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# Comparison of St. John's wort oil and thiocilline ointment on wound healing in a diabetic rat model

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## ABSTRACT

**Aims:** In diabetic patients, wound healing is impaired and wounds are often infected with multifactorial agents. This study aimed to compare the effectiveness of St. John's wort and ointment containing bacitracin-neomycin (thiocilline) to improve wound healing in a diabetic infected wound model.

**Methods:** Rats in which diabetes was induced by administering 60 mg/kg streptozotocin (STZ) were considered diabetic if their blood sugar levels were above 300 mg/dl 72 hours later. Group 1: Control (Non diabetic) group, Group 2: Diabetes group. During wound care, both groups were disinfected with povidone iodine (PI) and the right lumbar region of each rat was dressed with thiocilline and the left lumbar region was dressed with St. John's wort oil. Considering the wound healing period, the study was terminated after an average of 20 days. In histopathological examination, ulceration, necrosis, epithelialization, congestion, edema, polymorphous nucleated leukocyte (PNL), monocyte, fibroblast, and neovascularization were evaluated.

**Results:** In histopathological evaluation, there was a statistically significant decrease in ulceration and necrosis in the group treated with St. John's wort oil compared to the group given thiocilline (p=0.04). In terms of epithelialization, there was a statistically significant increase in the group dressed with St. John's wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant decrease in congestion and edema in the group treated with St. John's wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant increase in fibroblast and neovascularization in the group treated with St. John's wort oil compared to the group given thiocilline (p=0.02).

**Conclusion:** Histopathologic ally, epithelialization, fibroblast, and neovascularization, which have important functions in the wound healing process, increased in diabetic rats administered St. John's wort. Although it is used in traditional medicine due to its antidepressant effectiveness, we believe that St. John's wort can be used in wounds that develop in diabetic patients, as it has the potential to increase the wound healing process.

**Keywords:** Diabetes, rat, wound model, St. John's wort oil, thiocilline, wound healing

## INTRODUCTION

Problems in wound healing in diabetes can be summarized as a decrease in cellular infiltration, angiogenesis, granulation tissue, collagen amount and organization, and an increase in infectious complications.[1] Although the causes of wound healing problems that may occur in diabetes have not been fully explained, hyperglycemia is basically held responsible for this situation. It has been shown that high blood glucose inhibits cell proliferation and collagen production. In addition, situations such as decreased growth factors and fibroblast proliferation, increased apoptosis in wound tissue cells, decreased chemotaxis and phagocytosis and infection formation can be listed among the negative effects of hyperglycemia on wound healing.[2-4]

Wound healing is characterized by epithelial, endothelial, inflammatory cells, platelets and fibroblasts coming together and performing their normal functions in a certain order and order.[5-7] Wound healing continues as a rapid and regular process in healthy people. Clinically, wound healing is delayed in infections, diabetes, systemic steroid and radiation applications, and the use of chemotherapeutic agents. It is thought that this may be the result of inadequate release or delay in the release of growth factors that come into play at various stages of wound healing.[8]

The basic principles in topical wound care and treatment are to remove obstacles and provide an environment conducive

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to repair so that the skin can perform its repair function. This environment is possible by keeping the wound clean and protecting the wound surface by keeping it moist and insulated.[9] Daily topical antibiotic-based ointment or white petroleum jelly is widely used in clinical practice, especially for postoperative wound care. Topical antibiotic ointments are medications that are considered safe and effective for local wound treatment. In addition, these drugs support wound healing and provide a moist environment by minimizing the adhesion of bandages. Bacitracin, fusaric acid, gentamicin, mupirocin, neomycin sulfate, and polymyxin B sulfate are topical antibiotics commonly used in the United States and Europe.[10] Thiociline is an antibacterial ointment containing bacitracin+neomycin sulfate.[11]

In Turkiye, locally known as Binbirdelik grass, Kan grass, Kılıç grass, Mayasır grass, Yara grass, Kuzukır and in English St. Hypericum perforatum L., known as John's wort, is a plant belonging to the Hypericaceae family and growing in Europe, Asia, North Africa and the United States. It is used in traditional medicine due to its antidepressant effect.[12] It is widely used in the field of phytotherapy in various European countries. There are about 70 species in Turkiye. It is an herbaceous or bushy plant with bright yellow flowers. H. perforatum contains many compounds with biological activity such as chlorogenic acid, many flavonoids, naphthodianthrones and phloroglucinols.[13] Although St. John's wort is used in traditional medicine for its antidepressant activity, it has been reported that it has antiviral and antibacterial activities.[14,15] Diabetic wounds are often multi-bacterial and exhibit impaired healing. This study aims to compare the efficacy of St. John's Wort oil and an ointment containing bacitracin+neomycin (Thiocilline) in enhancing wound healing in a diabetic infected wound model.

## METHODS

The study was carried out with the permission of Mustafa Kemal University Ethics Committee (Date: 0X.0X.2015, Decision No: 07/5). The study was conducted in accordance with the ethical principles of the "Guide for the Care and Use of Laboratory Animals.".

This study utilized male Wistar Albino rats, aged 12-16 weeks. The rats were acclimatized to the experimental environment one week prior to the study. They were housed under standard conditions, with free access to tap water, a 12-hour light/dark cycle, approximately 55% humidity, and a temperature range of 20-22°C. The rats were fed standard rat chow.

### Sample Size Determination

The sample size for each group was determined based on statistical considerations to ensure the results would be interpretable and significant, accounting for potential animal loss during the experiments. Literature from previous studies was also reviewed to inform group sizes.

### Experimental Groups

A total of 20 Wistar Albino rats were randomly divided into two groups, each consisting of 10 animals:

**Group 1**: Control (Non-diabetic rats)

**Group 2**: Diabetic rats (Thiocilline and St. John's Wort oil treatment)

### Induction of Diabetes

Diabetes was induced in the experimental rats using a single intraperitoneal injection of streptozotocin (STZ) at a dose of 60 mg/kg, freshly dissolved in 0.9% NaCl. Seven days post-STZ administration, rats with a fasting blood glucose level of 300 mg/dl or higher, as measured by a glucometer (Gloated), were considered diabetic. Non-diabetic rats served as the control group.

### Surgical Procedures

All rats were anesthetized with a single intraperitoneal dose of 90 mg/kg Ketamine (0.1 ml) and 10 mg/kg Xylazine (0.2 ml). After achieving anesthesia, the dorsal skin of the rats was shaved. Two open wounds, approximately 2x3 cm in size, were created on each rat's back at a distance of 1.5 cm from the midline on both lumbar regions, with four full-thickness skin loss wounds spaced 0.5 cm apart (Figure 1).

**Figure 1**. Diabetic wound model

Wound dressing procedures were performed daily at the same time each day. After the wounds were created, rats were housed individually in separate cages. For wound care, both diabetic and non-diabetic rats were disinfected with povidone-iodine before dressing. In the dressing process, the right lumbar region of each rat was treated with Thiocilline, and the left lumbar region was treated with St. John's Wort oil. Considering the wound healing period, the study was terminated after approximately 20 days.

### Anesthesia and Tissue Collection

On the 20th day of the study, anesthesia was induced in the rats by administering a single intraperitoneal dose of 90 mg/kg Ketamine (0.1 ml) and 10 mg/kg Xylazine (0.2 ml). After achieving anesthesia, wound tissues, including a 0.5 cm margin of surrounding healthy tissue, were excised and fixed in 10% formalin for 72 hours for pathological examination.

### Histopathological Evaluation

Histopathological analysis was conducted by scoring ulceration, necrosis, epithelialization, congestion, edema, polymorphonuclear leukocytes (PNL), monocytes, fibroblasts, and neovascularization across three high-power fields (40X magnification) on the wound bed. Each sample was anonymized and assigned a number before being sent for pathological evaluation to ensure blinded assessment. The tissue sections were examined using a light microscope (Olympus CX31RTSF, Olympus Optical, Japan), and images of specific sections were captured digitally (Olympus E 330, Olympus Optical, Japan) to assess changes in the nerves and other histological features.

### Statistical Analysis

In examining the obtained data, it was evaluated using SPSS (The statistical package for social sciences) 15.0 statistical package program. Kruskal-Wallis was used to determine whether there was homogeneity and statistical difference between all groups. Student t test was used to determine which group caused the difference. In all groups, p values below 0.05 were considered statistically significant within the 95% confidence interval.

## RESULTS

Comparison of weight and blood glucose levels in the groups was shown in Table 1. The substantial reduction in weight observed in the DM group (342.7±57.4) compared to the control group (440.8±40.8) could be indicative of diabetes-related weight loss (p<0.01). The significantly higher blood glucose levels in the DM group (398.2±89.5) compared to the control group X(84.6±13.8) are consistent with the pathophysiology of diabetes mellitus (p<0.001).

**Table 1.** Comparison of weight and blood glucose levels in the groups

| | Control group | DM group | p |
|---|---|---|---|
| Weight (kg) | 440.8±40.8 | 342.7±57.4 | <0.01 |
| Blood glucose (mg/dl) | 84.6±13.8 | 398.2±89.5 | <0.001 |

DM: Diabetes mellitus

### Histopathological Findings

Comparison of histopathological parameters in the groups was shown in Table 2. In histopathological evaluation, there was a statistically significant decrease in ulceration and necrosis in the group treated with St. John's Wort oil compared to the group given thiocilline (p = 0.04). In terms of epithelialization, there was a statistically significant increase in the group dressed with St. John's Wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant decrease in congestion and edema in the group treated with St. John's Wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant increase in fibroblast and neovascularization in the group treated with St. John's Wort oil compared to the group given thiocilline (p=0.02). Although PNL and monocyte numbers decreased in the St. John's wort group compared to the thiocilline group, there was no statistical significance (p>0.05) (Table 2, Figure 2 and 3).

**Table 2.** Comparison of histopathological parameters in the groups

| | Control Thiocilline | Control St.John's wort oil | DM Thiocilline | DM St. John's wort oil | p |
|---|---|---|---|---|---|
| Ulceration | 0.16±0.4 | 0.12±0.3 | 0.15±0.35 | 0.10±0.25 | 0.04 |
| Necrosis | 0.14±0.2 | 0.10±0.15 | 0.13±0.18 | 0.08±0.12 | 0.04 |
| Epithelialization | 0.25±0.3 | 0.30±0.35 | 0.27±0.33 | 0.35±0.40 | 0.03 |
| Congestion | 0.20±0.25 | 0.15±0.20 | 0.18±0.22 | 0.10±0.15 | 0.03 |
| Edema | 0.22±0.3 | 0.18±0.25 | 0.20±0.27 | 0.15±0.20 | 0.03 |
| PNL | 0.18±0.2 | 0.16±0.18 | 0.17±0.19 | 0.15±0.17 | 0.06 |
| Monocyte | 0.12±0.15 | 0.10±0.12 | 0.11±0.13 | 0.09±0.11 | 0.05 |
| Fibroblast | 0.30±0.4 | 0.34±0.42 | 0.31±0.41 | 0.37±0.45 | 0.02 |
| Neovascularization | 0.25±0.3 | 0.30±0.35 | 0.27±0.33 | 0.35±0.40 | 0.02 |

DM: Diabetes mellitus

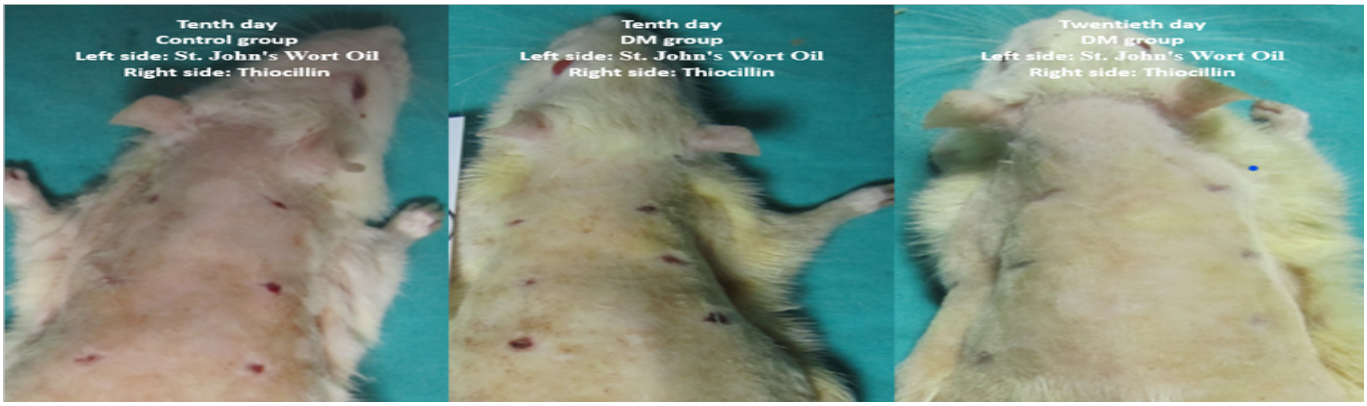


**Figure 2**. Morphological appearance of wound healing on the 10th and 20th days of treatment.

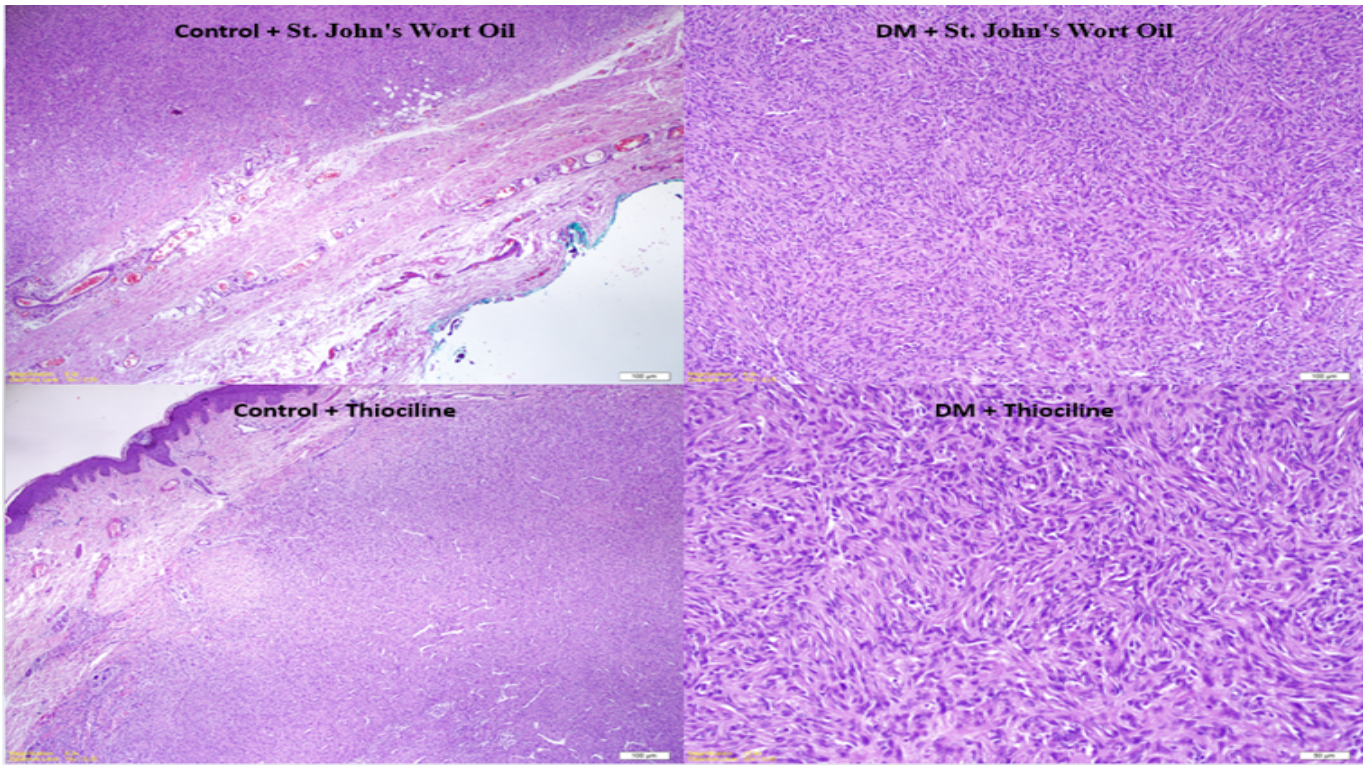


**Figure 3**. Histopathological appearance of wound healing in control and treatment groups.

## DISCUSSION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from inadequate insulin production or impaired insulin action. This condition often leads to impaired wound healing, frequently complicated by infections with various bacterial agents. This study aimed to compare the effectiveness of St. John's Wort oil (Hypericum perforatum) and thiocilline ointment (containing bacitracin and neomycin) in enhancing wound healing in a diabetic rat model.[16,17]

St. John's Wort oil has a longstanding history in herbal medicine for its beneficial effects on wound healing. The bioactive substances it contains, such as hypericin, hyperforin and flavonoids, offer many benefits, including anti-microbial, anti-inflammatory, and antioxidant properties.[13,18] Studies in the literature have shown its effectiveness in promoting epithelialization, reducing inflammation and accelerating the wound healing process.[19,20] Our findings are consistent with studies in the literature and show significant improvements in wound healing in diabetic rats treated with St. John's Wort oil. Compared to the thiocillin group, there was a significant reduction in ulceration and necrosis in the St. John's Wort oil group. Additionally, the significant increases in epithelialization and neovascularization observed in the St. John's Wort oil group indicate increased tissue regeneration and blood vessel formation, which are vital for effective wound healing.

Thiocillin, a compound containing neomycin and bacitracin, is widely used in routine practice due to its strong antibacterial properties.[10] Its anti-bacterial activity has a less significant effect compared to St. John's Wort oil on fundamental aspects of wound healing such as epithelialization, fibroblast proliferation and neovascularization. Our research revealed a significant reduction in edema and congestion in the group treated with St. John's Wort oil, demonstrating its potent anti-inflammatory effects.[21]

The wound healing effectiveness of St. John's Wort oil and its versatile effects can be attributed to physiological processes. Its anti-inflammatory effects help reduce edema and congestion often seen in diabetic wounds. Additionally, the antimicrobial properties of St. John's Wort oil can prevent infections and create an optimal environment for healing. St. John's Wort oil also supports fibroblast activity and neovascularization, which are necessary for tissue repair and regeneration.[22] Our study shows that St. John's Wort oil may be a valuable alternative or supplement to routine treatments such as thiocilline in the treatment of diabetic wounds. The significant effects of St. John's Wort oil on wound healing processes suggest that it may improve outcomes for diabetic patients. However, further clinical studies are needed to confirm these results and investigate potential side effects and best use practices of St. John's Wort oil in diabetic wound care.

Studies in the literature have shown the wound healing properties of St. John's Wort oil. [20,21,23-25] Özdemir et al.[23] reported that St. John's wort, thyme, and sage essential oils significantly increased wound healing in a rat model. These studies emphasize that St. John's Wort oil can be used as an effective agent in improving wound healing processes. Similarly, Arsic et al.[21] observed that creams containing St. John's Wort oil extract exhibited significant anti-inflammatory effects and accelerated wound healing in a sodium lauryl

sulfate-induced dermatitis model. Other studies have also highlighted the synergistic effects of combining herbal extracts.[23,24,26] Özdemir et al.[23] showed that the combination of St. John's Wort oil and Neem oil had a remarkable supportive impact on wound healing in pressure ulcer patients in intensive care units. Coban et al.[24] showed that composite films made from okra mucilage and methylcellulose, functionalized with Hypericum perforatum oil and gentamicin, exhibit enhanced wound dressing properties. Akturk et al.[26] showed that Hypericum perforatum oil (HPO) and vitamin A palmitate (VAP) incorporated into gelatin nanofibrous scaffolds, cross-linked with tannic acid (TA), effectively enhance wound healing. This aligns with our findings that St. John's Wort oil enhances epithelialization, fibroblast activity, and neovascularization, contributing to improved wound healing outcome. Hypericin and hyperforin, the main components of St. John's wort, are known to promote collagen synthesis, inhibit pro-inflammatory cytokines, and reduce oxidative stress. These effects are particularly beneficial for diabetic wounds, where chronic inflammation and oxidative stress inhibit the healing process. Additionally, St. John's Wort oil supports neovascularization, which is necessary to provide nutrients and oxygen to healing tissue, thus aiding tissue repair and regeneration. The increase in fibroblast proliferation observed in our study is very important for the development of granulation tissue and the accumulation of extracellular matrix components necessary for wound closure.[27,28]

### Limitations

This study has some limitations. The use of a single diabetic rat model in the study may not fully reflect the complex processes of wound healing in human diabetic patients. The short duration may be insufficient to observe the long-term effects of St. John's Wort oil and thiocilline on wound healing. However, the strength of our study is that it contributes to the limited body of research on wound healing, filling a critical gap in the literature and encouraging further research in this area. Another limitation of this study was the insufficient number of cases.

## CONCLUSION

In conclusion, St. John's Wort oil shows substantial potential for enhancing wound healing in a diabetic rat model, outperforming thiocilline in several crucial histopathological aspects. These results are consistent with existing research on the wound healing benefits of St. John's Wort oil and highlight the need for further studies to confirm its efficacy and safety in clinical settings. Incorporating St. John's Wort oil into wound care protocols could offer an effective, natural alternative for improving wound healing in diabetic patients.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Mustafa Kemal University Ethics Committee (Date: 29.05.2014, Decision No: 07/5).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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