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The Effect of Pantoprazole, a Proton Pump Inhibitor, on Wound Healing in L929 Fibroblast Cells

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Abstract

This study aimed to investigate the potential effects of pantoprazole on wound healing using the L929 fibroblast cell line. Specifically, its impact on cell viability, oxidative stress markers, and the in vitro wound healing process was evaluated. The L929 fibroblast cells were treated with pantoprazole at concentrations between 2.5 and 40 µM for 24 hours to assess cell viability. To evaluate oxidative balance, 2.5 µM pantoprazole was applied, and total antioxidant status (TAS) and total oxidant status (TOS) were measured. For wound healing analysis, a scratch assay was performed by creating a standardized wound area (0.9×1.8 mm), and cell migration toward the wound was evaluated at 24-, 36-, and 48-hours post-treatment. Pantoprazole showed a concentration-dependent cytotoxic effect at doses between 5 and 40 µM ($p<0.05$ to $p<0.001$), while 2.5 µM significantly enhanced cell viability ($p<0.01$). TAS levels were significantly increased ($p<0.05$), with no significant change in TOS ($p>0.05$). Wound closure was significantly improved at 48 hours in the pantoprazole-treated group ($p<0.05$), though earlier time points showed no statistical difference. At low concentrations, pantoprazole enhances fibroblast viability, boosts antioxidant status, and accelerates wound healing, indicating potential therapeutic utility in tissue repair and oxidative stress modulation.

Keywords

Pantoprazole, Wound Healing, Cytotoxicity, Oxidative Stress

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Proton Pompası İnhibitörü Olan Pantoprazolün L929 Fibroblast Hücrelerinde Yara İyileşmesi Üzerindeki Etkisi

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Özet

Bu çalışmanın amacı, pantoprazolün yara iyileşmesi üzerindeki potansiyel etkilerini L929 fibroblast hücre hattı kullanarak araştırmaktır. Özellikle, pantoprazolün hücre canlılığı, oksidatif stres belirteçleri ve in vitro yara iyileşme süreci üzerindeki etkileri değerlendirilmiştir. L929 fibroblast hücreleri, hücre canlılığını değerlendirmek amacıyla 2,5 ila 40 µM konsantrasyonlarında pantoprazol ile 24 saat süreyle muamele edilmiştir. Oksidatif dengeyi değerlendirmek için 2,5 µM pantoprazol uygulanmış; total antioksidan seviye (TAS) ve total oksidan seviye (TOS) ölçülmüştür. Yara iyileşmesini analiz etmek amacıyla, 0,9 × 1,8 mm boyutlarında standart bir yara alanı oluşturulmuş ve pantoprazol ile tedavi edilen hücrelerin yara bölgesine göçü 24., 36. ve 48. saatlerde değerlendirilmiştir. Pantoprazol, 5 ila 40 µM arasındaki konsantrasyonlarda doza bağlı anlamlı sitotoksik etki göstermiştir ($p<0,05$ ila $p<0,001$), buna karşılık 2,5 µM konsantrasyonunda hücre canlılığında anlamlı bir artış saptanmıştır ($p<0,01$). TAS seviyeleri anlamlı şekilde artarken ($p<0,05$), TOS seviyelerinde anlamlı bir değişiklik gözlenmemiştir ($p>0,05$). Pantoprazol uygulanan grupta yara alanı 48. saatte anlamlı olarak daha hızlı kapanmıştır ($p<0,05$), ancak 24. ve 36. saatlerde istatistiksel fark saptanmamıştır. Düşük konsantrasyonlarda pantoprazol, fibroblast canlılığını artırmakta, antioksidan düzeyleri yükseltmekte ve yara iyileşmesini hızlandırmaktadır. Bu bulgular, pantoprazolün doku onarımı ve oksidatif stres modülasyonunda potansiyel terapötik yararlar sağlayabileceğini göstermektedir.

Anahtar kelimeler

Pantoprazol,
Yara İyileşmesi,
Sitotoksisite,
Oksidatif Stres

1. INTRODUCTION

Ana başlıklar büyük harf ile yazılmalıdır. Bu alandaki Wound healing is a complex, multi-stage biological process in which various tissue and cell types interact harmoniously [1]. The initial step in this process involves sealing the damage to the skin's protective layer with a clot. Following this, skin cells migrate and converge at the wound edges. All cell types participate in wound healing, guided by mechanical and chemical signals. The formation of new blood vessels, known as angiogenesis, is a temporary process, while collagen deposition is permanent [2]. In addition, the time factor plays a significant role in wound healing. Healing duration varies based on several variables, including the type of wound, the individual's overall health status, the vascular structure, the cause of the wound, its location in the body, and the presence of infection [3]. Chronic wounds are defined as those that take longer than three months to heal or do not heal at all. In contrast, acute wounds typically heal more quickly and with fewer complications. Consequently, the primary objective is to promote prompt healing of wounds, as prolonged healing can result in complications such as chronic ulcers and pathological scar formation[4]. Therefore, it is essential to expedite the wound healing process, prevent the formation of permanent scars, and inhibit the development of non-healing chronic wounds.

Reactive oxygen species (ROS) can cause cellular damage while also supporting beneficial processes, such as wound healing, at low concentrations. The balance in ROS levels is crucial for maintaining cellular health [5,6]. Antioxidants provide this balance by converting ROS into harmless compounds. Both enzymatic and non-enzymatic antioxidants play a crucial role, particularly in the process of wound healing [7,8]. Therefore, there is a growing therapeutic interest in new pharmacological compounds with antioxidant effects [9,10]. However, the clinical information and therapeutic potential of these new compounds or drugs with antioxidant properties in wound healing have not yet been sufficiently clarified.

Proton pump inhibitors (PPIs) are a class of substituted benzimidazole sulfoxide group of drugs that have strong inhibitory effects on gastric acid secretion in the parietal cells of the stomach. PPIs perform their inhibitory effect by irreversibly binding to the hydrogen-potassium ATPase (H^+/K^+-ATPase) enzyme located in the apical membrane of gastric parietal cells [11]. These pharmacological properties make them widely used in the treatment of diseases associated with acid hypersecretion, such as gastroesophageal reflux disease, peptic ulcers, and Zollinger-Ellison syndrome [12]. Furthermore, in addition to inhibiting gastric acid secretion, PPIs may exhibit neuroprotective properties, the ability to modulate the process of apoptosis, as well as anti-inflammatory, antifibrotic and antioxidant effects [13,14]. PPIs have been demonstrated to eliminate ROS by activating antioxidant defense mechanisms and regulating the expression of heme oxygenase-1 (HO-1) in this process. Consistent with the reorganization of antioxidant defense systems, several studies have demonstrated that PPIs can inhibit the oxidative modification of proteins and lipids [15]. The observation that PPIs exhibit neuroprotective, anti-inflammatory, and antioxidant effects, in addition to their role in suppressing gastric acid secretion, has heightened interest in exploring the therapeutic potential of these agents. In this study, we aimed to investigate the effects of pantoprazole, a PPI, on wound healing in the L929 fibroblast cell line by examining its antioxidant and oxidant effects under in vitro conditions.

2. MATERIAL AND METHOD

2.1. Experimental Design

This study investigated the effects of pantoprazole on cell proliferation and antioxidant and oxidative parameters in a wound-healing model established using L929 fibroblast cells (Figure 1).

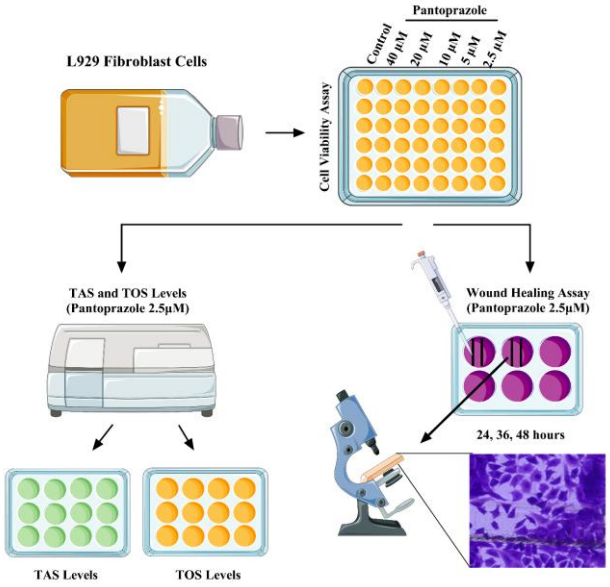

Figure 1. The experimental protocol of pantoprazole (The figure was created by Servier and is licensed under a Creative Commons Attribution 4.0 Unported License.).

2.2. Cell Culture and Chemicals

A healthy L929 fibroblast cell line was obtained from the American Type Culture Collection (ATCC). The cells were cultured in DMEM medium supplemented with 10% fetal bovine serum (FBS), 1% L-glutamine, and 1% penicillin-streptomycin in 25 cm^2 culture flasks. Cultures were maintained under sterile conditions at 37°C in a 5% CO_2 atmosphere. Passaging was performed when the cells covered approximately 80% of the culture surface. Experimental studies commenced from the third passage. Pantoprazole (Sigma-Aldrich Co., St. Louis, MO, USA) was dissolved in physiological saline. The drug solution was freshly prepared on each experimental day.

2.3. Cell Viability Assay

The effect of pantoprazole on cell viability was evaluated using the XTT assay [2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide]. For cytotoxicity analyses, 1.5×10^3 L929 cells were added to each well, and the plates were incubated overnight at 37°C in a 5% CO_2 atmosphere to allow the cells to adhere to the surface. The following day,

the medium was removed, and the wells were washed with phosphate-buffered saline (PBS). Different concentrations of pantoprazole, ranging from 40 to 2.5 µM, were then applied. After 24 hours of incubation, the cells were washed again with PBS. Then, 100 µL of colourless DMEM and 50 µL of XTT solution were added to each well, and the plates were incubated for 4 hours. The amount of formazan formed was measured at a wavelength of 450 nm, and cell viability was calculated as a percentage compared to the control group [16].

2.4. Preparation of Cell Homogenates

Cells from all groups were collected under sterile conditions and centrifuged at 2000 rpm for 10 minutes. The resulting cell pellets were suspended in PBS at pH 7.4 to a concentration of approximately 1×10^6 cells/mL [17]. Cell lysis was achieved through three freeze-thaw cycles, followed by centrifugation at 4000 rpm for 10 minutes at 4°C. The supernatants obtained were utilized for biochemical analyses. Total protein levels were quantified using the Bradford protein assay kit (SERVA, Heidelberg, Germany)[18].

2.5. Measurement of TAS and TOS Levels

Total antioxidant status (TAS) and total oxidant status (TOS) levels in cell supernatants were determined using the spectrophotometric automated assay method developed by Erel [19]. Measurements were conducted at wavelengths of 660 nm for TAS and 530 nm for TOS, with results expressed as µmol Trolox equivalent per mg of protein and µmol H_2O_2 equivalent per mg of protein, respectively. Total protein levels in the samples were measured using a Bradford protein assay kit (Merck Millipore, Germany) and subsequently normalized [20].

2.6. Wound Healing Assay

The wound healing assay was conducted using the Abcam wound healing kit (Wound Healing Assay, ab242285). This kit includes two sets of 24 wells, each creating wound areas measuring 0.9 × 1.8 mm. L929 fibroblast cells were plated in trans well plates following treatment with pantoprazole and incubated for 24, 36, and 48 hours. Cell migration was visualized using light microscopy, and proliferation rates were assessed by measuring the distance of migration within the wound area. The control wells contained untreated L929 cells cultured under identical conditions without exposure to pantoprazole. Both control and treated wells underwent the same wound creation protocol using the removable inserts provided by the kit to ensure consistent wound widths. This approach allowed for a direct comparison of migration rates between pantoprazole-treated and control cells, eliminating variability caused by manual scratching or inconsistent wound geometry [3].

2.7. Statistical analysis

Results are presented as mean values ± standard error of the mean (SEM). Data analysis was conducted using GraphPad Prism software (version 10.0; Boston, USA). XTT assay data were evaluated using one-way ANOVA and analyzed with independent t-tests for pairwise comparisons.

3. RESULTS

3.1. Effect of Pantoprazole on Cell Viability in L929 Cells

The effects of pantoprazole on cell viability were evaluated in L929 fibroblast cells. Treatment of L929 cells with pantoprazole concentrations ranging from 5 to 40 µM for 24 hours resulted in a significant, concentration-dependent cytotoxic effect on cell viability ($p < 0.05$ to $p < 0.001$; Figure 2). In contrast, treatment with 2.5 µM pantoprazole significantly increased cell viability compared to the control group ($p < 0.01$) (Figure 2).

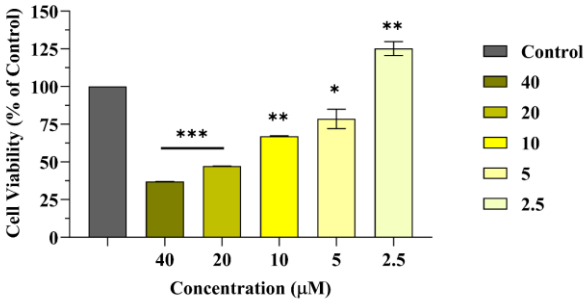

Figure 2. The effect of Pantoprazole on L929 cell viability. The data are given as mean ± SEM. *p < 0.05, **p < 0.01 and ***p < 0.001 as compared to the control group (n=3).

3.2. Effect of Pantoprazole on TAS and TOS levels in L929 Cells

To evaluate the effects of pantoprazole on antioxidant and oxidative parameters, L929 cells were incubated with pantoprazole at a concentration of 2.5 µM for 24 hours. As shown in Figure 3A, the administration of pantoprazole resulted in a significant increase in TAS levels compared to the control group ($p < 0.05$). In contrast, no statistically significant change was observed in TOS levels following pantoprazole administration ($p > 0.05$; Figure 3B).

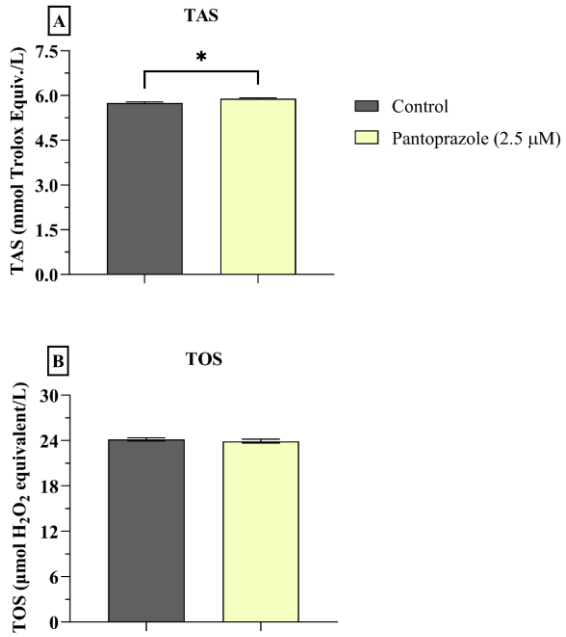

Figure 3. Effect of Pantoprazole on (A) TAS and (B) TOS levels in L929. The data are given as mean ± SEM. *p < 0.05 as compared to the control group (n=3). In panel (A), a broken Y-axis was applied to better visualize small differences between groups; values below 5 µmol Trolox eq/mg protein are not shown.

3.3. Effects of Pantoprazole on Wound Healing in L929 Cells

To create the wound healing model, a standardized wound area measuring 0.9 × 1.8 mm was established, and L929 cells were introduced into this area. Subsequently, 2.5 µM pantoprazole was administered to the cells, which were then incubated for 24, 36, and 48 hours. After each incubation period, the migration distances of the cells toward the wound area were measured. At 24 and 36 hours, an increase in the wound-healing process was observed in the pantoprazole-treated group compared to the control group; however, this difference was not statistically significant ($p > 0.05$; Figure 4). In contrast, at 48 hours, it was determined that the pantoprazole-treated cells migrated to the wound area more rapidly and closed the area more effectively than the control group, with this difference being statistically significant ($p < 0.05$; Figure 4).

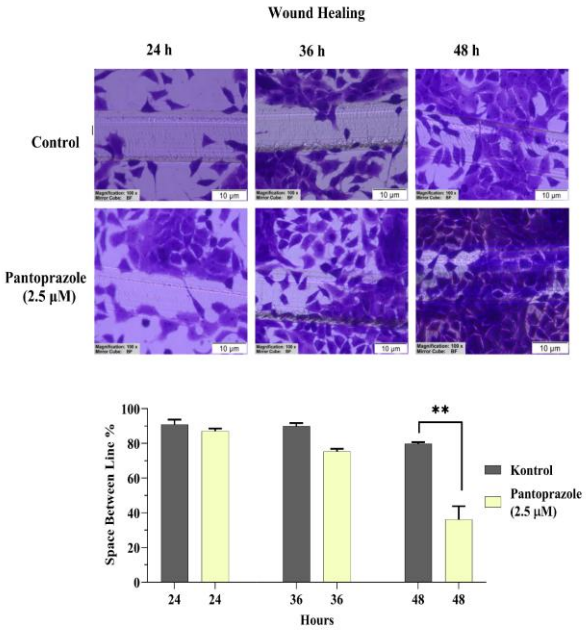

Figure 4. The effect of Pantoprazole on wound healing of L929 cell line at 24, 36 and 48 hours. Data are given as mean ± SEM. *p < 0.05, compared with the control group (n=3).

4. DISCUSSION AND CONCLUSION

Wound healing is the process by which the integrity of tissue is restored following physical damage. This complex process involves a series of cellular and molecular events that allow the tissue to regain its structure and function. Wound healing occurs in three distinct phases: hemostasis and inflammation, proliferation, and remodeling. Disruption of any of these phases can result in delayed healing or chronic wounds [21].

In this study, the cytotoxic, proliferative, antioxidant, and oxidant effects of pantoprazole on L929 fibroblast cells were evaluated using a wound healing model. While pantoprazole demonstrated cytotoxic effects at high concentrations, it exhibited cell proliferation-enhancing and antioxidant properties at lower concentrations (2.5 µM). However, treatment with 2.5 µM pantoprazole did not result in a significant change in oxidative stress parameters.

Preclinical studies indicate that PPIs have antitumor potential by influencing processes such as apoptosis, metastasis, and autophagy, in addition to their role in gastric acid suppression [22,23]. Moreover, there is growing interest in their application across various clinical fields due to their antifibrotic, antioxidant, and anti-inflammatory properties [24].

Many studies have demonstrated that PPIs may have a beneficial effect on wound healing. In a study conducted by Akimato et al. in 2005, it was found that the use of PPIs increased the expression of CXC chemokine receptor (CXCR4) mRNA in patients with gastric ulcers. This increase promoted vascular regeneration, maturation, and angiogenesis, thereby supporting the healing of ulcers [25]. In another in vitro experiment, the mouse gastric mucosal cell line GSM06 was used, and it was reported that the administration of lansoprazole, a PPI, increased

cell proliferation and migration. These findings suggest that lansoprazole promotes gastric mucosal healing by enhancing cell regeneration and that this effect may be associated with the activation of the p44/p42 MAPK pathway [26]. In our study, we observed that pantoprazole had a favorable effect on wound healing. However, the proliferative effect of PPIs on fibroblasts may appear contradictory to the antifibrotic and anti-inflammatory effects reported in previous studies. However, pantoprazole demonstrated a proliferative effect on fibroblasts at low concentrations and a cytotoxic effect at higher concentrations, which aligns with previous literature. Similar dose-dependent biphasic effects of pantoprazole have been reported in various cell models. Prause et al. demonstrated that low concentrations of pantoprazole (up to 10 µg/mL, ≈27 µM) enhanced viability and alkaline phosphatase activity in primary human osteoblasts, whereas higher concentrations reduced cell function [27]. In contrast, studies in gastric and colon cancer cells reported significant cytotoxicity and apoptosis induction at concentrations above 40 µM, highlighting a switch from proliferative to cytotoxic activity in a concentration-dependent manner [28,29]. These findings further support our observation that pantoprazole exhibits a dual, dose-dependent effect on fibroblast cells in the wound healing model. According to the findings of our study, pantoprazole, particularly at low concentrations, may be expected to accelerate wound healing through its proliferative effects during the second phase of healing. Furthermore, at high concentrations, it may facilitate a more favorable progression of the remodeling process by influencing the third phase of healing, potentially aiding in the prevention of poor wound healing and fibrotic formations.

Oxidative stress and antioxidant mechanisms play a crucial role in the wound healing process. Oxidative stress occurs due to an imbalance of ROS within cells, which can result in cellular damage, inflammation, and tissue degradation [30]. In the early stages of intermediate healing, an increase in ROS can promote cell proliferation and the formation of angiogenesis. However, elevated levels of ROS can lead to tissue damage [8]. Antioxidants are molecules that counteract the damage caused by ROS. In the later stages of wound healing, the body activates antioxidant defense systems to mitigate oxidative stress. Maintaining a balance between oxidative stress and antioxidant systems is crucial for successful tissue repair [31]. Studies have focused on the antioxidant effects of certain PPIs, such as pantoprazole, in reducing oxidative stress and preventing cellular damage [13,32]. In a study conducted by Taşkıran et al. on the toxicity of PTZ, it was observed that pantoprazole significantly reduced oxidative stress by exhibiting antioxidant effects in cells and stabilized cellular integrity by enhancing apoptosis[13]. In another study investigating the neuroprotective effects of pantoprazole against morphine tolerance, it was reported that pantoprazole significantly increased TAS while decreasing TOS [33]. In our study, we concluded that pantoprazole significantly increased antioxidant levels in fibroblast cells and accelerated the wound healing process. These findings suggest that pantoprazole significantly reduces the effects of oxidative stress by showing potent antioxidant properties and plays a crucial role in tissue repair.

In conclusion, pantoprazole enhanced wound healing in L929 fibroblast cells at low concentrations (2.5 µM), whereas higher doses exhibited cytotoxic effects. Low-dose pantoprazole significantly increased the total antioxidant status without affecting the total oxidant status, indicating that its wound-healing potential may be mediated through antioxidant mechanisms. These results suggest that pantoprazole promotes fibroblast proliferation and migration in a dose-dependent manner, supporting its potential role in tissue repair.

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