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ORIGINAL STUDY

Resveratrol and IL-6 Modulation of CXCL1 Expression and Viability in Human Breast Cancer Cell Lines

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ABSTRACT

This study aims to investigate, through in vitro methods, the molecular, immunofluorescent, and immunohistochemical effects of resveratrol and IL-6 on CXCL1 gene/protein expression in human breast cancer cells (MCF-7). MCF-7 and MCF-10A cell lines were cultured and divided into four groups: control, IL-6-treated, resveratrol-treated, and a combination-treated group. CXCL1 gene expression was assessed by real-time PCR (RT-PCR), while CXCL1 protein levels were analyzed using immunofluorescence and immunohistochemistry. Cell viability was quantified by MTS assay using ELISA. CXCL1 gene/protein was overexpressed in MCF-7 cells, especially in the IL-6-treated group, but reduced in both resveratrol and combination-treated groups. MTS assay showed increased cell viability in all IL-6 concentrations compared to control, with the highest value at 300 μM. Immunofluorescence revealed a significant increase in CXCL1 protein in the IL-6-treated group and a decrease in the resveratrol and combination groups. Immunohistochemistry confirmed that CXCL1 protein levels significantly declined in MCF-7 cells treated with resveratrol alone or in combination with IL-6, compared to untreated control cells. These findings indicate that IL-6 upregulates, while resveratrol downregulates, CXCL1 expression in breast cancer cells. Further research is recommended to assess the long-term safety and effects of IL-6 and resveratrol in mammals, as comprehensive safety data for prolonged use remain incomplete.

Keywords: MCF-7, RT-PCR, Cell viability assay, CXC chemokine family, Iraq

1. Introduction

Scientific researchers have studied resveratrol, as a naturally occurring polyphenolic compound, widely due to its ability to bind to numerous molecular targets throughout the body and exert diverse biological activities [1]. The sirtuin 1 (SIRT1) activation mechanism by resveratrol is emerging as a promising candidate for the prevention of processes that trigger endothelial dysfunctions [2]. Subsequently, the biological processes, circadian rhythms, endothelial functions, inflammation-immune function, cellular senescence, cell survival, and metabolism stress resistance have been altered by SIRT1 by its action of deacetylation on both histones and transcription factors and additional non-histone proteins [3]. The key barrier to applying *in vitro* resveratrol results in practical medical applications stems from its inadequate absorption properties through oral pathways [4]. Also, the anti-pathological effects of resveratrol include a protective role against inflammation together with cancer prevention and reduced occurrence of heart diseases [5]. However, the poor oral availability of resveratrol creates an issue between its high *in vitro* cell-based effectiveness and its minimal *in vivo* body response because the substance quickly breaks down inside the body [6].

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Interleukin-6 (IL-6) plays a complex role in the progression of various cancers, including colorectal, prostate, ovarian, and lung cancers, by promoting chronic inflammation, tumor cell proliferation, angiogenesis, and metastasis [7]. Elevated IL-6 levels are often associated with poor prognosis and resistance to therapy [7]. Resveratrol, on the other hand, has demonstrated anti-cancer activity across multiple cancer types by modulating pathways such as NF-κB, STAT3, and PI3K/AKT [8]. Several studies have also reported that resveratrol can inhibit IL-6-mediated signaling, thereby reducing inflammatory responses and tumor progression in models of lung, gastric, and prostate cancers [9]. However, limited studies have explored the direct interaction between IL-6 and resveratrol in breast cancer specifically, making this investigation particularly relevant [10].

The pleiotropic cytokine known as interleukin-6 operates as an intricate regulatory agent for diverse physiological functions because it executes both the pro-inflammatory and anti-inflammatory effects depending on particular situational contexts throughout target cell types [11]. As an essential inflammatory mediator, IL-6 activates numerous physiological processes which protect against infections and tissue injuries through acute phase reactions and modified immunological and hematopoietic activities [12]. The biological activities of IL-6 function occur through interactions with two essential molecules to regulate cellular processes that include lymphocyte chemokine and adhesion molecule production as well as liver cell acute-phase protein induction and blood neutrophil elevation [13–15]. The pathogenesis of several immune-mediated diseases shows IL-6 dysregulation because it acts as both a protective substance and as a damaging factor [16]. In addition, IL-6 has great roles in maintaining autoimmune processes by facilitating B-cell maturation and TH-17 differentiation which consolidates its significance in the development of various diseases [17]. Worldwide, anticancer therapy has been studied by thousands of preclinical researchers; however, little advance was made in clinical trials. Therefore, this study aims to *in vitro*, molecular and histological indications of the anti-cancer effects of resveratrol and IL-6 through modulation of CXCL1 in MCF-7 cells.

Human breast cancer manifests as an intricate condition that leads to uncontrolled proliferation in mammary epithelial cells. Worldwide, human breast cancer appears as the second reason causing mortality among women demanding early detection systems, effective and immediate treatment methods, and enhanced preventive measures [18–20]. The CXCL1 gene is a member of the CXC chemokine family which plays a pivotal role in growth stimulatory activity, neutrophil-activating protein 3, inflammation, angiogenesis, and tumorigenesis [21, 22]. The increased levels of the CXCL1 gene can foster the microenvironment conducive to the development and progression of tumours, supporting the recruitment of inflammatory immune cells, and directly promoting tumour cell proliferation and survival [23, 24]. In this study, findings revealed a higher level of CXCL1 gene expression in tumour MCF-7 cells when compared to normal MCF-10A cells. In comparison with the findings of other studies, Zou et al. [25] found that overexpression of CXCL1 in breast cancer is related to poor prognosis of a patient since it is associated with decreased patient survival, disease recurrence, and tumour grade. *In vivo*, breast cancer xenografts confirmed that CXCL1 silencing in tumour-related macrophages can result in a marked decrease in growth and metastatic burden of breast cancer; while, the overexpression of CXCL1 in breast cancers might cause basal-like subtype, metastasis to lymph nodes, and poor overall survival [26]. Korbecki et al. [27] described the clinical importance and role of the CXCL1 gene in the cancer process among various types of cancer and demonstrated molecularly the contribution of the CXCL1 gene to radioresistance and chemoresistance in selected cancers.

2. Materials and methods

2.1. Cell culture

As described by other studies, MCF-7 and MCF-10A cells were cultured in supplemented RPMI 1640 and DMEM media, respectively, incubated at 37°C in the presence of 5% CO_2, and they achieved on sub-confluent monolayers [28–30].

2.2. Cell viability assay (MTS assay)

To determine the viability of MCF-7 and MCF-10A cells, the CellTiter 96® AQueous One Solution Cell Proliferation Assay kit was used as the manufacturer's protocol. The absorbance was measured at 490 nm using an ELISA plate reader. For experiments involving resveratrol, DMSO was used as the solvent. Control cells for these experiments received an equivalent volume of DMSO (final concentration: 0.1%) to account for any solvent-related effects. All treatments were performed in triplicate (n = 3).

2.3. RNA isolation

Total RNA was extracted from MCF-7 and MCF-10A cells using TRIzol™ Reagent (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA), following the manufacturer's instructions. The collected supernatant was kept in a new tube [31].

2.4. RT-PCR

Cells were treated with IL-6 (100 ng/mL), resveratrol (100 μM), or a combination of both for 24 hours. Following treatment, total RNA was extracted and CXCL1 mRNA expression was quantified via RT-PCR. Each experimental condition was performed in triplicate (n = 3). Following the manufacturer instructions of iScript cDNA Synthesis Kit, RNA was used to synthesize cDNA, which was amplified using two sets of primers [Human-*CXCL1* (F: 5′-ATC CCT CAA AGT TCA GTG T-3′) and (R: 5′-ACG GTT GAG GTA GTC TGA-3′) and Human-*GAPDH* (F: 5′-AAT CCC ATC ACC ATC TTC CA-3′) and (R: 5′-TGG ACT CCA CGA CGT ACT CA-3′)] in preparation of PCR MasterMix tubes that tested using the StepOnePlus™ RT-PCR Systems.

2.5. Immunohistochemistry

Tissue sections were prepared and incubated with the primary antibody against CXCL1 (1:200 dilution), followed by a biotinylated secondary antibody (1:500 dilution), horseradish peroxidase (HRP), chromogen, and haematoxylin and eosin staining, as previously described [32].

2.6. Immunofluorescence

Cells were seeded and immunolabeled with the primary anti-CXCL1 antibody at a dilution of 1:200, incubated overnight at 4°C. After washing, cells were incubated with the appropriate fluorophore-conjugated secondary antibody (Alexa Fluor®488, 1:500 dilution) for 1 hour at room temperature in the dark. Nuclei were counterstained with DAPI (1 μg/mL) [33].

2.7. Measurement of CXCL1

CXCL1 was measured using a multiplex bead-based assay as described by the manufacturer of the Bio-Plex Pro Kit (Bio-Rad, USA).

2.8. Statistical analysis

One-way ANOVA in the GraphPad Prism Software was used to detect significant differences at $p < 0.05$ [34].

3. Results and discussion

Significantly ($p < 0.05$), a higher level of CXCL1 gene expression was shown in MCF-7 cells in comparison with MCF-10A cells (Fig. 1). Each experiment was performed in triplicate (n = 3), and data are presented as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$).

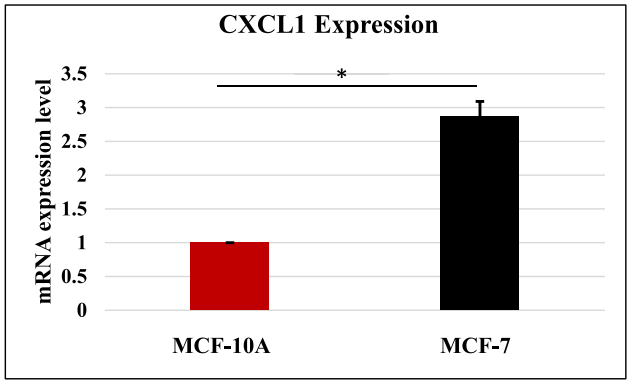

Fig. 1. CXCL1 mRNA expression in MCF-10A and MCF-7 cells. Relative mRNA levels of CXCL1 were measured using RT-PCR in normal (MCF-10A) and breast cancer (MCF-7) cell lines. Data are presented as mean ± SEM (n = 3). (*) indicates statistically significant difference ($p < 0.05$) compared to MCF-10A.

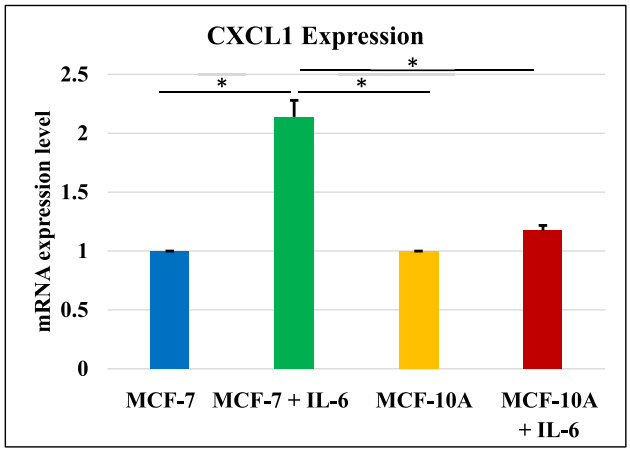

Fig. 2. Effect of IL-6 treatment on CXCL1 mRNA expression in MCF-10A and MCF-7 cells. Cells were treated with IL-6 or left untreated, and CXCL1 gene expression was quantified via RT-PCR. Data are shown as mean ± SEM (n = 3). (*) indicates significant difference ($p < 0.05$) compared to the respective untreated control group. Note: Expression levels were normalized to their respective untreated controls within each cell line, and are not intended to reflect absolute cross-cell-type expression differences.

Quantitatively, the findings of RT-PCR revealed that the CXCL1 gene was overexpressed significantly ($p < 0.05$) in MCF-7 cells treated with IL-6 in comparison with those observed in a group of MCF-10A treated with the pro-inflammatory IL-6 as well to other MCF-7 and MCF-10A non-treated groups with IL-6 (Fig. 2).

The findings of the MTS assay revealed that the cell viability of MCF-7 was increased significantly at all concentrations of IL-6 in comparison with control; however, the highest value of cell viability was seen at a concentration of 300 in comparison with others;

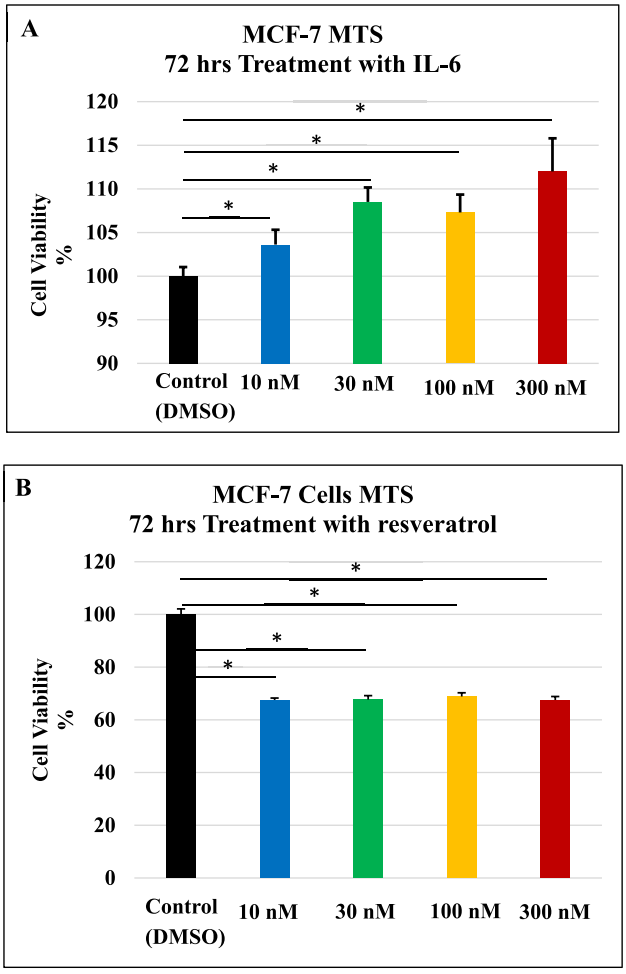

Fig. 3. Effect of IL-6 (A) and resveratrol (B) on the viability of MCF-7 cells. Cell viability was assessed using the MTS assay after treatment with various concentrations of IL-6 (A) or resveratrol (B). Resveratrol was solubilized in DMSO (stock solution: 100 mM), and diluted to a final concentration of 100 μM in culture medium. The final DMSO concentration in all treated and control wells was 0.1%.Values are expressed as mean ± SEM (n = 3). (*) indicates significant difference ($p < 0.05$) compared to the control group (A) or DMSO-treated group (B).

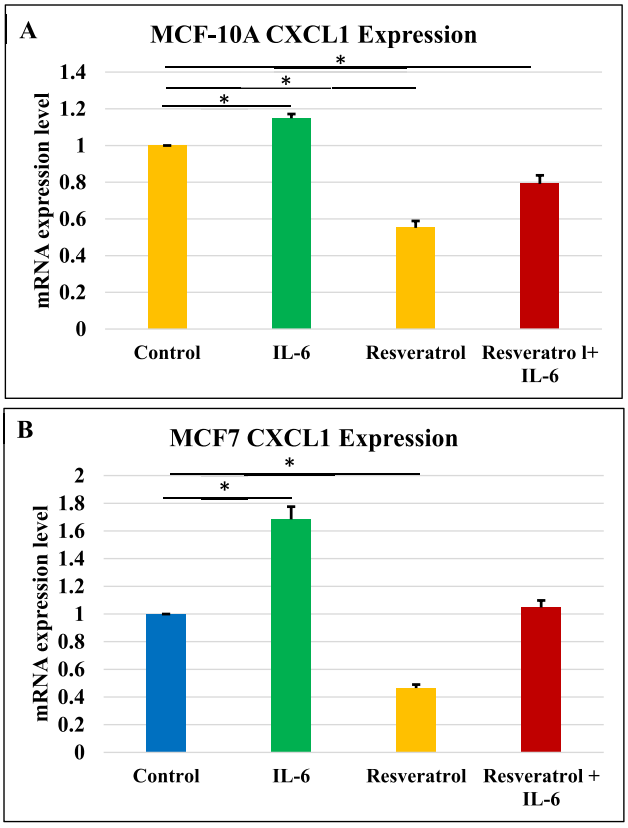

Fig. 4. *CXCL1* mRNA expression in response to IL-6 and resveratrol in MCF-10A (A) and MCF-7 (B) cells. Cells were treated with IL-6 (100 ng/mL), resveratrol (100 μM), or both for 24 hours. *CXCL1* mRNA levels were measured using RT-PCR and normalized to GAPDH. Data are presented as mean ± SEM from three independent experiments (n = 3). (*) indicates statistically significant difference ($p < 0.05$) compared to the untreated control.

10, 30, and 100 (Fig. 3A). In study groups exposed to different concentrations of resveratrol (Fig. 3B), the findings were reduced significantly ($p < 0.05$) in all resveratrol concentrations in comparison with the value of DMSO. However, no significant variation ($p > 0.05$) was seen between the values of various concentrations of resveratrol (Fig. 3B).

In comparison to the control group, the levels of mRNA expression in the CXCL1 gene were showed a significant elevation ($p < 0.05$) in MCF-10A cells that treated with IL-6 but reduced significantly ($p < 0.05$) in a group treated with resveratrol as well as the group treated with a combination of resveratrol and IL-6 (Fig. 4A). In MCF-7 cells, the mRNA expression of the CXCL1 gene was increased significantly ($p < 0.05$) in a group treated with IL-6 and decreased significantly in a group treated with resveratrol. However, no significant variation ($p > 0.05$) was seen in a group treated with a combination of resveratrol and IL-6 in comparison with the control group (Fig. 4B).

Subsequently, the level of CXCL1 protein in MCF-10A was decreased significantly ($p < 0.05$) in a group treated with resveratrol but not ($p > 0.05$) in groups treated with IL-6 as well as a group treated with a combination of resveratrol and IL-6 in comparison with the control group (Fig. 5A). The level of CXCL1 protein in MCF-7 was increased significantly ($p < 0.05$) in a group treated with IL-6 but decreased significantly ($p < 0.05$) in groups treated with resveratrol as well as a group treated with a combination of resveratrol and IL-6 in comparison with the control group (Fig. 5B).

In MCF-10A cells, the findings of immunofluorescence showed that the levels of CXCL1 protein were increased significantly ($p < 0.05$) in a group treated with IL-6; but not altered significantly ($p > 0.05$)

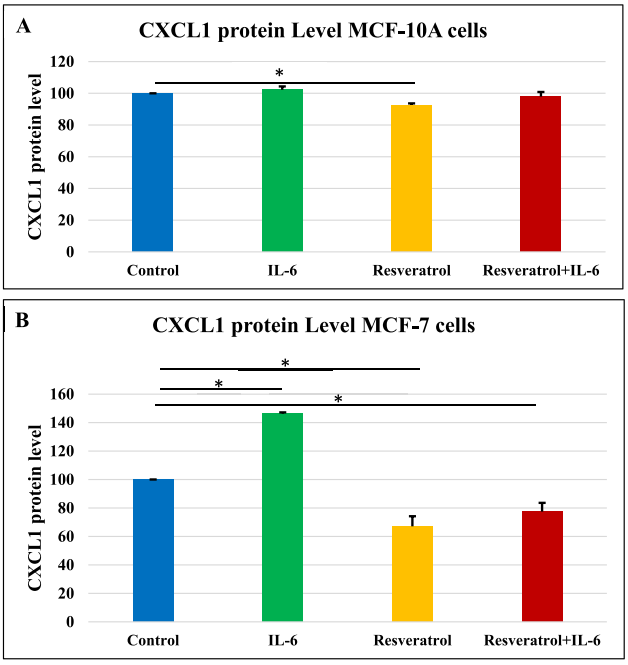

Fig. 5. CXCL1 protein levels in MCF-10A (A) and MCF-7 (B) cells following treatment. Protein levels were determined using a multiplex bead-based assay after treatment with IL-6, resveratrol, or both. Data are expressed as mean ± SEM (n = 3). (*) indicates significant difference ($p < 0.05$) compared to the control group.

in groups treated with resveratrol as well as in a group treated with a combination of IL-6 and resveratrol. A significant strong reaction ($p < 0.05$) of DAPI was seen in all study groups; IL-6, resveratrol, and a combination of IL-6 and resveratrol in comparison with the control group. However, a higher value ($p < 0.05$) was detected in a group treated with resveratrol in comparison with values of a group treated with IL-6 as well as a group treated with a combination of IL-6 and resveratrol. In groups of CXCL1-DAPI, the findings of a group treated with IL-6 and a group treated with a combination of IL-6 and resveratrol were elevated significantly ($p < 0.05$) in comparison with the control group, but not for a group of resveratrol, in which, the values were differed insignificantly ($p > 0.05$), (Fig. 6A).

For groups of MCF-7 cells, the findings of immunofluorescence recorded that the levels of CXCL1 protein were increased significantly ($p < 0.05$) in a group treated with IL-6, while significant decreases ($p < 0.05$) were shown in a group treated with resveratrol as well as in a group treated with a combination of IL-6 and resveratrol. A significant strong reaction ($p < 0.05$) of DAPI was seen in a group treated with IL-6, but not ($p > 0.05$) in a group treated with resveratrol as well as in a group treated with a combination of IL-6 and resveratrol in comparison with the control group. However, the higher value was detected in a group treated with IL-6 in comparison with values of a group treated with resveratrol as well as to value of a group treated with a combination of IL-6 and resveratrol. In groups of CXCL1-DAPI, a significant strong reaction ($p < 0.05$) of DAPI was seen in a group treated with IL-6, but not ($p > 0.05$) in a group treated with resveratrol as well as in a group treated with a combination of IL-6 and resveratrol in comparison with the control group. However, the higher value was detected in a group treated with IL-6 in comparison with values of a group treated with resveratrol as well as to value of a group treated with a combination of IL-6 and resveratrol (Fig. 6B).

The findings of immunohistochemistry revealed that the levels of CXCL1 protein were decreased significantly ($p < 0.05$) in cells of MCF-7 in comparison with those identified in cells of MCF-7 (Fig. 7).

In MCF-7 cells, this study identified molecularly, immunologically and immunohistochemically the presence of significant elevation in *CXCL1* gene expression in the group treated with IL-6. Ahuja et al. [35] found that IL-6 can mediate pulmonary injury *via* production of CXCL1 in mice, and *CXCL1* was inhibited by using the CXCR2-dicient and anti-CXCL1 antibodies. Roy et al. [36] detected that IL-6 upregulates the expression of *CXCL1* in the brain of mice that experimentally have encephalomyelitis. Parkunan et al. [37] hypothesize the contribution of IL-6 and CXCL1 in the rapid recruitment of neutrophils, explosive inflammation and tissue damage. In other *in vitro* and *in vivo* studies, the findings demonstrated the overexpression of *CXCL1* that stimulates the overexpression of IL-6 [38, 39]. Hou et al. [40] reported that the elevated level of CXCL1 and IL-6 is a feature in the pathogenesis of different diseases.

Herbal products have attracted marked significance in the last decades by the scientific communities due to their potential activity towards several inflammatory diseases and cancers [41–43]. In the current study, the findings of molecular, immunological and immunohistochemical diagnostic assays detected that the overexpression of the *CXCL1* gene can be reduced apparently in MCF-7 cells treated with resveratrol as mentioned by various researchers [44–47]. Ko et al. [48] mentioned that resveratrol can impact the various stages of cancer from initiation and promotion to progression. Other researchers found that resveratrol can inhibit events linked to the initiation of tumours by suppressing the formation of free radicals in cancerous cells [49, 50], and excellent scavengers of hydroxyl, superoxide, and radicals generated within the cells [51–53]. In addition, resveratrol can inhibit TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin)-induced expression of cytochrome P450 1A1 and 1B1 genes as well as their catalytic actions in breast cancer

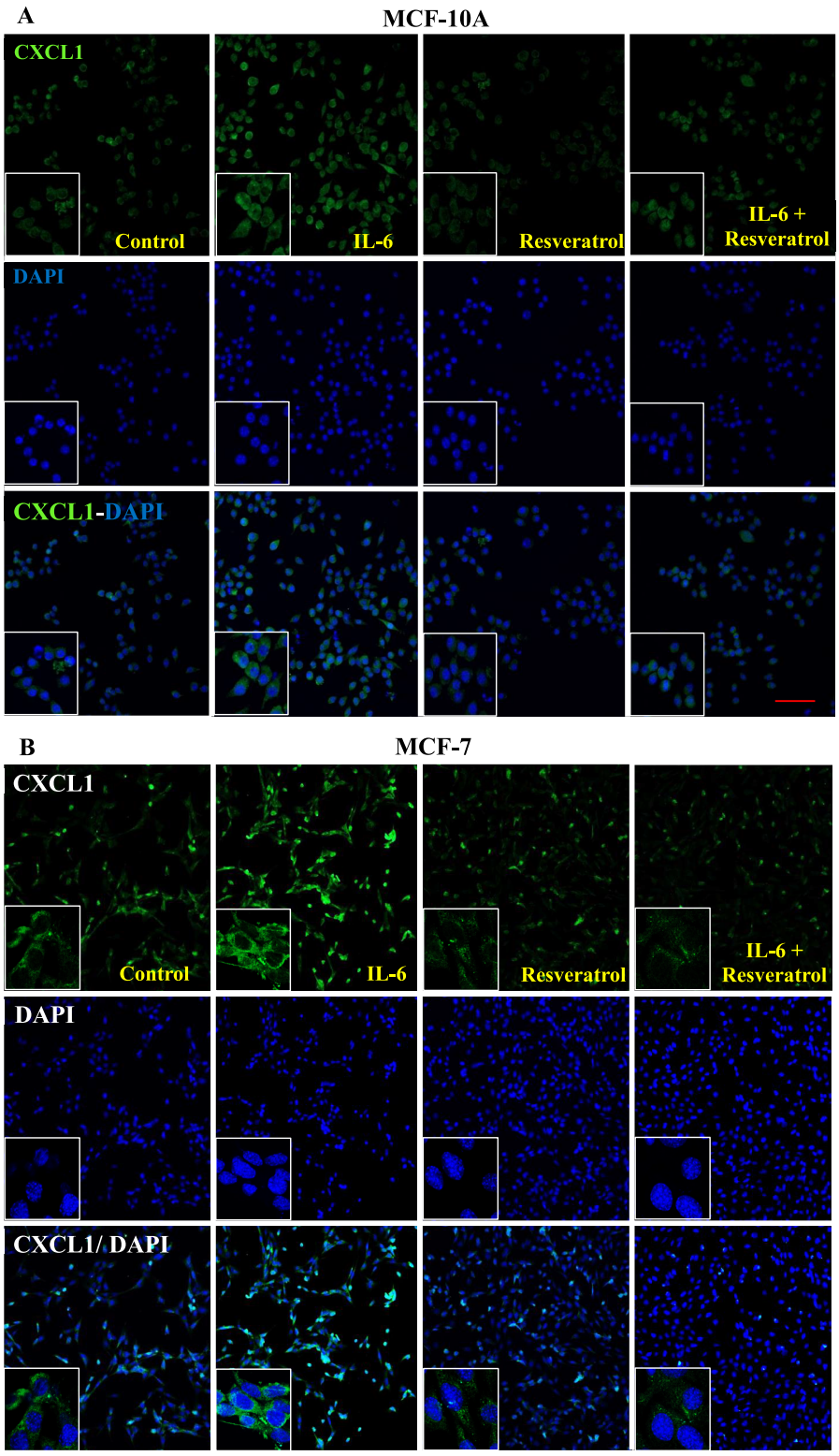

Fig. 6. Immunofluorescence analysis of CXCL1 and DAPI in MCF-10A (A) and MCF-7 (B) cells. Cells were treated with IL-6, resveratrol, or a combination of both, then stained for CXCL1 (green) and nuclei using DAPI (blue). Merged images (CXCL1-DAPI) show protein localization and nuclear morphology. Data are representative of three independent experiments. Scale bars represent 100 μm.

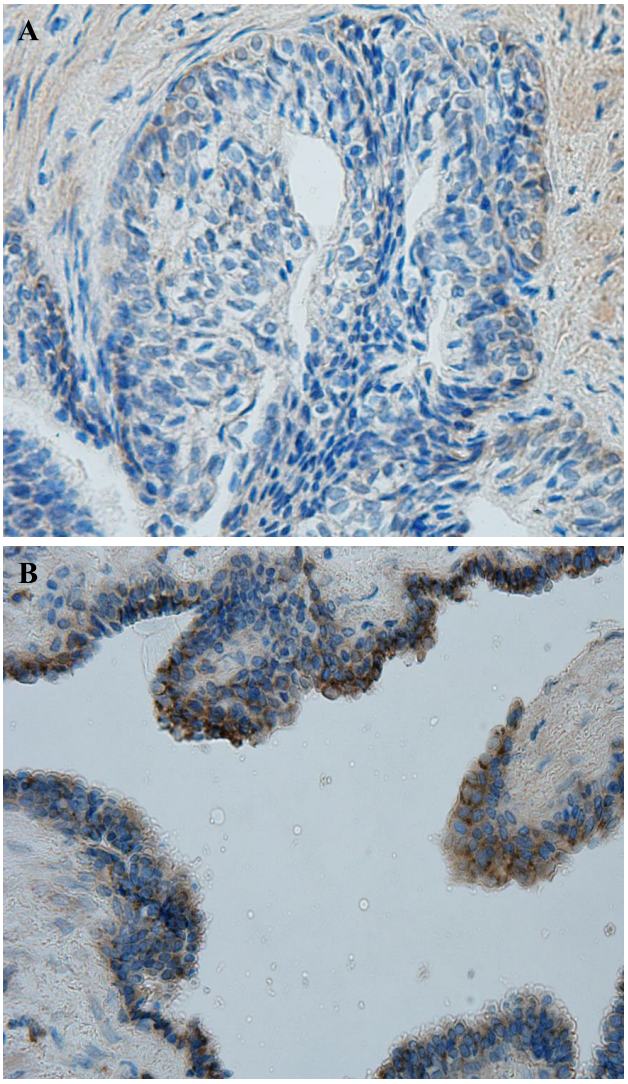

Fig. 7. Immunohistochemical detection of CXCL1 protein in MCF-10A (A) and MCF-7 (B) cells. Cells were stained to visualize CXCL1 protein expression using immunohistochemistry. Representative images show cytoplasmic localization of CXCL1, with positive staining indicated by brown chromogen. Scale bars represent 50 μm.

(MCF) cells [54–56]. Mikuła-Pietrasik et al. [57] demonstrated that resveratrol and its synthetic derivatives can exert the opposite effects on mesothelial cell-dependent angiogenesis. However, the anticancer effects of resveratrol *in vivo* and *in vitro* have been proven and mediated by different mechanisms like autophagy, kinase signalling pathways, cell cycle arrest, and apoptosis [58].

4. Conclusion

This study demonstrates that IL-6 and resveratrol regulate and significantly reduce *CXCL1* gene expression in human breast cancer (MCF-7) cells. Further studies are needed to evaluate the long-term safety and biological consequences of IL-6 and resveratrol use in vivo, particularly with prolonged administration. Future research should focus on elucidating the specific molecular pathways involved in *CXCL1* regulation—such as the roles of NF-κB, MAPK, and STAT3 signaling—and their potential as therapeutic targets in breast cancer treatment.

Conflict of interests

No.

Ethical approval

Not applicable.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conception: A,H,A; E,M,A,A; K,A,A
Design: A,H,A; E,M,A,A
Supervision: A,H,A
Literature: K,A,A
Review: A,H,A; K,A,A
Writing: K,A,A
Critical Review: A,H,A

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