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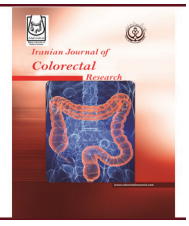

Salinomycin Triggers Human Colorectal Cancer HCT116 Cell Death by Targeting Unfolded Protein Responses and Autophagy Pathways

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Abstract

Background: Autophagy and the unfolded protein response (UPR) are important pathways in colorectal tumorigenesis and drug resistance, rendering them as potential therapeutic targets for treating this cancer. As an ionophoric polyether antibiotic, salinomycin has anti-cancer effects and overcomes drug resistance in cancer cells. Considering the minimal information on the molecular action mechanism of salinomycin in colorectal cancer (CRC), this study was designed to investigate the effect of this compound on autophagy and UPR pathways in CRC cells.
Methods: The in vitro cytotoxicity of salinomycin on CRC cell line HCT116 was determined using the MTT assay by treating the cells with different concentrations of salinomycin for 24 and 48 h. The gene expression analysis of three main autophagy biomarkers (*Beclin1*, *LC3,* and *P62*) and two UPR biomarkers (*XBP-1s* and *CHOP*) was performed using quantitative real-time polymerase chain reaction (RT-PCR). Data were analyzed with GraphPad Prism 8 software.
Results: Salinomycin had cytotoxic effects on HCT116 cells in a time- and dose-dependent manner. The expression analysis of the UPR and autophagy-related genes showed UPR activation at both 24 h and 48 h (increase of *XBP-1s* and *CHOP*), autophagy activation at 24 h (increase of *Beclin 1*, *LC3II,* and decrease of *P62*), and autophagy flux inhibition at 48 h (increase of *Beclin 1*, *LC3II* and *P62*).
Conclusion: The anti-cancer activity of salinomycin against the HCT116 cell line seems to be through triggering cell death by targeting UPR and autophagy pathways. Further studies are required to confirm our results.

Keywords: Salinomycin, Colorectal cancer, Autophagy, Unfolded protein response

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Introduction

The enhanced prevalence of colorectal cancer worldwide and increased drug resistance have made this disease a significant health concern (1). Different molecular signaling pathways are involved in colorectal tumorigenesis and drug resistance. The unfolded protein response (UPR) and autophagy are among these mechanisms (2).

The UPR is an adaptive mechanism related to the endoplasmic reticulum (ER), which is activated in response to cellular stresses like hypoxia and starvation. Three ER transmembrane protein sensors that mediate the UPR include pancreatic ER eIF2α kinase (PERK), activating transcription factor 6 (ATF6), and inositol requiring kinase 1 (IRE1) (3). In normal conditions, the main ER chaperone, glucose-regulating protein 78 (GRP78), binds to and suppresses the above three arms. However, the accumulation of unfolded or misfolded proteins during stress conditions perturbs ER homeostasis and triggers UPR by separating GRP78 from these arms (4). Activated PERK phosphorylates eukaryotic initiation factor 2α (eIF2α), which induces CCAAT/Enhancer-Binding Protein Homologous Protein (CHOP). The Xbox binding protein (XBP1) transcription factor is induced by activated IRE1 and upregulates UPR stress genes. After GRP78 release, ATF6 also translocates to the Golgi and is cleaved by proteases. Finally, it forms an activated transcription factor to upregulate UPR-related genes (3). As the downstream signaling of the UPR, the expression of chaperones is increased to assist protein folding, and the protein load of the ER is decreased by translation attenuation and mRNA degradation (4).

As a lysosome-dependent mechanism, autophagy is also induced under stress conditions, promoting the degradation and recycling of dysfunctional cellular components. During autophagy, defective organelles and proteins are engulfed in a vesicle structure called an autophagosome. The fusion of an autophagosome with a lysosome makes an autolysosome in which the compounds are degraded by lysosomal enzymes (5). Different signaling molecules regulate autophagy, which can be used as the biomarkers of this pathway. Examples include autophagy-related gene (ATG) proteins, Beclin1, LC3B, and P62. Beclin1 is a marker of autophagy initiation (6).

Microtubule-associated protein 1 light chain 3B (LC3) plays a critical role in autophagosome maturation. ATG proteins promote LC3 to LC3II conversion, which is a marker of autophagy flux. The autophagy substrate, sequestosome-1 (SQSTM1/P62), is another indicator of autophagy flux, which induces the degradation of ubiquitinylated protein substrates (5). Activation of UPR and autophagy maintains cellular homeostasis during stresses. However, under severe continuous stresses, downstream signaling causes the cells to undergo autophagy-mediated cell death and apoptosis (CHOP/JNK pathway) (7). These pathways work as double edge swords in tumor cells. On the one hand, they cause the adaptation of tumor cells to adverse conditions of hypoxia, nutrient deprivation, and acidosis, and contribute to tumor growth and survival. On the other hand, they activate tumor cell death signaling. These dual roles make autophagy and UPR potential therapeutic targets for cancer treatment (8, 9). In this regard, the anti-cancer effects of different compounds, which activate or inhibit these pathways, have been studied in different cancer types.

Salinomycin is an ionophoric polyether antibiotic that is produced by *Streptomyces albus* (10). The anti-cancer stem cell effect of salinomycin was first described by Gupta et al. in 2009 (11). Then, various studies described the anti-cancer effects of this compound in different malignancies such as brain (12), lung (13), liver (14), breast (15), prostate (16), and colorectal cancers (17). Interestingly, salinomycin was able to overcome drug resistance and sensitize cancer cells to chemotherapeutic agents such as cisplatin (18), temozolomide (19), doxorubicin (20), and gemcitabine (21). In some previous studies, the effect of salinomycin on autophagy activation and cell death has been reported in breast (22, 23), melanoma (24), glioma (25), colorectal (23), and non-small cell lung cancer (NSCLC) cells (26). Salinomycin also activated the UPR pathway in bladder (27), prostate (16), and breast cancer cells (28).

Considering the importance of the UPR pathway in colorectal tumorigenesis and drug resistance and the low information content on the effect of salinomycin on this pathway, we aimed to explore the role of salinomycin in the UPR pathway in HCT116 CRC cells. We also evaluated the autophagy pathway following salinomycin treatment in HCT116 cells.

Materials and Methods

Cell Culture

The CRC cell line HCT116 was purchased from the National Cell Bank of Iran (Pasteur Institute, Tehran, Iran). Cells were cultured in RPMI 1640 medium containing 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin in a humidified CO2 (5%) incubator at 37 °C.

MTT Cytotoxicity Assay

Salinomycin's in vitro anti-proliferative activity on the HCT116 cell line was assessed using the standard MTT assay according to the previously described protocol (29). In brief, HCT116 cells were seeded into 96 well plates (2×10^3 cells/well). After reaching 80% confluency, the cells were treated with salinomycin in the concentration range of 0.1 to 1000 µM for 24, 48, and 72 hours (h). Then, cells were incubated with MTT reagent (5 mg/ml, 20 µM) for 4 h, and absorbance was measured at 570 nm using an ELISA reader (Mikura Ltd.). Finally, the half-maximal inhibitory concentration (IC50) values were determined through cell-survival plots.

Gene Expression Analysis

To evaluate the effect of salinomycin on autophagy- and UPR-related genes, the quantitative real-time polymerase chain reaction (RT-PCR) was applied. For this purpose, cells were treated with desired concentrations of salinomycin (1 and 10 µM) for 24 and 48 h. Then, according to the manufacturer's instructions, total RNA was extracted using the RNX-Plus RNA extraction kit (Cinnagen, Iran). The purity and concentration of the isolated RNA were determined by the optical density (260/280 nm ratio) using the NanoDrop spectrophotometer (Thermo Scientific, USA). The integrity of the obtained RNA was also assessed by gel electrophoresis under denaturing conditions. The cDNA was synthesized using a cDNA Synthesis Kit (Thermo Fisher Scientific, USA). Finally, SYBR green-based RT-qPCR (Amplicon, USA) was applied for gene amplification using specific primers (metabion, Germany) (Table 1) and by the ABI real-time PCR 7500 system.

Statistical Analysis

Data were analyzed by GraphPad Prism 8 software (GraphPad Prism, RRID: SCR_002798) using one-way or two-way ANOVA followed by Tukey's or Bonferroni's post-hoc test.

Data are described as mean±standard deviation (SD) of three replicates (n=3). A P value<0.05 was considered significant.

Results

The Cytotoxicity of Salinomycin on HCT-116 Cells

The antiproliferative activity of salinomycin was evaluated by the MTT assay after treatment of HCT116 cells with different concentrations of the salinomycin (0.1, 1, 10, 50, 100, and 1000 µM). The results indicated that salinomycin significantly induced HCT116 cell death in a time- and dose-dependent manner. According to Figure 1, salinomycin concentrations of 1 and 10 µM and exposure times of 24 h and 48 h were selected as proper doses and exposure times for subsequent experiments.

The Effect of Salinomycin on the UPR Pathway in HCT116 Cells

To understand the effect of salinomycin on the UPR pathway, the mRNA levels of two UPR-related genes including the C/EBP homologous protein (CHOP) and spliced X-box binding protein 1 (XBP-1s) were determined by RT-PCR. As illustrated in Figure 2, 1 µM and 10 µM salinomycin significantly increased the *CHOP* expression compared to the time-matched control after 24 h (by 1.94- and 2.81-folds, respectively) and 48 h (by 3.55- and 5-folds, respectively). Salinomycin also significantly increased *XBP-1s* expression at concentrations of 1 µM and 10 µM after 24 h (by 2.97- and 3.46-folds, respectively) and 48 h (by 3.56- and 4.66-folds, respectively) compared with the control group.

The Effect of Salinomycin on the Autophagy Pathway in HCT116 Cells

To investigate the effect of salinomycin on the autophagy pathway, HCT116 cells were treated with 1 and 10 µM salinomycin for 24 and 48 h, after which the mRNA levels of autophagy biomarkers *Beclin1*, *LC3,* and *P62* were assessed using RT-PCR.

Table 1: The primer sequences of autophagy and unfolded protein response (UPR) markers

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
LC3 βII	AACGGGCTGTGTGAGAAAAC	AGTGAGGACTTTGGGTGTGG
P62	AATCAGCTTCTGGTCCATCG	TTCTTTTCCCTCCGTGCTC
Beclin-1	AGCTGCCGGTTATACTGTTCTG	ACTGCCTCCTGTGTCTTCAATCTT
CHOP	GCTCTGATTGACCGAATGG	TTCTGGGAAAGGTGGGTAG
XBP-1s	TGCTGAGTCCGCAGCAGGTG	GCTGGCAGGCTCTGGGGAAG-
GAPDH	CGACCACTTTGTCAAGCTCA	AGGGGTCTACATGGCAACTG

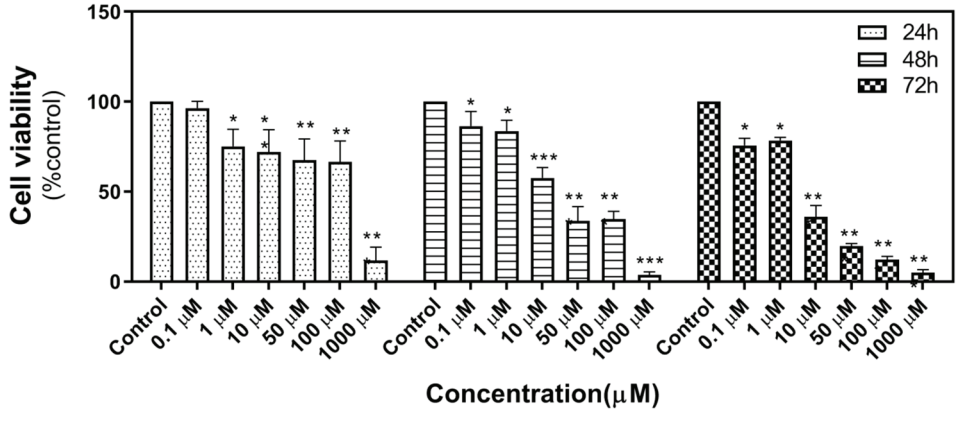

Figure 1: The effect of salinomycin on the growth of HCT-116 colon cancer cells. The cells were exposed to different concentrations of salinomycin for 24 h, 48 h, and 72 h. Cell viability was assessed by the MTT assay. Data are reported as mean±SD of three independent assays (n=3, *P<0.05; **P<0.01; ***P<0.001).

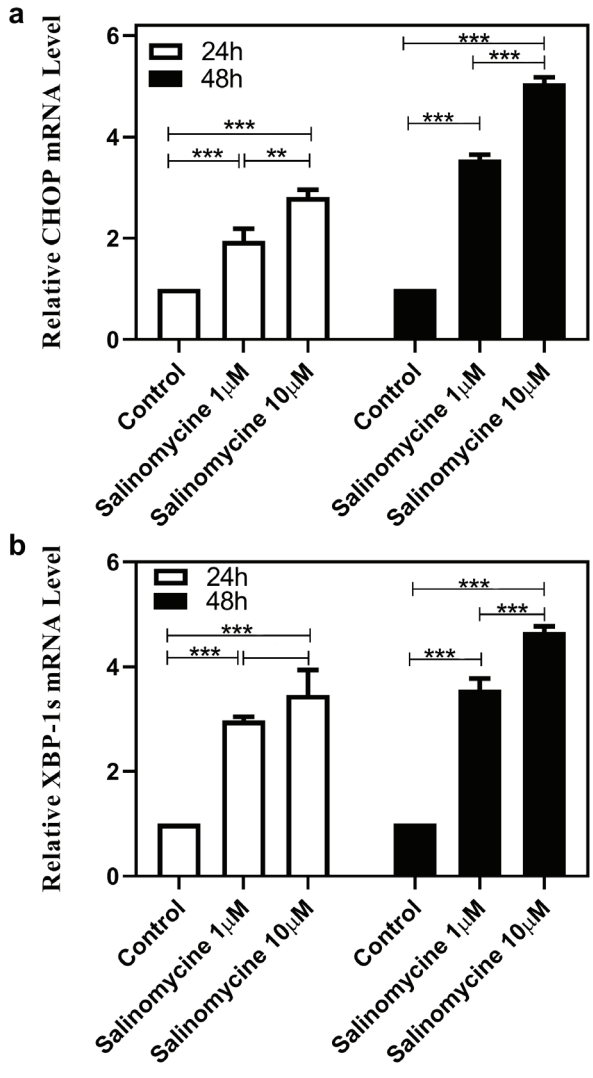

Figure 2: The relative mRNA expression levels of *CHOP* (a) and *XBP-1s* (b) in HCT-116 cells after 24 and 48 h of treatment with salinomycin. Salinomycin increased the expression levels of *CHOP* and *XBP-1s*. Data are reported as mean±SD of three independent assays (n=3, *P<0.05; **P<0.01; ***P<0.001).

As presented in Figure 3, in HCT116 cells treated with 1 and 10 µM salinomycin, the mRNA expression of *Beclin-1* increased significantly compared with the control after 24 h (1.21- and 1.45-folds, respectively) and 48 h (2.26- and 3.27-folds, respectively) (Figure 3a). *LC3βII* expression also significantly increased with 1 and 10 µM salinomycin after 24 h (1.16- and 1.3-folds, respectively) and 48 h (1.55- and 2.2-folds, respectively) (Figure 3b). In addition, the *P62* mRNA level fell with 1 and 10 µM concentrations (0.48- and 0.3-folds, respectively) at 24 h compared with the time-matched control. However, significant enhancement of *P62* expression was observed at 1 and 10 µM concentrations of salinomycin after 48 h (3.21- and 4.6-folds, respectively) (Figure 3c).

Discussion

This study described a time- and dose-dependent cytotoxic effect of salinomycin on the human CRC HCT116 cell line. Increased levels of UPR biomarkers *CHOP* and *XBP-1s* were seen after 24–48 hours of treatment with salinomycin. The increase of *Beclin1* and *LC3II* and decrease of *P62* also indicated the activation effect of salinomycin at 24h after treatment. However, the increase of *Beclin1*, *LC3II,* and *P62* indicated the inhibitory effect of salinomycin on autophagy flux at 48 h of treatment. To our knowledge, this is the first description of salinomycin's effect on the UPR and autophagy pathway in the CRC HCT116 cell line.

Available evidence illustrates the important roles of UPR and autophagy pathways in tumorigenesis, cancer progression, metastasis, and drug resistance (30-32). However, few studies have addressed the effect of salinomycin on the UPR pathway. In this regard, Yu et al. described the salinomycin-mediated induction of ER stress, UPR, and apoptosis by suppressing Nrf2 signaling in prostate cancer cells (16). Yuan and colleagues also revealed that salinomycin suppressed lysine (K)-specific demethylase 1A (KDM1A) expression and bladder tumor growth and activated the UPR and apoptosis in the T24 cell line (27). Salinomycin also suppressed the breast stem-like cancer cells by induction of ER Ca^{2+} release, ER stress, and UPR activation (28). Similarly, our results are consistent with the above studies, and salinomycin treatment activated the UPR pathway in the CRC HCT116 cells.

Salinomycin's role in autophagy activation has also been demonstrated in previous studies. Accordingly, in a study on non-small cell lung cancer (NSCLC) cells, salinomycin activated endoplasmic reticulum

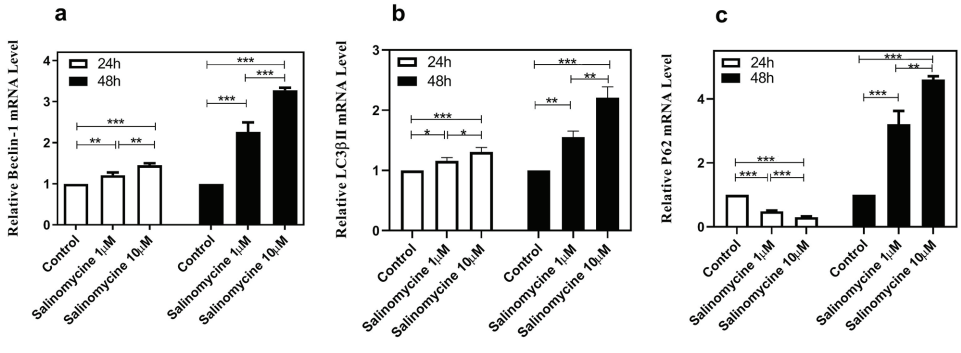

Figure 3: The relative mRNA expression levels of *Beclin-1* (a), *LC3βII* (b) and *P62* (c) in HCT-116 cells after 24 and 48 h of treatment with salinomycin. Salinomycin induced the expression levels of *Beclin-1*, *LC3βII,* and *P62*. Data are reported as mean±SD of three independent assays (n=3, *P<0.05; **P<0.01; ***P<0.001).

stress and autophagy by inhibiting the AKT1/mTOR pathway, which finally led to autophagy-mediated cell death (26). Activation of autophagy has also been reported in CRC (SW620) and breast cancer (MCF-7) cell lines (23). Salinomycin also induced endoplasmic reticulum stress, autophagy, and apoptosis in glioma cell lines (25).

Consistent with the above-mentioned studies, we observed autophagy activation in the HCT116 cell line at 24 h following treatment with salinomycin. Although the increase in *Beclin 1* indicated autophagy induction at 48 h after salinomycin treatment, the increase of *P62,* along with the increase of *LC3,* indicated suppression of the late stage of autophagy (autophagy flux). The inhibitory effect of salinomycin on autophagy flux has also been reported in previous studies. In this regard, salinomycin maintained and expanded the progenitor phenotype of breast cancer stem cells and inhibited their tumorigenicity by inhibiting autophagy flux (22). The salinomycin-mediated inhibition of autophagy flux and autophagic cell death was also observed in melanoma cell lines (24).

Inhibition of autophagy flux at 48 h after salinomycin treatment, along with the activation of *CHOP* in the UPR pathway, may indicate the role of salinomycin in mediating HCT116 cell death/apoptosis. In summary, according to the available evidence and the results of the present study, it seems that UPR and autophagy-mediated cell death can be considered as the mechanisms to explain the anti-cancer effects of salinomycin in the CRC HCT116 cell line.

Conclusion

Salinomycin presented anti-CRC activity against the HCT116 cell line in a time- and dose-dependent manner. The UPR and autophagy may be considered the main signaling pathways targeted by this antibacterial compound in CRC cells. Further in vivo studies will contribute to a better understanding of the exact action mechanism of salinomycin in CRC and confirm our results.

Authors' Contribution

The conception and design of the study: P.M. Acquisition of data: M.Z., M.S. Analysis and interpretation of data: M.S., S.D., M.Z. Drafting the article and revising it critically for important intellectual content: M.Z., P.M. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest: None declared.

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