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Topical buspirone accelerates wound healing in rats through modulation of inflammation, angiogenesis, and collagen formation

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ABSTRACT

Objective(s): Cutaneous wound healing is a complex, multistep process that requires coordinated regulation of inflammation, cell proliferation, extracellular matrix deposition, and angiogenesis. This study evaluated the effects of topical buspirone, a partial 5-HT1A receptor agonist, on wound healing in a rat excisional wound model.

Materials and Methods: Full-thickness dorsal wounds were created in Wistar rats and treated with topical 0.5% buspirone, 1% phenytoin, vehicle, or left untreated. Wound contraction was assessed macroscopically, and hydroxyproline content, TNF-α, and TGF-β levels were measured to evaluate collagen deposition and inflammatory and fibrotic responses. Histopathological analysis and a chick chorioallantoic membrane (CAM) assay were also performed.

Results: Buspirone treatment significantly accelerated wound contraction at all time points compared with the control, vehicle, and phenytoin groups ($P<0.001$). Hydroxyproline levels were significantly increased, indicating enhanced collagen deposition. In addition, TNF-α levels were reduced, whereas TGF-β levels showed a moderate increase, suggesting balanced modulation of inflammation and fibrosis. Histological findings demonstrated improved re-epithelialization and dermal organization in the buspirone-treated group. Enhanced angiogenesis was also observed in the CAM assay.

Conclusion: Overall, topical buspirone may promote wound healing through coordinated effects on inflammation, collagen synthesis, tissue organization, and angiogenesis. This suggests that buspirone is a potential therapeutic agent for wound healing.

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Introduction

Cutaneous wound healing is a dynamic, tightly regulated process with overlapping phases, including hemostasis, inflammation, proliferation, and remodeling (1). Successful repair requires precise coordination of multiple cellular and molecular events, including inflammatory regulation, fibroblast migration, angiogenesis, extracellular matrix deposition, and re-epithelialization (2). Disruption of these processes can impair healing and may lead to chronic wounds or excessive scar formation (3, 4).

Chronic and non-healing wounds represent a significant global health burden and are associated with reduced quality of life (5). Chronic wounds commonly develop in conditions characterized by impaired tissue repair, such as diabetes mellitus, vascular insufficiency, prolonged pressure exposure, infection, and aging (6, 7). In addition to persistent pain and limited mobility, these wounds often require long-term clinical management and repeated interventions, placing substantial strain on healthcare systems (5, 6).

Although various wound dressings and advanced therapies are available, many fail to control prolonged inflammation or fully restore normal tissue structure adequately. This highlights the need for more effective therapeutic strategies that target key mechanisms of tissue repair (7, 8).

Recent studies have suggested a role for serotonin (5-hydroxytryptamine, 5-HT) in peripheral tissue repair and skin regeneration (9, 10). Serotonin has been shown to regulate immune cell function, including dendritic cells and macrophage polarization (11, 12). It may also influence fibroblast activity and angiogenesis during tissue repair (10, 13).

Serotonin receptors, including 5-HT1A, are involved in modulation of inflammatory responses, vascular tone, and immune cell activity (14-18). Buspirone, a 5-HT1A partial agonist, is a widely used anxiolytic with a well-established safety profile (19, 20). Owing to its extensive clinical use and well-characterized pharmacological profile, buspirone

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was selected as a clinically relevant agent to investigate the contribution of 5-HT1A receptor activation to wound healing (21, 22). However, its potential role in cutaneous wound healing, particularly in topical formulations, has not been sufficiently explored. Given the advantages of topical drug delivery in wound management, including direct application to the wound site and reduced systemic exposure, the effects of topically administered buspirone were investigated in the present study.

Accordingly, the present study aimed to investigate the effects of topical buspirone on cutaneous wound healing in rats using macroscopic, biochemical, histopathological, and angiogenic assessments.

Materials and Methods

Buspirone ointment preparation

Buspirone powder was obtained from Tehrandarou Pharmaceutical Company (Tehran, Iran). Buspirone ointments were prepared using the levigation method. Briefly, the required quantity of buspirone was accurately weighed and pulverized in a mortar to obtain a fine powder. A small quantity of Eucerin was added gradually to levigate the powder and form a smooth paste. The remaining Eucerin base was incorporated incrementally with continuous geometric dilution until a homogeneous ointment was obtained. The final preparation was transferred into a suitable container and stored at room temperature until use. A preliminary pilot study was conducted to determine the optimal concentration of buspirone for topical application. Three concentrations (0.5%, 1%, and 2% w/w) were evaluated using a within-subject experimental design. Wound contraction and overall healing quality were assessed macroscopically. Based on comparative evaluation, the 0.5% buspirone formulation demonstrated superior wound healing performance compared to the higher concentrations (1% and 2%), and was therefore selected for use in the main experimental study.

Animals and experimental design

Twenty adult Wistar male and female rats (*Rattus norvegicus*), weighing 200±20 g and aged 8-12 weeks, were used in this study. Animals were maintained under standard laboratory conditions (22±2 °C, 12 hr light/dark cycle) with free access to food and water. All experimental procedures were approved by the Ethics Committee of Hamadan University of Medical Sciences (ethical approval No; IR.UMSHA.AEC.1403.022) and were carried out in accordance with institutional guidelines for the care and use of laboratory animals. The animals were randomly assigned to four groups (5 per group): (1) buspirone-treated group (0.5% topical formulation), (2) positive control (phenytoin 1% cream), (3) vehicle control (Eucerin base), and (4) untreated control.

Wound induction and treatment protocol

Animals were anesthetized with ketamine (60 mg/kg) and xylazine (10 mg/kg) via intraperitoneal injection. After shaving and disinfection with 70% ethanol, two full-thickness excisional wounds (1×1 cm) were created on the dorsal surface of each animal using a sterile template. Although a standardized 1 1 cm excisional template was used, the wound margins became irregular during the early inflammatory phase, which may result in apparent variations in measured wound area over time. Wound size was therefore quantified based on surface area tracing rather than geometric assumptions. Postoperative analgesia was administered using piroxicam (0.5 mg/kg, IP) for three consecutive days. Animals were monitored daily throughout the study. The treatments were applied topically twice daily, and wound healing was monitored for approximately 13 days. On this day, the animals were euthanized, and tissue samples were collected for further studies.

Wound evaluation

The wounded areas were assessed every three days using digital photography with a standardized scale. Images were analyzed using ImageJ software, and the percentage of wound contraction was calculated relative to the initial wound size (day 1).

Histopathological analysis

Skin biopsies were collected on days 7 and 13, fixed in 10% formalin, and processed for histological examination. A blinded pathologist evaluated tissue sections under light microscopy for inflammatory cell infiltration, fibroblast proliferation, angiogenesis, granulation tissue formation, and re-epithelialization.

Biochemical and molecular analyses

Hydroxyproline content, as an indicator of collagen deposition, was measured using a commercial colorimetric assay kit (KIAZIST Life Sciences, Iran) according to the manufacturer's instructions.

Rat tumor necrosis factor-α (TNF-α) (ZellBio, Germany) and rat transforming growth factor-beta (TGF-β) (MyBioSource, USA) ELISA kits were used according to the manufacturer's instructions. Protein concentrations were calculated from the corresponding standard curves and expressed as pg/mL or µg/mg tissue, as appropriate.

Evaluation of the effect of buspirone on angiogenesis

The angiogenic activity of buspirone was evaluated using a modified chick chorioallantoic membrane (CAM) assay based on a previously described method (23). Fertilized chicken eggs were incubated at 37 °C and 45% humidity for 7 days. After vascular development, a small window was created in the eggshell, and buspirone solution (0.5%, 50 µl) was applied through the opening. The window was sealed, and the eggs were re-incubated for 24 hr. Vascular development was photographed and re-evaluated after an additional 24 hr of incubation. Control eggs underwent the same procedure without drug administration (n=8).

Statistical analysis

Statistical analyses were performed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD). Normality was assessed using the Kolmogorov–Smirnov test. One-way and two-way ANOVA followed by Tukey's *post hoc* test was used for intergroup comparisons. Statistical significance was defined as $P<0.05$.

Results

Effect of topical buspirone on wound contraction rate

Wound closure was evaluated on days 1, 3, 7, 10, and 13 following treatments. As illustrated in Figure 1, wound closure progressed more rapidly in the buspirone-treated group than in the phenytoin, vehicle, and control groups.

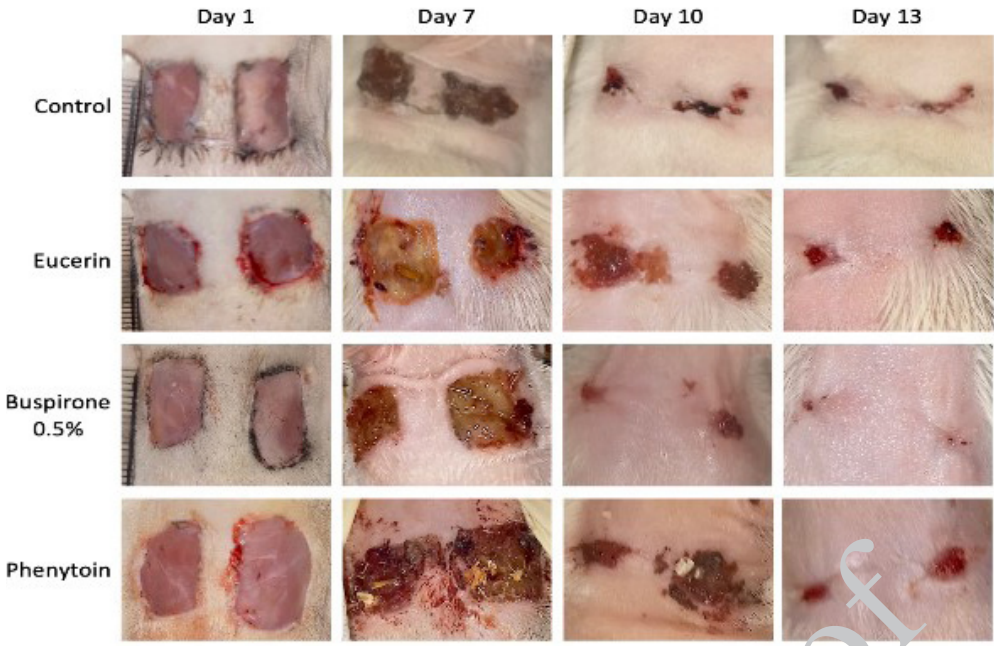

Figure 1. Representative photographs of mouse wound healing progression in different treatment groups (control, Eucerin, buspirone 0.5%, and phenytoin) on days 1, 7, 10, and 13 post-injury

Topical buspirone significantly (P<0.001) accelerated wound contraction compared to the control, vehicle, and phenytoin-treated groups at all time points (Figure 2). On day 3, wound closure reached 45.83% in the buspirone group, compared with 23.97% in the control and 38.18% in the phenytoin group. The difference increased over time, with contraction rates of 93.86% in the buspirone group versus 82.45% and 69.48% in the phenytoin and control groups, respectively, on day 10. By day 13, nearly complete wound closure (97.65%) was observed in the buspirone-treated group, whereas wound closure remained markedly incomplete in the other experimental groups.

Topical buspirone treatment resulted in visibly accelerated wound contraction and improved healing compared to the control, vehicle (Eucerin), and phenytoin-treated groups.

Two-way ANOVA revealed significant effects of both time and treatment on wound contraction (P<0.001), with time accounting for 78.90% of the total variance (F = 325.5) and treatment accounting for 11.20% (F = 46.71). *Post hoc* Tukey analysis confirmed significantly greater contraction in the buspirone group compared to the control, vehicle, and phenytoin groups across all evaluated time points (P<0.001) (Figure 2).

Effect of topical buspirone on hydroxyproline content

Hydroxyproline levels were measured on days 7 and 13 as an index of collagen deposition (Figure 3A). On day 7, the buspirone-treated group showed significantly higher hydroxyproline levels compared to the control, vehicle, and phenytoin groups (P<0.0001). This trend persisted on day 13, with the highest levels observed in the buspirone group. Although the vehicle group exhibited a moderate increase on day 13, no significant difference was detected between the phenytoin and control groups at this time point.

Effect of topical buspirone on TGF-β levels

Tissue levels of TGF-β were assessed on days 7 and 13 to evaluate fibrotic signaling (Figure 3B). On day 7,

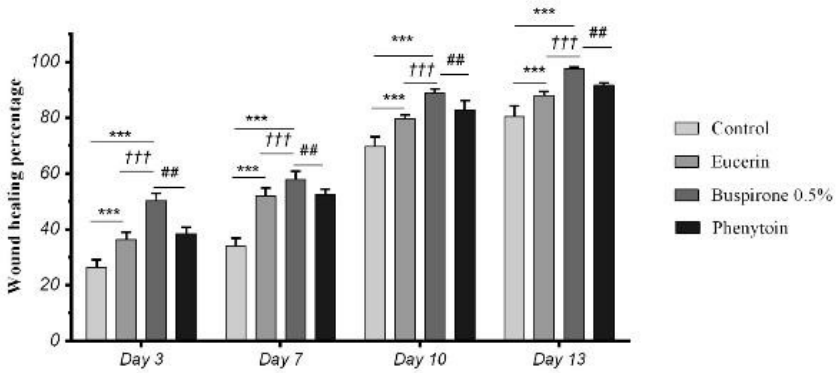

Figure 2. Effect of topical buspirone on mouse wound contraction over time

Percentage of wound closure was measured on days 3, 7, 10, and 13 in control, vehicle (Eucerin), buspirone (0.5%), and phenytoin-treated groups. Buspirone-treated animals exhibited significantly greater wound contraction compared to the control, vehicle, and phenytoin groups at all evaluated time points. Data are presented as mean±SEM (n=5 per group). Statistical analysis was performed using two-way ANOVA followed by Tukey's *post hoc* test. ***P<0.001 vs control; †††P<0.001 vs vehicle; ##P<0.01 vs phenytoin.

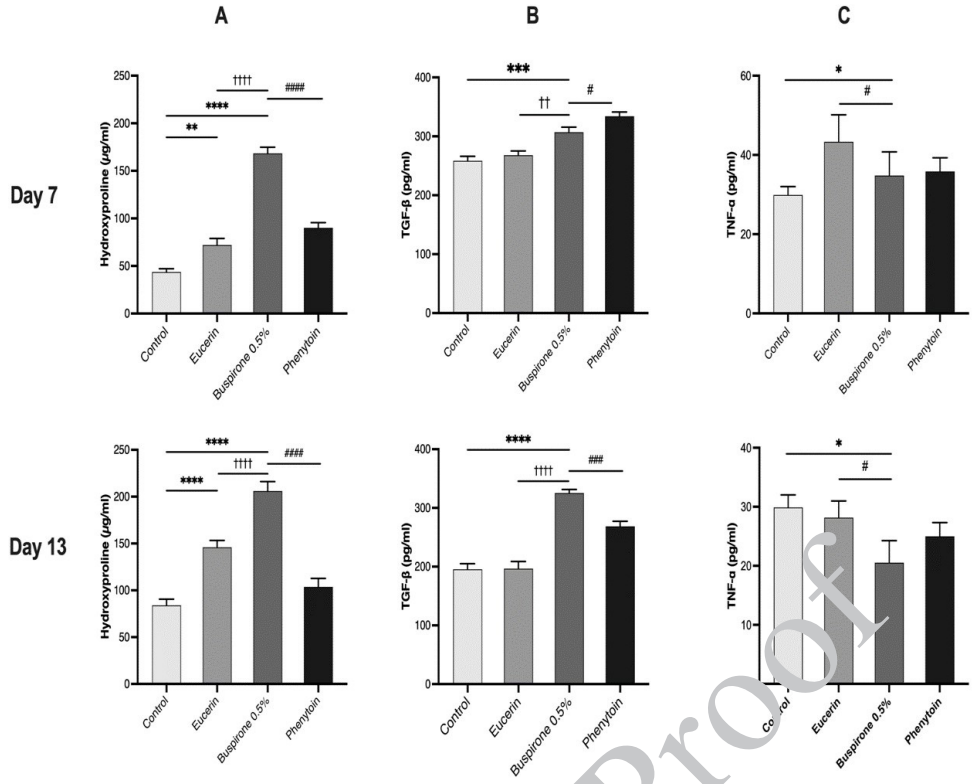

Figure 3. Effects of topical buspirone on collagen deposition, fibrotic signaling, and inflammation during wound healing in mice
(A) Hydroxyproline content (µg/ml), (B) transforming growth factor-beta (TGF-β, pg/ml), and (C) tumor necrosis factor-alpha (TNF-α, pg/ml) levels were measured in wound tissue on days 7 and 13 in control, vehicle (Eucerin), buspirone 0.5%, and phenytoin-treated groups. Data are expressed as mean±SEM. **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001 versus control; †*P*<0.05, ††*P*<0.01, ††††*P*<0.0001 versus indicated groups; #*P*<0.05, ###*P*<0.001 versus indicated groups.

TGF-β levels were significantly elevated in both buspirone and phenytoin-treated groups compared to the control (*P*<0.0001), with a greater increase observed in the phenytoin group. A similar pattern was observed on day 13, where both treatment groups maintained higher TGF-β levels than control, while no significant difference was detected between vehicle and control groups.

Effect of topical buspirone on TNF-α levels

TNF-α levels were measured to assess the inflammatory response during wound healing (Figure 3C). Two-way ANOVA demonstrated significant effects of both time and treatment (*P*<0.001), with time accounting for 54.83% and treatment for 18.39% of total variance. On day 7, TNF-α levels in the buspirone group were significantly lower than in the control and vehicle groups (*P*<0.05), and this reduction persisted on day 13. No significant differences were observed between buspirone and phenytoin groups at either time point. Across all groups, TNF-α levels decreased over time, with significantly lower levels on day 13 compared to day 7 (*P*<0.001). The lowest TNF-α levels were observed in the buspirone group.

Buspirone 0.5% significantly increased hydroxyproline levels on both day 7 and day 13 compared to the control, vehicle, and phenytoin groups, which indicates enhanced collagen deposition. TGF-β levels were significantly elevated in both buspirone and phenytoin groups relative to the control at both time points, with phenytoin showing the highest levels. TNF-α levels were significantly reduced in the buspirone-treated group compared to the control and vehicle groups at both time points, with an overall decrease observed across all groups from day 7 to day 13.

Histopathological evaluation

Histopathological analysis was performed on days 7 and 13 to assess tissue regeneration and structural organization (Figure 4). On day 7, all groups exhibited fibrin clot formation over the wound surface, with varying thicknesses. Keratinocyte migration from the wound edges was evident in the phenytoin-treated group and was more pronounced in the buspirone-treated group. In contrast, only minimal migration was observed in the vehicle group, while the control group showed little to no evidence of epithelial cell movement. Dermal remodeling was also more apparent in the buspirone group, accompanied by areas of dermal Vacuolization. By day 13, epidermal regeneration was observed in all groups; however, the extent of healing differed markedly. The control group exhibited incomplete wound closure, with a thin and poorly developed neo-epidermis. In contrast, complete epithelialization was observed in all treated groups.

The phenytoin and vehicle groups demonstrated moderate epidermal organization, with the phenytoin group showing a more defined multi-layered structure. The most advanced tissue architecture was observed in the buspirone-treated group, characterized by a thick, well-organized epidermis with distinct rete ridges and clear differentiation between papillary and reticular dermis. No skin appendages, such as hair follicles, were observed in any group on day 13. Additionally, there was no histological

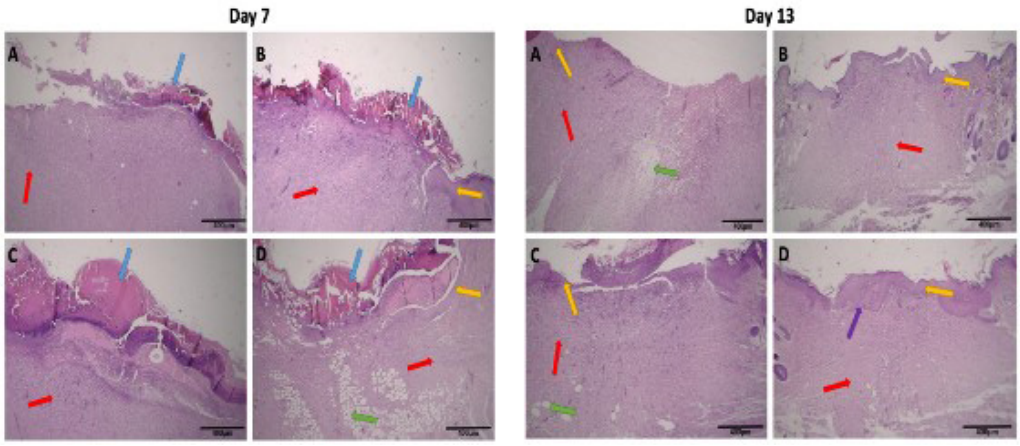

Figure 4. Histopathological evaluation of mouse wound healing following topical treatments on days 7 and 13 (H&E staining, scale bar=400 µm)
Representative photomicrographs of wound tissues from four experimental groups: (A) untreated control, (B) phenytoin-treated, (C) vehicle (Eucerin)-treated, and (D) buspirone (0.5%)+vehicle-treated animals. On day 7, all groups exhibited fibrin clot formation (blue arrows) of varying thickness over the wound surface. Keratinocyte migration from wound edges (yellow arrows) was evident in the phenytoin group and more pronounced in the buspirone-treated group. In contrast, minimal or absent migration was observed in the vehicle and control groups, respectively. Dermal remodeling (red arrows) was more prominent in the buspirone group, along with areas of dermal vacuolization (green arrows).

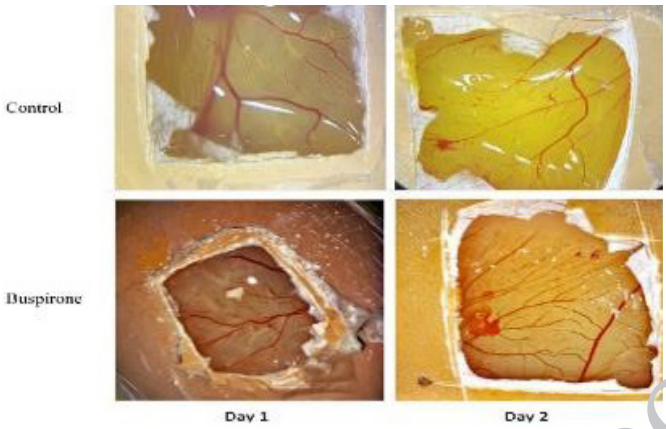

Figure 5. Representative images demonstrating the effect of 24-hr buspirone treatment on angiogenesis in the chick chorioallantoic membrane (CAM) assay

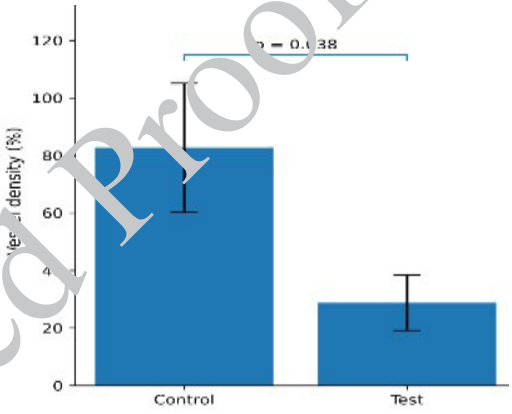

Figure 6. Quantitative analysis of angiogenesis in the chick chorioallantoic membrane (CAM) assay
Vessel density was determined as the percentage of the selected region of interest occupied by blood vessels. Data are presented as mean±SD

evidence of hypertrophic scar or keloid formation in any of the experimental groups.

Effect of buspirone on angiogenesis

CAM assay analysis revealed that treatment with buspirone significantly increased vessel density after 24 hr compared with the control group, suggesting enhanced angiogenic activity (Figure 5). Semi-quantitative analysis of CAM images demonstrated a marked increase in vessel density in the test group compared with the control group. The mean vessel density was 82.64 ± 22.40% in the buspirone-treated group and 28.87±9.60% in the control group. Statistical analysis using Welch's unpaired t-test revealed a significant difference between groups (P=0.038), indicating that treatment significantly stimulated angiogenesis in the CAM model (Figure 6).

Discussion

The present study demonstrates that topical buspirone accelerates cutaneous wound healing through coordinated effects on multiple aspects of the repair process, including wound contraction, collagen deposition, inflammatory regulation, tissue organization, and angiogenesis.

Wound healing is a complex and tightly regulated process involving interactions between cytokines, growth factors, and extracellular matrix components (24-26). Wound contraction is a key indicator of healing progression and is primarily driven by fibroblast activity and myofibroblast-mediated remodeling of the extracellular matrix (27). In the present study, buspirone-treated wounds exhibited significantly faster contraction compared to the control, vehicle, and phenytoin groups, which may be associated with enhanced fibroblast activity and improved extracellular matrix organization. *In vitro* and *in vivo* studies have demonstrated that serotonin signaling has been implicated in peripheral tissue repair, where it influences cell proliferation, migration, vascular responses, and fibro-proliferative processes (13, 28). In particular, activation of the 5-HT1A receptor has been associated with improved coordination of cellular processes required for efficient wound closure (10, 22). In addition, serotonin has been shown to promote keratinocyte and fibroblast proliferation and migration, which are essential for re-epithelialization and wound healing (29). The superior healing observed with buspirone suggests that it may influence multiple stages of

the repair cascade.

Collagen deposition, assessed by hydroxyproline content, was significantly increased in the buspirone-treated group. Collagen is the primary structural protein responsible for tissue strength and integrity, and its synthesis is a hallmark of the proliferative phase of healing (2, 8). The elevated hydroxyproline levels observed in this study suggest enhanced extracellular matrix formation and maturation. Previous *in vitro* and *in vivo* studies have demonstrated that serotonin modulates fibroblast activity and collagen synthesis, supporting a potential role for serotonergic signaling in tissue repair. This regulatory effect is believed to occur via serotonin receptors expressed on fibroblasts, leading to activation of intracellular pathways that control cell proliferation, migration, and extracellular matrix production. In particular, serotonin may enhance the synthesis of collagen and other matrix components that are essential for wound strength and structural restoration. These findings suggest that serotonergic signaling could play a significant role in the proliferative phase of wound healing, contributing to granulation tissue formation and tissue remodeling (10, 12, 22, 30, 31).

Inflammation is an essential early phase of wound healing; however, its timely resolution is critical for progression to tissue regeneration (1, 8, 26). In the present study, buspirone significantly reduced TNF-α levels. TNF-α is a key pro-inflammatory cytokine that, when persistently elevated, can impair healing and inhibit collagen synthesis (32, 33). In addition, TNF-α interferes with fibroblast differentiation and extracellular matrix production, thereby negatively affecting wound contraction and tissue strength (33, 34). The reduction of TNF-α observed in the buspirone group may therefore facilitate the transition from the inflammatory to the proliferative phase.

TGF-β plays a central role in wound repair by regulating fibroblast proliferation, myofibroblast differentiation, and extracellular matrix synthesis (35). It acts as a key switch that coordinates the transition from the inflammatory phase to tissue formation by promoting fibroblast activation and collagen deposition while also influencing extracellular matrix remodeling (36). In this study, both buspirone and phenytoin increased TGF-β levels; however, the increase was more moderate in the buspirone group. This suggests a more controlled activation of the healing cascade rather than an excessive fibrotic response. Such balanced modulation may be beneficial, as tightly regulated TGF-β signaling supports effective tissue regeneration, whereas sustained or overactivation is associated with fibrosis, excessive collagen accumulation, and abnormal scar formation (35).

Histopathological findings further supported the beneficial effects of buspirone, showing enhanced keratinocyte migration, improved dermal remodeling, and the formation of a well-organized epidermis with distinct rete ridges. Topical serotonin (5-HT) has been shown to promote key keratinocyte functions during the proliferative phase of wound healing, including enhanced cell survival and migration, in a dose-dependent manner. These effects translate into accelerated re-epithelialization, as evidenced by faster wound closure in both *in vitro* and *in vivo* models (30). The improved structural organization observed in this study suggests not only faster but also higher-quality tissue repair. These findings are consistent with a more coordinated regenerative response, in which epithelial and dermal components mature in parallel to restore normal skin architecture.

Angiogenesis is another critical component of wound healing, providing oxygen and nutrients to regenerating tissue (29). Platelet-derived mediators, such as serotonin, have been shown to contribute to vascular remodeling and tissue regeneration (37). The enhanced neovascularization observed in the CAM assay supports a pro-angiogenic effect of buspirone, which may further contribute to its overall healing activity.

The observed effects are likely mediated through the pharmacological action of buspirone as a partial agonist of the 5-HT1A receptor. Serotonin receptors, including 5-HT1A receptors, are expressed in the skin and on several cell types involved in wound healing, such as keratinocytes, fibroblasts, macrophages, and endothelial cells (38, 39). Activation of these receptors has been associated with modulation of inflammation, promotion of cellular proliferation and migration, angiogenesis, and re-epithelialization (22, 40). Furthermore, disruption of the skin barrier at the wound site may facilitate percutaneous absorption of buspirone. 5-HT1A receptor signaling has anti-inflammatory and cytoprotective effects that may promote the shift from the inflammatory phase to the proliferative phase of wound healing (10, 12). In addition, serotonin pathways can support angiogenesis and extracellular matrix remodeling, which are key processes in tissue repair (10, 39). Therefore, the wound-healing effects observed in the present study may result from direct local activation of cutaneous 5-HT1A receptors. At the same time, systemic absorption through the compromised skin barrier may also contribute to the therapeutic response. Although the extent of systemic absorption was not evaluated in this study, both local and systemic serotonergic mechanisms may be involved in mediating the observed effects.

This study has several limitations that should be considered. First, the findings are based on an animal model and may not be directly applicable to human wound healing. Second, although changes in inflammatory and fibrotic markers were observed, the underlying cellular and molecular mechanisms were not directly investigated. In addition, the relatively small sample size may have limited the study's statistical power. Moreover, both male and female rats were included in this study; however, due to the limited sample size per group, sex-specific analyses were not performed. Given the known influence of sex hormones on wound healing, this represents a limitation of the current study, and future investigations with larger cohorts are required to assess potential sex-dependent effects. However, no obvious sex-related trend was observed upon visual inspection of the data. Finally, the use of ELISA kits designed for rat cytokines may introduce variability due to potential cross-species differences and should be interpreted with caution.

Conclusion

Topical buspirone enhances wound healing by accelerating wound contraction, increasing collagen deposition and angiogenesis, modulating inflammatory and fibrotic mediators, and improving histological organization. These findings suggest that buspirone may be a candidate adjunct for wound management.

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Authors' Contributions

P T conceived and designed the study. M Z, F M, and M M conducted data collection and processing, experiments, and analysis and interpretation of results. All authors prepared the draft manuscript and visualizations. M Z and P T critically revised the article. P T provided supervision and funding acquisition. All authors gave final approval of the version to be published.

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Data Availability

The datasets generated and/or analyzed in this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no competing interests.

Declaration

The authors used ChatGPT (OpenAI) solely for language editing of the manuscript. The authors reviewed all revisions and take full responsibility for the final content.

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