Original Article

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Royal Jelly Enhances Skin Wound Healing in Mice Model by Modulating Glutathione Peroxidase Activity and CCL2 Chemokine Gene Transcription

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ABSTRACT

Background & Objective: Wound healing can be impaired by diabetes and aging, leading to delays, scarring, or infections. There is a need for improved treatments to expedite wound healing. Complementary and alternative medicine often utilizes natural remedies for disease management. Royal jelly (RJ), a natural bee product, is a food supplement known for its beneficial biomedical properties. CCL2 exhibits angiogenic properties and has been observed to promote tissue regeneration. Glutathione peroxidase (GPx) plays a critical role in tissue repair by preventing apoptosis and tissue damage caused by excessive reactive oxygen species (ROS) production. This study investigates the application of Royal Jelly to accelerate skin wound healing through modulation of GPx activity and CCL2 expression.

Materials & Methods: Thirty mice were divided into six groups. Royal jelly treatment (2.5, 10, and 40 mg/kg) was administered orally. Following the treatment period, GPx activity was measured in blood samples, and the transcription level of the CCL_2 gene was assessed in healing wound tissue samples using real-time PCR. Evaluation of epithelial tissue formation and the presence of inflammatory and fibroblastic cells was conducted in prepared wound tissue sections.

Results: Analysis of wound diameter revealed that oral administration of RJ (10 and 40 mg/kg) significantly accelerated wound healing ($P=0.0198$). Moreover, GPx activity in the royal jelly groups (2.5, 10, and 40 mg/kg) was significantly lower (43.8, 68.6, and 31.1, respectively) compared to the PC group ($P=0.0001$). Additionally, CCL2 mRNA levels in the royal jelly groups (2.5, 10, and 40 mg/kg) were significantly higher (1.9, 6.6, and 15.2 times, respectively) than in the PC group ($P<0.05$). Administration of 40 mg/kg of royal jelly significantly increased fibroblast cells in tissue sections.

Conclusion: Royal jelly, as a complementary food drug, facilitates wound healing by promoting the proliferation and migration of fibroblasts, regulating ROS production, and stimulating CCL_2 gene transcription.

Keywords: Wound Healing, Glutathione Peroxidase, CCL2 chemokine, Royal jelly

Introduction

The wound healing process comprises sequential phases of homeostasis, inflammation, proliferation, and regeneration. Disruptions or delays in any of these phases, often associated with diabetes and aging, can impede wound healing or lead to excessive scar formation. Hence, comprehending the mechanisms involved in wound healing is pivotal for developing novel and enhanced treatments to expedite this process (1).

Mitochondria serve as the primary source of small oxygen-derived molecules referred to as reactive oxygen species (ROS), which play a dual role in wound healing. While ROS can cause cellular damage, they are also vital for promoting wound healing (2, 3). ROS production at the wound site is essential for combating

pathogens and facilitating wound healing processes. Neutrophils and macrophages release ROS and cytokines during the inflammatory phase, aiding pathogen destruction and supporting angiogenesis, cell migration, and proliferation (4). However, excessive ROS production can trigger the activation of pro-apoptotic proteins, leading to adjacent tissue damage through cell death and necrosis (5). Antioxidants function to prevent ROS-induced damage to crucial molecules such as proteins or DNA. These antioxidants can be categorized into non-enzymatic types, including vitamin E, vitamin C, glutathione, and flavonoids, and enzymatic types, such as superoxide dismutase, catalase, glutathione peroxidases, and thioredoxin-1 and -2. They convert ROS into stable molecules like H_2O and O_2 (3). Glutathione peroxidases (GPXs), belonging to the selenoprotein family, are integral to wound healing by detoxifying hydrogen peroxide. Recent research indicates a decrease in GPX1 levels during the early stages of wound healing, resulting in reduced activity in wounded control and immunocompromised rats (6).

Chemokines in wounds play a critical role in wound healing by regulating angiogenesis and inflammatory cells' release of cytokines and growth factors. Neutrophils and macrophages in the wound promote the recruitment of inflammatory cells that release growth factors with pro-angiogenic properties, facilitated by the pro-inflammatory chemokine CCL2 (MCP-1) (1). CCL2, a chemokine responsible for recruiting macrophages and monocytes during angiogenesis, is essential for the normal progression of wound healing (7). Additionally, CCL2 enhances the expression of MMP-1 and TIMP-1 in fibroblasts, thereby regulating matrix production and regeneration (8). Studies have shown that CCL2 knockout mice exhibited reduced re-epithelialization due to decreased macrophage infiltration (7).

Complementary and alternative medicine (CAM) has emerged as a significant area of interest for treating various diseases (9). Royal jelly (RJ), a natural bee product, has garnered attention in traditional and modern medicine. Worker bees produce RJ, also known as Queen Bee Jelly, which comprises water (60–78%), proteins (9–18%), carbohydrates and lipids (7–18% and 3–8% respectively), mineral salts (0.8–3%), and small amounts of polyphenols, vitamins, and enzymes. While queen larvae are exclusively fed RJ, worker bee larvae receive RJ only during the initial three days of their lives. RJ serves as a vital nutraceutical and dietary supplement, enhancing the nutritional content of the human diet (10). It is recognized as a food supplement with numerous biological properties, including anti-cancer, anti-allergic, anti-inflammatory, and immune-regulatory effects (11, 12).

Given the reported therapeutic effects of RJ and the roles of glutathione peroxidase and CCL2 in the wound healing process, this study aimed to evaluate the impact of orally administered RJ on skin wound healing by examining glutathione peroxidase activity levels, CCL2 gene mRNA expression, and tissue indices in a mouse wound model.

Materials and Methods

Laboratory Animals

Thirty healthy male laboratory mice weighing 20±2 grams (Research and Educational Institute of Pasteur, Karaj, Iran) were utilized for this research. The laboratory animals were handled according to maintenance and testing guidelines. Before experimentation, approval was obtained from the National Committee of Ethics in Biomedical Research (IR.IAU.VARAMIN.REC.1400.013). All experimental procedures adhered to relevant regulations. Mice were acclimated to the laboratory environment for one week in standard cages under standard conditions (temperature 22±2°C, 12-hour light-dark cycle).

Animal grouping

The mice were randomly divided into six groups, each containing five mice: control, patient control, experimental control, and three experimental groups (13). The control group received no treatment. An excisional wound was prepared without further treatment in the patient control group. The experimental control group received RJ (40 mg/kg) without an excisional wound. After excisional wound preparation, the three experimental groups received different concentrations of RJ (2.5, 10, and 40 mg/kg). Each mouse was housed in a cage, and treatments were administered for nine days. RJ was dissolved in drinking water to achieve the desired concentration (14).

Excisional wound preparation

To induce a skin wound, mice were intraperitoneally injected with ketamine (80 mg/kg) and xylazine (10 mg/kg) for anesthesia. After ensuring complete anesthesia, the hair on the back of the neck was shaved, and the site was sterilized with 70% ethanol. Two identical circular skin wounds (diameter 5-7 mm) were created in the prepared area. The wounds were washed with sterile normal saline, and each mouse was returned to its cage.

Collection of Blood and Tissue Samples

Treatment of mice was terminated on day 9 after excisional wound preparation. First, all mice were euthanized, and blood samples were collected from their hearts. Subsequently, in mice with wounds, both wounds and approximately 1 mm of surrounding skin were excised. One wound was designated for histological examination, while the other was used for gene expression evaluation. A skin sample was obtained from the same site using a punch in mice without wounds.

Evaluation of CCL_2 mRNA level

The obtained wound tissue was homogenized for RNA extraction, which was performed using a Column RNA isolation kit (DENAzist, Iran). RNA quality and concentration were assessed using a Nanodrop device (Thermo Fisher Scientific, USA). cDNA synthesis was carried out using a 2-step 2XRT-PCR Premix kit (Biofact, Korea) according to the manufacturer's instructions, with cDNAs stored at -20°C.

The relative mRNA level of the CCL_2 gene in tissue samples was determined using real-time PCR with a 2-step 2X RT-PCR Premix (BioFactTM, South Korea) and Real-time PCR cycler (Rotor-Gene). The β-actin gene served as the housekeeping gene, and primers for CCL_2 (forward: 5'-TGA TCC CAA TGA GTA GGC TGG AG-3' and Reverse: 3'-ATG TCT GGA CCC ATT CCT TCT TG-5') and β-actin (Forward: 3'-GTG CTA TGT TGC TCT AGA CTT CG-5' and Reverse:3'-ATG CCA CAG GAT TCC ATA CC-5') were designed using NCBI primer-blast. The real-time PCR temperature and time program comprised initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at 60°C for 25 s, and extension at 72°C for 30 s, with a final extension at 72°C for 7 minutes. CTs average was calculated using REST software (version 2009).

GPx Activity Assay

GPx activity was measured using a GPx activity assay kit (Nundsalamat, Iran) based on consuming NADPH by glutathione reductase. Plasma samples were subjected to the assay according to the kit instructions. Briefly, a plasma sample (40 µL) was added to 950 µL of NADPH assay reagent, and the reaction was initiated by adding 10 ml of tert-butyl hydroperoxide solution (30 mM). Absorbance decrement was recorded at 340 nm for 3 min, and GPx activity was calculated in units per gram of protein, with one enzyme unit defined as the quantity of enzyme generating one micromole of NADP+ from NADPH in a minute (15).

Tissue Processing

The second wound of mice was utilized for histological studies. Skin wound tissue was fixed using 10% paraffin and sectioned using a Manual Rotary Microtome-CUTX100 (Pouya Abzar Azma). Hematoxylin and eosin (HE) staining was performed according to the manufacturer's instructions (Sigma-Aldrich), and slides were evaluated using light microscopy for gross observation.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism software. Data were expressed as mean ± standard deviation. Ordinary one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used for comparisons among different groups, with differences considered statistically significant at $P<0.05$.

The effect of oral administration of RJ on wound healing was assessed by daily measurement of wound diameter, glutathione peroxidase enzyme activity, relative CCL_2 gene mRNA levels, and tissue indices in blood and tissue samples.

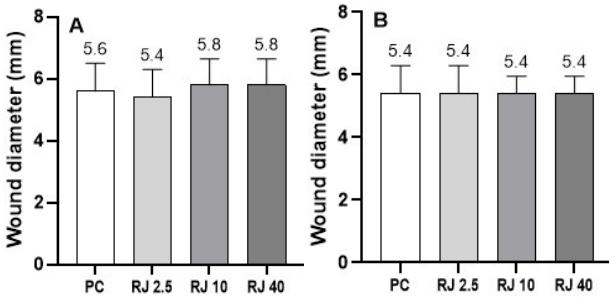
Wound Diameter Evaluation

RJ compared to the patient control group ($P=0.0198$). The concentration of 2.5 mg/kg did not significantly accelerate wound healing. However, concentrations of 10 and 40 mg/kg resulted in a one-

Results

Changes in wound diameter were monitored over the 9-day experiment period. The alterations in wound diameter on days 1, 3, 6, and 9 were compared among RJ-treated (experimental) groups and the patient control group (Figure 1). Results indicated a reduction in wound diameter only on the ninth day in groups treated with 10 and 40 mg/kg of

centimeter reduction in wound diameter compared to the patient control group, suggesting an acceleration in wound healing.



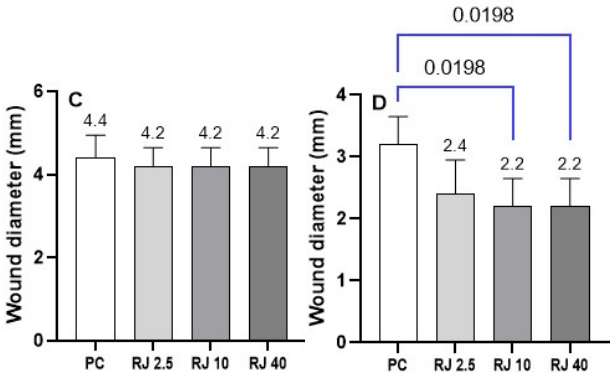


Figure 1. Changes in wound diameter over 9 days of treatment. A; day 1, B; day 3, C; day 6, and D; day 9 after excisional wound preparation. In treated groups, accelerated wound healing is observed on day 9 in RJ (10 and 40 mg/kg), PC; patient control, RJ; royal jelly. Numbers on top of lines represent *P* values.

GPx Activity

The results of GPx activity measurement in mouse serum at the end of the experimental period are presented in (Figure 2). The patient control group exhibited the highest GPx activity (128.3 U/L), while the experimental control group showed the lowest activity (11.5 U/L). No significant difference was observed in GPx activity between the intact group (17.2 U/L) and the experimental control group (*P=0.54*), indicating that RJ did not affect GPx activity in mice without skin lesions. Wound presence increased GPx activity in the patient control group compared to the intact group (*P<0.0001*). In the experimental groups, GPx activity was lower than that in the patient control group (*P<0.0001*), suggesting that oral RJ administration accelerated wound healing, resulting in decreased GPx activity at the end of the treatment period compared to the control group. Furthermore, GPx activity was dose-dependent on RJ concentration (2.5, 10, and 40 mg/kg), decreasing (84.5, 59.7, and 31.1 U/L, respectively) with increasing RJ concentration. Thus, increasing RJ concentration accelerated wound healing, leading to a gradual decrease in GPx activity.

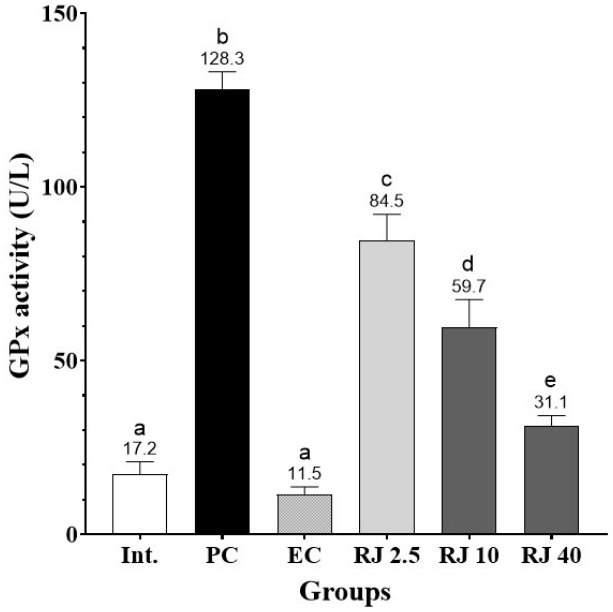


Figure 2. GPx activity on day 9 after excisional wound preparation. GPx activity is high in the PC group and decreases with RJ treatment. Data in each column represent the mean GPx activity in groups ± SD. Int; intact, PC; patient control, EC; experimental control; and RJ (2.5, 10, and 40) represent RJ (2.5, 10, and 40 mg/kg, respectively). Similar letters atop columns indicate *P>0.05*, while different letters denote significant differences from other columns.

CCL_2 mRNA Levels

The mRNA level of the CCL_2 gene in the different groups was compared to the intact group (Figure 3). The relative mRNA level in the patient control group increased 2.7 times compared to the intact group (*P=0.0004)*, indicating that wound formation enhances CCL_2 gene transcription. No significant difference was observed between the experimental control (2.3-fold) and intact groups (*P=0.12*), suggesting that oral administration of 40 mg/kg of RJ does not impact CCL2 gene transcription in healthy skin cells.

In the experimental groups, the relative mRNA levels of CCL_2 (5.6-, 10.3-, and 18.9-fold) were significantly increased compared to the experimental control group

(*P<0.05*). This suggests that RJ administration enhances wound healing by upregulating CCL2 gene expression. Furthermore, the mRNA level of the CCL_2 gene in the experimental groups increased (5.6-, 10.3-, and 18.9-fold) with increasing RJ concentration (2.5, 10, and 40 mg/kg, respectively; *P<0.05*), indicating a dose-dependent effect of RJ on CCL_2 gene transcription in skin wound tissue. The expression of the CCL_2 gene in the experimental groups was significantly higher than that in the experimental control group (*P<0.0001*), suggesting that RJ's effect on CCL_2 gene expression in wounded tissue exceeds that in healthy tissue. This indicates that RJ enhances CCL_2 gene expression by influencing other factors produced during wound occurrence, suggesting a synergistic effect between RJ and these factors.

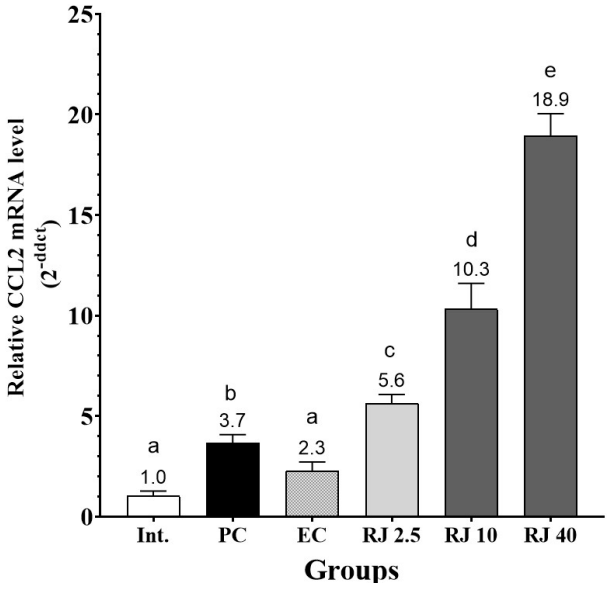


Figure 3. mRNA level of CCL_2 gene in wound tissue. Data in each column represent the relative CCL2 mRNA level mean in groups ± SD. Int; intact, PC; patient control, EC; experimental control; and RJ (2.5, 10, and 40) represent Royal jelly (2.5, 10, and 40 mg/kg, respectively). Similar letters atop columns indicate *P>0.05*, while different letters denote significant differences from other columns.

Histological Evaluation Results

Tissue samples obtained at the end of the treatment period (9th day) underwent histological investigation. Hematoxylin-eosin staining was performed, and wound healing indicators, including epidermal cell migration, inflammatory cell infiltration, and the presence of fibroblastic cells, were examined using a light microscope. Scoring from 0 to 4 was assigned based on the degree of progress (Figure 4) (16). The epithelial tissue formation was evaluated by assessing the thickening of cut edges, migration of epithelial cells, cut area bridging, and keratinization degree (Figure 5A). Results revealed bridging of the cut area and keratinization in all groups, with no significant differences indicating a superior effect of RJ on this index.

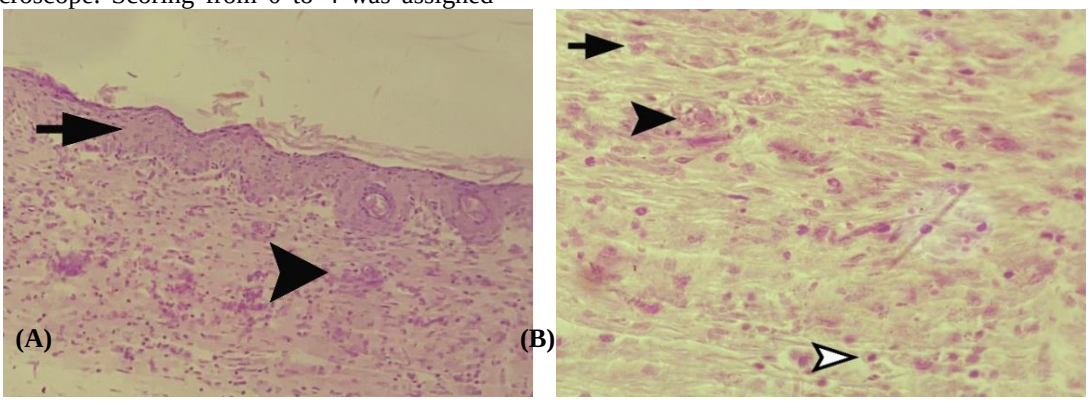


Figure 4. Hematoxylin-eosin staining of skin wound tissue sections from the experimental group (40 mg/kg). (A) The arrow indicates the complete formation of the epidermis, while the arrowhead highlights the high number of inflammatory cells infiltrating the area (10X). (B) There is the presence of numerous fibroblasts (arrow), newly formed blood vessels (black arrowhead), and notable inflammatory cell infiltration (arrowhead) (40X).

The presence of inflammatory cells was assessed across five levels: absence, less than 25%, 25-50%, 50-75%, and more than 75%. The results did not indicate a significant change in the presence of inflammatory cells following treatment with RJ (Figure 5B).

The presence of fibroblastic cells was evaluated using the following scoring system: non-presence (score zero), presence around the tissue (score one), presence in budding tissue (score 2), moderate presence (score 3), and prominent presence (score 4). Results showed that treatment with RJ (40 mg/kg) increased the presence of fibroblastic cells (ranging from medium to prominent) compared to the patient control group (ranging from medium to budding tissue) (Figure 5C).

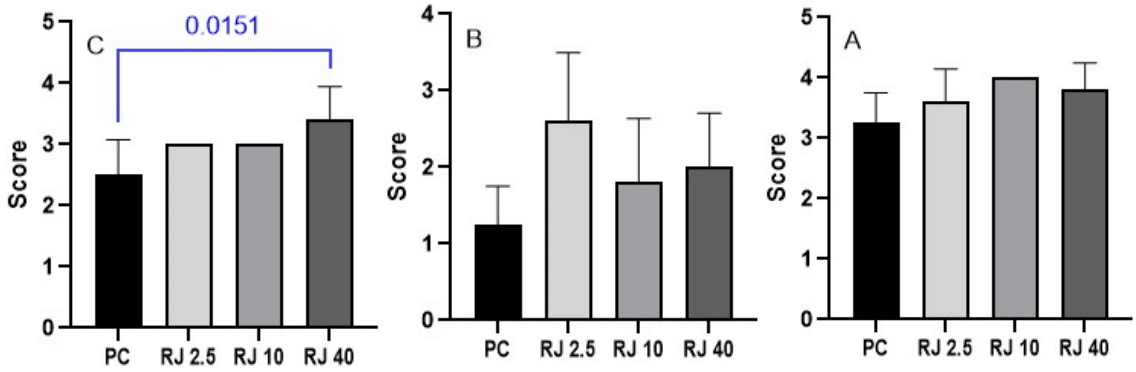


Figure 5. Scoring of wound healing indices. (A) Epithelial tissue formation, (B) Presence of inflammatory cells, and (C) fibroblastic cells. PC; Patient control, RJ; Royal jelly. Data in each column represent the mean score in groups ± SD. Numbers on top of lines represent *P* values.

Discussion

In recent years, there has been increasing interest in complementary nutrition approaches, particularly wound healing,due to certain foods' reported biochemical and molecular effects (17). In this study, we evaluated the effects of oral consumption of RJ on skin wound healing, GPx levels, CCL_2 gene transcription, and tissue indices.

Our findings from wound diameter measurements demonstrated that consumption of 10 and 40 mg/kg of RJ accelerates wound healing, particularly evident in the later stages of the treatment period (days 7 to 9) (Figure 1). This acceleration may be attributed to RJ's promotion of cell migration, fibroblast proliferation, angiogenesis, and extracellular matrix protein production, such as collagen (18, 19). Lin et al. have similarly highlighted RJ's role in enhancing wound closure and cell proliferation, leading to successful wound healing (20). Consistently, Shirzad et al. reported visibly improved wound healing with high doses of RJ (21).

GPx is pivotal in regulating H_2O_2 concentration, mitigating its harmful effects (22). Our examination of GPx activity revealed lower levels in RJ-treated groups compared to the patient control group by the treatment's end (Figure 2). This inverse relationship with RJ concentration contrasts with studies demonstrating increased GPx activity post-antioxidant treatment (23, 24). Woo et al. observed a rise in GPx1 protein levels during cutaneous injury healing (25). Jato et al. noted increased GPx levels in diabetic rats, decreasing with wound healing progression (26). Given ROS's crucial role in wound healing, our results suggest RJ's acceleration of wound healing may reduce ROS levels, thus lowering GPx activity. RJ's antibacterial properties may also aid immune function, modulating ROS production and reducing GPx activity (27-31) Rasik and Shukla linked lower antioxidant levels to slower wound healing (32).

CCL_2 gene transcription increased with RJ dose, consistent with Ishida et al. (33). Lower CCL_2 expression in conditions like type 2 diabetes correlates with slower wound healing (33). Platelet-secreted CCL_2 at wound sites stimulates keratinocytes and fibroblasts, promoting extracellular matrix and blood vessel formation. CCL_2's role in angiogenesis and epithelial regeneration is crucial, supported by studies showing its significant wound healing stimulation (34, 35). Our histological findings confirmed increased fibroblast presence in RJ-treated wounds, corroborating accelerated wound healing and RJ's effect on CCL_2 expression.

Conclusion

In conclusion, our findings indicate that royal jelly consumption regulates ROS levels in wounds and enhances signals promoting fibroblast migration and growth through increased CCL_2 gene transcription. Elevated CCL_2 expression stimulates the formation of extracellular matrix and new blood vessels, ultimately accelerating wound closure. Thus, royal jelly emerges as a promising dietary supplement for expediting wound healing.

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Authors' Contribution

Study concept and design: Mehdi Ebrahimi; acquisition of data: Mohammad Sadegh Ghashghaie; analysis and interpretation of data: Mehdi Ebrahimi; drafting of the manuscript: Mehdi Ebrahimi; critical revision of the manuscript for important intellectual content: Mehdi Ebrahimi, Maryam Eidi; statistical analysis: Mehdi Ebrahimi; administrative, technical, and material support: Mehdi Ebrahimi; Study supervision: Mehdi Ebrahimi.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This study was performed as the M.Sc. thesis of the first author and no additional funding was used.

Ethics Approval and consent to participate

Before experimentation, approval was obtained from the National Committee of Ethics in Biomedical Research (IR.IAU.VARAMIN.REC.1400.013).

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