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Research Article / Araştırma Makalesi

EVALUATION OF THE EFFECTS OF SULFAMETHOXAZOLE ON ENDOTHELIAL AND FIBROBLAST CELLS

SÜLFAMETOKSAZOLÜN ENDOTEL VE FİBROBLAST HÜCRELERİ ÜZERİNDEKİ ETKİLERİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: *Sulfamethoxazole (SMX) is a sulfonamide derivative drug used in the treatment of bacterial infections. The potential role of SMX not only in the treatment of infections but also in tissue regeneration and wound healing has aroused interest in its potential therapeutic applications. In this study, we aimed to determine the effects of SMX on fibroblast and endothelial cell viability, migration and collagen gene expression.*
Material and Method: *In this study, HUVEC was used as endothelial cell line and L929 as fibroblast cell line. Cell viability was evaluated by MTT assay, migration inhibition by wound healing assay and COL1A1 gene expression by qRT-PCR method.*
Result and Discussion: *SMX was found to show some positive effects on endothelial and fibroblast cells to promote wound healing, but some concentrations may negatively affect cellular processes. More detailed in vitro research is needed to expand the therapeutic areas in which SMX is used.*
Keywords: *Endothelial cell, fibroblast cell, sulfamethoxazole, wound healing*

ÖZ

Amaç: *Sülfametoksazol (SMX), bakteriyel enfeksiyonların tedavisinde kullanılan bir sülfonamid türevi ilaçtır. SMX sadece enfeksiyon tedavisinde değil, aynı zamanda doku rejenerasyonu ve yara iyileşmesindeki olası rolüyle de potansiyel terapötik uygulama alanları ilgi uyandırmaktadır. Bu çalışmada SMX'in fibroblast ve endotel hücrelerinin canlılığı, migrasyonu ve kollajen gen ekspresyonu üzerindeki etkilerinin belirlenmesi amaçlanmıştır.*
Gereç ve Yöntem: *Bu çalışmada, endotel hücre hattı olarak HUVEC ve fibroblast hücre hattı olarak ise L929 kullanıldı. Hücre canlılığı MTT testi ile, migrasyon inhibisyonu yara iyileşme testi ile ve COL1A1 gen ekspresyonu ise qRT-PCR yöntemi ile değerlendirildi.*
Sonuç ve Tartışma: *SMX'in, endotel ve fibroblast hücrelerinde yara iyileşmesini destekleyecek bazı olumlu etkiler gösterdiği ancak bazı konsantrasyonların hücresel süreçleri olumsuz etkileyebileceği bulundu. SMX'in kullanıldığı terapötik alanlarının genişletilebilmesi için daha ayrıntılı in vitro araştırmalara ihtiyaç duyulmaktadır.*
Anahtar Kelimeler: *Endotelyal hücre, fibroblast hücresi, sülfametoksazol, yara iyileşmesi*

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INTRODUCTION

Sulfamethoxazole (SMX) is a sulfonamide-derived drug that acts as a structural analog of para-aminobenzoic acid (PABA), competitively inhibiting PABA to block the synthesis of dihydrofolic acid, a key step in tetrahydrofolate production, by targeting and inhibiting the enzyme dihydropteroate synthase [1,2]. Folate metabolism consists of a series of interconnected reaction mechanisms in several steps, with both the cytoplasm and mitochondria forming the common ground [3]. Tetrahydrofolate, an intermediate formed during these steps, is the physiologically active form of folic acid. Intermediates formed from tetrahydrofolate are important for anabolic pathways such as thymidine, purine synthesis, conversion of the amino acid serine to the amino acid glycine and the methionine cycle [1,3]. Tetrahydrofolate is also an important cofactor in bacterial DNA synthesis [1]. The combination of sulfamethoxazole with trimethoprim is used for many indications. It is used orally or intravenously for the treatment of urinary tract infection, acute otitis media, treatment and prophylaxis of Pneumocystis pneumonia, infectious diarrhea due to enterotoxin-producing E. coli, shigellosis caused by S. flexneri or S. sonnei [4]. Trimethoprim inhibits the enzyme dihydrofolate reductase, which synthesizes tetrahydrofolic acid from dihydrofolic acid in folic acid synthesis [1]. The trimethoprim-sulfamethoxazole combination has been studied for many activities. A study by Hee-Yun et al. significantly improved the survival rate in melanoma skin cancer in immunodeficient mouse models and was shown to reduce tumor weight and growth and vascular endothelial growth factor levels. The same study also showed that it increased the rate of caspase-3, 8 and 9 [5]. Ritu et al. observed that the combination of sulfomethoxazole and selenium reduced elevated liver enzyme levels in rats with diethylnitrosamine-induced hepatocellular carcinoma [6]. Mohamed et al. showed that newly synthesized sulfamethoxazole derivatives have carbonic anhydrase inhibitor (I, II, IX and XII) activities. At the same time, one of these derivatives stops some cell cycle stages of MCF7 cancer cells and induces apoptosis and also has a strong cytotoxic effect [7]. Another study demonstrated the efficacy of sulfamethoxazole on skin and soft tissue infections [8].

Fibroblast cells play a crucial role in the synthesis of the extracellular matrix (ECM) and contribute to the structural integrity of connective tissue [9,10]. Fibroblasts produce essential substances and proteins such as collagen, elastin, laminin, glycosaminoglycans and elastin, which are contained in the ECM. Apart from these, they play a major role in physiological and pathological processes such as tissue repair and wound healing [10,11]. During wound healing, granulation tissue is formed by fibroblasts reaching the site and subsequent angiogenic sprouting of adjacent blood vessels [12]. Endothelial cells and fibroblasts work together so that blood vessels can grow efficiently [13]. They also work together to ensure ECM synthesis and vascularization for the successful regeneration of tissues [14]. In addition, it has been observed that there is a connection between fibroblast cells and endothelial cells in the regulation of the inflammatory response [15]. In addition to the clinically approved indications of the sulfamethoxazole-trimethoprim combination, there are some studies evaluating its effectiveness in wound-related processes. In a study conducted by Bowen et al., the use of the sulfamethoxazole-trimethoprim combination in the treatment of wound infections was supported [8]. The aim of this study is to investigate the clinical indications of SMX, a clinically approved drug, as well as its effect on wound healing process on mouse fibroblast cell line (L929) and human endothelial cell line (HUVEC). Explaining the beneficial effects of SMX, in addition to its positive effects on wound healing, will help to revise its uses in order to expand its range of applications.

MATERIAL AND METHOD

Cell Culture

L929 cells (ATCC, Manassas, USA) were grown in DMEM containing 10% FBS, 1% penicillin/streptomycin and 2 mM L-glutamine. HUVEC cells were grown in RPMI complete medium containing 10% FBS, 1% penicillin/streptomycin and 2 mM L-glutamine. Cells were incubated at 37°C, 5% CO_2 and 100% humidity. The medium was changed regularly until the cells reached 80% confluency.

Cell Viability Analysis

The viability effects of SMX on HUVEC and L929 cell lines were evaluated by a spectrophotometer using the MTT procedure. Both cells were seeded in 96-well plates at 5000 cells per well. Six wells were used for all three drug doses. Cells were then incubated for 24 hours at 37°C in an incubator containing 5% CO_2. During the incubation period, SMX was dissolved in 100 µl DMSO and doses were prepared using DMEM/RPMI medium. The doses used in the MTT assays were prepared such that the maximum DMSO concentration did not exceed 1%. The DMSO concentration used as a positive control was also 1%. At the end of the incubation period, 100 µl of the previously prepared drug doses of 1, 10, 50, 100, 250, 500 µM and 1 mM for SMX were added to the wells. At the end of the 24- and 48-hour exposure periods starting with the application of these doses, 10 µl each of MTT solution (Biotium) was added to the volumes in all wells. The plates to which MTT solution was added were incubated for 4 hours in the dark in an incubator at 37°C. At the end of this time, 200 µl Dimethyl sulfoxide (DMSO) was added to each well to dissolve the purple-colored formazan crystals. Absorbance values were then measured at 630 nm using a microplate reader (BioTek Synergy H1, USA). The cells in the wells to which the drug dose was not added were considered as control group and the viability values of these wells were evaluated as 100%.

Migration Analysis

For migration analysis, cells were seeded to 24-well plates with a volume of 500 µl and 10^5 cells/well in all wells. After the seeded cells covered 90% of the plate surface, the doses decided by MTT assay (1 µM-50 µM-100 µM) were added and the bottom of the plates were scratched with a pipette tip. Among the doses tested in the MTT assays, the three lowest concentrations that did not show significant cytotoxicity and covered a relatively broad range were selected for migration and gene expression analyses. For each cell (HUVEC and L929), three wells were used for all three drug doses. At 0 and 24 hours, images of the wells were obtained using a Leica DM IL microscope (Leica, Wetzlar, Germany). Cell-free areas in the images were calculated for each cell line and drug dose using ImageJ program and expressed as percentage. After obtaining the images from the migration assay, crystal violet staining was also performed. For this procedure, cells were seeded into 24-well plates. Once the cells covered approximately 90% of the well surface, SMX was added at concentrations of 1 µM, 50 µM, and 100 µM. Subsequently, the bottoms of the wells were scratched using a pipette tip. After a 24-hour incubation period, each well was washed with 1x PBS, and 100% methanol was added. Following the evaporation of methanol, 0.5% crystal violet solution was added to each well. After staining, the cells were examined and images of the wells were captured using a Leica DM IL microscope.

Gene Expression Analysis

In order to perform *COL1A1* gene expression analyses; L929 and HUVEC cells were seeded to 6-well plates with 10^5 cells in each well. Analyses were performed at 24 hours. SMX doses were 1, 50 and 100 µM, respectively. RNA from cells collected from 6 wells was combined. Total RNA was isolated using Bluezol (SERVA, Germany). Timed PCR was performed using the Lightcycler® 96 system (Roche Diagnostic Systems, Indianapolis, IN) and A.B.T.TM 2X One-Step qRT-PCR Master Mix (with SYBR) (ATLAS Biotechnology, Turkey). For each 20 µl of PCR reaction, 2 µl RNA (1 µl: 20 ng/ml), 10 µl of master mix, 0.5 µl of forward and reverse primer (10 µM each), and 7 µl H_2O were added. The final concentration for the primers was 10 µM. The L929 primer sequences were as follows: *COL1A1* (F: TGACTGGAAGAGCGGAGAGAGT - R: GTTCGGGCTGATGTACCAGT) GAPDH (F: CTGCCCAGAACATCATCCCT - R: GTCCTCAGTGTAGCCCAAGA). The HUVEC primer sequences were as follows: *COL1A1* (F: GCTACTACCGGGCTGATGAT - R: ACCAGTCTCCATGTTGCAGA) GAPDH (F: GTCTCCTCTGACTTCAACAGCG - R: ACCACCCTGTTGCTGTAGCCAA). The threshold cycle (Ct) value of the GAPDH gene was used to standardize the data and samples were analyzed in triplicate [16].

Statistical Analysis

The data in this study are presented as mean±SD. GraphPad Prism version 10 (GraphPad Software, USA) was used for plotting the graphs and statistical analyses. Two-way ANOVA was used for statistical analysis. The control group consisted of untreated cells. Bonferroni post-hoc test was applied to compare the differences between the groups. $P<0.05$ significance level was considered statistically significant which is indicated with an asterisk (*). The significance levels in the analyses were defined as *$p<0.05$, **$p<0.01$, ***$p<0.001$, and ****$p<0.0001$.

RESULT AND DISCUSSION

Effect of SMX on Viability of HUVEC and L929 Cells

The effects of SMX on the viability of L929 and HUVEC cells were evaluated for 24 and 48 hours. After 24 hours of 1 μM SMX exposure, the HUVEC cell line showed 111.8% viability compared to the control group. 10, 50, 100, 250, 500 μM and 1 mM exposure of SMX for 24 hours resulted in 105.34%, 109.41%, 106.77%, 103.37%, 105.84% and 106.67% viability rates respectively (Figure 1a). 48 hours of SMX exposure at doses of 1, 10, 50, 100, 250, 500 μM and 1 mM resulted in 89.45%, 86.89%, 86.29%, 84.49%, 89.40%, 91.82% and 85.93% viability respectively, compared to the control group (Figure 1b). SMX caused an increase in the viability of endothelial cells at 24 hours. At 48 hours, no significant decrease in viability levels was observed.

In the L929 cell line, after 24 hours of exposure to 1μM SMX, the viability rate was 103.06% at 1 μM compared to the control group, while with the other exposure doses of 10, 50, 100, 250, 500 μM and 1 mM showed the viability rates were 95.45%, 89.46%, 99.97%, 99.73%, 102.94% and 101.70%, respectively (Figure 1d). After 48 hours of exposure, 95.37%, 91.58%, 90.29%, 93.43%, 90.19%, 89.64% and 86.31% viability rates were observed at exposure doses of 1, 10, 50, 50, 100, 100, 250, 500 μM and 1 mM, respectively (Figure 1e). SMX did not significantly reduce the viability of fibroblast cells at 24 and 48 hours; however, viability levels were lower at 48 hours.

In both cell lines, the highest viability rate at 24 hours was observed at 1μM concentration. At 48 hours, the highest viability percentage was observed at a 500 μM concentration in the HUVEC, whereas in the L929, it was observed at a 1 μM concentration. Microscopic images of HUVEC and L929 cells are presented in Figure 1c and Figure 1f, respectively.

SMX increased the viability of endothelial cells at the specified concentrations after 24 hours of treatment. Following 48 hours of exposure, no significant reduction in viability was observed. Previous studies have reported that TMP-SMX improves survival rate in melanoma skin cancer, improves immunity, reduces tumor growth and reduces vascular endothelial growth factor (VEGF) levels in immunodeficient mouse models [5]. Given this information, in addition to having a suppressive effect on cancer cells, SMX also causes an increase in viability and migration abilities of healthy endothelial cells, which may contribute to the treatment process with its positive effects on healthy cells besides increasing immunity in cancer chemotherapy. In fibroblast cells, an increase in viability was observed at 1 μM, 500 μM and 1 mM concentrations at 24 hours, while SMX did not significantly decrease the viability at other concentrations and at 48 hours. The viability percentages observed across the wide range of concentrations tested, along with the absence of solubility issues for SMX, suggest that this drug may have a biphasic effect. However, further studies are needed to confirm this.

Effect of SMX on Migration of HUVEC and L929 Cells

The effects of SMX on the migration capacity of fibroblast and endothelial cells were investigated using 1, 50 and 100 μM concentrations. After 24 hours of incubation, the HUVEC cell line showed a 21.9% closure percentage in the control group, whereas 38.1% at 1 μM concentration, 30.4% at 50 μM concentration and 32.2% at 100 μM concentrations (Figure 2b). In L929 cell line, the closure percentage was 8.5% in the control group, whereas it was 13.5% at a 1 μM concentration, 0.4% at a 50 μM concentration, and 4.7% at a 100 μM concentration (Figure 2d). These percentages are consistent with the data obtained from migration images (Figure 2b). Crystal violet staining data are presented in the supplementary materials (Supplementary figure 1).

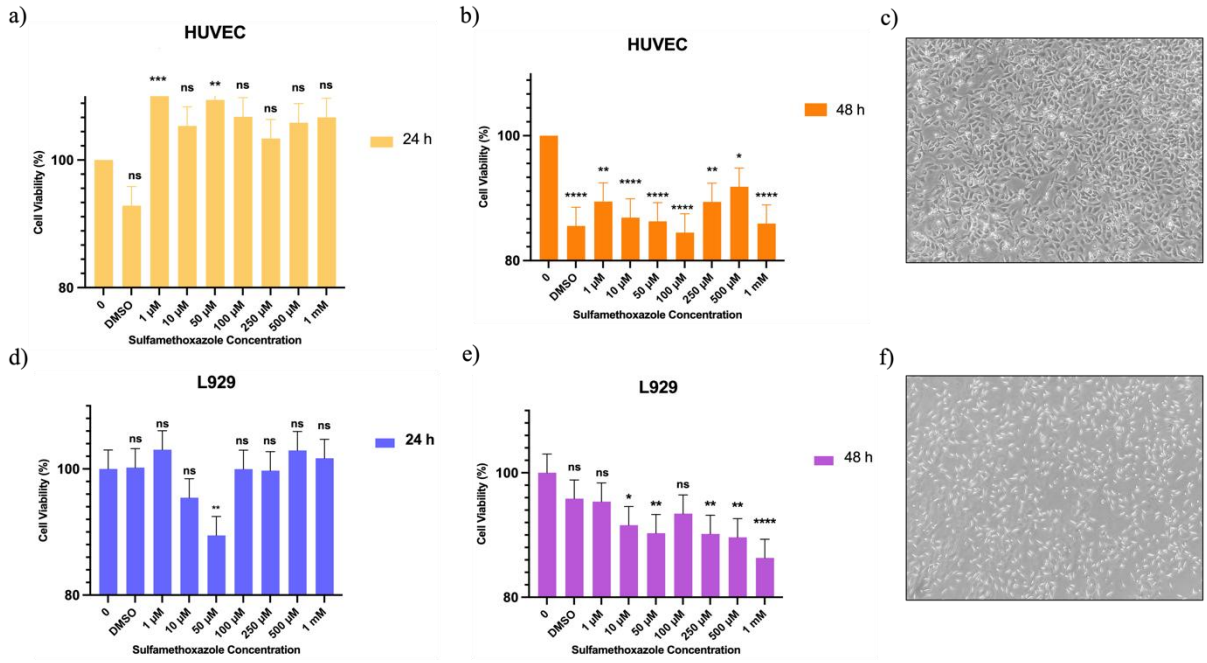

Figure 1. Effect of SMX on the viability of HUVEC (a-b) and L929 (d-e) cells after 24 and 48 hours of treatment at a dose range of 1µM-1 mM, (n=6). The image of HUVEC (c) and L929 (f) cells under a light microscope (5X)

Accordingly, SMX increased the migration ability of HUVEC cells compared to the control group, but the same increase was not observed in L929 cells. The increase in migration ability in L929 cells was observed only at 1µM concentration of SMX. Similar to cell viability, an increase in the migration ability of endothelial cells was also observed at selected concentrations. In fibroblast cells, migration ability increased at 1µM dose concentration, where an increase in cell viability was observed, while a decrease in migration ability was observed at other doses. In a study, it was observed that co-trimoxazole did not show a cytotoxic effect on the L929 cell line [17]. In a study by Dragostin et al., wound dressings combining chitosan and sulfamethoxazole-both exhibiting antimicrobial and antioxidant effects and high biodegradability-were shown to possess the essential properties of good wound dressing materials [18]. Another study involving sulfadiazine, a sulfonamide derivative active ingredient like SMX, combined with chitosan demonstrated that the prepared polyelectrolyte complexes, due to their strong bacteriostatic effects and prolonged drug release, could serve as suitable drug delivery systems during wound healing [19]. Similarly, in a study conducted on non-infected animal models, sulfonamide group antibiotics were observed to enhance re-epithelialization, fibroblast proliferation, and extracellular matrix production during the wound healing process [20]. These studies provide promising insights into the potential applications of sulfamethoxazole in the wound healing process.

Effect of SMX on *COL1A1* Expression

Collagen is the most abundant protein in the body, a component of the extracellular matrix, which acts as a regulator in the wound healing process [21]. Collagen type 1 alpha 1 (*COL1A1*) is a gene involved in many cellular processes such as cell proliferation, metastasis and apoptosis and encodes the α1 chain of type I collagen [22,23]. The effects of SMX on *COL1A1* gene expression in HUVEC and L929 cell lines were analyzed at concentrations of 1 µM, 50 µM, and 100 µM. After 24 hours of treatment in the HUVEC cell line, *COL1A1* expression levels were measured as 1.052, 0.420, and 0.290, respectively (Figure 3a).

In the L929 cell line, *COL1A1* expression levels at 1 µM, 50 µM, and 100 µM concentrations were measured as 0.410, 0.391, and 0.194, respectively. The results indicate that SMX increased *COL1A1* gene expression only at a 1 µM concentration in the HUVEC cell line, whereas it inhibited

COL1A1 expression at all tested concentrations in the L929 cell line and at 50 µM and 100 µM concentrations in the HUVEC cell line (Figure 3b).

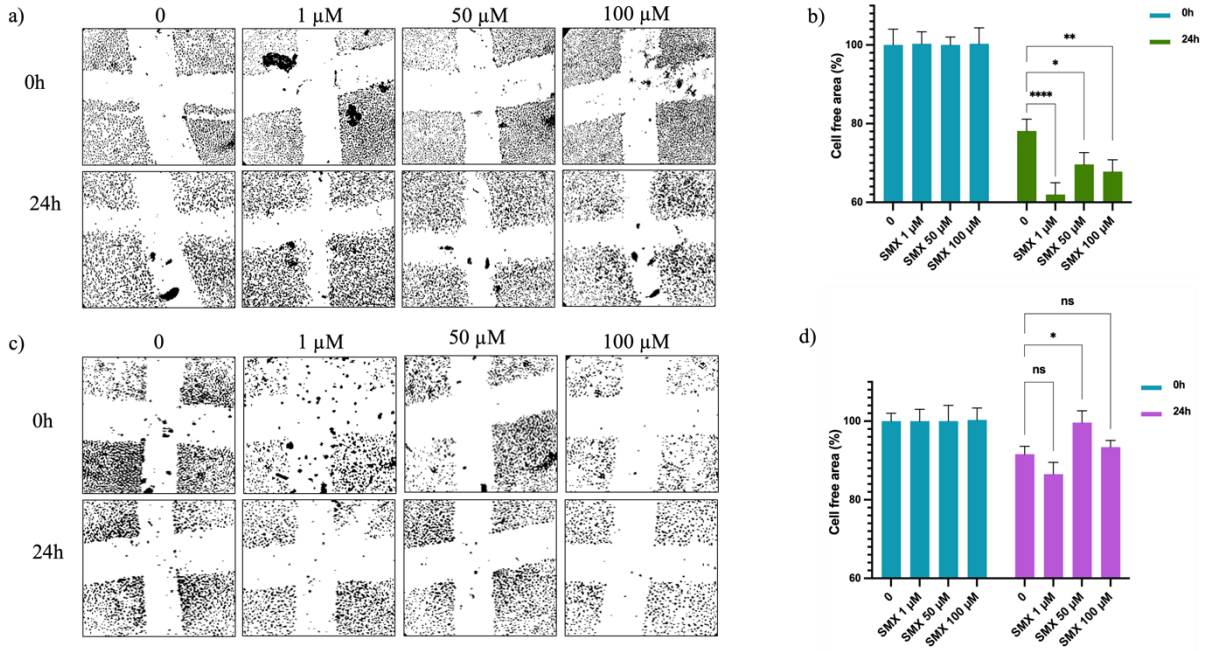

Figure 2. Data and graphs (b-d) for microscope images (a-c) showing the effects of SMX on migration in HUVEC and L929 cells at doses of 1, 50 and 100 µM at 0 and 24 hours, respectively (n=3)

Wound healing is a process consisting of many steps including hemostasis, inflammation, growth, re-epithelialization and remodeling. In this process, endothelial cells, especially in the formation of new blood vessels, and fibroblast cells that provide connective tissue formation in the remodeling phase work together in the wound cavity and contribute to wound healing [24,25]. SMX increased *COL1A1* expression in endothelial cells only at a concentration of 1 µM, but a decrease in the expression of this gene was observed at other doses and in fibroblast cells. Hypotheses regarding the role of SMX in enhancing endothelial function independent of *COL1A1* expression can be tested by examining other genes and pathways known to contribute to vascular repair and tissue remodeling. For example, matrix metalloproteinases (MMPs) are enzymes involved in ECM degradation and are essential in angiogenesis and endothelial cell migration [26]. Similarly, integrins, transmembrane receptors that mediate cell-ECM interactions, play a crucial role in endothelial cell adhesion, survival and migration during vascular remodeling [27]. TGF-β family members are also essential regulators of endothelial function as they modulate processes such as cell proliferation, differentiation and ECM production and have been shown to interact with both MMPs and integrins in a context-dependent manner [28]. Future studies could investigate the expression levels and activities of these gene families following SMX treatment to determine whether SMX promotes endothelial repair through these alternative pathways.

In conclusion, this study demonstrated that SMX enhances the viability and migration ability of HUVEC cells at specific concentrations, particularly after 24 hours of exposure. In fibroblast cells, these effects were more limited and observed only at the 1 µM concentration. SMX increased *COL1A1* expression exclusively in endothelial cells at 1 µM, whereas decreased expression was noted at other doses and in fibroblast cells. These findings suggest that SMX may have a concentration- and cell-type-specific role in promoting wound healing by supporting endothelial cell function. However, the observed effects appear to be independent of *COL1A1* expression, indicating the involvement of alternative molecular pathways. Future studies should explore the specific molecular mechanisms underlying SMX's effects, particularly focusing on angiogenesis-related pathways, ECM remodeling, and immune

modulation. Moreover, in vivo studies using wound healing models are needed to validate these in vitro findings and assess the therapeutic potential of SMX in tissue regeneration. Further studies are needed to elucidate pathways to better understand the mechanisms underlying the action of SMX and its potential application in regenerative medicine.

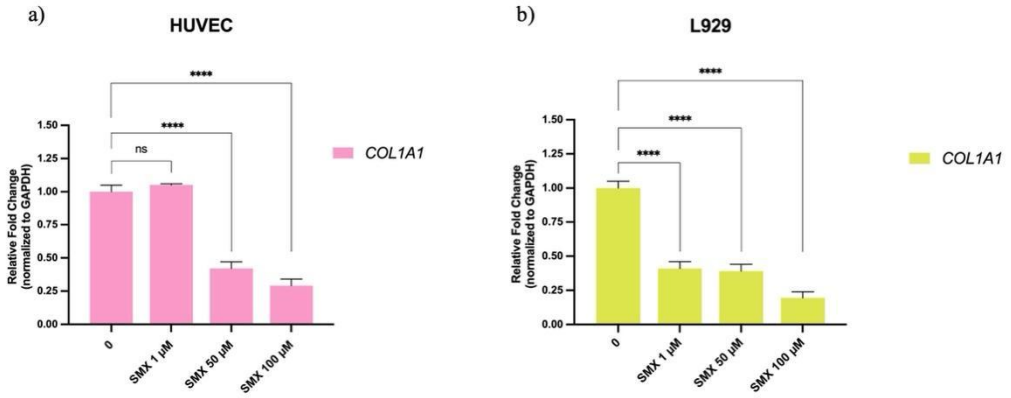

Figure 3. Effects of SMX on *COL1A1* gene expression in HUVEC and L929 cell line. Data are presented as mean±SD, and fold changes were normalized using GAPDH (n=3)

AUTHOR CONTRIBUTIONS

Concept: M.B.Ş., D.K., A.E.; Design: M.B.Ş., D.K., A.E.; Control: M.B.Ş., D.K., A.E.; Sources: M.B.Ş., D.K., A.E.; Materials: D.K., A.E.; Data Collection and/or Processing: M.B.Ş., D.K.; Analysis and/or Interpretation: M.B.Ş., D.K., A.E.; Literature Review: M.B.Ş., D.K., A.E.; Manuscript Writing: M.B.Ş., D.K., A.E.; Critical Review: M.B.Ş., D.K., A.E.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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