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Synergistic effects of zinc oxide and ellagic acid on macrophage infiltration, angiogenesis, and collagen deposition in excisional wounds healing

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ABSTRACT

Objectives: The combination of zinc oxide (ZnO) and ellagic acid (EA) in wound dressings offers synergistic benefits for wound healing due to their complementary antimicrobial, antioxidant, anti-inflammatory, and tissue regenerative properties. This study aimed to evaluate the effects of ZnO-EA dressing on macrophage infiltration, angiogenesis, and collagen density in excisional wounds on days 3 and 7 post-treatment.

Materials and methods: This in vivo posttest-only experimental study involved twenty *Rattus norvegicus* with excisional dorsal wounds, randomly assigned to two groups: a control group receiving ZnO dressing and a treatment group receiving ZnO-EA dressing. Each group was evaluated at day 3 and day 7, resulting in four observation subgroups. Tissue samples were collected to assess macrophage infiltration and angiogenesis using Hematoxylin and Eosin staining, and collagen density using Masson's Trichrome staining. Histological evaluation was performed under a light microscope at 400× magnification.

Results: Treatment with ZnO-EA resulted in significant increase in macrophages infiltration, the number of newly formed blood vessels, and collagen density in the treatment group compared to the ZnO group on both days 3 and 7 ($p < 0.05$).

Conclusion: The application of a ZnO wound dressing enriched with EA significantly enhances macrophage infiltration, angiogenesis, and collagen deposition during the wound healing process.

1. Introduction

Wound healing remains a significant challenge in clinical practice, particularly when the healing process is delayed, increasing the risk of secondary infections and complications.[1] Complete wound closure typically requires a minimum of seven days; however, prolonged healing can lead to chronic inflammation, bacterial colonization, and impaired tissue regeneration.[2] To mitigate these risks, various therapeutic strategies have been developed, including the use of wound dressings that not only protect the wound site but also deliver active compounds with antimicrobial, anti-inflammatory, and regenerative properties.[3,4]

Zinc oxide (ZnO) has been extensively studied for its therapeutic role in wound healing, especially when integrated into dressing materials.[5,6] Its well-documented antimicrobial and anti-inflammatory properties contribute to a favorable wound environment by reducing bacterial colonization and modulating local immune responses.[7,8] Studies have shown that ZnO-containing dressings, such as hydrocolloid formulations with 6 % ZnO, significantly reduce bacterial counts and promote granulation tissue formation.[9] Additionally, ZnO emulsions and ZnO nanoparticles embedded in alginate dressings have demonstrated accelerated wound closure and improved management of chronic wounds, including diabetic ulcers.[5]

Ellagic acid (EA), a natural polyphenol found in various fruits and plants, has also demonstrated potent wound healing activity[10] It promotes fibroblast proliferation and migration, enhances collagen synthesis, and facilitates angiogenesis.[11] EA exerts strong antioxidant and

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anti-inflammatory effects by inhibiting oxidative stress and suppressing pro-inflammatory mediators.[12,13] Recent advances in biomaterials have enabled the incorporation of EA into hydrogels and film-based wound dressings, allowing sustained release and targeted delivery at the wound site, further enhancing its therapeutic efficacy.[14,15]

The combination of ZnO and EA presents a promising approach in wound management due to their complementary biological activities. Both agents exhibit antimicrobial properties, targeting a broad spectrum of pathogens, and may act synergistically to reduce the risk of infection and microbial resistance. Their anti-inflammatory effects via down-regulation of cytokines such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), and inhibition of nuclear factor kappa B (NF-κB) signaling, support a timely transition from the inflammatory to the proliferative phase of healing. Additionally, both compounds possess antioxidant capacities, contributing to reduced oxidative stress and improved tissue regeneration. ZnO also facilitates epithelial regeneration and hemostasis, while EA enhances vascular stability and collagen remodeling. Although each compound has demonstrated wound-healing benefits individually, the potential synergistic effect of their combined application in vivo remains insufficiently explored. This study therefore sought to investigate whether incorporating EA into a ZnO dressing enhances key parameters of wound healing, like macrophage infiltration, angiogenesis, and collagen deposition.

Given the favorable biocompatibility and biological activity of ZnO and EA, combining these agents may provide synergistic benefits for wound repair. We hypothesized that a ZnO-EA dressing would enhance macrophage infiltration, angiogenesis, and collagen deposition more effectively than ZnO alone in an excisional wound model. Therefore, this study aimed to evaluate the in vivo effects of ZnO-EA on key phases of wound healing, including inflammatory cell infiltration, neovascularization, and collagen formation.

2. Materials and methods

2.1. Animal model

This laboratory-based experimental study employed a post-test control group design to assess the effects of ZnO combined with EA on wound healing parameters. Twenty healthy male Wistar rats *(Rattus norvegicus),* aged 12–15 weeks and weighing 200–300 g, were obtained from the Animal Laboratory Unit, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia. The sample size was calculated using the Lemeshow formula for comparing two independent means, with a two-sided $\alpha = 0.05$ and statistical power of $1 - \beta = 0.80$. by this calculation each group in each time of observation obtained 5 rats.

Animals were housed in polypropylene cages (40 × 30 × 15 cm) with stainless-steel wire lids, containing autoclaved wood-shavings bedding, with one rat per cage. Environmental conditions were controlled at 22–25 °C with 50–60 percent relative humidity and a 12-h light/dark cycle. Rats were provided ad libitum access to standard pellet chow and clean water.

2.2. Preparation of zinc oxide and ellagic acid mixture

A homogeneous mixture was prepared by combining 87.5 g of ZnO powder (Zinc oxide, Sigma Aldrich. Cat #1088490500) with 12.5 g of EA (ellagic acid 90 % (Xi'an Biof-Technology Co., Ltd. China)) on a mixing pad using a stainless-steel spatula. This mixture was then blended with coconut fatty acids (JIC89, Indonesia) in a 1:1 ratio, ensuring uniform consistency suitable for topical application.

2.3. Excisional wound induction and treatment

Following a seven-day acclimatization period, the rats were randomly assigned into four subgroups (five animals per group). Before wound induction, animals were fasted for 12 h. General anesthesia was administered intramuscularly using ketamine hydrochloride (80 mg/kg) and xylazine hydrochloride (10 mg/kg). The dorsal fur was shaved and disinfected by applying 70 percent ethanol three times, allowing 30 s contact time between applications.

A sterile ruler and skin marker were used to delineate a 10 × 10 mm wound area on the dorsal surface. A full-thickness excisional wound was created using a No. 15 scalpel to a depth of approximately 2 mm, reaching the fascia layer. Wound depth was standardized visually to the fascia and by using the scalpel blade depth as a reference guide. The wound was rinsed with sterile normal saline.

The ZnO-EA dressing was applied topically as a thin, uniform layer sufficient to completely cover the wound surface (approximately 10 × 10 mm). The control group received a comparable topical application of ZnO alone. Dressings were applied once at the time of wound creation and were not replaced during the study period. A 20 × 20 mm piece of hypoallergenic medical tape was gently pressed around the wound margins to secure the dressing and prevent displacement. Following dressing application, each rat was housed individually to avoid interference with the wound site. Animals were randomly allocated to treatment groups using simple randomization, with group assignments generated prior to wound induction to ensure equal distribution across experimental conditions.

Animals were euthanized at 72 h (day 3) and 168 h (day 7) after treatment application using an overdose of ketamine–xylazine (0.6 mL; intraperitoneal). A full-thickness skin specimen encompassing the wound and a uniform 0.5 mm margin of surrounding healthy tissue was excised to ensure consistent sampling across animals. Excised tissue was rinsed gently with distilled water, laid flat on filter paper to prevent curling, and immediately fixed in 10 % neutral buffered formalin at room temperature. A fixative-to-tissue volume ratio of approximately 10:1 was maintained, and samples were immersed for 24 h before routine histological processing.

2.4. Histological analysis

Fixed dorsal skin tissues were processed, embedded in paraffin, and sectioned at 4 μm thickness using a rotary microtome. For evaluation of macrophage infiltration and angiogenesis, sections were stained with Hematoxylin and Eosin (H&E) (Sigma-Aldrich, USA; Cat. No. H3136 and E4009). Collagen deposition was examined using Masson's Trichrome staining kit (Sigma-Aldrich, USA; Cat. No. HT15). Staining was performed according to the manufacturer's protocols, including standard sequential immersion in hematoxylin, eosin, and trichrome reagents with appropriate washing steps between stages.

Macrophages were identified based on characteristic morphology, including large oval or kidney-shaped nuclei and abundant eosinophilic cytoplasm. Blood vessels were counted by identifying luminal structures lined by endothelial cells and containing or capable of containing erythrocytes. Five randomly selected high-power fields (400 ×) were examined per slide. Collagen density was quantified using ImageJ software (NIH, version 1.53) by converting images to grayscale, applying a fixed threshold to isolate collagen fibers, and calculating the percentage of collagen-positive area relative to the total tissue area. All histological evaluations and quantitative analyses were performed by an investigator blinded to treatment group allocation to minimize observer bias.

2.5. Statistical analysis

Data were analyzed using GraphPad Prism 10 (Mac version). Each group consisted of five animals per time point (n = 5 on day 3 and n = 5 on day 7), and five high-power fields (400 ×) were analyzed per animal per parameter.

Normality was evaluated with the Shapiro-Wilk test and homogeneity of variance with Levene's test. For normally distributed and homogeneous data, an independent *t*-test was applied. Due to software output format, p-values are presented as significance thresholds (*p <

0.05 or **p < 0.01 or ***p < 0.001 or ****p < 0.0001), with p < 0.05 considered statistically significant.

3. Result

3.1. Macrophages

On histological examination, the macrophages infiltration was noticeably higher in the group treated with ZnO-EA compared to the group treated with ZnO, at both day 3 and day 7 post-wounding (Fig. 1A). This observation was supported by quantitative analysis which showed a significant increase in macrophage infiltration in the ZnO-EA group on both day 3 and day 7 **(p < 0.01)** (Fig. 1B). No significant difference was observed within each group between day 3 and day 7. These results indicate that the addition of EA to Zn dressings promotes a sustained pro-healing inflammatory response by increasing macrophage infiltration during the early and mid-stages of wound healing.

3.2. Angiogenesis

Similarly, the formation of newly blood vessel was markedly enhanced in the ZnO-EA group compared to the ZnO group (Fig. 2A). Histological examination revealed a greater number of newly formed vascular structures in the ZnO-EA at both 3 and 7 days after wounding. Quantitative assessment confirmed a significant increase in neovascularization in the ZnO-EA relative to the ZnO at both time points (p < 0.01) (Fig. 2B). Consistent with the macrophage findings, no significant differences were observed within each group between day 3 and day 7. These results suggest that EA supplementation promotes angiogenesis during the early and mid-phases of wound healing.

3.3. Collagen density

In addition to enhanced vascularization, the deposition of collagen fibers was significantly greater in the ZnO-EA compared to the ZnO group (Fig. 3A). Histological analysis showed denser and more organized collagen bundles in the ZnO-EA-treated wounds at both 3- and 7-days post-wounding. Quantification of collagen density showed a significant increase in the ZnO-EA group at both time points (p < 0.001), with no significant change observed within each group between day 3 and day 7 (Fig. 3B). These findings support that EA facilitates extracellular matrix remodeling and promotes collagen synthesis during wound healing.

4. Discussion

Zinc oxide (ZnO) enhances wound healing by modulating the immune response and promoting tissue regeneration.[16] When applied as a wound dressing, ZnO activates innate immune cells, particularly macrophages and neutrophils, through interactions with Toll-like receptors such as TLR6.[17,18] This activation triggers downstream signaling pathways, including MAPK and NF-κB, [19] leading to the production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) that are essential for early wound defense and debris clearance.[20] ZnO-induced reactive oxygen species (ROS) further act as signaling mediators that amplify immune activation and support cell recruitment to the injury site.'[21,22]

Beyond immune activation, ZnO-generated ROS promote the expression of vascular endothelial growth factor (VEGF),[23] thereby stimulating angiogenesis and improving blood supply to the healing tissue. In parallel, ZnO enhances fibroblast migration and collagen deposition while exerting antimicrobial effects, collectively creating a favorable microenvironment for efficient tissue repair and wound closure.

Ellagic acid (EA), a polyphenolic compound found in fruits like pomegranates and berries, exhibits several mechanisms when applied topically as a wound dressing, enhancing the healing process by modulating immune cell activity and promoting angiogenesis. [11] EA influences macrophage and neutrophil functions through various signaling pathways. In macrophages, EA has been shown to modulate the expression of cytokines and chemokines, thereby influencing the inflammatory response. [24] For instance, it can reduce the production of pro-inflammatory cytokines such as IL-6 and TNF-α, while increasing anti-inflammatory cytokines like IL-10, thereby promoting a balanced immune response. Additionally, EA can inhibit the activation of NF-κB and MAPK pathways, which are crucial in the inflammatory process, [24] leading to decreased expression of adhesion molecules and reduced recruitment of neutrophils to the site of injury.

EA also plays a role in angiogenesis, the angiogenesis, which is essential for tissue repair during wound healing. It has been reported to stimulate VEGF-induced endothelial cell proliferation, migration, and tube formation by directly interacting with VEGFR-2, thereby interfering with angiogenesis processes. Although this study did not quantitatively assess re-epithelialization, histological observations showed no

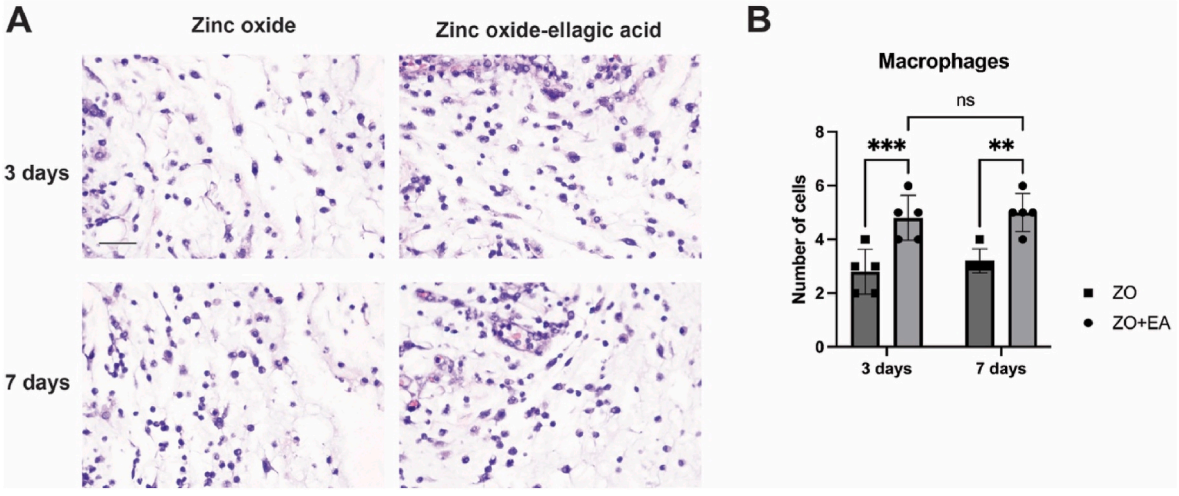

Fig. 1. Macrophage infiltration in excisional wounds treated with ZnO and ZnO-EA dressing. (A) Representative H&E-stained tissue sections showing macrophage distribution at day 3 and day 7 post-wounding (400 × magnification). Increased macrophage presence is observed in the ZnO-EA group at both time points. Scale bar = 50 μm. (B) Quantification of macrophages per field. Data are expressed as mean ± SD (n = 5). **p < 0.01, ***p < 0.001 ns = not significant; using independent *t*-test. ZnO = zinc oxide; ZnO-EA = zinc oxide with ellagic acid.

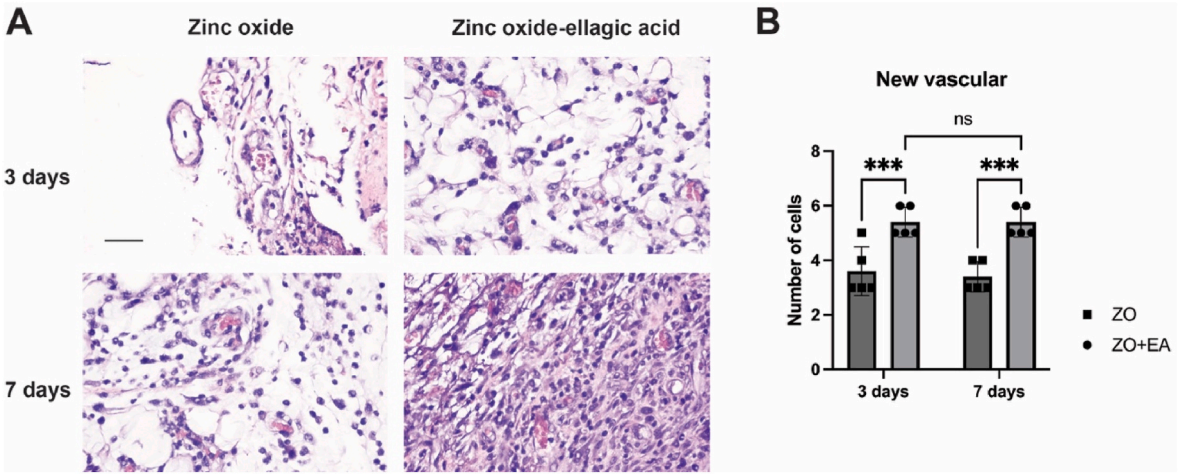

Fig. 2. EA enhances new vascular formation in healing tissues. (A) Representative hematoxylin and eosin-stained sections of tissue from the ZnO and ZnO-EA groups at 3 and 7 days after injury. Angiogenesis are visible and appear more abundant in the ZnO group. Scale bar: 50 μm. (B) Quantification of new vessel numbers per high-power field. Data are presented as mean ± standard deviation (n = 5). ***p < 0.001 compared to control; ns: not significant; using independent *t*-test. ZnO = zinc oxide; ZnO-EA = zinc oxide with ellagic acid.

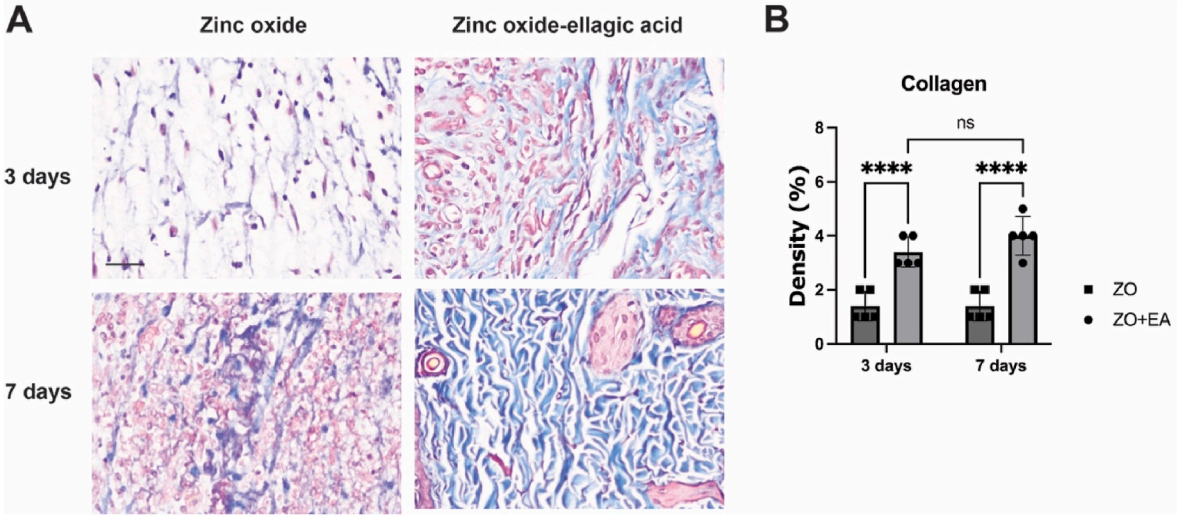

Fig. 3. Histological evaluation and quantification of collagen deposition. (A) Representative images of collagen fibers stained by Masson's trichrome in the control and ZnO groups at 3- and 7-days post-wounding. Blue staining indicates collagen fibers. Scale bar = 50 μm. (B) Quantitative analysis of collagen density showing a significant increase in the ZnO-EA group compared to the ZnO at both 3 and 7 days (***p < 0.001), with no significant difference between days within each group (ns); using independent *t*-test. Data are presented as mean ± SD (n = 5). ZnO = zinc oxide; ZnO-EA = zinc oxide with ellagic acid. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

evidence of delayed epithelial coverage or abnormal tissue reactions in the ZnO-EA group. No adverse effects, such as necrosis, excessive inflammatory infiltrate, or granulomatous response, were observed. The relatively small sample size, consistent with exploratory in vivo wound-healing studies, may limit statistical power and generalizability. In addition, full blinding was not feasible during wound creation and treatment application due to procedural constraints, although histological evaluation and image analysis were performed in a blinded manner. Future research incorporating standardized quantitative scoring of re-epithelialization, larger sample sizes, and full blinding protocols will enhance the robustness of these findings and support further translational evaluation of ZnO-EA wound dressings.

This study provides in vivo evidence that combining ZnO–EA enhances key wound-healing endpoint parameters beyond what has been reported for ZnO alone. Unlike conventional single-agent dressings, the ZnO–EA formulation is designed to address microbial control, inflammation modulation, oxidative stress reduction, and extracellular matrix formation simultaneously. In the present study, however, evaluation was limited to selected histological parameters, including macrophage infiltration, angiogenesis, and collagen deposition, while other healing outcomes such as re-epithelialization were not quantitatively assessed. Taken together, these findings suggest that ZnO–EA dressings may offer a practical and biologically grounded approach to accelerate wound repair and could serve as a foundation for developing next-generation topical biomaterials for clinical wound management.

5. Conclusion

In this in vivo rat wound model, direct histological comparison between ZnO–EA and ZnO dressings demonstrated increased macrophage infiltration, angiogenesis, and collagen deposition in the ZnO–EA–-treated wounds; however, these findings should be interpreted in light of the relatively small sample size. The use of standardized histological quantification across predefined high-power fields further strengthens

the reliability of these observations.

Patient's/Guardian's consent

This study did not involve human participants, and therefore, informed consent were not required.

Ethical clearance

This study was approved by the Health Research Ethics Committee, Faculty of Dental Medicine, Universitas Airlangga, Indonesia (Approval No. 0677/HRECC.FODM/VII/2024). All procedures followed institutional guidelines for the care and use of laboratory animals and complied with the National Guidelines for the Care and Use of Laboratory Animals in Indonesia and the internationally accepted principles for laboratory animal use and care.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Intan Nirwana reports financial support was provided by Airlangga University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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