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Effects of Fisetin on Cutaneous Full Thickness Wound Healing in a Rat Model

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ABSTRACT

Cutaneous wound healing is a complex biological process involving inflammation, proliferation, and tissue remodeling. Fisetin, a dietary flavonoid found in fruits and vegetables, is known for its potent antioxidant and anti-inflammatory properties. However, its therapeutic potential in wound healing has not been previously explored. This study aimed to evaluate the effects of topical fisetin on skin wound healing in a rat model. Forty male rats were randomly divided into four groups: control (no treatment), olive oil (vehicle), treatment 1 (T1; 10 mg/kg fisetin in olive oil), and treatment 2 (T2; 20 mg/kg fisetin in olive oil). A full-thickness dorsal wound (20 mm) was created in each rat. Treatments were administered topically for 14 days. Wound contraction was measured on days 3, 6, 9, 12, and 14. Oxidative stress markers malondialdehyde (MDA), Total oxidant status (TOS), superoxide dismutase (SOD), and total antioxidant capacity (TAC) were assessed on day 14, and histological evaluation using H&E staining was performed on days 7 and 14. Fisetin significantly accelerated wound contraction, particularly in the T2 group. MDA and TOS levels were significantly reduced, while SOD and TAC were elevated in fisetin-treated groups compared to controls. Histopathological analysis revealed reduced inflammatory cell infiltration, enhanced collagen deposition, and re-epithelialization, especially in the T2 group. Topical application of fisetin markedly improves cutaneous wound healing by modulating oxidative stress and enhancing tissue regeneration. These findings suggest fisetin as a promising natural agent for promoting skin repair and warrant further investigation in clinical settings.

Introduction

The skin, the largest organ of the body, serves multiple critical roles. It acts as a guard shield, protecting against pathogens and mechanical strain, while also regulating body temperature. Moreover, it enables the perception of touch, pressure, vibration, and pain.[1] Regrettably, skin damage can occur following trauma, burns, diabetes mellitus, and surgical procedures making rapid and effective wound healing a critical goal.[2] Wound healing involves an intricate sequence of coordinated cellular and molecular stages that begin immediately following an injury. This process seeks to repair the skin's structural integrity and functionality within a reasonable timeframe. The stages encompass hemostasis, inflammation, cellular proliferation, and the remodeling of the extracellular matrix.[3] Regrettably, specific conditions —including ischemia, infection, coexisting systemic disorders, and the use of corticosteroids— can interfere with the normal progression of wound healing. This disruption

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often leads to unfavorable complications.[3] Under normal wound healing conditions, limited quantities of reactive oxygen species (ROS) aid in cellular growth and act against microbial threats. The body's antioxidant system maintains balance by controlling these ROS levels. In contrast, chronic wounds are marked by an overproduction of ROS that overwhelms the natural antioxidant defenses, leading to sustained inflammation.[4] This extended inflammatory phase interferes with tissue repair and harms newly generated cells. Because of ROS's detrimental impact on healing, using antioxidants may offer a promising therapeutic strategy.[4] Hence, several studies aim to investigate wound healing acceleration.

Medicinal plants are among the most readily available medicines and their use has few side effects.[5] Fisetin, a significant phytoflavonoid, exhibits notable antioxidant, anti-Parkinson's, and anticancer properties. Fisetin (3,7,3′,4′-tetrahydroxyflavone 1), a prominent flavonoid, is widely acknowledged as a bioactive compound derived from plants, showing promise as a therapeutic agent against various free radicals. This compound is commonly found in vegetables such as onions and cucumbers, fruits including persimmons, apples, and strawberries, as well as in wine and nuts, with concentrations ranging from 2 to 160 mg/g and an estimated average daily consumption of 0.4 mg. Nutritional supplements enriched with higher doses of fisetin have been developed, demonstrating a range of pharmacological effects, such as antioxidant and anti-inflammatory properties. By neutralizing and scavenging free radicals, fisetin also promotes apoptosis, induces cell cycle arrest, and inhibits cyclin-dependent kinases (CDKs) in human cancer cell lines.[6]

No previous study has investigated effects of topical fisetin on wound healing. Therefore, the present study aimed to investigate the therapeutic effects of fisetin on cutaneous wounds in a rat model.

Materials and Methods

Animals and Groups

Forty healthy male Wistar albino rats (10-12 weeks old) with approximate weight of 250 g were purchased from Urmia University of Medical Sciences. Animals were maintained in standard conditions including temperature of 25 ± 2 °C, humidity of 60%, and 12 h dark/light cycle. All rats were kept in the mentioned conditions one week before experiments to get accustomed to the conditions. Animals were provided free access to the tap water and pellet diet. All experiments were approved by the animal Ethics Committee of Urmia University and their guidelines were followed. All rats were randomly divided in to four equal groups of ten in each group as follow: Control group (C): Animals in this group were not topically treated following wound creation. Olive oil group (O): Following wound creation in this group, rats were topically treated with 100 µl of olive oil for 14 days. Treatment group 1 (T1): After wound creation, 10 mg/kg fisetin was dissolved in 100 µl of olive oil and used topically for 14 days.[7,8] Treatment group 2 (T2): Following wound induction, rats were topically treated with fisetin 20 mg/kg dissolved in 100 µl of olive oil for 14 days.[9,10]

Wound Creation

After intraperitoneal administration of ketamine 10% (80 mg/kg, Bremer Pharma, Warburg, Germany) in combination with xylazine 2% (10 mg/kg, Alfasan, Woerden, The Netherlands) the hair on the rat's dorsal surface was shaved, and the surgical area was aseptically prepared using Povidone Iodine 10%.

A circular, full-thickness wound with a diameter of 20 millimeters was then excised in the thoracic region between the scapulae, using a No. 10 scalpel blade. This excision encompassed the total removal of both the epidermal and dermal layers. Treatments were performed based on the groups described before. Half of the animals were sacrificed on day 7 using an overdosage of ketamine/xylazine and skin samples were taken for oxidative stress and pathology and the others were euthanized on day 14. Wound area was assessed on days 3, 6, 9, 12, and 14 using a digital camera (Canon, Ōita, Japan) and measuring tool of Adobe Acrobat 9 Pro was utilized to analyze images.

Oxidative Stress Parameters Assessment

Tissue samples were collected and maintained at -20 °C freezer until subsequent experiments were performed. Subsequently, the samples were homogenized using a homogenizer and centrifuged. Thereafter, the supernatant was separated and utilized for oxidative stress parameters. Oxidative stress parameters including total oxidant status (TOS), malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC) were evaluated using Navand Salamat assay kits (Navand Salamat, Urmia, Iran).

Histopathological Assessments

In this research, hematoxylin and eosin (H&E) was performed for evaluation of skin tissues. The H&E staining procedure was conducted as follows: tissue specimens were extracted from the fixative solution (10% neutral buffered formalin) and encased in paraffin wax to form tissue blocks. Subsequently, sections with a thickness of 4 mm were sliced. Following deparaffinization, the staining process was executed. An experienced pathologist, blinded to the prior experimental stages, evaluated the resulting pathology slides. In each slide 10 fields were evaluated with the magnification of ×400.

Statistical Analysis

All data were analyzed using SPSS version 25 (SPSS Inc. in Chicago, IL, USA). Initially, data were checked for distribution using one-sample Kolmogorov-Smirnov test. Data with normal distribution were analyzed using one-way ANOVA and Tukey post hoc and non-normally distributed data were examined using Kruskal-Wallis test. $p < 0.05$ was considered significant.

Results

Table 1 shows wound area contraction in different study groups. Based on the table, a significant difference was observed between all groups and the control groups on various days. Moreover, T2 group significantly reduced wound area compared to the O and T1 groups on days 3, 6, 12, and 14.

Oxidative stress biomarkers are presented at Figure 1. Based on Figure 1 (A), no significant differences were observed between the control and olive oil group ($p > 0.05$). While a significant reduction in the concentration of the MDA was found between treatment groups and the control group ($p < 0.05$). Moreover, the T2 group significantly reduced the levels of the MDA compared to the T1 group ($p < 0.05$). TOS significantly decreased in the O, T1, and T2 groups in comparison to the C group ($p < 0.05$). The T2 group significantly reduced TOS levels compared to the C group ($p < 0.05$) Figure 1 (B). Levels of SOD remarkably increased in the T2 group compared to the C group ($p < 0.05$) Figure 1 (C). Due to the Figure 1 (D), TAC was significantly increased in all groups compared to the C group ($p< 0.05$). Significant increments in the levels of the TAC were observed in both treatment groups compared to the C group ($p < 0.05$). Furthermore, the High dose treated group significantly increased the levels of TAC compared to the low dose group ($p < 0.05$).

Histopathological evaluation of skin tissues stained with Hematoxylin and Eosin (H&E) was conducted on days 7 and 14 post-wounding to assess the impact of fisetin treatment on cutaneous wound healing (Figure 2). On day 7, the control group (C) displayed dense inflammatory cell infiltration and disorganized collagen fibers, indicative of an active inflammatory phase and delayed tissue remodeling. Similarly, the olive oil-treated group (O) exhibited moderate inflammatory infiltration and loose connective tissue, with no substantial improvement compared to the control. In contrast, the T1 group (10 mg/kg fisetin) showed a noticeable reduction in inflammatory cells and early signs of collagen fiber alignment. The T2 group (20 mg/kg fisetin) demonstrated the most significant histological improvements at this time point, including minimal inflammatory infiltrates and more organized collagen deposition, suggesting accelerated transition into the proliferative phase of healing. By day 14, the control and olive oil groups still showed signs of ongoing inflammation and incomplete remodeling, with irregular collagen fibers and scattered inflammatory cells. However, tissues from both fisetin-treated groups (T1 and T2) exhibited markedly improved histological features. Particularly in the T2 group, there was clear evidence of advanced wound healing, characterized by well-organized, dense collagen fibers, reduced inflammatory cell presence, and re-epithelialization of the wound area.

Discussion

Following tissue disruption, wounds occur and may lead to infection and discomfort. Mechanisms involved in wound healing consists of angiogenesis, production of collagen and development of scar.[11] Recently, several studies focused on traditional and complementary methods to improve and accelerate wound healing.[12,13] This research aimed to investigate the treatment effects of fisetin in an excisional wound model in rat.

Oxidative stress indicators including MDA, SOD, TAC, and TOS reveal redox status of the body and its effects on wound healing. MDA is an important reflective of lipid peroxidation and increased levels of MDA leads to oxidative damage to cell membranes, hinders wound healing and harm regenerating tissue.[14] Superoxide radicals are neutralized by SOD. When SOD activity is reduced, oxidative stress occurs aligned with impaired neovascularization, and slower wound closure, especially in aged or compromised individuals.[15] The overall ability of the body to neutralize free radicals is measured by TAC. Reduction in the levels of TAC signifies weakened antioxidant defense and more vulnerability to the oxidative damage, which may delay tissue repair.[16] Conversely, total oxidant status (TOS) measures the cumulative burden of oxidative agents; elevated TOS levels correlate with prolonged inflammation and tissue

Table 1. Effect of fisetin on circular excision wound contraction area (mm^2) in various studied groups.

Groups	Day 3	Day 6	Day 9	Day 12	Day 14
C	312.43 ± 8.14	243.22 ± 7.75	101.35 ± 5.90	67.21 ± 4.45	48.45 ± 2.15
O	236.88 ± 7.25^{a}	158.16 ± 5.35^{a}	66.37 ± 4.97^{a}	51.26 ± 3.07^{a}	25.95 ± 2.67^{a}
T1	228.63 ± 9.74^{a}	152.61 ± 4.98^{a}	52.31 ± 4.38^{ab}	47.36 ± 3.17^{a}	24.44 ± 2.74^{a}
T2	97.86 ± 6.33^{abc}	73.42 ± 4.12^{abc}	44.28 ± 4.11^{ab}	28.67 ± 0.55^{abc}	12.89 ± 1.26^{abc}

Control (C), olive oil (O), T1 and T2 are indicative of various doses of fisetin. ^{a} indicates significant difference with the C group. ^{b} shows significant difference with the O group. ^{c} indicates significant difference with the T1 group.

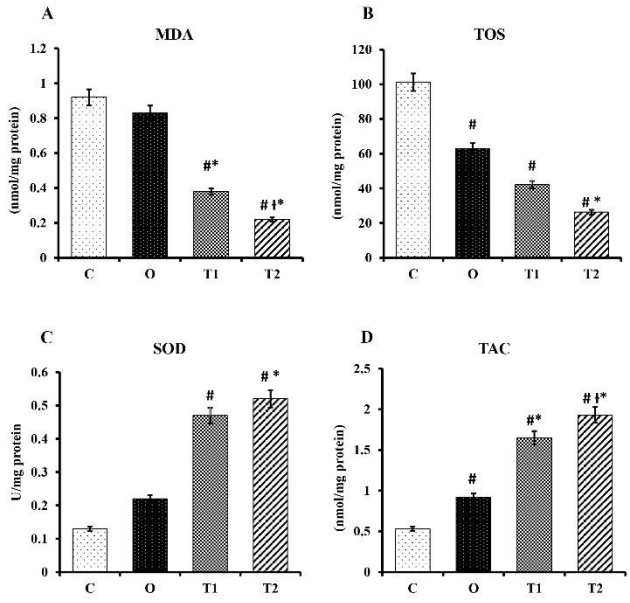

Figure 1. Oxidative stress evaluation in different groups of the study. A: MDA, B: TOS, C: SOD, and D: TAC. #: The mean difference is significant at the $p < 0.05$ level vs control group.*: The mean difference is significant at the .05 level vs olive oil. #: The mean difference is significant at the .05 level vs T1 group.

injury, contributing to chronic, non-healing wounds.[17] Overall, mentioned parameters indicate oxidative stress dynamics in the wound environment and their implications for healing outcomes.

Fisetin, a noteworthy flavonoid, is commonly found in various foods consumed by humans, such as fruits and vegetables including strawberries, apples, persimmons, onions, and cucumbers, with strawberries boasting the greatest concentration at 160 µg/g.[18] Sahu *et al*. (2014) investigated the effects of fisetin on cisplatin-induced nephrotoxicity in rats, finding that fisetin in both doses could significantly reduce BUN and creatinine. Moreover, oxidative stress indicators such as GSH, GST, CAT, SOD, and vitamin C levels significantly increased compared to the cisplatin-control group.[19] Another study focused on beneficial effects of fisetin on diabetic cardiomyopathy, and revealed a significant reduction in the levels of MDA and protein carbonyl, and notably increment in the levels of GSH, SOD, and CAT.[20] Effects of fisetin on aflatoxin-B1 induced hepatocellular carcinoma in rats was evaluated in an investigation conducted by Maurya *et al*. (2015), findings indicated that fisetin significantly increased levels of ROS, total glutathione, SOD, CAT, and GPx.[21] Wound healing effects of *Annona muricata* leaves was assessed in a study and oxidative stress markers were measured. CAT, SOD, and GPx were significantly increased in the treatment group compared to the control group and concentration of MDA was reduced significantly.[22] Silymarin as a potent antioxidant was employed in a rat model of cutaneous wound healing and serum antioxidant levels significantly increased and MDA levels decreased in the treatment group compared to the control group.[23] In a wound healing model, quercetin was employed as an antioxidant, finding significant reduction in MDA levels and increment in the levels of SOD and CAT.[24] In agreement with previous mentioned studies, in the present study MDA and TOS were significantly reduced and SOD and GPx increased in the treatment groups compared to the olive oil and control groups.

Healing effects of olive leaf extract ointment and dermaheal ointment on cutaneous wound in diabetic rats was investigated and findings revealed reduced inflammatory reaction and increased angiogenesis in the treatment group on day 7 and formation of epidermis layer and adnexa on day 14.[25] Galactomannan derived from *Delonix regia* seeds was examined in a study on cutaneous wound healing and treatment groups on day 7 indicated formation of granulation tissue, enhanced angiogenesis, mild collagen deposition, and decreased inflammatory reaction. Moreover, re-epithelialization was predominant on day 14 in the treatment group.[26] healing effects of graphene oxide-cellulose nanocomposite on skin wound healing was studied by Soliman *et al*. (2021) and results revealed reduced inflammatory reaction in the treatment group and increment in the number of blood vessels on day 7 and improvement in the epithelization on day 21.[3] Effects of quercetin in three different doses was evaluated on wound healing in a mice model and H&E slides indicated improved wound repair in the low, medium and high dose quercetin groups compared to the non-treated groups with disappearing muscular necrosis and scar tissue formation on day 5. Additionally, numbers of lymphocytes and neutrophils reduce in the wounds treated with quercetin on day 8.[27] Consistent with previous studies, in the present study reduced inflammatory infiltration, and improved collagen deposition was observed on day 7 in the H&E slides. Moreover, well-organized, dense collagen fibers, reduced inflammatory cell presence, and re-epithelialization of the wound area were detected in the fisetin-treated group on day 14.

The main aim of the present study was to investigate the effects of fisetin on cutaneous wound healing in rats. Findings revealed that treatment with fisetin significantly increased wound contraction, reduced oxidative stress biomarkers, and improved wound healing in the microscopic slides by reducing inflammatory cells infiltration, increased angiogenesis and collagen deposition. One limitation of the present study was that gene expression and protein expression were not assessed.

Conflict of Interest

None.

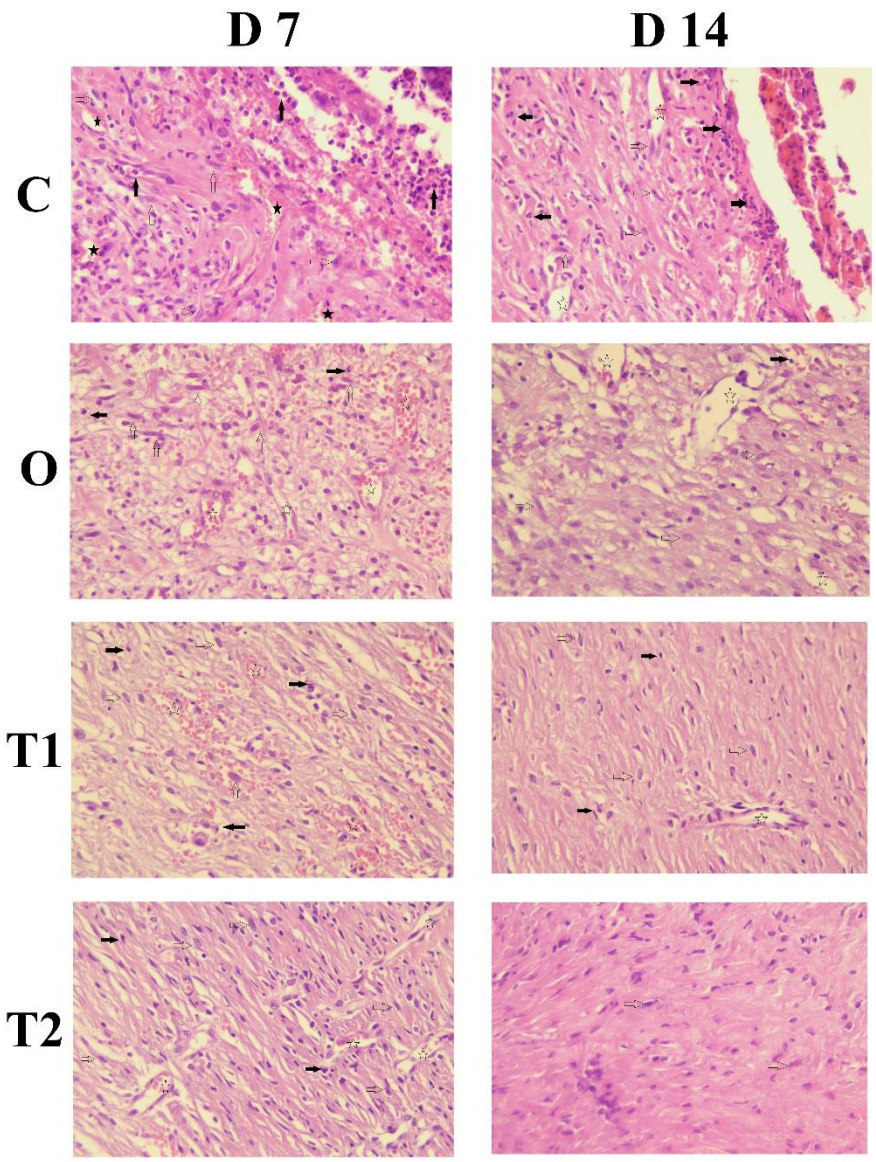

Figure 2. Histopathological evaluation of skin wound healing in different study groups on days 7 and 14 post-wounding (hematoxylin and eosin staining, magnification ×400). Stars indicate blood vessels, blank arrows represent fibroblasts, and filled arrows show neutrophils. Representative images show the tissue morphology in the Control (C), Olive oil (O), Treatment 1 (T1; fisetin 10 mg/kg), and Treatment 2 (T2; fisetin 20 mg/kg) groups. On day 7 (D7), the Control group exhibited dense inflammatory cell infiltration and disorganized collagen fibers, indicating an active inflammatory phase. The Olive oil group showed moderate inflammatory infiltration with limited collagen organization. In the T1 group, reduced inflammatory cells and early collagen fiber alignment were observed. The T2 group demonstrated minimal inflammatory infiltration with better-organized collagen fibers, suggesting accelerated progression to the proliferative phase. By day 14 (D14), the Control and Olive oil groups still exhibited signs of persistent inflammation and incomplete tissue remodeling, with irregular collagen deposition. In contrast, the T1 and especially the T2 groups showed markedly improved wound healing, characterized by reduced inflammation, dense and organized collagen deposition, and advanced re-epithelialization.

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