNA methylation and histone deacetylation are heritable, these

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epi-genetic changes are reversible, which is an opportunity for cancer treatment. Histone deacetylase inhibitors (HDACIs) are a group of anticancer compounds for the treatment of cancers. They increase acetylation by inhibiting the HDAC activity. Structurally, these compounds are divided into the four groups of compressing hydroxamates (e.g., vorinostat), benzamides (e.g., MS-275), cyclic peptides (e.g., romidepsin), and aliphatic acids (e.g., valproic acid, or VPA). Alternatively, these compounds can be classified by their affinity for HDACs (4). The apoptotic effects of these agents have been reported in numerous human cancers. It has been shown that sodium butyrate (NaB), SAHA, and TSA are able to induce apoptosis in both S-type (SH-EP, SK-N-AS) and N-type (IMR32, LAN-1, and SH-SY5Y) neuroblastoma (NB) (5). In vitro studies have indicated that NaB and TSA induce strong apoptosis in the cancer cell lines of the breast, cervix, and brain (6). Several studies have also shown that TSA can induce apoptosis in the human glioblastoma cell lines U-343 MG, GBM-29, and U-343 MGa Cl. 2:6 (7). Some researchers have demonstrated that NaB can induce apoptosis in hepatocellular cancer (HCC) HepG2 and glioblastoma C6 cell lines (8). Previously, we reported the effects of TSA (9-13) and VPA (14, 15) on HCC and colon cancer, respectively. Recent studies have shown that HDACIs induce apoptosis via both the intrinsic and extrinsic pathways (16). Since epi-drugs such as TSA can inhibit cell growth and induce apoptosis in a tissue based on the concentration of drugs and the time of treatment, the effect of each dose of a compound, each time of treatment, or each experimental cell line could be a topic of novelty for research (17-20).

The aim of the current in vitro study is to investigate the effects of TSA on the intrinsic apoptotic pathway (Bid, BimEL, Noxa, Bcl-xL, RIP, Mcl-1, XIAP), p21/Waf1/Cip1 (p21), p53, and histone deacetylases (HDACs) 1, 2 and 3 in human neuroblastoma LAN-1, human glioblastoma GBM-29, human HCC SMMC7721, and human colon cancer COLO 201 cell lines.

Materials and Methods

Materials

Neuroblastoma LAN-1, human glioblastoma GBM-29, human HCC SMMC7721, and human colon cancer COLO 201 cell lines were purchased from the National Cell Bank of Iran-Pasteur Institute. The TSA, kits and materials were obtained as provided for our previous works (21, 22). TSA was dissolved in dimethyl sulfoxide (DMSO) and prepared a work stock solution. The cells were maintained as explained in our previous works (21, 22).

Cell culture and cell viability

The LAN-1, GBM-29, SMMC7721, and COLO 201 cells were cultured in conditions similar to those mentioned previously (21, 22). The LAN-1 and GBM-29 cells were treated with TSA (0, 25, 50, 75, 100, and 200 nM), and the SMMC7721 and COLO 201 cells were treated with TSA (0, 1, 2.5, 5, 10, and 20 μM) for 24 hours except in the control groups; the control cells were treated with the equal amounts of DMSO as a solvent. After 24 hours, the cell viability was determined by the MTT assay according to the standard protocols. Finally, the optical density was detected by a microplate reader at the wavelength of 570 nM.

Cell apoptosis assay

To determine LAN-1, GBM-29, SMMC7721, and COLO 201 cell apoptosis, the cells were seeded at the density of 3 × 105 cells per well and incubated for 24 hours. Then, the cells were treated with TSA based on IC50 values for 24 hours except in the control groups; the control cells were treated with the equal amounts of the DMSO solvent. Subsequently, as in our previous study

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(13), the apoptotic cells were investigated by flow cytometry.

Real-time Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

The qRT-PCR was done to determine the relative expression levels of the Bid, BimEL, Noxa, Bcl-xL, RIP, Mcl-1, XIAP, p21, p53, and HDACs 1 2, and 3 genes. The LAN-1, GBM-29, SMMC7721, and COLO 201 cells were cultured at the density of 3×10^5 cells per well and treated with TSA for 24 hours. This was done based on the concentrations and IC50 values demonstrated in Table I. The control groups were treated with the solvent. Then, qRT-PCR was done as in our previous work (13). The primer sequences (23-30) are indicated in Table II.

Ethical Consideration

This study was supported and approved by the Ethics Committee of Jahrom University of Medical Science. The ethics certificate code number is IR.JUMS.REC.1399.078.

Results

Cell viability

The viability of the LAN-1, GBM-29, SMMC7721, and COLO 201 cells treated with TSA was evaluated with the MTT assay as explained in Section 2. As indicated in Figure 1, TSA could induce significant cell growth inhibition in all the cell lines in a dose-dependent manner ($P < 0.0001$).

Cell apoptosis assay

To identify the apoptotic cells, LAN-1, GBM-29, SMMC7721, and COLO 201 cells were treated with TSA for 24 hours and then stained with annexin-V-(FITC) and PI. As indicated in Figures 2, 3 and 4 (part A), TSA induced cell apoptosis significantly ($P < 0.0001$). In addition, the LAN-1 cell line was more sensitive to TSA than the other cell lines, and the percentage of the apoptotic cells in it was more than that in the other cell lines (Figure 4, part B). Based on the statistical analysis, a significant difference existed between the experimental (treated) and the control (untreated) groups (Figure 4, part C3).

Gene expression

The result of qRT-PCR indicated that TSA could increase the expression levels of Bid, BimEL, Noxa, p21, and p53 genes and decrease those of Bcl-xL, RIP, Mcl-1, XIAP, HDACs 1, 2 and 3 significantly (Figure 5).

Table I: IC50 values of TSA was determined by MTT assay in different cell lines including LAN-1, GBM-29, and SMMC7721.

Cell line	Duration (in hours)	IC50 value	LogIC50	R squared
LAN-1	24	61.48 nM	1.789	0.9818
GBM-29	24	81.64 nM	1.911	0.9817
SMMC7721	24	4.726 µM	0.6745	0.9224
COLO 201	24	4.906 µM	0.6903	0.6567

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Table II: The primer sequences of Bid, BimEL, Noxa, Bcl-xL, RIP-1, Mcl-1, XIAP, p21, p53, and HDACs 1, 2 and 3

Primer	Primer sequences (5' to 3')	Product lent/bp	Reference
Bid		169	23
Forward	TGGTGTTTGGCTTCCTCCAA		
Reverse	GAATCTGCCTCTATTCTTCCC		
BimEL		100	23
Forward	GAGCCACAAGACAGGAGC		
Reverse	CCATTGCACTGAGATAGTGG		
Bcl-xL		220	23
Forward	GCGACGACTTCTCCCGC		
Reverse	GCGATGTTGTCCACCAGG		
Noxa		233	24
Forward	ATGAATGCACCTTCACATTCCTCT		
Reverse	TCCAGCAGAGCTGGAAGTCGAGTGT		
RIP1		106	25
Forward	AGAAAGTGTAGAAGAGGACGTG		
Reverse	AGGTACTGCCACACAATCAAG		
Mcl-1		79	26
Forward	GGGCAGGATTGTGACTCT CATT		
Reverse	GATGCAGCTTTCTTGGTTTATGG		
XIAP		368	27
Forward	GTGACTAGATGTCCACAAGG		
Reverse	GTTGAGGAGTGTCTGGTAAG		
p21		270	28
Forward	AAGACCATGTGGACCTGTCACTGT		
Reverse	AGGGCTTCCTCTTGGAGAAGATCA		
P53		121	28
Forward	TAACAGTTCCTGCATGGGCGGC		
Reverse	AGGACAGGCACAAACACGCACC		
HDAC1		374	29
Forward	AACCTGCCTATGCTGATGCT		
Reverse	CAGGCAATTCGTTTGTCAGA		
HDAC2		314	29
Forward	GGGAATACTTTCCTGGCACA		
Reverse	ACGGATTGTGTAGCCACCTC		
HDAC3		328	29
Forward	TGGCTTCTGCTATGTCAACG		
Reverse	GCACGTGGGTTGGTAGAAGT		
GAPDH		172	30
Forward	GAAGGTGAAGGTCGGAGTC		
Reverse	GAAGATGGTGATGGGATTTC		

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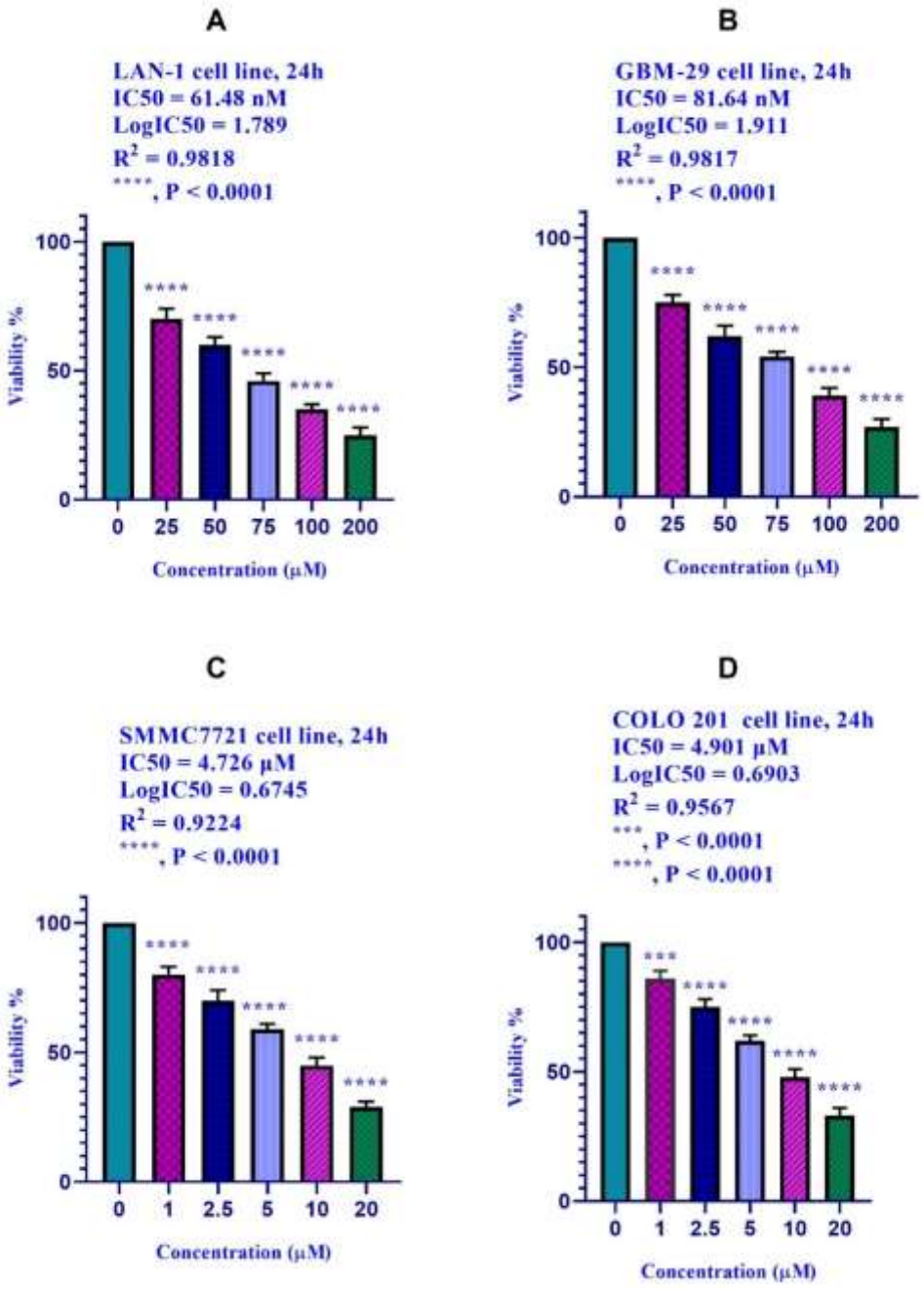

Figure 1. The effect of TSA on LAN-1, GBM-29, SMMC7721, and COLO 201 cell viability: Each experiment was conducted in triplicate. The mean values from the three experiments are reported with ± standard errors of the mean. An asterisk (*) indicates a significant difference between the experimental and the control groups. Ic50s and P values are also shown in parts A, B, C and D.

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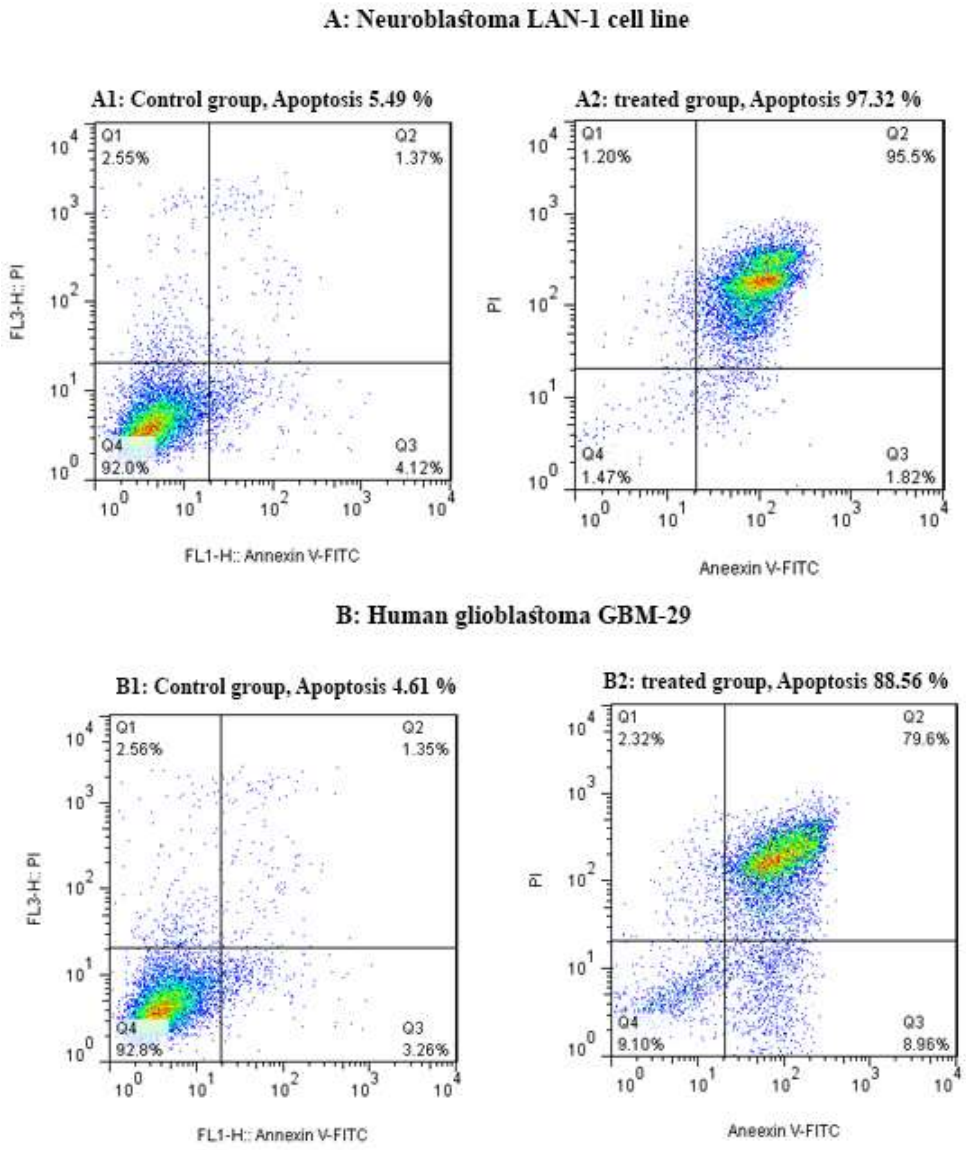

Figure 2. The apoptotic effect of TSA on LAN-1 and GBM-29 cell lines: TSA was demonstrated to induce significant cell apoptosis after 24 hours of treatment.

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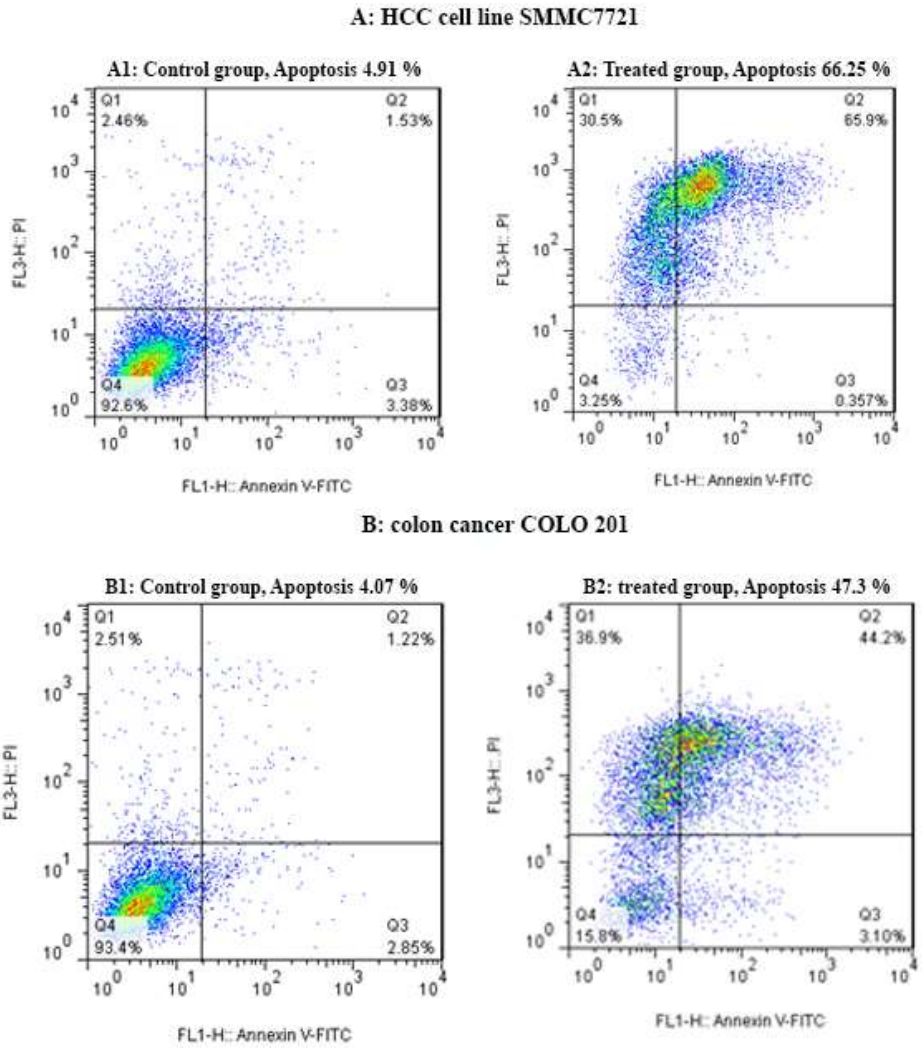

Figure 3. The apoptotic effect of TSA on SMMC7721 and COLO 201 cell lines: The results indicated that TSA could induce a significant cell apoptosis after 24 hours.

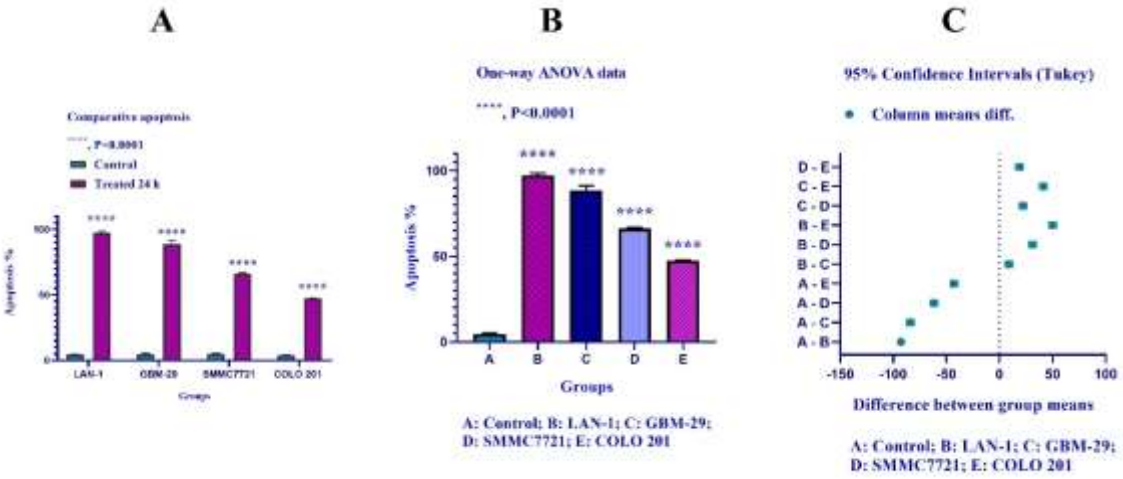

Figure 4. The apoptotic effect of TSA on LAN-1, GBM-29, SMMC7721, and COLO 201 cell lines: TSA induced significant cell apoptosis in all the cell lines after 24 hours of treatment (A). Also, the LAN-1 cell line was more sensitive to TSA than the other cell lines (B). Based on the statistical analysis, there was a significant difference between the experimental and the control groups (C).

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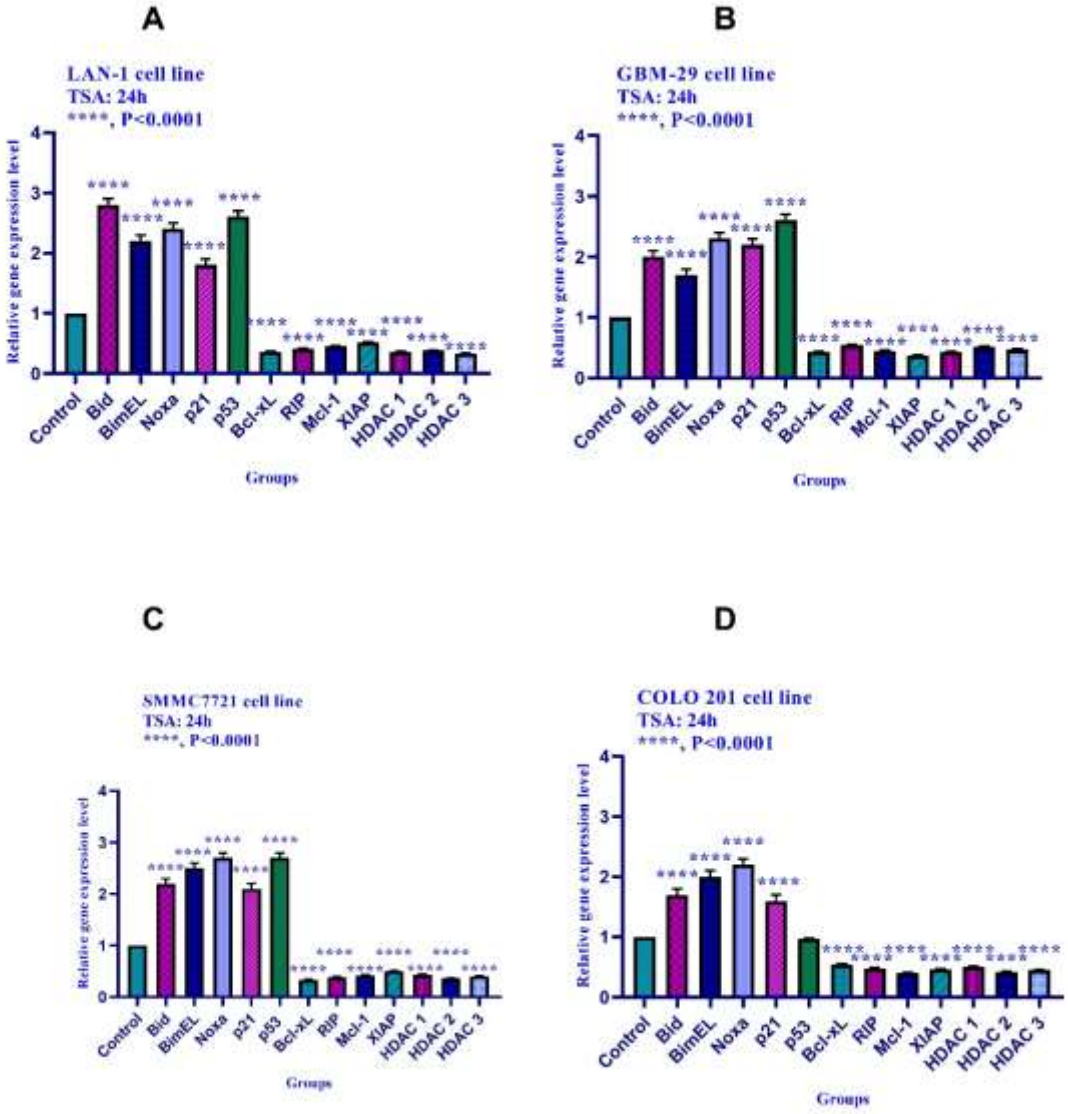

Figure 5. The relative expression levels of Bid, BimEL, Noxa, Bcl-xL, RIP, Mcl-1, XIAP, p21, p53, and HDACs 1, 2 and 3 genes in the LAN-1, GBM-29, SMMC7721, and COLO 201 cells treated with TSA versus control groups: As indicated, there were significant differences between the experimental and the control groups. An asterisk (*) indicates a significant difference. $P < 0.0001$.

Discussion

Several molecular apoptotic pathways have been reported for HDACIs, one of which is the intrinsic/mitochondrial pathway. Recent experimental works have shown that these compounds enhance mitochondrial apoptosis in a p53-dependent manner in the medulloblastoma cell line (31). In this regard, it has been shown that HDACIs activate the intrinsic apoptotic pathway via the upregulation of several Bcl-2 family genes (32). As observed in this study, TSA induced significant apoptosis and cell growth inhibition in all the treated cell lines. This compound up-regulated the expression levels of Bid, BimEL, Noxa, p21, and p53 genes but down-regulated the expression levels of Bcl-xL, RIP, Mcl-1, XIAP, HDACs 1, 2 and 3 significantly. According to the findings of the present study, TSA can induce cell apoptosis via a

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mitochondrial (intrinsic) apoptotic pathway in LAN-1, GBM-29, SMMC7721, and COLO 201 cell lines. Furthermore, TSA had no significant effect on the p53 gene expression in colon cancer COLO 201line. Previously, we reported that valproic acid and TSA could induce apoptosis through the inhibition of histone deacetylase 1 and the re-activation of CIP/KIP family genes (p21, p27, and p57) in the SW480 colon cancer cell line [15]. In the present study, TSA was found to induce apoptosis by regulating the intrinsic apoptotic pathway, p21/Waf1/Cip1, and p53 in human neuroblastoma, glioblastoma, hepatocellular carcinoma, and colon cancer cell lines. Inconsistent with this finding, several researchers have reported that TSA plays its role by up-regulating the expression of pro-apoptotic genes (such as BIM) and down-regulating anti-apoptotic genes in the pancreatic cancer cell lines HPAF, CFPAC1, Panc1 PC, PSN1, Miapaca2, RT45P1, Paca44, and T3M4 (33). Similarly, it has been shown that TSA mediates its apoptotic effect via the mitochondrial pathway in the human prostatic cancer DU145 cell line (34). The same effect has been reported for sodium butyrate (NaBt), as another histone deacetylases inhibitor in pancreatic cancer cell lines (ASPC-1 and PANC-1) (35). Regarding the lung cancer H157 cell line, a decreased expression of anti-apoptotic proteins has been observed in TSA-treated cells (36). In the lung cancer H157 cell line, TSA triggers apoptosis by activating the intrinsic pathway along with the Fas/FasL system and the extrinsic pathway along with mitochondrial dysfunction (37). In MM1S myeloma cells, TSA treatment down-regulates the expression of the anti-apoptotic Bcl-2 proteins (38). Similar to our results, it has been reported that HDACIs activate the mitochondrial pathway in neuroblastomas (39). They induce apoptosis in human glioblastoma cells with a decrease in the anti-apoptotic BcL-x1 protein and an increase in the pro-apoptotic factor (40). Besides, Apoptosis is induced via the mitochondrial pathway by a shift in the bax/bcl-2 ratio in HCC (41).

As reported in this article, TSA up-regulated the p53 gene expression in LAN-1, GBM-29, and SMMC7721 cell lines, whereas it had no significant effect on this gene in the COLO 201 cell line. It means that TSA can play its role through two apoptotic pathways, including p53-dependent, and independent pathways. Additionally, a minimal apoptotic effect was seen in the COLO 201 cell line. It may be concluded that TSA can induce a strong apoptotic effect through a p53-dependent pathway.

Contrary to our results, several experimental studies have reported that HDACIs can induce apoptosis through the activation of the extrinsic apoptotic pathway (42). Meanwhile, numerous in vivo studies have shown that HDACIs mediate their apoptotic effects via both the intrinsic and extrinsic apoptotic pathways in the colon, breast, hematopoietic, central nervous system, melanoma, lung, ovarian, renal, prostatic, and stomach cancer cell lines (43).

Taken together, HDACIs can affect cell apoptosis through extrinsic and intrinsic pathways. Therefore, the evaluation of the extrinsic apoptotic pathway on human neuroblastoma LAN-1, human glioblastoma GBM-29, human HCC SMMC7721, and human colon cancer COLO 201 cell lines is recommended.

Conclusion

In summary, our findings demonstrated that TSA can play its apoptotic role via an intrinsic (mitochondrial) apoptotic pathway in human neuroblastoma LAN-1, human glioblastoma GBM-29, human HCC SMMC7721, and human colon cancer COLO 201 cell lines. Furthermore, it induces apoptosis through both p53-dependent and independent pathways.

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Conflict of interest
The authors declare no conflict of interest.

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