



Jjoba Oil Hastens Dexamethasone Induced Delayed Wound Healing: A Preclinical Study

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Abstract

Background: Wound healing is a complex, multifactorial process in which poor healing in chronic wounds has emerged as the most significant complication in recent years. Jojoba oil (JO) has been traditionally used for its medicinal properties, especially for skin disorders. Studies suggested its potential wound-healing activity in-vitro. However, the underlying mechanism by which JO promotes the rejuvenating process is unclear in-vivo. The present study was aimed at evaluating the wound-healing activity of JO in both normal and delayed healing.

Methods: Excision wounds were inflicted by surgical method on the anesthetized rats. Animal wounds were explored for their healing activity by photography in-vivo. Expression of ERK, collagen, VEGF and PDGF was investigated using western blot.

Results: Topical administration of JO (0.5 ml/wound, twice a day) showed significant wound healing activity. All groups demonstrated a significant increase ($p < 0.001$) in wound contraction percentage except dexa+JO versus control. 100% wound closure was seen on day 12 in JO treated group when compared to the control which showed complete closure on day 15. We found that JO-treated animals showed an increase in the expression of collagen, VEGF, PDGF and ERK whereas dexamethasone displayed no expression. In the histopathology and Masson trichrome staining, the control group showed granulation tissue with no scab and epithelium, dexamethasone group exhibited the presence of less granulation tissue when compared with the control and treatment groups. The JO group depicted mature granulation tissue with more epithelial growth and the dexa+JO group, showed granulation tissue with little epithelial growth when compared, with the JO group. Masson trichrome staining showed matured collagen in the JO group when compared with the diseased group.

Conclusion: These findings suggest that JO activates ERK signaling, collagen formation, VEGF, PDGF expression which shows the plausible potential of JO in accelerating the healing process, more efficiently in delayed wound healing.

Introduction

Wound healing is a complex, firmly regulated process which is essential for skin's barrier function to remain intact.¹ A fully healed wound is one that has returned to its original anatomical form, function, and appearance within a fair amount of time, normally after a simple injury. It may also be described as a wound that has healed completely without the need for drainage or dressing.² Some wounds, on the other hand, do not heal in a timely and orderly fashion, leading to permanent, non-healing wounds. Delay in wound healing remains a major problem³ and is associated with diseases like diabetes, obesity and hypertension.⁴ Delayed wounds start off as acute wounds with a fibrin clot, but they get caught in an inflammatory process for a long time. It has been suggested

that the prolonged inflammatory process induces an increase in the levels of matrix metalloproteases (MMPs), plasmin, thrombin and elastase like proteases which destroy extracellular matrix (ECM) components thus damaging growth factors, and their receptors, all of which are essential in the healing process.⁵ Examples of chronic wounds include ulcers such as venous ulcer, diabetic foot ulcer, pressure ulcers, ischemic ulcers and infected wounds such as surgical or traumatic wounds. There are some agents that delay the wound healing process including non-steroidal anti-inflammatory drugs (NSAIDs). Delayed wound healing can be life-threatening to patients under steroid therapy.

According to both anecdotal and empirical evidence, many natural products have wound healing

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properties.⁶ Jojoba (*Simmondsia chinensis*) is one such herb that has piqued the interest of many scientists with respect to wound healing mechanisms. Jojoba liquid wax (jojoba oil) is made up of a combination of long chain fatty alcohols and acids like oleic acid, linoleic acid, arachidonic acid, palmitoleic acid, and others, all of which contribute to wound healing.⁷⁻⁹ Its unique chemical structure, which includes high viscosity, oxidative stability, and low volatility, makes it a versatile commodity with a wide range of industrial and medicinal applications.¹⁰ In vitro experiments highlighted minimal cytotoxic effects of jojoba oil (JO) on fibroblasts and immortalized human keratinocytes (HaCaT),¹¹ implying that JO can be categorized as a non-toxic agent that can be used safely for both external applications on healthy skin and on wound dressings. Fibroblasts normally migrate to the wound site to begin the proliferative phase of repair and deposition of matrix, while keratinocytes are involved in the re-epithelialization phase. It was seen that JO notably accelerated closure of wound by acting on fibroblasts and keratinocytes. JO also had the ability to induce collagen 1 synthesis in fibroblasts.¹¹ These findings were sufficient to warrant further research on in-vivo studies of JO.

Mitogen activated protein kinase (MAPK) signaling is involved in regulating the migration and proliferation of cells. Extracellular signal regulated kinase (ERK) has been extensively studied as one of the important signal pathways of various cell migration, through activation of MAPK.¹²⁻¹⁵ ERK/MAPK signaling also gets activated during skin injury and ERK/MAPK has shown its effect directly on keratinocyte migration in *in-vitro* models. The down regulation of this pathway ultimately decreases the cell migration and proliferation thus making skin repair critical. ERK pathway regulates the expression of collagen and other growth factors and JO according to previous studies has been reported to enhance collagen synthesis. Studies also suggested that the mechanism behind the action of JO is regulation of phosphoinositide 3 kinase -mammalian target of rapamycin (P13K-mTOR) pathway. Upregulation of pathways enhances the healing process by increasing epithelial cell migration and proliferation.¹¹ Thus, we hypothesized that JO may hasten wound healing by accelerating cell migration and proliferation. This research was proposed to investigate the possible wound healing effects of JO, given its widespread cosmetic use and dermatological properties on dexamethasone(dexa)-induced delayed wound healing.

Methods

Animal studies were carried out according to the Committee for Control and Supervision of Experiments on Animals (CCSEA) guidelines. Animal experiments were performed at Central Animal Research Facility, MAHE, Manipal. Animal studies were approved by Institutional Animal Ethics Committee (IAEC/KMC/43-2021). Forty-eight healthy inbred albino rats of the Wistar strain (150-200 g) were used. All animals were housed at controlled

room temp (23±2°C) and were provided with food and water *ad libitum*. The surgical intervention for excision wound model was carried out by using ketamine (80mg/kg) and xylazine (10 mg/kg) as anesthesia.¹⁶

Chemicals

JO (cold pressed, virgin and unrefined) was obtained from Urban Botanics Pvt. Ltd. Dexona vial (dexamethasone), ketamine and xylazine vials were obtained from Radha Medicals, Manipal.

Excision wound model

Wound size of 500 mm² was excised by surgical method on the dorsal region, 5 cm away from the ear of the animal. After hemostasis, the Wistar rats were placed back in cages and test compound were administered.⁴

Wound contraction area measurement

The percent of wound area contraction is measured using the following method

Percentage Wound contraction = [(initial wound size (Day 0) – specific day wound size (Day 2, 4, 6, 8, 10, 12, 15))/ initial wound size (day 0)] ×100

Period of epithelialization measurement

Complete epithelialization is considered as the scab to fall off, without leaving any raw wound behind and the number of days required was considered as the period of epithelialization.

Experimental design and evaluation of wound healing

Based on reference 4 with some modifications done, animals were divided into four groups of six each. The first group was kept as control for normal wound healing, the second group was controlled for delayed wound healing (0.17 mg/kg Dexamethasone given intramuscularly (IM)) consecutively for the first four days and then on alternate days. The third group involved tests for normal healing (0.5 ml/wound of 100% Jojoba oil, twice daily). Fourth group was test for delayed healing (0.17 mg/kg Dexamethasone IM, consecutively for the first four days and then on alternate days.⁴ A topical dose of 0.5 ml/wound of 100% JO oil, twice daily).

Excision wounds were inflicted by surgical method in rats under ketamine and xylazine anesthesia. A 15-day dosing period was given to rats in groups 2, 3 and 4. The area of the wound was measured every alternate day, using the Image J software and the wound contraction percentage was calculated. After 15 days of treatment, animals were euthanized by cervical dislocation using ether as anesthesia,¹⁷ and the wound tissues were collected and stored in -80 °C deep freezer for western blotting and in 10% formalin for histopathology and Masson trichrome staining.

Western blotting

Wound tissue samples were homogenized using

radioimmunoprecipitation assay buffer (RIPA) buffer for lysis of cells with protease inhibitor and phosphatase inhibitor. The obtained lysate was centrifuged at 16000 rpm for 20 min, supernatant was collected, and protein levels were estimated using Pierce bicinchoninic acid (BCA) Protein Assay kit (Thermo fisher Scientific). Fifty μg of proteins were separated using 10% sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE), then transferred onto PVDF membrane. The membranes were blocked using 3% bovine serum albumin (BSA) in 1X tris-buffered saline with 0.1% Tween[®] 20 detergent (TBST) for 2hrs. The membranes were washed three times, 10 min each using TBST then incubated with the primary antibodies at 4 °C overnight, followed by incubation with horseradish peroxidase conjugated anti IgG Secondary antibody. The primary antibodies for phosphorylated extracellular signal-regulated kinase (p-ERK), ERK, Collagen-1 and 3, VEGF, alpha tubulin (House Keeping), HRP Secondary antibody (Goat anti-rabbit IgG) were purchased from E-labScience. The blots were detected using ECL solution (Westar Antares, Cyanagen, Bologna, Italy). Quantification of protein bands' intensities was conducted using Gel documentation system (Syngene GBox Chemi XRQ).¹⁸

Histological assessment of wound healing

For granulation tissue formation, angiogenesis, epidermal regeneration, inflammatory cell infiltration, and collagen deposition, the tissue sections were stained with Masson trichome and Haematoxylin and eosin staining.¹⁹ Scoring was done from mild to moderate in order to indicate the level of healing in dexamethasone induced delayed wounds. Scoring for histology was represented as +, ++,

+++, - (+Mild, ++ Moderate, +++ Extensive, - Absent).

Statistical analysis

Data was presented as Mean \pm SEM. The wound contraction percentage was analyzed and compared by two-way analysis of variance (ANOVA) test followed by post hoc Bonferroni's test. Western blot data was analyzed using one-way analysis of variance followed by post hoc Tukey test.

Results

Figure 1 depicts the representative images of the wounds of four groups. The progress of wound healing on days 2, 4, 6, 8, 10, 12 and 15 can be seen. In the normal healing groups (control and JO), the wounds from the JO group showed faster contraction compared to the wounds of the control group. In the delayed healing groups (dexamethasone alone and dexa+JO), dexamethasone group showed delayed healing when compared to control and the wounds of the dexa+JO healed faster compared to the wounds of dexamethasone alone.

On days 8 and 10, a significant difference ($p < 0.001$) in percentage wound contraction was observed in dexa+JO treated rats when compared to dexamethasone alone. On day 10, a significant difference ($p < 0.001$) in percentage wound contraction was noted in JO-administered rats when compared to dexamethasone. On day 15, all the groups demonstrated significant increase ($p < 0.001$) in percentage wound contraction except dexa+jojoba oil versus control. 100% wound closure was seen on day 12 in Jojoba treated group when compared to control which showed complete closure on day 15. However, the period of wound closure was delayed in dexamethasone treated



Figure 1. Representative photographs of excision wounds of control, jojoba oil, dexamethasone and dexa+JO groups on various days of wound healing (n=6).

groups. i.e., dexamethasone alone and dexa+JO groups when compared to control groups. On day 15 jojoba showed significant increase in wound closure ($p < 0.00001$) when compared with dexamethasone alone and with dexa + jojoba (Figure 2).

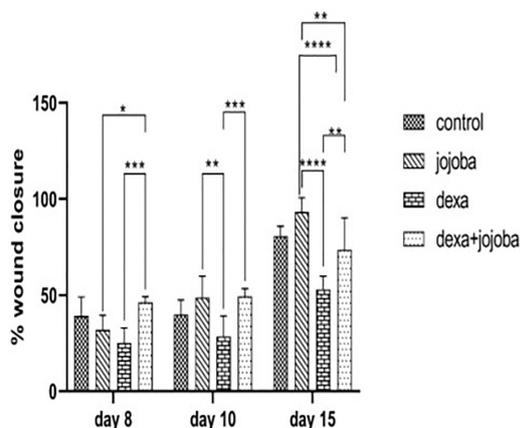


Figure 2. Effects of Jojoba oil on the contraction of the wound in normal & delayed wounds. Where * $p < 0.1$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Data was presented as Mean \pm SEM & $n=6$. The percentage of wound contraction was analyzed and compared by two-way analysis of variance (ANOVA) test followed by post hoc Bonferroni's test. Comparison is done between groups.

Effect of Jojoba oil on ERK, VEGF, Collagen expression by Western blot

Extracellular signal-regulated kinase (ERK) is a signaling pathway which helps in the regulation of cellular processes like cell growth, proliferation, apoptosis and helps in wound healing through MAP signaling. In this study, we found that in the dexamethasone group, phosphorylation of ERK and expression of VEGF, Collagen was decreased significantly compared to the normal control, and jojoba group as well as JO+dexa group significantly increased the phosphorylation of ERK and expression of VEGF and collagen (Figure 3).

Effect of Jojoba oil on histopathological changes on wound healing process in dexamethasone induced delayed wound healing

Epidermal regeneration, granulation tissue formation, fibroblast proliferation, angiogenesis and collagen deposition are the pillars of wound healing. The present study involved the histopathology of day 15 samples to observe the acceleration of healing with JO. Epidermal regeneration, fibroblast proliferation, angiogenesis and collagen deposition were observed in jojoba oil treated groups (Figures 4-6).

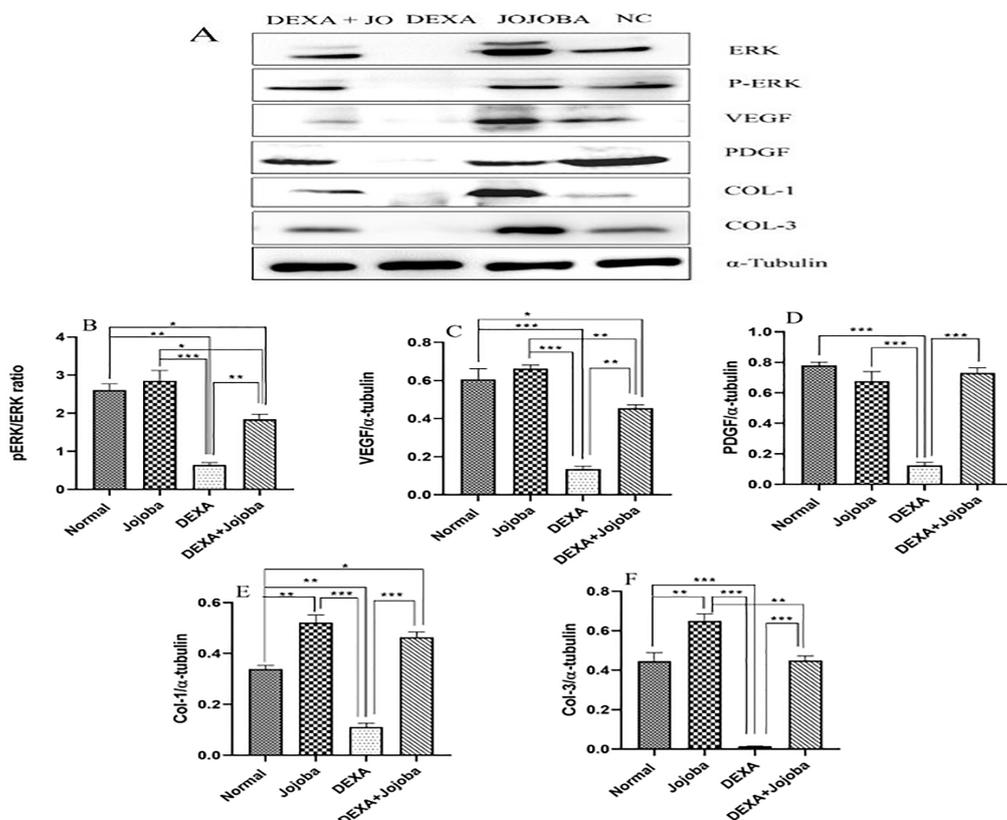


Figure 3. Effect of Jojoba oil on ERK, VEGF, PDGF, COL-1, COL-3 Expression. (A) Representative images of the blots; (B) p-ERK/ERK ratio; (C) VEGF/ α -tubulin ratio; (D) PDGF/ α -tubulin ratio; (E) Col-1/ α -tubulin ratio; (F) Col-3/ α -tubulin ratio. Data is represented as Mean \pm SEM; *** $P < 0.001$, ** $P < 0.01$, * $P < 0.1$ when compared with normal control, treated and dexa groups. Sample data ($n=6$) was analyzed by One Way ANOVA using Tukey as post hoc test.

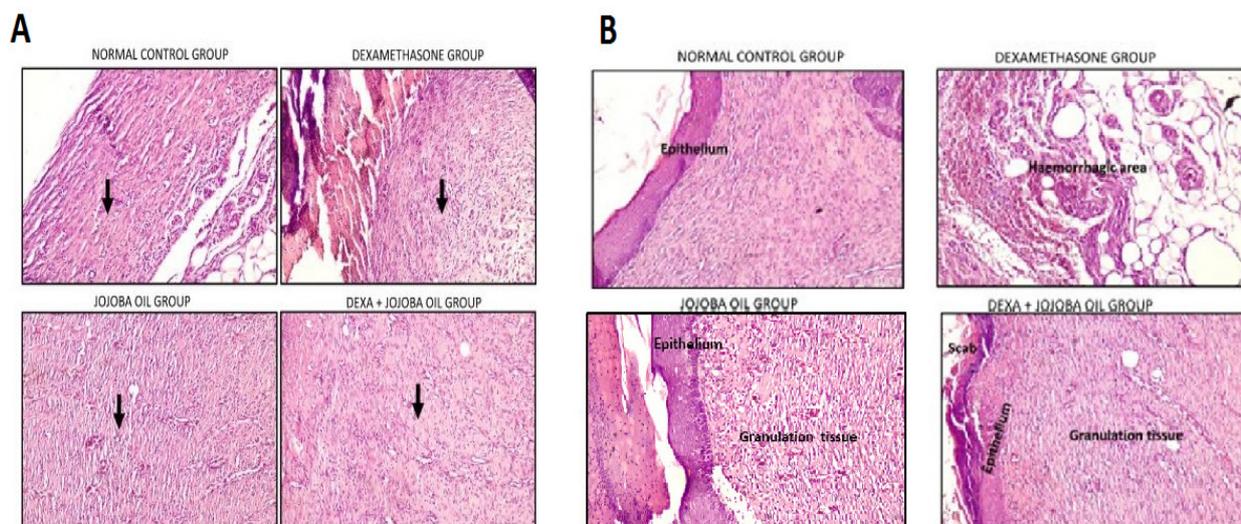


Figure 4. Effect of JO on histopathology (Haematoxylin & Eosin staining). Arrows in Figure A indicate the formation of granulation tissue at 100x. Figure B showing epithelium, haemorrhagic areas and granulation tissue at 100X.

Discussion

Our findings present a scientific evaluation of properties of jojoba oil on dexamethasone induced delay in wound healing and because jojoba oil is a non-toxic substance and has a unique chemical structure, 25% similar to human sebum, causes rapid re epithelialization, collagen, and new blood vessels formation. Jojoba oil is beneficial and has traditional as well as folklore use in the cosmetic and skin care industry.²⁰ Our findings suggest that jojoba oil has fast and effective healing capacity, for use in both normal and delayed wounds.

Wound healing is a multifactorial process that involves collagen synthesis, re-epithelialization, cell migration, and cell proliferation. Delayed wound healing has become a clinical issue in recent years, and synthetic therapeutic compounds are too expensive, which has drawn our attention towards natural compounds. Due to its

exceptional properties, including providing a light feeling and containing natural omega-9 and vitamin E, jojoba oil is widely used in beauty cosmetics. Jojoba oil can be safely applied to skin injuries, thus aiding in skin rejuvenation. An in-vitro study has shown that jojoba oil has the capability to stimulate collagen-1 synthesis in fibroblasts. The MAPK signaling pathway, especially Extracellular signal-regulated kinase (ERK), plays a vital role in cell migration and proliferation. Jojoba oil has already been studied in vitro and has been reported to activate the PI3-Akt-mTOR pathway in both fibroblasts and keratinocytes, which is an integral part of wound healing. However, its activity in in-vivo dexamethasone-induced delayed wounds has not been elucidated. Hence, this study was undertaken to determine whether jojoba oil has the capacity to heal dexamethasone-induced delayed wounds.

We performed an excision wound model and treated the

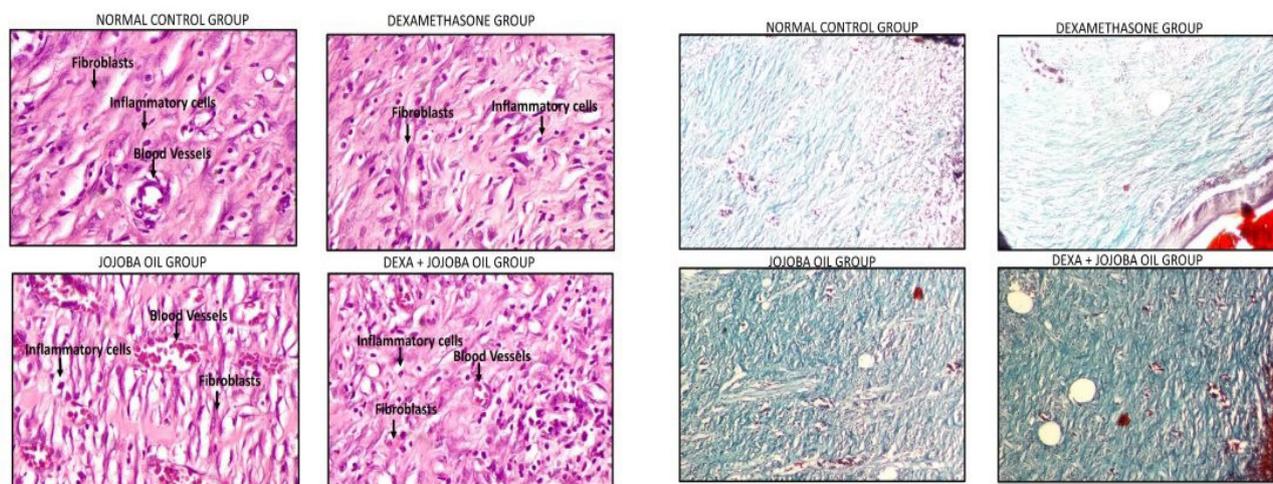


Figure 5. Effect of JO on histopathology (Haematoxylin & Eosin staining). Figure showing Fibroblast, inflammatory cells and blood vessels at 400x.

Figure 6. Effect of JO on collagen deposition by Masson trichrome staining. Images captured at 100X.

animals for 15 days. On days 2, 4, 6, 8, 10, 12, and 15, animals were monitored for wound closure, and images were taken using a digital camera. The images were analyzed using Image J software. On days 8 and 10, a significant difference ($p < 0.001$) in percentage wound contraction was observed in rats treated with dexamethasone+JO compared to those treated with dexamethasone alone. On day 10, a significant difference ($p < 0.001$) in percentage wound contraction was noted in rats administered with JO compared to those treated with dexamethasone alone. On day 15, all groups demonstrated a significant increase ($p < 0.001$) in percentage wound contraction except for the dexamethasone+jojoba oil group compared to the control. Complete wound closure was observed on day 12 in the jojoba-treated group, compared to the control group, which showed complete closure on day 15.

It has been reported by Rodrigues *et al.*²¹ that VEGF and its signaling molecule ERK, which regulate inflammation and angiogenesis, are decreased in chronic wounds. It has also been observed that there is low expression of collagen 1 and collagen 3 in chronic wounds. Previous studies by Ranzato *et al.*¹¹ showed that jojoba oil accelerates wound closure by acting on both fibroblasts and keratinocytes in normal wounds, and the mechanism behind this is through the PI3K–Akt–mTOR pathway. The wound tissues collected on day 15 were subjected to western blot analysis, which revealed that jojoba oil increased the expression of phospho-ERK, VEGF, and PDGF compared to the dexamethasone-treated group, and the expression of collagen-1 and collagen-3 compared to the control and dexamethasone-treated groups. These findings provide insight into how jojoba oil accelerates healing in delayed wounds by activating ERK/MAPK signaling.

Collagen is important for skin healing as it helps in the formation of the extracellular matrix, which plays a vital role in the healing of acute or delayed wounds. Re-epithelialization is crucial for wound healing, as the cellular and molecular processes involved are important in healing. It is the ability of the wound to heal properly and swiftly by coordinating the proliferation and migration of keratinocytes present at the wound area. From the western blot analysis, Masson trichome staining, and histopathological images, we observed that jojoba oil increased the formation of new blood vessels, re-epithelialization, myofibroblasts formation, and collagen synthesis.

Histopathology and Masson trichome staining in the control group showed the wound area with scab, neutrophilic aggregates, granulation tissue consisting of inflammatory cells (lymphocytes), fibroblasts, and new blood vessels (angiogenesis). The dexamethasone group showed the wound area with epithelial formation and scab. The scab area showed the presence of cell debris and neutrophilic aggregates. Some areas showed discontinuous epithelium, 7-11 layers in thickness. The granulation tissue consisted of inflammatory cells (lymphocytes), fibroblasts, and new blood vessels (angiogenesis). Impairment of granulation tissue formation is observed in chronic wounds. Systemic

steroids cause wounds to heal with incomplete granulation tissue and reduced wound contraction. In the JO group, the epithelium was seen above the granulation tissue and was 3 to 8 layers in thickness. The granulation tissue seen beneath the epithelium was more mature, consisting of few inflammatory cells (lymphocytes), fibroblasts, and new blood vessels (angiogenesis). The dexamethasone + JO group showed the wound area with scab consisting of cell debris and neutrophilic aggregates. The epithelium was discontinuous with 3 to 8 layers in thickness. The granulation tissue seen beneath the epithelium consisted of a few inflammatory cells (lymphocytes), fibroblasts, and new blood vessels (angiogenesis). The JO group showed the presence of mature granulation tissue with significant epithelial growth. Similarly, the dexamethasone+JO group also showed granulation tissue with limited epithelial growth compared with jojoba oil treatment. Masson trichome staining showed mature collagen in the JO group compared with the diseased group. Thus, it can be concluded that jojoba treated groups showed significant granulation tissue formation and formation of new blood vessels compared to the disease control, indicating that jojoba oil can promote wound healing in delayed wound healing conditions.

Our findings present a scientific evaluation of the properties of jojoba oil on dexamethasone-induced delay in wound healing, and because jojoba oil is a non-toxic substance with a unique chemical structure, 25% similar to human sebum, it causes rapid re-epithelialization, collagen, and new blood vessels formation. Jojoba oil is beneficial and has traditional as well as folklore use in the cosmetic and skincare industry. Our findings suggest that jojoba oil has fast and effective healing capacity for use in both normal and delayed wounds.

Conclusion

The JO group depicted mature granulation tissue with more epithelial growth and matured collagen when compared with the diseased group. It also increased the expression of collagen, VEGF, PDGF and ERK. JO counteracts the dexamethasone-induced delay in wound healing but has no beneficial action on normal healing. This alludes to a promising topical agent for the treatment of delayed wounds as seen in diabetic patients.

Ethical Issues

Animal studies have been approved by the Institutional Animal Ethics Committee, KMC, MAHE, Manipal (IAEC/KMC/43-2021).

Author Contributions

Farmiza Begum: Investigation, Writing - Original Draft. Pooja J Kotian: Investigation, Writing - Original Draft. Snigdha Hiremath: Investigation. Atharva Ramdasi: Investigation, Writing - Original Draft. Apoorva Sharma: Investigation. Fathima Beegum: Investigation. Prasada Chowdhari Gurram: Investigation, Madhavan Nampoothiri G: Conceptualization, Writing - Review &

Editing. Krishnadas Nandakumar: Conceptualization, Writing - Review & Editing, Rekha R Shenoy: Investigation, Conceptualization.

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Conflict of Interest

The authors declare no conflict of interest.

References

- Han G, Ceilley R. Chronic Wound Healing: A Review of current management and treatments. *Adv Ther.* 2017;34(3):599. doi:10.1007/S12325-017-0478-Y
- Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. *Clin Dermatol.* 2007;25(1):9-18. doi:10.1016/J.Clindermatol.2006.09.007
- Enoch S, Elaine Price P, Price PB, Director Chp. cellular, molecular and biochemical differences in the pathophysiology of healing between acute wounds, chronic wounds and wounds in the aged. *World Wide Wounds.* 2004;13:1-17
- Rao MC, Sudheendra AT, Nayak PG, Paul P, Kutty GN, Shenoy RR. Effect of Dehydrozingerone, a half analog of curcumin on dexamethasone-delayed wound healing in albino rats. *Mol Cell Biochem.* 2011;355(1-2):249-56. doi:10.1007/S11010-011-0861-Y/METRICS
- Schultz GS, Chin GA, Moldawer L, Diegelmann RF. Principles of Wound Healing. In: Fitridge R, Thompson M, editors. *Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists.* Adelaide (AU): University of Adelaide Press; 2011.
- de Fátima A, Modolo LV, Sanches AC, Porto RR. Wound healing agents: the role of natural and non-natural products in drug development. *Mini Rev Med Chem.* 2008;8(9):879-88. doi:10.2174/138955708785132738
- Oh SY, Lee SJ, Jung YH, Lee HJ, Han HJ. Arachidonic acid promotes skin wound healing through induction of human MSC migration by MT3-MMP-mediated fibronectin degradation. *Cell Death Dis.* 2015;6(5):e1750. doi:10.1038/cddis.2015.114
- Weimann E, Silva MBB, Murata GM, Bortolon JR, Dermargos A, Curi R, et al. Topical anti-inflammatory activity of palmitoleic acid improves wound healing. *PLoS One.* 2018;13(10):e0205338. doi:10.1371/journal.pone.0205338
- Cardoso CR, Souza MA, Ferro EA, Favoreto S Jr, Pena JD. Influence of topical administration of n-3 and n-6 essential and n-9 nonessential fatty acids on the healing of cutaneous wounds. *Wound Repair Regen.* 2004;12(2):235-43. doi:10.1111/j.1067-1927.2004.012216.x
- Wisniak J. Jojoba oil and derivatives. *Prog Chem Fats Other Lipids.* 1977;15(3):167-218. doi:10.1016/0079-6832(77)90001-5
- Ranzato E, Martinotti S, Burlando B. Wound healing properties of jojoba liquid wax: An in vitro study. *J Ethnopharmacol.* 2011;134(2):443-9. doi:10.1016/j.jep.2010.12.042
- Lee S, Kim MS, Jung SJ, Kim D, Park HJ, Cho D. ERK activating peptide, AES16-2M promotes wound healing through accelerating migration of keratinocytes. *Sci Rep.* 2018;8(1):14398. doi:10.1038/s41598-018-32851-y
- He M, Xue ZM, Li J, Zhou BQ. Breviscapine inhibits high glucose-induced proliferation and migration of cultured vascular smooth muscle cells of rats via suppressing the ERK1/2 MAPK signaling pathway. *Acta Pharmacol Sin.* 2012;33(5):606-14. doi:10.1038/aps.2012.6
- Seger R, Krebs EG. The MAPK signaling cascade. *FASEB J.* 1995;9(9):726-35.
- Makino T, Jinnin M, Muchemwa FC, Fukushima S, Kogushi-Nishi H, Moriya C, et al. Basic fibroblast growth factor stimulates the proliferation of human dermal fibroblasts via the ERK1/2 and JNK pathways. *Br J Dermatol.* 2010;162(4):717-23. doi:10.1111/j.1365-2133.2009.09581.x
- Alsareii SA, Ahmad J, Umar A, Ahmad MZ, Shaikh IA. Enhanced in vivo wound healing efficacy of a novel piperine-containing bioactive hydrogel in excision wound rat model. *Molecules.* 2023;28(2):545. doi:10.3390/molecules28020545
- Tan WS, Arulsevan P, Ng SF, Mat Taib CN, Sarian MN, Fakurazi S. Improvement of diabetic wound healing by topical application of Vicenin-2 hydrocolloid film on Sprague Dawley rats. *BMC Complement Altern Med.* 2019;19(1):20. doi:10.1186/s12906-018-2427-y
- Begum F, Manandhar S, Kumar G, Keni R, Sankhe R, Gurram PC, et al. Dehydrozingerone promotes healing of diabetic foot ulcers: a molecular insight. *J Cell Commun Signal.* 2023;17(3):673-88. doi:10.1007/s12079-022-00703-0
- Wu X, Yang L, Zheng Z, Li Z, Shi J, Li Y, et al. Src promotes cutaneous wound healing by regulating MMP-2 through the ERK pathway. *Int J Mol Med.* 2016;37(3):639-48. doi:10.3892/ijmm.2016.2472
- Jojoba oil: uses, benefits and risks – forbes health. <https://www.forbes.com/health/body/jojoba-oil/>. Accessed on September 2023.
- Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: A cellular perspective. *Physiol Rev.* 2019;99(1):665. doi:10.1152/PHYSREV.00067.2017