Sarcouncil Journal of Applied Sciences

ISSN(Online): 2945-3437

Volume- 06| Issue- 09| 2026

Research Article **Received:** 15-08-2026 | **Accepted:** 10-09-2026 | **Published:** 25-09-2026

Study the Effect of Zinc Oxide Nano-particles on the Corneal Defect in the Rabbit Model

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Abstract: Corneal injury can result in persistent epithelial defects, inflammation, stromal fibrosis, vascularization, and impaired corneal transparency. The present study evaluated the therapeutic potential of zinc oxide (ZnO) nanoparticles in promoting corneal wound healing in an experimental rabbit model. Sixteen healthy adult male rabbits were randomly divided into two equal groups: a ZnO nanoparticle-treated group and a control group. Experimental corneal injury was induced in the right eye of each animal by surgical removal of the corneal epithelium. Following injury, the treatment group received ZnO nanoparticles at a concentration of 10 µg/200 µL, whereas the control group received normal saline. All animals received antibiotic treatment, and conjunctival flap and tarsorrhaphy procedures were performed. Clinical and histopathological evaluations were conducted at one and two weeks after treatment. Histopathological examination of the control group revealed marked epithelial disruption, stromal edema, inflammatory-cell infiltration, vascularization, and collagen disorganization. In contrast, the ZnO-treated group demonstrated progressive restoration of the corneal epithelium, improved stromal organization, reduced inflammatory-cell infiltration, and comparatively normal collagen alignment by the second week. At one week, the ZnO-treated corneas showed a thickness of 550.7 ± 0.6 µm, 6.8 ± 0.9 keratocytes, and 16.2 ± 1.4 inflammatory cells, whereas by two weeks these values were 410.2 ± 0.5 µm, 3.4 ± 0.4 keratocytes, and 4.2 ± 0.3 inflammatory cells, respectively. Significant differences were observed between the treatment and control groups ($P < 0.05$). Clinically, ZnO treatment was associated with reduced corneal opacity and improved corneal architecture compared with the control group. The findings suggest that topical ZnO nanoparticles may promote corneal repair and reduce inflammatory and fibrotic changes following acute corneal injury. Further studies are warranted to establish their safety, optimal dosage, and molecular mechanisms of action in corneal wound healing.

Keywords: Zinc oxide nanoparticles; Corneal injury; Corneal wound healing; Rabbit model; Corneal epithelium; Histopathology; Stromal fibrosis; Inflammation; Nanomedicine; Ocular therapy.

INTRODUCTION

The current study aimed to evaluate the potential of zinc oxide nanoparticles for the repair of acute corneal defects. This was done using sixteen mature male rabbits. The treatment and control groups each had eight animals allocated at random. The animals were put to sleep using a mixture of 50 mg of ketamine hydrochloride and 5 mg of xylazine hydrochloride per kg of body weight. In the all animals the cornea were induced of injury by surgical blade in epithelial layer only, then make conjunctival flap and tarsorrhaphy.

After that the control group, the animals were treated with normal saline immediately by dropping, while in the treated group the animals were treated with zinc oxide also immediately all animals receive antibiotic for five days, clinical evaluation in control group revealed, severe ulceration, moderate opacity, corneal neovascularization and conjunctival congestion. While in treatment group showed, mild opacity, with normal the architecture of all eye structure.

In comparison to the control groups, the histopathological examination, which was carried out at 1 and 2 weeks during the trial, showed that the treatment groups had the best corneal injury healing until the completion of the study. The results in control group revealed, severe corneal epithelium disruption, stromal fibrosis, collagenous disorder with profuse inflammatory cell infiltration. Rather in the treatment group showed, complete corneal epithelium repair, normal collagenous alignment with keratocyte infiltration. In conclusion, the study confirmed that the dropping of zinc oxide nanoparticles improved and accelerated the corneal healing process in contrast to the control groups, which showed higher fibrosis formation with corneal epithelial disruption. The acute treatment as well as control groups' mean values of the VEGF (vascular endothelial growth factor) gene were recorded in the molecular assessment, which revealed down-regulation of the gene level until the study's conclusion.

The eye is a crucial sensory organ that dates back to the Cambrian period of life. It may be roughly split into two parts and has several levels. The cornea and sclera make up the outer layer; the iris, choroids, and ciliary body make up the middle layer; and the retina makes up the inner layer. Among the segments are the anterior, which specializes in light perception, as well as the

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DOI- https://doi.org/10.5281/zenodo.22965536

posterior, which specializes in light sensing. The clear, jelly-like fluid that fills the inner spaces between the anterior and posterior regions is referred to as aqueous and vitreous humor, respectively. The eye consists of an opening system (pupil), lens system (lens), and film system (retina), which is similar to artificial devices such as cameras (Guyton and Hall, 2000).

The cornea, along with the lens, is the most important part of the ocular surface that allows light to enter the eye and focus onto the retina for the best possible visual acuity. It is responsible for about two thirds of the refractive optical power. One-sixth of the outside layer of the eye is made up of the cornea, a transparent, spherical material that covers the iris, pupil, and anterior chamber and serves as the outer window. The limbus, conjunctiva, and sclera encircle the cornea, which is found on the outside of the eye (DelMonte and Kim, 2011).

After these traumas, there is no effective way to stop corneal scarring, which frequently leads to blindness and visual loss. Medical treatments, such as corticosteroids applied topically and non-steroidal anti-inflammatory drugs, have a high incidence of ocular issues and are unsuccessful in preventing corneal fibrosis and reducing stromal scarring, according to Kwok et al. (2019). Additionally, another technique for treating visibly significant corneal stromal scarring was corneal transplantation. Nonetheless, tissue is severely lacking globally (Gain et al., 2016). Furthermore, blindness can result from corneal transplant-related complications like infection, bleeding, glaucoma, detached retinas, and graft failure. As a result, vision scientists and clinicians are very interested in an effective and deliverable alternative therapy which can lessen corneal scarring.

These days, one of the most significant areas of material science and nanotechnology is nanomedicine (Augustine et al., 2014). Metal nanoparticles have been employed in a variety of biological applications throughout the past decade, such as antiviral therapy, anticancer therapy, antibiotic therapy, & diagnostic and therapeutic fields (semiconductors and quantum dots). Zinc oxide (ZnO) is an inorganic material that has been approved by the FDA because of its intrinsic ability to neutralize UV radiation, stability, and safety (Zhang et al., 2013). It has a lot of applications. According to Rasmussen et al. (2010), ZnO nanoparticles have potential in biological applications such as drug transport, antimicrobial, antigen, gene, biosensor, and tissue engineering. According to Ayan et al., ZnO nanoflowers may also be encouraging angiogenesis through endothelial cell migration and proliferation (Barui et al., 2012; Augustine et al., 2014). Furthermore, they claim that in reaction to ROS, europium hydroxide [EuIII (OH)3] nanorods cause angiogenesis. (Patra et al., 2011).

MATERIALS AND METHODS

Experimental Animals

For this investigation, sixteen healthy adult male local breed rabbits weighing between 1.5 and 2 kg and aged between 1 and 1.5 years were enlisted. According to the protocol, standard condition for feeding all animas in healthy status.

Experimental Design

Keratectomy in sixteen adult male rabbits were induced by using surgical bade. The animals were randomly divided into two equal categories (A and B), each consisting of eight individuals. In group (A) (the therapy group), zinc oxide was given directly to the ocular sores. The animals in group (B) received the same treatment for their wounds as those in group (A), however the control group's wounds were treated with regular saline.

ZnO Nanoparticles Synthesis

To synthesize nanoparticles of (ZnO), using green method was applied. For this purpose, mg zinc acetate was utilized as a precursor. After that, the extract solutions are filtered, and the eluted extract solution is isolated for use in the production of (ZnO). The eluent solution can be dried to concentrate solid extracts or utilized directly for (ZnO) production. Plant extracts and zinc precursors are then reacted at different pH and temperature levels.

The nine-part of pure extract 100mg added to 10mg of 0.45 M zinc acetate dihydrates) ratios were mixed with 10mL of 0.45 M NaOH, respectively. The three complex mixtures were then stirred constantly for 2 hrs applying a magnetic stirrer at 900rpm until appearing yellow precipitate formation, then added surfactant of TPGS at concentration 0.05 in order to coating and stability of the product as well as reduce particle size the steering persistence for 60 min. next, the solution was transferred to prob sonication with altitude 80 at cycle 1:1. For 30 minutes, the suspension was centrifuged at 12,000 g. Water was used to resuspend the pellet. The ZnO nanoparticle suspension was filtered through the Whatman filter paper in a glass cylinder, washed with ethanol and

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distilled water to remove impurities, and then oven-dried at 50°C for two hours. The obtained powder has yellow color characteristics that were grinding manually via a mortar and pestle (Arciniegas-Grijalba *et al.*, 2017; Jasim *et al.*, 2019) (Figure 1).

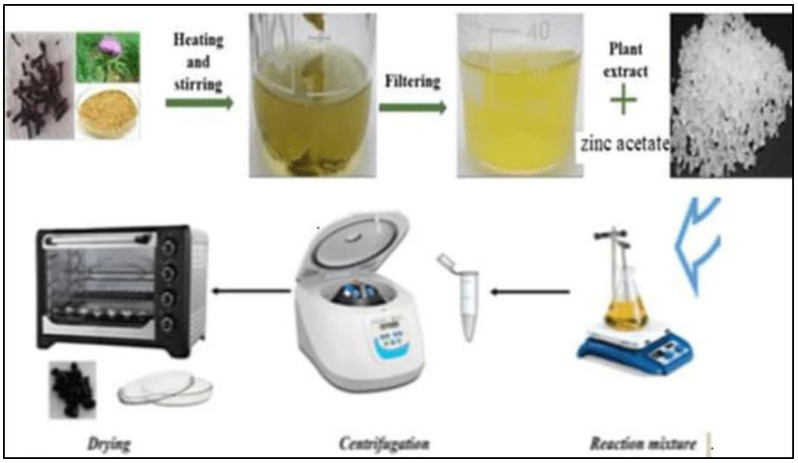

Figure (1): Show synthesize nanoparticles of ZnO, using green method.

Inducing of Corneal Injuries

Intramuscular injections of 50 mg/kg ketamine hydrochloride and 5 mg/kg xylazine hydrochloride were used to sedate the rabbits, and surgical bade was used to make ocular incisions. Then, the right eye was prepared aseptically by adding of a drops of 1:20 dilution butadiene solution then proparacaine hydrochloride 0.5% was used as local anesthetic medication. After that, the axial cornea of right eye were induce the removable of epithelium until the level of stromal layer, all groups undergo to the conjunctival flap (Figure 2: A and B). ZnO nanoparticles at a concentration of 10 µg/200 µl Phenytoin were applied to the wound of group (A) (Pitiakoudis et al., 2004), whereas group (B) received normal saline as a control group. Additionally, all groups underwent tarsorrhaphy (Figure 3: A and B).

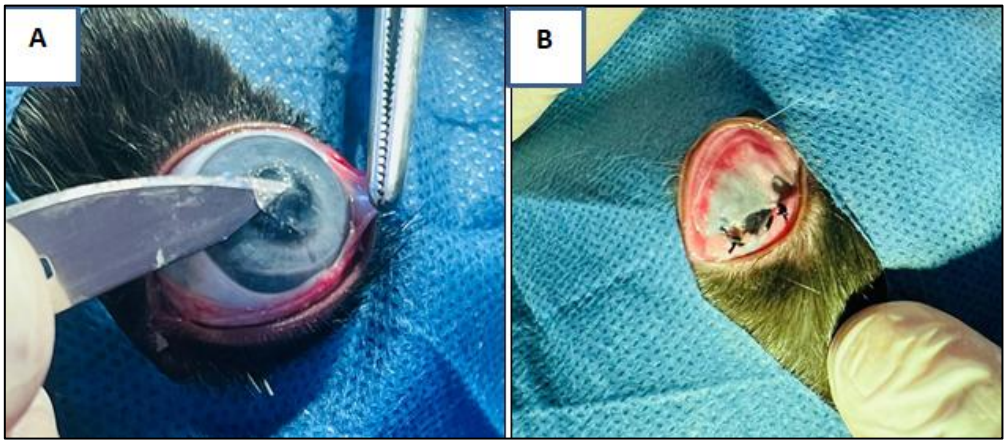

Figure (2): Show protocol of inducing corneal injury (**A**),and conjunctival flap(**B**).

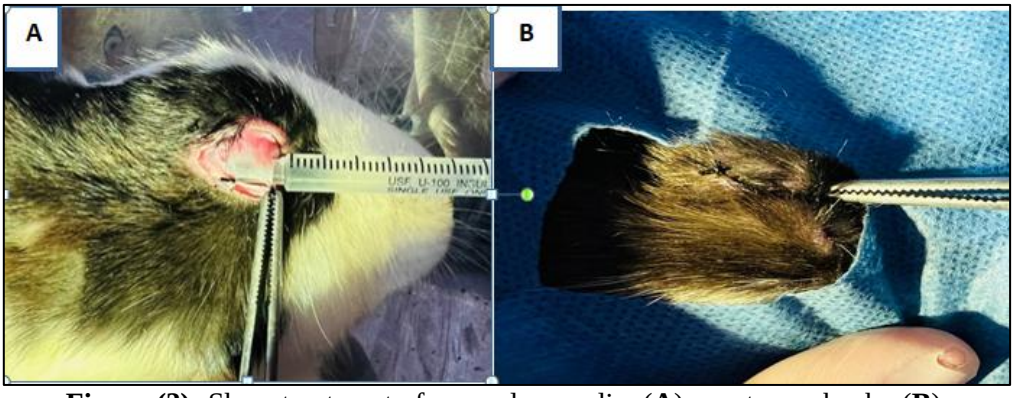

Figure (3): Show treatment of corneal wounding(**A**), eye tarsorrhaphy (**B**).

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Histopathological Evaluation

Histopathological evaluation was conducted on 1 and 2 weeks post-treatment (4 animals/period). The animals were euthanized and the eye ball was harvested from the orbit and soaked in modified Davison's fluid for 24hours and then fixed in 10% natural buffered formalin. Sharp dissection was used to cut the cornea in half, and the material from the incision site was preserved in 10% neutral formalin for a full day at room temperature before being paraffin-embedded and cut into 4µm slices. The paraffin slices were then stained using the standard hematoxylin and eosin (H&E) technique (Feldman and Wolfe, 2014). Light microscopy & microphotography were used to study tissue sections using a Future Win Joe microscopic camera. The Fiji image analyzer system was used to analyze and score the pictures (Schindelin et al., 2015).

RESULTS AND DISCUSSION

In acute control group (**B**), one week post-injection of normal saline, the histopathological examination of the corneal tissue biopsies revealed marked accumulation of inflammatory cells, irregular thickness with severe disruption of corneal epithelium, obvious corneal edema, sub-epithelial hemorrhage and stromal angiogenesis as well as stromal collagen irregularity **(Figure 4)**. One week after NS injection, the histopathological analysis of the corneal tissue biopsies in the acute control group (B) showed significant irregularities in the corneal epithelium, including a focal increase in basal epithelium, cellular fibrotic deposition, and severe disruption of the corneal epithelium structure, primarily in the interior portion. Significant stromal congestion with many thin-walled capillaries was another observed (Fig. 4). There was a significant difference between the control and ZO therapy groups ($P<0.05$). The cornea's thickness was 884.04±1.2, the number of keratocytes was 5±0.7, and the mean cellular infiltration (leukocytes) was 25.6±1.1. The sections of group (**B**), two weeks post-dropping of normal saline showed, complete loss of basal epithelium and bowman layer associated with marked stromal edema and areas of necrotic stromal mainly which was recognized anteriorly, scattered inflammatory cellular infiltration of PMNC and macrophage were also observed in superficial necrotic stroma with focal folds formation of epithelium surface. Other corneal feature showed evidence of vascularization and mild cellular infiltration mainly macrophage in interior stromal associated with hypo cellular collagenous corneal stroma in deeper layer (Fig. 4-4). There were significant changes between the (ZO) treatment group as well as the control group at $P<0.05$ in the corneal thickness (558.3±0.7), the number of keratocytes (1.6±0.4), and the number of cellular infiltration (leukocytes) in the surface of the cornea (4.2±0.3).

In acute treatment group (**A**) one week post treatment revealed the presence of mild irregular epithelization with lack of partial epithelial layer, mild sub epithelial hemorrhage with moderate stromal angiogenesis, profuse inflammatory cellular infiltration with stromal collagenous irregularity (figure 5). The thickness of the cornea was 550.7±0.6, the number of keratocytes was 6.8±0.9, and the number of cellular infiltration (leukocytes) at the cornea was 16.2±1.4. These changes were significant ($P<0.05$) between the acute (ZO) treatment group and the control group.

The sections in group (**A**) two weeks post treatment revealed restoration of stratified epithelial that sitting on straight basement membrane and regular stromal with evidence of thick collagen bundles with few keratocytes while some still separated and intact endothelial layer, other sections showed normal stratification and projection of basal cells to corneal stroma that exerted proprial lamellar appearance mainly in central portion (Figure 6). The corneal thickness (410.2±0.5), the number of keratocytes (3.4±0.4), and the number of cellular infiltration (inflammatory leukocytes) in the cornea were all significantly different ($P<0.05$) between the ZO treatment group and the control group. Hassan and others (2011). As an extracellular protein, collagen plays a significant role in the tissue that forms granulation throughout the healing process of wounds. Interestingly, it is essential to both the hardness of the incision and the impartiality of the tissue matrix. The regulated synthesis, deposition, and subsequent maturation of new collagens are essential for the healing of wounds (Puratchikody et al., 2006). This study supports the findings of Hassan et al. (2021). ZnO-NRs effectively construct a multilayer of collagen layers in the wall of the vessel with red blood cells, as shown by a score of +4, which denotes that a large vascular encompasses more than four red blood cells and multilayered blood vessels, comprising layers of collagen in vessel walls. The approach for zinc oxide nanoparticles has a reasonable mechanism. Who thought that ZnO nanoparticles may have a significant impact on the production of

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ROS, particularly H2O2? Hydrogen peroxide may be produced in cells by a variety of massive methods. The direct creation of O_2 and its reaction with water is one of these processes (Fridovich, 1975). Another is the conversion of superoxide to H2O2 by the cell's superoxide dismutase enzyme (Bancroft et al., 2013).

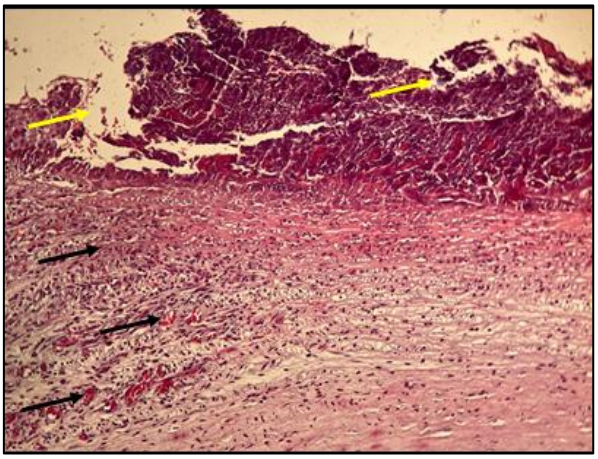

Figure. 4: Histopathological section of cornea one week post- dropping of normal saline in (control group) showed focal epithelium detachment (yellow arrow), and evidence of numerous capillaries in the superficial stroma accompanied with stromal fibrosis (black arrow) (H and E X10).

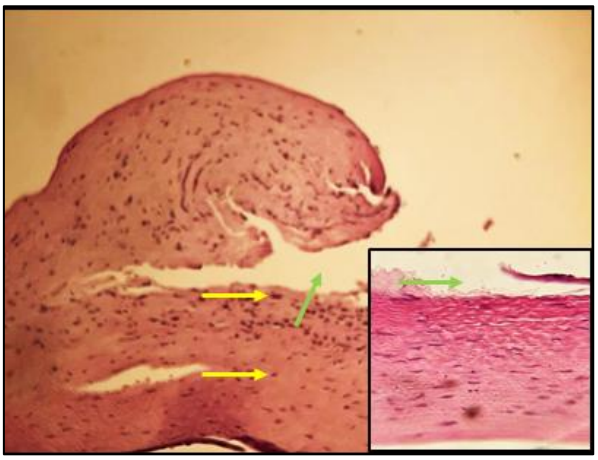

Figure. 5: Histopathological section of cornea, two weeks post dropping normal saline in (control group) shows complete disruption of epithelial layer (green arrow), mixed inflammatory infiltration (PMNC and macrophage) (yellow arrow) and moderate stromal fibrosis (black arrow) (H and E X10).

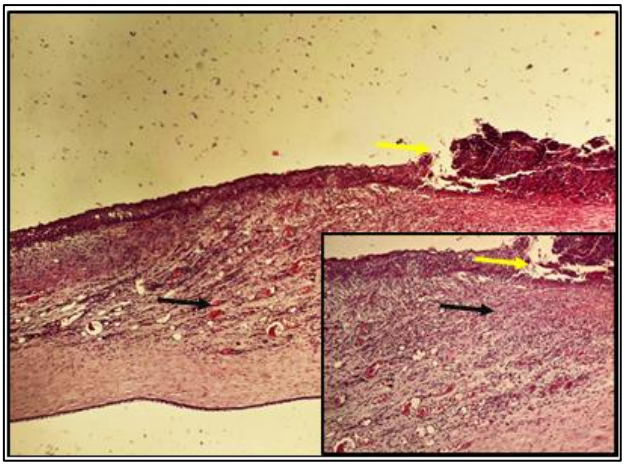

Figure. 6: Histopathological section of cornea one week post- treatment with zinc oxide in (treatment group) showed partial epithelium detachment (yellow arrow), and moderate of numerous angiogenesis in the stroma accompanied with stromal fibrosis (black arrow) (H and E X10,40).

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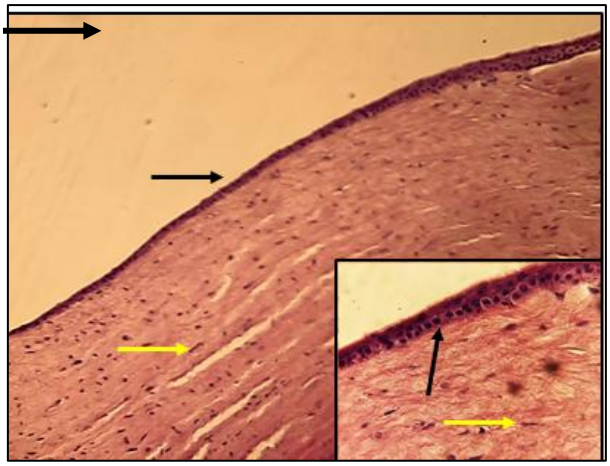

Figure. 7: Histopathological section of cornea, two weeks post treatment with zinc oxide (treatment group) shows corneal surface lining with multilayer epithelium(black arrow) prominence of keratocyte and regular stromal collagen (yellow arrow) (H and E X40).

CONCLUSION

The present study demonstrates that topical zinc oxide nanoparticles may enhance corneal wound healing in experimentally induced corneal defects in rabbits. Compared with the control group, ZnO-treated corneas showed improved epithelial regeneration, reduced inflammatory-cell infiltration, less stromal fibrosis, and better collagen organization. These findings suggest that ZnO nanoparticles have potential as a therapeutic agent for promoting corneal repair and reducing post-injury complications. Further studies are required to determine their optimal dose, safety, and underlying mechanisms

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Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:
Abed, H. H. “Study the Effect of Zinc Oxide Nano-particles on the Corneal Defect in the Rabbit Model." *Sarcouncil Journal of Applied Sciences* 6.9 (2026): pp 1-8.

Publisher: SARC Publisher