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Gene Expression Analysis of Inflammation, Proliferation, and Tissue Repair in Fibroblasts Treated with Ishtx-k Toxin and Mucilage

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ABSTRACT

The present study was conducted to investigate the effects of a combination derived from okra extract and the sea anemone toxin Ishtx-K under cell culture conditions. Fibroblasts are one of the most important cells involved in tissue repair. Modulation of fibroblast growth rate is useful for wound-healing management. In this study, in order to more precisely evaluate alterations in gene expression under in vitro conditions, cell cultures treated with mucilage and the Ishtx-K peptide were employed. Real-time RT-PCR assays were performed to analyze the expression changes of key genes associated with inflammation and tissue repair, including *FGF1*, *TAC3*, *NF-κB*, and the two long non-coding transcripts *H19* and *NEAT1*. Statistical analysis was performed in the P≤ 0.05 significant range. The results demonstrated that treatment with okra mucilage and the Ishtx-K peptide reduced the expression of NF-Kb (fold change/FC= 0.47, P= 0.000), one of the most important regulators of inflammation. Significant alterations were also observed in the expression of *FGF1* (overexpression to 4.2-fold, P= 0.000) and a decrease of about 50% in *TAC3* in the group treated with mucilage, indicating stimulation of regenerative processes and modulation of pathways associated with tissue repair. In addition, diminished expression changes of the non-coding transcripts *H19* and *NEAT1*, confirmed their potential roles in the molecular mechanisms underlying cell signaling related to cell growth and cell physiology, were FC= 0.2-0.25 in the mucilage-treated group for two molecules, P= 0.000 and about 0.39 for LncRNA *NEATA1* in the mucilage-toxin combined treated group, P= 0.000. The combined application of the plant-derived and peptide-based compounds exhibited greater efficacy in reducing inflammation and improving the regenerative process compared with individual treatments. These findings suggest that the combined therapy presented in this study, through modulation of inflammatory and molecular pathways, may represent a novel and effective therapeutic approach for some important process in tissue repair.

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Introduction

Fibroblast cells play the most important role in the tissue repair process, such as wound healing. Studies have shown that timely and appropriate wound management can substantially prevent complications and reduce treatment costs (Guo and DiPietro, 2010). When the skin is damaged by external factors, its normal structure becomes disrupted, resulting in the loss of a portion of the tissue and subsequent wound formation. A wound is generally defined as epithelial damage that leads to impairment of tissue integrity (Afsharian and Rahimnejad, 2021). The severity of injury and underlying conditions significantly influence

wound healing and tissue regeneration. Disruption of the skin barrier rapidly initiates a complex wound healing response in which fibroblasts play a central role. Upon injury, inflammatory signals such as cytokines and growth factors, including TGF-β, PDGF, and IL-1β, activate resident quiescent fibroblasts and promote their transition into an activated phenotype, which is essential for tissue repair and extracellular matrix (ECM) remodeling (Chang *et al.,* 2025). Fibroblast activation is a tightly regulated and multifactorial process influenced by the inflammatory microenvironment of the wound and the crosstalk with immune cells such as macrophages and neutrophils. These immune cells secrete cytokines and chemokines that modulate fibroblast behavior, enhancing their migration, proliferation, and ECM production during tissue repair (Correa-Gallegos *et al.,* 2021). However, persistent or dysregulated fibroblast activation can lead to excessive ECM deposition and ultimately contribute to pathological scar formation (Moretti *et al.,* 2022). Despite the development of various therapeutic strategies for wound healing, including tissue grafting, cell-based therapies, and advanced wound dressings, no single approach has yet been recognized as an ideal and universally effective treatment for all types of wounds. This limitation highlights the need for approaches that specifically target key cellular mediators of wound repair, particularly fibroblasts and their regulatory signaling pathways (Berry *et al.,* 2024). The use of medicinal plants and plant-derived extracts in wound healing has long been recognized (Shedoeva *et al.,* 2019). Plant secondary metabolites, such as phenolics, alkaloids, fatty acids, glycosides, and polysaccharides, contribute to wound repair through their anti-inflammatory and antioxidant properties, as well as by promoting collagen synthesis and cellular regeneration (Ibrahim *et al.,* 2018). Okra (Abelmoschus esculentus) is a medicinal plant that has attracted considerable attention due to its high mucilage content and nutritional value (Coughlin *et al.,* 2021). Okra mucilage is mainly composed of acidic polysaccharides, including monosaccharides such as glucose, galactose, rhamnose, and galacturonic acid (Elkhalifa *et al.,* 2021). From a biological perspective, one of the key biological properties of okra mucilage is its ability to regulate inflammatory responses. The polysaccharides present in okra mucilage can modulate immune cell activity and reduce the production of pro-inflammatory cytokines, thereby controlling the intensity of inflammation at the site of injury. This anti-inflammatory effect plays an important role in preventing chronic inflammation and facilitating the transition to the tissue repair phase (Wang *et al.,* 2025). In addition, okra mucilage can help reduce oxidative stress and protect cells against reactive oxygen species-induced damage, thereby preventing the amplification of inflammatory responses and maintaining the balance of the wound microenvironment (Sipahi *et al.,* 2021). Animal venoms are complex mixtures of biochemical compounds whose composition depends on the venom-producing species (Utkin, 2015). Sea anemone venom contains both proteinaceous components (peptides and proteins) and non-proteinaceous compounds such as quaternary ammonium compounds, purines, and biogenic amines (Frazao *et al.,* 2012). Many of these venom-derived peptides have attracted considerable attention due to their potential therapeutic applications. Among them, the ShK peptide, isolated from *Stichodactyla helianthus*, is a 35-amino-acid peptide and a potent inhibitor of the Kv1.3 potassium channel. It also affects other potassium channel isoforms in tissues such as the heart and brain (Chang *et al.,* 2018). In the present study, the Ishtx-K toxin, similar to Shtx-K from *Stichodactyla haddoni*, was used. This toxin was extracted from a specimen collected in the Persian Gulf and consists of a signal peptide, a propeptide, and a mature peptide. At the molecular level, several genes involved in the regulation of inflammation and tissue regeneration, including NF-κB, Fibroblast growth factor 1(FGF1), TAC3, NEAT1, and H19, play important roles in controlling the wound healing process and the activity of involved cells. NF-κB is a key regulator of inflammation and wound healing, activated after tissue injury. It controls inflammatory gene expression and contributes to cell survival, proliferation, and tissue repair, but excessive activation may impair healing (Liu *et al.,* 2022). FGF1 is a member of the fibroblast growth factor family and is involved in tissue repair and regeneration. It contributes to cell proliferation and migration, extracellular matrix remodeling, angiogenesis, and granulation tissue formation,

thereby supporting wound healing (Farooq *et al.*, 2021). The TAC3 gene encodes neurokinin B, a member of the tachykinin family involved in neurogenic inflammation. Through its receptor NK3R, it affects immune and inflammatory responses (Wang *et al.*, 2025). *NEAT1* is involved in regulating cellular responses to stress and inflammation and contributes to the modulation of cytokine expression under tissue injury conditions. This lncRNA also coordinates immune responses during tissue repair processes (De Domenico *et al.*, 2025). lncRNA H19 is involved in inflammation and tissue repair. It regulates inflammatory responses, affects immune cells such as macrophages, and participates in processes related to tissue regeneration and wound healing (Li *et al.*, 2023). The main goal of this study is to present a new strategy based on toxin, mucilage, and combined mediated regulation and modulation of fibroblast behavior in wound repair and inflammation *in vitro* conditions.

Materials and Methods

Recombinant Ishtx-k protein production

The recombinant vector generated by ligating the Ishtx-k fragment (117 bp) into the pET32b(+)Rh plasmid was transformed into competent *E. coli* BL21(DE3) cells using the heat-shock method. Presence of the recombinant vector containing the *Ishtx-k* gene fragment in the bacterial cells, confirmed by colony PCR – using specific T7-forward: 5'TAATACGACTCACTATAGGG and T7-reverse:5' GTTTCTTAGCAGGTTCCACAGG primers. The PCR products were analyzed by electrophoresis on a 1% agarose gel. The transformed cells were cultivated in LB medium supplemented with ampicillin (1μg/mL final concentration) until reaching an OD_{600}= 0.5. Protein expression was induced by the addition of 100 mM IPTG, followed by incubation at 30°C for 2 h. After cell lysis and centrifugation, the soluble and insoluble fractions were separated. To determine whether the expressed protein was present in the soluble or insoluble phase, the resulting suspensions were analyzed by SDS-PAGE electrophoresis. Finally, purification was performed from the soluble fraction using a Ni-NTA affinity column. The purified sample was subsequently analyzed by SDS-PAGE to evaluate the efficiency of the purification process. Also, the concentration of the purified protein was determined using the Bradford method (Kruger, 2002).

Extraction of Okra Mucilage

Okra mucilage was extracted by boiling (95°c) of 100gr okra in distilled water for 20 min. The resulting extract was then filtered and sterilized using a 0.22 μm syringe filter. Finally, this extract was eluted in 50% V/V sterile distilled water and used for cell culture analysis.

Cell culture

The HGF3-PI53 cell line was obtained, and the cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin antibiotics at 37°C in a humidified atmosphere containing 5% CO_2. To evaluate the effects of the Ishtx-k peptide and mucilage on the growth of HGF3-PI53 cells, a 6-well plate was used, and the cells were divided into four treatment groups. In the negative control group, the cells were cultured without mucilage or peptide treatment. In the peptide-treated group, the cells were treated with 20 μL of the Ishtx-k peptide. In the mucilage and peptide-treatment group, two wells were first coated with 500 μL of mucilage, and subsequently, the cells together with 20 μL of the Ishtx-k peptide were added to the wells. In the mucilage-treated group, two wells were initially coated with 500 μL of mucilage, after which the cells were seeded into the wells. Cell growth was monitored daily for 6 days, and images were captured using an optical microscope.

RNA extraction and cDNA synthesis

RNA was extracted from treated HGF3-PI53 cells using the RNX-Plus kit buffer (Sinaclon, Iran) according to the manufacturer's instructions. The quality of the extracted RNA was evaluated by electrophoresis on a 1% agarose gel. cDNA synthesis was performed using the extracted RNA with a cDNA synthesis kit (Pars Tous, Iran) and Oligo(dT) and Random Hexamer primers according to the manufacturer's instructions.

Real-time PCR assay

Real-time PCR was carried out using an ABI system and a 2X Real-Time PCR Master Mix containing SYBR Green dye (Biofact, South

Korea), according to the manufacturer's protocol. This assay was performed to evaluate gene expression in treated cell samples. Human ACTB was used as the reference gene. Experimental groups were defined as follows: C1 (control group), M1 (mucilage-treated group), P1 (Ishtx-k peptide-treated group), and MP1 (combined mucilage and peptide treatment group). Information regarding the primer sequences of target and reference genes is provided in Table 1. Finally, relative gene expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

Table 1. Primer sequences used in the Real-time PCR assay.

Primer names	Oligomers (5′→3′)	Target gene	Amplicon (bp)	Tm (ºC)	Accession number
AactF	CACCCGCCGCCAGCTCACC	*Human ActB*	124	64	*NM_001101.5*
ActR	CACGATGGAGGGGAAGACGG				
Fnkb	AGGACATGGTGGTTGGCTTTG	*NFkB*	122	60	AY521463.1
Rnkb	CAGAAGTCCAGGATTATAGCC				
F H19ZM	GGGATTTTACAGCAAGGAGG	*LncRNAH19*	134	57	NR_130973.1
R H19ZM	AGCGGTTAGGGCATACAGTG				
FNea	CTGCCAGTGTGAGTCGTAG	*LncRNANEAT1*	129	56	NR_003513.3
RNea	CCTAAGCCTCTGGAATTCAC				
FTAC3mr	CTGTTCGCGGCTGTCCTCG	*TAC3*	139	60	XM_021174976.2
RTAC3mr	CGTAGAGTCTCCGAAGCAGG				
FFGF1hm	GGAGCGACCAGCACATTCAG	*FGF1*	140	60	NM_010197.3
RFGF1hm	ACATTCCTCATTTGGTGTCTG				

TA = Temperature annealing

Statistical analysis

In this study, statistical analyses were performed using GraphPad Prism software (version 10). For normally distributed data, one-way ANOVA was used to compare mean values among different groups. In all tests, a p-value of less than 0.05 was considered statistically significant.

Gene network construction

Gene interaction networks related to cell proliferation and tissue repair were analyzed and constructed using Cytoscape software (version 3.10.3) in combination with KEGG, Reactome, and STRING databases. Based on the obtained data, a gene network was generated with a focus on the studied genes, including *NF-κB*, *lncRNA H19*, *lncRNA NEAT1*, *TAC3*, and *FGF1*.

Results

Transformation and selection of *E. coli* BL21

The initial culture of *Escherichia coli* BL21 resulted in the formation of isolated single colonies on LB agar medium. These colonies were used as the primary source for the preparation of competent cells. Following transformation and subsequent plating on LB agar medium supplemented with ampicillin, multiple colonies of transformed bacteria were formed (Fig. 1A). Several colonies grown on ampicillin-containing agar medium were randomly selected and screened using colony PCR. Electrophoresis of the PCR products on a 1% agarose gel revealed a DNA band of approximately 666 bp in all examined colonies (Fig. 1B), corresponding to the presence of the Ishtx-k gene in the pET32b(+)RH plasmid.

Expression and purification

SDS-PAGE analysis confirmed the presence of the Ishtx-k peptide with an approximate molecular weight of 22 kDa (Fig. 2B) in both soluble and insoluble fractions. In the preliminary electrophoretic analysis of proteins extracted from recombinant bacteria, the pre-induction sample corresponds to cells harvested prior to the initiation of recombinant protein expression. The insoluble fraction contains proteins that, following cell lysis, were aggregated or formed inclusion bodies and therefore remained in the insoluble phase, whereas the soluble fraction consists of proteins that remained in the soluble phase after cell lysis and were successfully extracted. Following purification of the protein from the soluble fraction using a Ni-NTA affinity column, the purified sample was analyzed by

SDS-PAGE (Fig. 2C). In the analysis of samples before and after purification, the total lysate represents the total cellular protein content prior to purification, while the pre-induction sample corresponds to cells harvested before the initiation of recombinant protein expression. The elution fractions correspond to the purification step, during which the target protein, after binding to the column and washing, was eluted and collected in fractions 2-4. Ishtx-k protein appeared as a single band with an approximate molecular weight of 22 kDa on the gel. Based on the constructed standard curve, the concentration of the Ishtx-k protein was calculated to be 1.113 µg/µL.

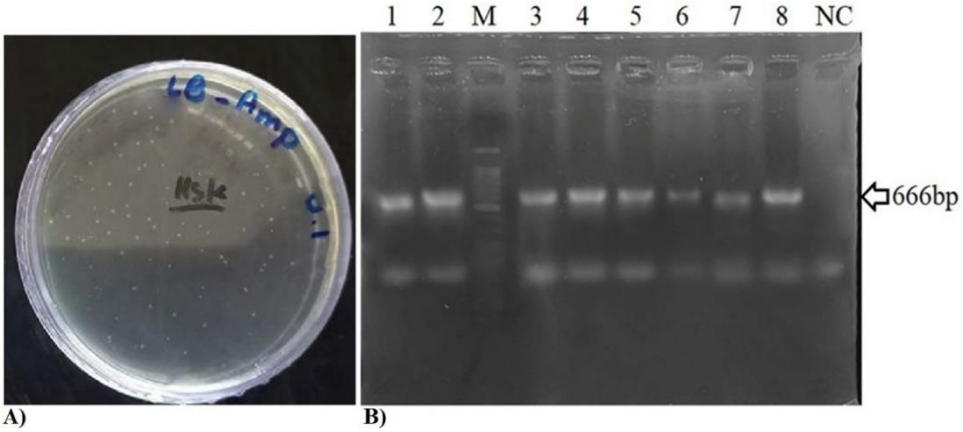

Fig. 1. Transformation and selection of recombinant *E. coli* BL21: A) LB agar plate showing transformed colonies with the recombinant pET32b-RH+Ishtx-k; B) Agarose gel electrophoresis of colony PCR products from the selected colonies. M: 100 bp DNA ladder; lanes 1-9: PCR amplicons resolved on a 1% agarose gel.

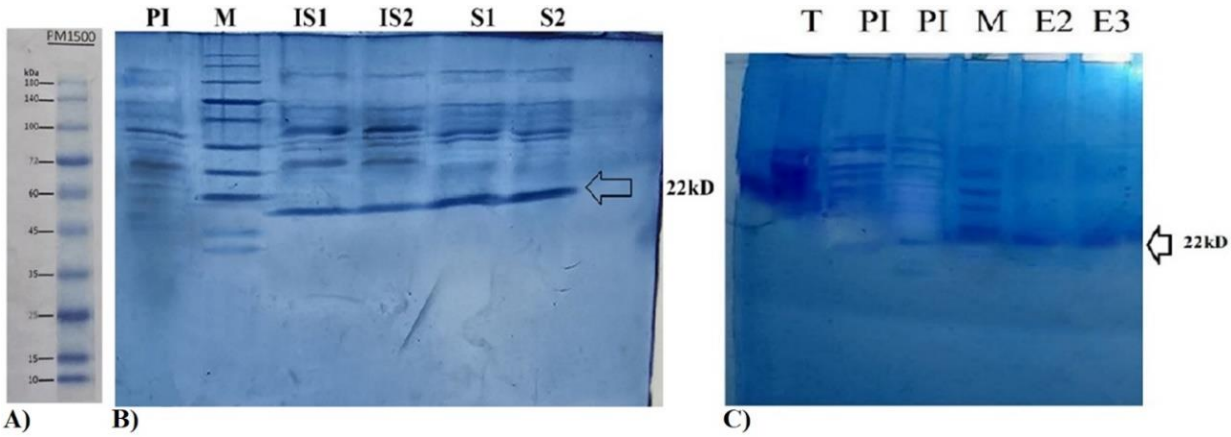

Fig. 2. Expression and purification analysis of recombinant protein by SDS-PAGE electrophoresis: A) Protein size marker; B) Preliminary electrophoretic analysis of protein extracted from recombinant bacteria (PI: pre-induction, M: protein molecular weight marker, IS1 and IS2: insoluble fraction, S1 and S2: soluble fraction); C) Electrophoretic analysis of proteins extracted before and after purification using a Ni-NTA column (T: total lysate, PI: pre-induction, M: protein molecular weight marker, E2 and E3: eluted purified proteins of fractions 2-4).

Ishtx-k and mucilage effects on cell growth

The results related to the growth and morphology of HGF3-PI53 cells in different treatment groups are shown (Fig. 3). In the negative control group, cells exhibited normal growth and showed appropriate morphology in terms of both cell number and structure. In the peptide group, no significant change in cell growth was observed compared with the negative control group. In the mucilage group, when the culture surface was coated with mucilage, the number of growing cells was lower than that in the negative control

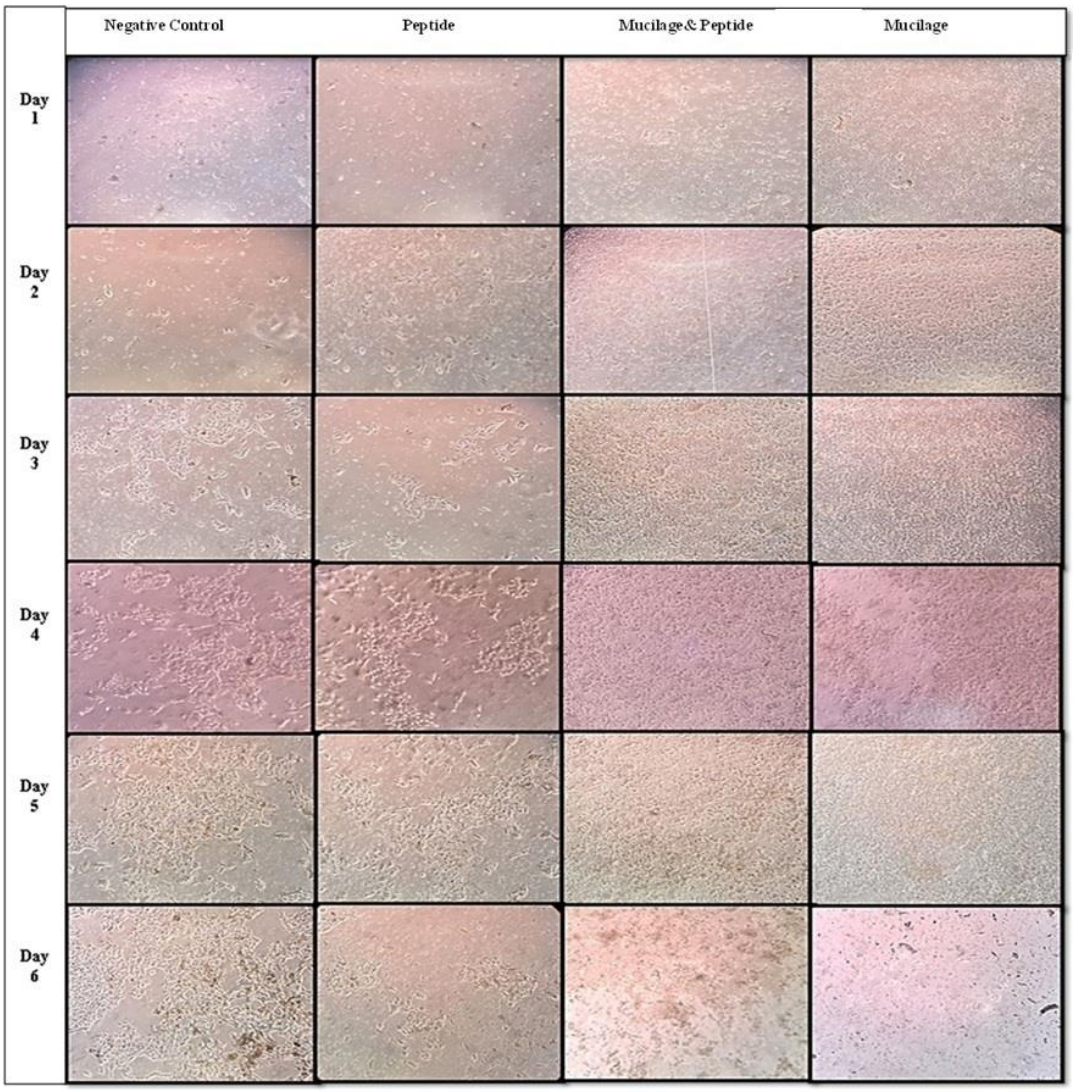

Fig. 3. Cell growth under different treatments: Microscopic images of the HGF3-PI53 cell cultures over 6 days under different treatment conditions. Attachment of the cell to the surface coated with mucilage was observed. However, the number of them was fewer than that of the control group.

group. In the combined mucilage and peptide group, results similar to those observed in the mucilage-only group were obtained.

Real-time PCR analysis

The quality of RNA extracted from the cell samples was evaluated by electrophoresis on a 1% agarose gel. The presence of clear 28S and 18S rRNA bands indicated the high quality of the extracted RNA.

The effects of different treatments on the expression of lncRNA H19, lncRNA NEAT1, FGF1, TAC3, and NF-κB were evaluated in fibroblast cells. *ACTB* was used as the reference gene. The melting curve analysis showed a single peak for each gene, confirming the specificity of the reactions. The gene expression results in cells are presented (Fig. 4A- E).

Statistical analysis was performed in the $p \leq 0.05$ significant range. The results demonstrated that treatment with okra mucilage and the Ishtx-K peptide reduced the expression of *NF-Kb* (fold change/FC= 0.47, p= 0.000), one of the most important regulators of inflammation (Fig. A). Also increased expression observed for *FGF1* gene (Fig. B) by overexpression to 4.2-fold, p= 0.000. and decreasing of the gene expression (about 50%) in *TAC3* (Fig. C) in the group treated with mucilage. As presented in Figure 4D, lncRNA *NEAT1* showed a significant reduction in

expression in all treatment groups compared with the control group (FC= 0.26 for mucilage-treated cells, FC= 0.8 for toxin-treated cells, and 0.4 in the combined treated group, p= 0.000). More severe reduction in lncRNA *H19* expression was seen in the group treated with mucilage and its combination with the peptide (Fig. 4E: FC= 0.2 and FC= 0.34, respectively, p= 0.000).

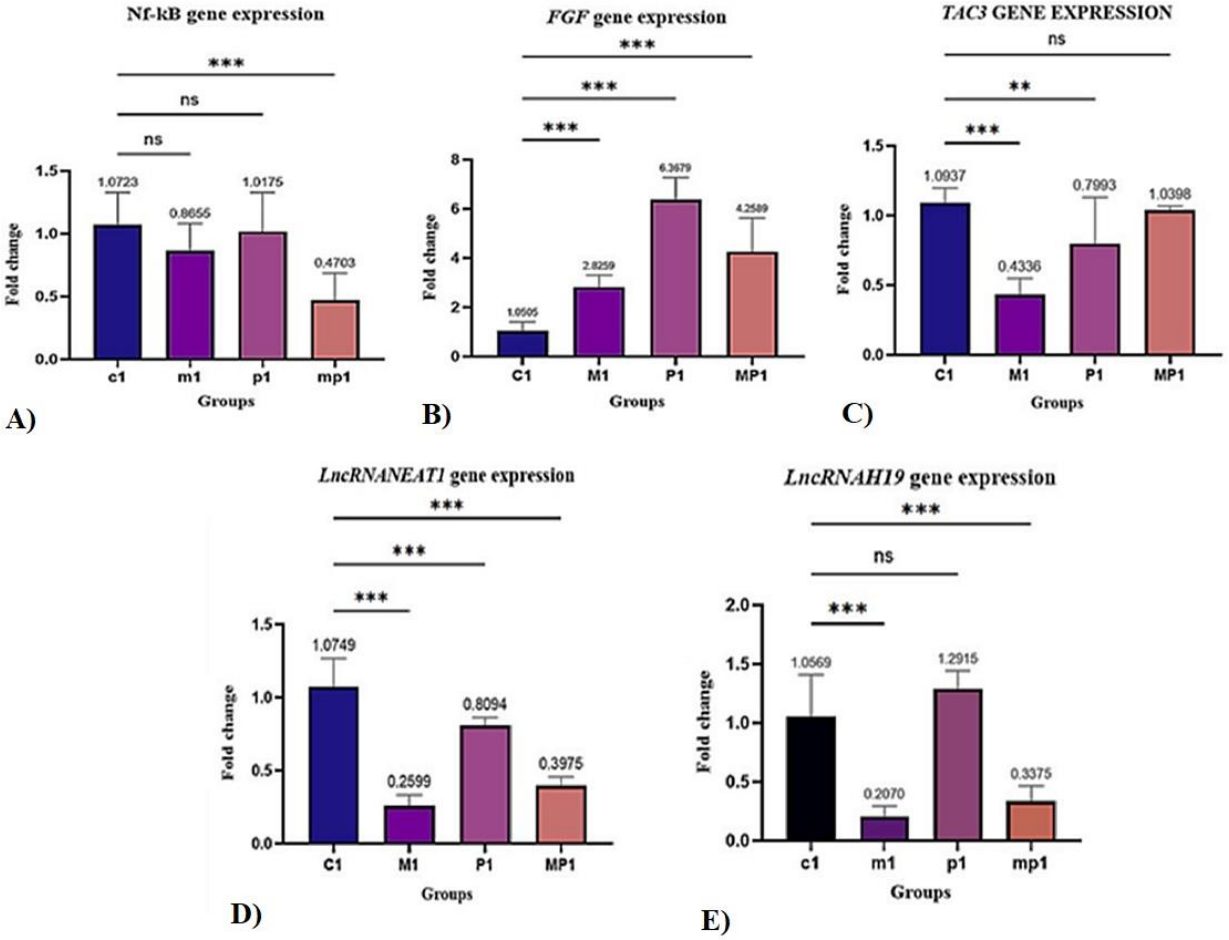

Fig. 4. Gene expression in HGF3-PI53 cells determined by Real-time PCR: Asterisks indicate significant differences compared with the control group (p≤ 0.01*, p≤ 0.001**, p≤ 0.000***), and ns indicates non-significant differences (p> 0.05).

Gene Network

The analysis of the constructed network (Fig. 5) revealed the presence of a functional triangle among *MMP9*, *TGF-β*, and *IL-6*, highlighting the relationship between inflammation and tissue differentiation factors. In addition, *lncRNA NEAT1* exerts an indirect inhibitory role on *miR-17*, indicating the involvement of both coding and non-coding molecules in the regulation of inflammation and the formation of fibrotic and necrotic structures during the tissue repair process.

Discussion

In this study, the effects of the Ishtx-k peptide and okra mucilage were evaluated under in vitro conditions. Numerous studies have investigated the therapeutic potential of peptides as well as the development of wound dressings for the management of wound healing–related complications (Guo *et al.*, 2024). Mucilage, as a complex polysaccharide, has attracted attention in various fields, including its application as a dietary supplement, a food matrix component,

and a biomaterial for tissue repair (De Oliveira Filho *et al.*, 2021). The findings demonstrated that mucilage alone exhibited no cytotoxic effects and showed no direct interaction with cells; however, it appeared to function as a relatively inert scaffold capable of regulating cell proliferation. The reduced cell growth observed on mucilage-coated surfaces was likely related to limited interactions between the cells and the extracellular matrix. This observation may also indicate mild inhibitory effects on cell proliferation that require further investigation (Yilmaz *et al.*, 2023). The Ishtx-k peptide showed no adverse effects on cell growth under cell culture conditions and, consistent with previous studies, demonstrated anti-inflammatory and scar-reducing properties (Song *et al.*, 2020).

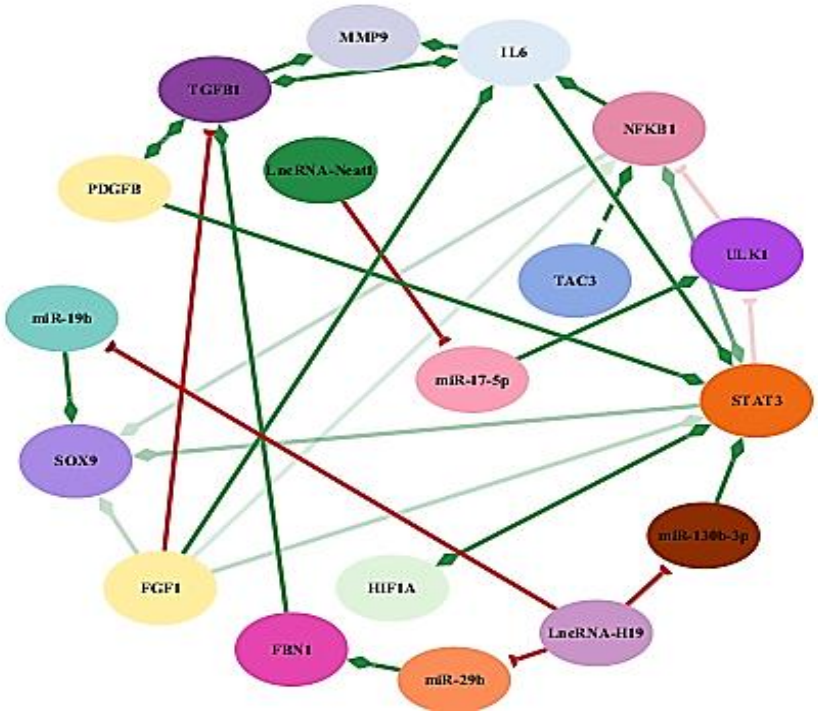

Fig. 5. Interaction network between the investigated genes and other genes involved in wound healing.

Gene expression analysis revealed that, at the cellular level, the combination of mucilage and peptide significantly reduced NF-κB expression, suggesting a potential anti-inflammatory effect of this combination, whereas mucilage alone did not induce a significant reduction. FGF1 expression was elevated in all groups treated with mucilage and peptide, which under in vitro conditions may be associated with stimulation of fibroblast activity and cellular proliferation. Regarding regulatory genes, mucilage alone and in combination with the peptide markedly reduced the expression of *LncRNAH19* and *LncRNANEAT1*, which may be attributed to the inhibitory effects of mucilage on cellular activity or cell population density. Numerous studies have shown that increased *NEAT1* expression is associated with the stimulation of fibrosis and inflammation in epithelial cells and fibroblasts, while its downregulation exerts anti-inflammatory effects (Zhang *et al.*, 2022). Furthermore, it has been confirmed in previous studies that increased H19 expression promotes inflammation and fibrosis in fibroblasts and epithelial cells, whereas its downregulation exhibits anti-inflammatory effects (Mu *et al.*, 2021). In contrast, treatment with the peptide alone tended to increase LncRNAH19 expression, although the change was not statistically significant. In addition, reduced TAC3 expression in the mucilage- and peptide-treated groups further supports the anti-inflammatory potential of these compounds (Khorasani *et al.*, 2020).

In this study, the relationship between genes indicative of inflammation, proliferation, and cell survival with other genes, especially those we

studied, was manually visualized using Cytoscape software. If we put the research findings next to the designed gene network, considering the results of the expression of genes such as *NF-κB*, *IL-6*, and *TGF-β*, and LncRNAs studied in the study, we can be optimistic that the use of the combination of mucilage and Ishtx-k toxin, in addition to reducing inflammation and modulating cell proliferation, will probably be able to help prevent the scar from remaining by better regulating wound healing *In vivo* conditions. Furthermore, alterations in the expression of genes such as *H19* and *TAC3* may directly or indirectly contribute to the regulation of inflammatory pathways and wound healing processes.

Conclusion

In this study, herbal-derived compounds and peptide-based therapy were investigated for their potential roles in the cellular and molecular regulation of cell growth. The findings suggest that mucilage may act as a modulating agent during the cell growth process, and its combined application with the Ishtx-k toxin may offer promising potential for the development of a suitable ointment for skin care strategies.

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Availability of data and materials

All data produced and presented throughout the study are included in the manuscript.

Conflict of interests

The authors declare no conflict of interest.

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