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Efficacy and safety of topical doxycycline reduce MMP-9 expression towards populations with corneal alkali burn

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ABSTRACT

Introduction: Alkali ocular injury causes disintegration of the cornea by changes in pH level, proteolysis, ulceration, and impairment of collagen synthesis. Doxycycline was found to alter the remodeling of human conjunctival and skin fibroblasts. Doxycycline also reduced collagenolytic degradation of the cornea due to chemical injury by inhibiting matrix metalloprotease (MMP) activity, including in other non-infectious corneal ulcers. This study aimed to determine the efficacy and safety of topical doxycycline to manage corneal alkali burns. A systematic review was conducted in adherence to the PRISMA statement.

Method: Searching was conducted in five databases and inclusion and exclusion criteria were applied afterwards. Three studies were found, considered good, and eligible for inclusion after appraisal using SYRCLE critical appraisal tools for animal studies. All studies used mice models.

Result: We found a significant reduction of IL-1β, IL-6, MMP-8, MMP-9, α-SMA, and NF-κB by doxycycline usage starting from two days of usage. In addition, mRNA angiogenic factors and corneal neovascularization decreased after doxycycline usage. This contributes to better corneal repair after trauma, reflected by better corneal healing and opacity scores after doxycycline usage compared to other groups.

Conclusion: Doxycycline management improved outcomes for patients with corneal alkali burn by decreasing inflammatory cytokine and promoting tissue repair.

Keywords: *alkali, burn, chemical, cornea, doxycycline*.
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INTRODUCTION

Alkali ocular injury is defined as trauma toward eye integrity caused by alkali burn. Alkali injury is a serious condition that requires immediate treatment. It could cause permanent damages such as corneal scarring and blindness even though it is immediately treated.[1–4] Various efforts were made to restore corneal clarity, such as corneal transplantation. However, the long-term result has not been satisfying up to date.[5] Alkali corneal injury was more prevalent than acid ocular injury. A study in The United States from 2010 to 2013 showed that there was 144,149 chemical ocular injury throughout the period with median age of 32 years old and 56.6% male. The study found that alkali injuries were more prevalent than acid injuries (53.6% vs 46.4%).[6]

Alkali ocular injury causes disintegration of the cornea by changes in pH level, proteolysis, ulceration, and impairment of collagen synthesis. Alkali is considered lipophilic and can penetrate the eye faster compared to acid. Therefore, it could infiltrate ocular surface tissues, which could induce saponification within cells. This process should have induced an inflammatory response, represented by secretion of proteolytic enzymes, thus worsening the damage. Alkali also could penetrate the anterior chamber, causing cataracts. In addition, it could extend to the ciliary body and trabecular meshwork, causing more damage to the eye. Severe damage due to alkali injury could deplete pluripotent limbal stem cells, leading to limbal stem cell deficiency. This will result in increased corneal opacification and neovascularization, complicating its surface healing. Intraocular pressure will increase as a result of cornea and sclera shrinkage and contraction.[7–9] Inflammatory event also contributes to worsening corneal trauma due to alkali burn. A study found immediate tumor necrosis factor alpha (TNF-α) expression after exposure to alkali burn, which could lead to ocular cell apoptosis, worsening the condition.[10]

Alkali ocular injury should be managed by following some steps. The first step is to evaluate and treat immediately using isotonic saline or ringer lactate to restore ocular pH. It could take up to 20 liters of fluid to normalize ocular pH. This step is followed by acute phase treatment aimed at maintaining corneal epithelium integrity, balancing collagen synthesis and lysis, and preventing complications. The integrity of corneal epithelium is

Table 1. Keywords being used for literature searching

Database	Keywords
PubMed	("Doxycycline"[Mesh]) AND ("Corneal Injuries"[Mesh])
Wiley Online	"doxycycline" AND (("alkali" OR "base") AND ("cornea" OR "ocular" OR "eye"))
ProQuest	"doxycycline" AND (("alkali" OR "base") AND ("cornea" OR "ocular" OR "eye"))
Cochrane Library	"doxycycline" AND (("alkali" OR "base") AND ("cornea" OR "ocular" OR "eye"))
Science Direct	"doxycycline" AND (("alkali" OR "base") AND ("cornea" OR "ocular" OR "eye"))

maintained using tear substitutes, bandage soft contact lenses, retinoic acid, epidermal growth factor or fibronectin. Ulcers could be reduced and prevented by ascorbate or collagenase inhibitors. Inflammation could be managed with corticosteroids. In addition, topical antibiotics, which cover a broad spectrum of bacteria, cycloplegic, and antiglaucoma, are necessary. Patients who have not achieved intact corneal epithelium within three weeks should be managed in late reparation treatment as they risk vision loss. It could be done by keratoplasty, amniotic membrane transplantation, tissue adhesives, and conjunctival or tenons advancement. All stabilized eyes after corneal injury should go to the rehabilitation phase, in which medications are continued and tapered off.[10,11]

Doxycycline is a semisynthetic tetracycline antibiotic that serves as a broad-spectrum antibiotic. It was found in the early 1960s and has been used in various cases, such as pulmonary fibrosis, chronic periodontitis, and nasal polyps.[12–15] Doxycycline was also found to alter the remodeling of human conjunctival and skin fibroblasts.[16,17] In addition to the cornea, doxycycline negatively affected corneal scar production by inhibiting neovascularization and inflammatory cell infiltration.[18,19] Doxycycline was also found to reduce collagenolytic degradation of the cornea due to chemical injury by inhibiting matrix metalloprotease (MMP) activity, including in other noninfectious corneal ulcers.[20] However, there was still not enough evidence of the effect of doxycycline on corneal injury caused by alkali burns. In addition, even though more practical and have fewer side effects, topical doxycycline research is still new compared to systemic doxycycline for alkali corneal burn. Therefore, we conducted this study to find the relationship between topical doxycycline administration and corneal healing after corneal alkali injury. The findings of this study were expected to help clinicians and researchers provide care to patients and conduct further research on this field of study.

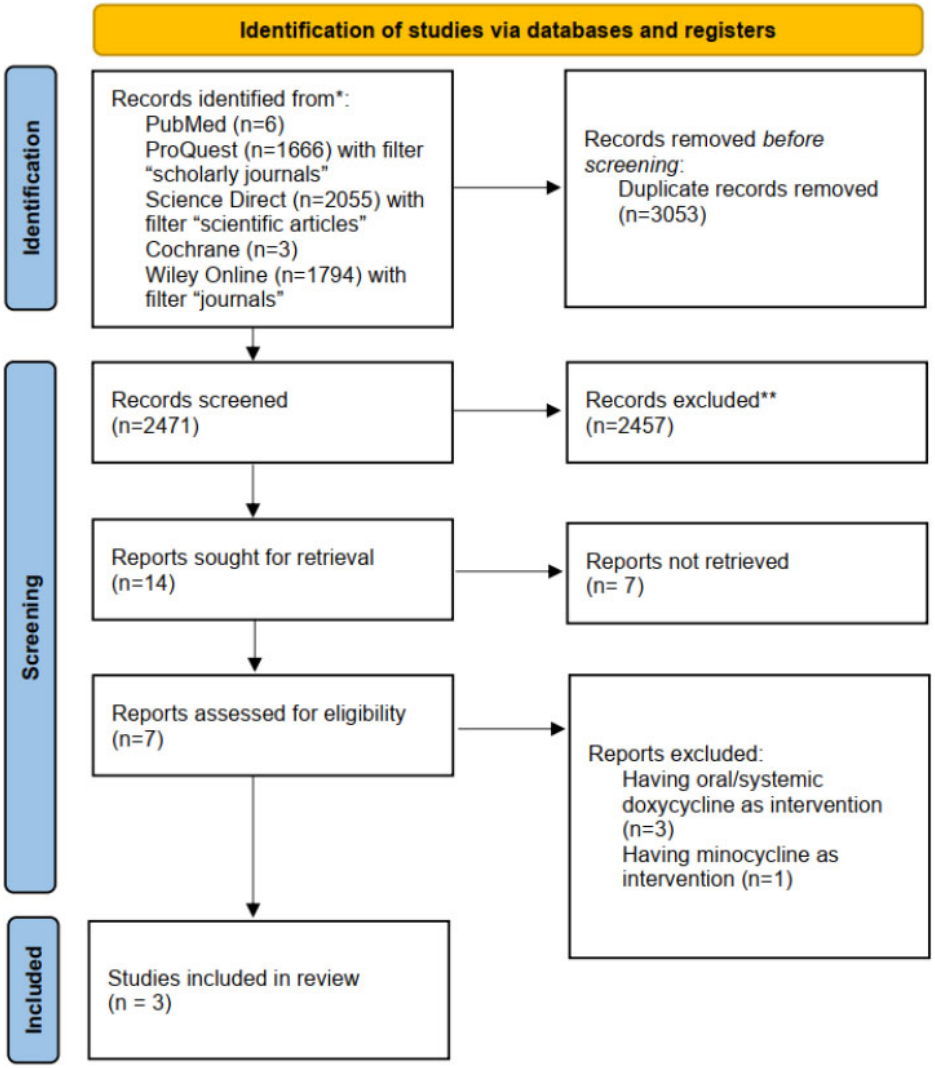

Figure 1. Literature searching and inclusion of studies based on the PRISMA statement.[21]

METHODS

We conducted a systematic review based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[21] We determined the population of corneal alkali burns injury, the intervention of topical doxycycline, control of other medication (double-armed) or none (single-armed), and outcome of efficacy and safety. Searching was conducted on PubMed, Wiley Online, ProQuest, Cochrane Library, and Science Direct using keywords described in Table 1.

Studies found will be assessed for eligibility for inclusion using criteria. Authors set inclusion criteria as follows: (1) clinical trial on human/animal model;

Table 2. Critical appraisal results of included study using SYRCLE tools[23]

Item	Type of bias	Review question	Bian *et al.*[18]	Yi *et al.*[24]	Khoshdel *et al.*[25]
1	Selection	Was the allocation sequence adequately generated and applied?	Y	Y	NI
2		Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Y	Y	NI
3		Was the allocation adequately concealed?	Y	Y	NI
4	Performance	Were the animals randomly housed during the experiment?	Y	Y	Y
5		Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	NI	NI	NI
6	Detection	Were animals selected at random for outcome assessment?	Y	Y	Y
7		Was the outcome assessor blinded?	NI	NI	NI
8	Attrition	Were incomplete outcome data adequately addressed?	NA	NA	NA
9	Reporting	Are reports of the study free of selective outcome reporting?	Y	Y	Y
10	Other	Was the study apparently free of other problems that could result in high risk of bias?	Y	Y	Y
		What is the overall quality of the study?	Good	Good	Fair
		Is this study eligible for inclusion?	Yes	Yes	Yes

(2) studying population of corneal trauma; (3) studying topical doxycycline as intervention; (4) studying efficacy and/or safety as an outcome. In addition, the authors decided to exclude studies that met these criteria: (1) involving a population with co-occurrence of other trauma (e.g., acid trauma, physical trauma); (2) inaccessible studies; (3) studies written not in English.

Selected studies will be included and appraised using Newcastle-Ottawa Scale for critical appraisal of the human model and the SYRCLE risk of bias tool for animal model.[22,23] Studies will be grouped into good, fair, or poor quality studies. Included studies will be extracted for study characteristics, including authors, year, location, study design, aim, sample size, sample characteristics, and study outcomes. In addition, studies will be qualitatively analyzed for study outcomes to synthesize information about the objective of this study. To control bias, all of these processes (searching, selection, inclusion, appraisal, extraction, analysis) were conducted by XX independent reviewers (AA, BB, CC), with all discrepancies met throughout the processes discussed to achieve final decisions.

RESULTS

We found three studies after thorough searching and inclusion (Figure 1).[18,24,25] All studies involved animal models, which were done in mice models.

All studies were appraised using SYRCLE critical appraisal tools and considered eligible after thorough appraisal and evaluation (Table 2). There was one study whose full paper could not be retrieved (Khoshdel *et al.*).[25] However, information acquired from the abstract was sufficient to be extracted in this study. All studies were conducted in Asia with various comparators but involving doxycycline. It was noted that there were various changes in cytokines in all studies. Studies by Bian *et al.* and Yi *et al.* found that there was a decrease in MMP-9 after the use of doxycycline for two and three days, respectively. In addition, the study by Bian *et al.* noted a decrease in IL-1β, IL-6, and MMP-9 after two days of administration. In contrast, the study by Yi *et al.* reported a decrease of α-SMA and NF-κB three and seven days after administration.[18,24] Khoshdel et al. showed decreased TNF-α and Rel- α activity after 7 and 28 days on both NAC and NAC + doxycycline groups. In addition, the same study found less expression of angiogenic factors and corneal neovascularization levels in the doxycycline combination arm.[25] All thorough results and study characteristics can be seen in Table 3.

DISCUSSIONS

Fully integrated corneal keratocytes are transparent due to their stationary status. However, corneal injury disrupts the integrity of the cornea and transforms keratocytes into myofibroblasts.[26] Corneal myofibroblast mainly consists of overexpressed α-SMA.[27] various cytokines and growth factors play roles in corneal healing after alkali trauma. Among them, TGF-β1 plays the most important role as it alters tissue regeneration.[28,29] TGF-β1 is severely upregulated after injury to induce the transformation of keratocytes into myofibroblasts, impacting corneal recovery.[30,31] TGF-β1 is accounted as a potent chemotactic factor for various cells such as monocytes, neutrophils, and macrophages.[32,33] TGF-β1 also stimulates MMP-9 expression in corneal tissue.[34] NF-κB contributed to compete with TGF-β1 to take control of MMPs expression.[35] MMP-9 contributed to the degradation of the cornea's basement membrane, which could promote pathologic ulcer and perforation of the corneal stroma.[36] While NF-κB is accounted for angiogenesis mediator, contributing to the cornea's transparency

and clarity.[37] Therefore, overexpression of TGF-β1 has been suggested as the hallmark of corneal opacification mechanism after corneal alkali injury as it contributes to myofibroblasts accumulation which produces more opaque crystalline compared to normal keratocytes.[38]

Doxycycline has been used in various circumstances involving impairment of corneal integrity because it serves as an immunomodulator and prevents neovascularization. Doxycycline was found to enhance corneal wound healing and disrupts neovascularization and inflammation after trauma, especially alkali burns.[19,39] Due to its properties, doxycycline does not only applicable for alkali burn but for various ocular problems. The study by Wang *et al.* showed that a combination of oral doxycycline and topical corticosteroids was proven to help the outcome of corneal erosion treatment, with 71% of patients did not develop any symptoms afterward.[40] Study by McElvanney *et al.* showed that oral doxycycline could stabilize corneal rupture and prevent a perforation in patients with pseudomonas keratitis.[41] Study conducted by Peng *et al.* stated that doxycycline usage was proven effective in inhibiting fibrosis in choroidal neovascularization of laser-injured mice.[42] Another study showed that doxycycline could improve allograft survival in mice with alkali corneal burns. The same study also suggests that doxycycline inhibited corneal neovascularization and corneal bed inflammation, thus providing a greater healing platform.[43]

Wound healing in corneal tissue involves a cascade of events consisting of re-epithelization and keratinocyte proliferation, followed by migration, differentiation, and extracellular matrix remodeling.[44] Cornea is dominated by three types of cells: surface epithelial, stromal keratocytes, and endothelial. All three cells were purposed to promote wound healing in all phases of corneal wound healing.[44,45] However, TGF-β1, which could be found abundantly in tears, will penetrate corneal stroma in case of trauma and provoke keratocyte differentiation to myofibroblasts. Therefore, overexpression of TGF-β1 could worsen corneal damage as too many myofibroblasts on corneal

Table 3. Study characteristics and results

Author	Year	Location	Aim	Sample	Sample size	Intervention	Control	Outcome
Bian *et al.*[18]	2015	China	Investigate the efficacy of dexamethasone and doxycycline in controlling inflammation and MMP production in a combined model of alkali burn associated with dry eye	Female C57BL/6 mice aged 6-8 weeks	28 per group	-2 ul dexamethasone 0.1% - 2 ul doxycycline 0.025% - Balanced salt solution	Naïve	- Dexamethasone decreased IL-1β, IL-6, MMP-8, -9, -13, and TIMP-1 after 2 days (p<0.05) - Dexamethasone increased MMP-8 after 2 days (p<0.05) - Doxycycline decreased IL-1b, IL-6, MMP-8, -9 after 2 days (p<0.05) - Neutrophil infiltration and myeloperoxidase activity were increased in the control group post injury - Better corneal healing and opacity scores in the doxycycline group compared to the control group (p<0.05)
Yi *et al*[24]	2019	China	Evaluate the wound healing effect of doxycycline and its underlying mechanisms in a mice model of corneal alkali burn	Mice	42 per group	1g/L doxycycline eye drops	Naïve	- Increase of TGF-β1 at 3, 7, and 14 days after treatment in the control group (p<0.05) - Lower MMP-9, alpha-SMA, and NF-κB expression at 3 and 7 days after treatment in the doxycycline group (p<0.05) - Increased SOD enzyme activity on day 28 in both groups (p<0.05)
Khoshdel *et al*[25]	2022	Iran	Analyze the single and combined effects of NAC and doxycycline on the inflammatory and angiogenic factors in mice model of the alkali-burned cornea	Mice	-	0,5% NAC + 12,5 ug/mL doxycycline eye drops	0,5% NAC	- Decrease of TNF-α and Rel-α genes on days 7 and 28 in both groups (p<0.05) - Decrease of mRNA level of angiogenic factors and corneal neovascularization level on intervention arm (p<0.05)

Abbreviations: NAC = n-acetyl cysteine, IL = interleukin, MMP = matrix metalloproteinase, TIMP = tissue inhibitor of metalloproteinase, TGF = transforming growth factor, SMA = smooth muscle actin, NF = nuclear factor, SOD = superoxide dismutase

stroma could cause a hazy cornea.[46–49] MMP-9 could also alter the process of corneal wound healing. MMP-9 is accounted for angiogenesis and wound healing of various ocular trauma. MMP-9 is found in the injured cornea but not in the healthy cornea. MMP-9 was also identified in the population with alkali burns.[50–52] According to a study, MMP-9 was proven to induce basal epithelial cell migration, thus intervening in subepithelial basement membrane region remodeling.[53-56] Therefore, disruption towards MMP-9 and TGF-β1 expression by doxycycline in patients with corneal alkali burn and suppression of other immunomodulatory cytokines/chemokines could benefit wound healing and clinical outcomes. All three reports did not show any side effects of doxycycline, which also stated its safety to be used on all animal models.

This study was initiated to assess the effectiveness of doxycycline in the population with alkali corneal burns. The findings of this study could be used as a hallmark to advance studies involving human subjects. As the animal model limited this study, we recommend further studies to involve human populations with corneal alkali burn to make better and stronger findings, thus research in this field would be relevant.

CONCLUSION

Topical doxycycline was proven effective in the mice population's corneal wound healing after alkali burn by suppressing immunomodulatory cytokines and/or chemokines, especially TGF-β1 and MMP-9. These findings should be used as the foundation to advance the human population to provide better evidence and level of study.

CONFLICT OF INTEREST

There have been no competing interests regarding this manuscript.

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ETHICAL STATEMENT

This manuscript has followed the Committee on Publication Ethics (COPE) and International Committee of Medical Journal Editors (ICMJE) guidelines regarding publication ethics.

AUTHOR CONTRIBUTION

All authors contribute to the design, intelligent content description, literature quest, data collection, data processing, manuscript writing, manuscript editing, and manuscript review. The corresponding author is the guarantor and constructs the concept of the manuscript.

REFERENCES

1. McCulley JP. Chemical injuries. In: The Cornea: Scientific Foundations and Clinical Practice. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1987. p. 527–42.
2. Wagoner MD. Chemical injuries of the eye: current concepts in pathophysiology and therapy. Surv Ophthalmol. 1997;41(4):275–313.
3. Pfister RR. Chemical trauma. In: The Cornea: Scientific Foundations and Clinical Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 781–96.
4. Schrage NF, Langefeld S, Zschocke J, Kuckelkorn R, Redbrake C, Reim M. Eye burns: an emergency and continuing problem. Burns. 2000 Dec;26(8):689–99.
5. Gupta N, Farooqui JH, Patel N, Mathur U. Early Results of Penetrating Keratoplasty in Patients With Unilateral Chemical Injury After Simple Limbal Epithelial Transplantation. Cornea. 2018 Oct;37(10):1249–54.
6. Haring RS, Sheffield ID, Channa R, Canner JK, Schneider EB. Epidemiologic Trends of Chemical Ocular Burns in the United States. JAMA Ophthalmol. 2016 Oct 1;134(10):1119–24.
7. Paterson CA, Pfister RR. Intraocular pressure changes after alkali burns. Arch Ophthalmol. 1974 Mar;91(3):211–8.
8. Fagerholm P, Lisha G. Corneal stem cell grafting after chemical injury. Acta Ophthalmol Scand. 1999 Apr;77(2):165–9.
9. Tuft SJ, Shortt AJ. Surgical rehabilitation following severe ocular burns. Eye (Lond). 2009 Oct;23(10):1966–71.
10. Cade F, Paschalis EI, Regatieri CV, Vavvas DG, Dana R, Dohlman CH. Alkali burn to the eye: protection using TNF-α inhibition. Cornea. 2014 Apr;33(4):382–9.
11. Singh P, Tyagi M, Kumar Y, Gupta KK, Sharma PD. Ocular chemical injuries and their management. Oman J Ophthalmol. 2013;6(2):83–6.
12. Smith VA, Cook SD. Doxycycline-a role in ocular surface repair. Br J Ophthalmol. 2004 May;88(5):619–25.
13. Hua F, Li XH, Li MM, Zhang CY, Liu HJ, Sun T, et al. Doxycycline attenuates paraquat-induced pulmonary fibrosis by downregulating the TGF-β signaling pathway. J Thorac Dis. 2017;9(11):4376–86.
14. Shin JM, Park JH, Park IH, Lee HM. Doxycycline inhibits TGF-β1-induced extracellular matrix production in nasal polyp-derived fibroblasts. Int Forum Allergy Rhinol. 2016 Mar;6(3):256–63.
15. Caton J, Ryan ME. Clinical studies on the management of periodontal diseases utilizing subantimicrobial dose doxycycline (SDD). Pharmacol Res. 2011 Feb;63(2):114–20.
16. Moore AL, desJardins-Park HE, Duoto BA, Mascharak S, Murphy MP, Irizarry DM, et al. Doxycycline Reduces Scar Thickness and Improves Collagen Architecture. Ann Surg. 2020 Jul;272(1):183–93.
17. Li H, Ezra DG, Burton MJ, Bailly M. Doxycycline prevents matrix remodeling and contraction by trichiasis-derived conjunctival fibroblasts. Invest Ophthalmol Vis Sci. 2013 Jul 12;54(7):4675–82.
18. Bian F, Pelegrino FSA, Henriksson JT, Pflugfelder SC, Volpe EA, Li DQ, et al. Differential Effects of Dexamethasone and Doxycycline on Inflammation and MMP Production in Murine Alkali-Burned Corneas Associated with Dry Eye. Ocul Surf. 2016 Apr;14(2):242–54.
19. Su W, Li Z, Lin M, Li Y, He Z, Wu C, et al. The effect of doxycycline temperature-sensitive hydrogel on inhibiting the corneal neovascularization induced by BFGF in rats. Graefes Arch Clin Exp Ophthalmol. 2011 Mar;249(3):421–7.
20. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. Cornea. 2000 May;19(3):274–7.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.
22. Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Medical Research Methodology. 2014 Apr 1;14(1):45.
23. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;26(14):43.
24. Yi Q, Zou WJ. The Wound Healing Effect of Doxycycline after Corneal Alkali Burn in Rats. J Ophthalmol. 2019;2019:5168652.
25. Khoshdel AR, Emami Aleagha O, Shahriary A, Aghamollaei H, Najjar Asiabani F. Topical Effects of N-Acetyl Cysteine and Doxycycline on Inflammatory and Angiogenic Factors in the Rat Model of Alkali-Burned Cornea. J Interferon Cytokine Res. 2022 Feb;42(2):82–9.
26. Torricelli AAM, Wilson SE. Cellular and extracellular matrix modulation of corneal stromal opacity. Exp Eye Res. 2014;129:151–60.
27. Jester JV, Ho-Chang J. Modulation of cultured corneal keratocyte phenotype by growth

factors/cytokines control in vitro contractility and extracellular matrix contraction. Exp Eye Res. 2003 Nov;77(5):581–92.
28. Sriram S, Tran JA, Zieske JD. Cornea As a Model for Testing CTGF-Based Antiscarring Drugs. Bone Tissue Regen Insights. 2016;7.
29. Tandon A, Tovey JCK, Sharma A, Gupta R, Mohan RR. Role of transforming growth factor Beta in corneal function, biology and pathology. Curr Mol Med. 2010 Aug;10(6):565–78.
30. Chen M, Matsuda H, Wang L, Watanabe T, Kimura MT, Igarashi J, et al. Pretranscriptional regulation of Tgf-beta1 by PI polyamide prevents scarring and accelerates wound healing of the cornea after exposure to alkali. Mol Ther. 2010 Mar;18(3):519–27.
31. Takahashi H, Igarashi T, Fujimoto C, Ozaki N, Ishizaki M. Immunohistochemical observation of amniotic membrane patching on a corneal alkali burn in vivo. Jpn J Ophthalmol. 2007;51(1):3–9.
32. Saika S. TGF-beta signal transduction in corneal wound healing as a therapeutic target. Cornea. 2004 Nov;23(8 Suppl):S25-30.
33. Saika S, Yamanaka O, Nishikawa-Ishida I, Kitano A, Flanders KC, Okada Y, et al. Effect of Smad7 gene overexpression on transforming growth factor beta-induced retinal pigment fibrosis in a proliferative vitreoretinopathy mouse model. Arch Ophthalmol. 2007;125(5):647–54.
34. Behzadian MA, Wang XL, Windsor LJ, Ghaly N, Caldwell RB. TGF-beta increases retinal endothelial cell permeability by increasing MMP-9: possible role of glial cells in endothelial barrier function. Invest Ophthalmol Vis Sci. 2001 Mar;42(3):853–9.
35. Ebihara N, Nakayama M, Tokura T, Ushio H, Murakami A. Expression and function of fibroblast growth factor-inducible 14 in human corneal myofibroblasts. Exp Eye Res. 2009 Aug;89(2):256–62.
36. Daniels JT, Geerling G, Alexander RA, Murphy G, Khaw PT, Saarialho-Kere U. Temporal and spatial expression of matrix metalloproteinases during wound healing of human corneal tissue. Exp Eye Res. 2003 Dec;77(6):653–64.
37. Taheri F, Bazan HEP. Platelet-activating factor overturns the transcriptional repressor disposition of Sp1 in the expression of MMP-9 in human corneal epithelial cells. Invest Ophthalmol Vis Sci. 2007;48(5):1931–41.
38. Jester JV, Moller-Pedersen T, Huang J, Sax CM, Kays WT, Cavangh HD, et al. The cellular basis of corneal transparency: evidence for 'corneal crystallins'. J Cell Sci. 1999 Mar;112 (Pt 5):613–22.
39. Dan L, Shi-long Y, Miao-li L, Yong-ping L, Hong-jie M, Ying Z, et al. Inhibitory effect of oral doxycycline on neovascularization in a rat corneal alkali burn model of angiogenesis. Curr Eye Res. 2008 Aug;33(8):653–60.
40. Wang L, Tsang H, Coroneo M. Treatment of recurrent corneal erosion syndrome using the combination of oral doxycycline and topical corticosteroid. Clin Exp Opthalmol. 2008;36(1):8–12.
41. McElvanney AM. Doxycycline in the management of pseudomonas corneal melting: two case reports and a review of the literature. Eye Contact Lens. 2003 Oct;29(4):258–61.
42. Peng X, Xiao H, Tang M, Zhan Z, Yang Y, Sun L, et al. Mechanism of fibrosis inhibition in laser induced choroidal neovascularization by doxycycline. Exp Eye Res. 2018 Nov;176:88–97.
43. Ling S, Li W, Liu L, Zhou H, Wang T, Ye H, et al. Allograft survival enhancement using doxycycline in alkali-burned mouse corneas. Acta Opthalmol. 2013;91(5):369–78.
44. Ljubimov AV, Saghizadeh M. Progress in corneal wound healing. Prog Retin Eye Res. 2015 Nov;49:17–45.
45. Saghizadeh M, Kramerov AA, Svendsen CN, Ljubimov AV. Concise Review: Stem Cells for Corneal Wound Healing. Stem Cells. 2017 Oct;35(10):2105–14.
46. Honma Y, Nishida K, Sotozono C, Kinoshita S. Effect of transforming growth factor-β1 and -β2 onin vitroRabbit corneal epithelial cell proliferation promoted by epidermal growth factor, keratinocyte growth factor, or hepatocyte growth factor. Exp Eye Res. 1997;65(3):391–6.
47. Nishida K, Sotozono C, Adachi W, Yamamoto S, Yokoi N, Kinoshita S. Transforming growth factor-β1, -β2 and -β3 mRNA expression in human cornea. Curr Eye Res. 1995;14(3):235–41.
48. Medeiros C, Marino GK, Santhiago MR, Wilson SE. The Corneal Basement Membranes and Stromal Fibrosis - PubMed. Invest Ophthalmol Vis Sci. 2018;59(10):4044–53.
49. Zieske JD, Hutcheon AE, Guo X, Chung EH, Joyce NC. TGF-beta receptor types I and II are differentially expressed during corneal epithelial wound repair. Invest Ophthalmol Vis Sci. 2001 Jun;42(7):1465–71.
50. Kawashima Y, Saika S, Miyamoto T, Yamanaka O, Okada Y, Tanaka S, et al. Matrix metalloproteinases and tissue inhibitors of metalloproteinases of fibrous humans lens capsules with intraocular lenses. Curr Eye Res. 2000 Dec;21(6):962–7.
51. Matsubara M, Girard MT, Kublin CL, Cintron C, Fini ME. Differential roles for two gelatinolytic enzymes of the matrix metalloproteinase family in the remodelling cornea. Dev Biol. 1991 Oct;147(2):425–39.
52. Gao M, Sang W, Liu F, Yu H, Zhou R, Belin MW, et al. High MMP-9 Expression May Contribute to Retroprosthetic Membrane Formation after KPro Implantation in Rabbit Corneal Alkali Burn Model. J Ophthalmol. 2016;2016:1094279.
53. Mohan R, Rinehart WB, Bargagna-Mohan P, Fini ME. Gelatinase B/lacZ transgenic mice, a model for mapping gelatinase B expression during developmental and injury-related tissue remodeling. J Biol Chem. 1998 Oct 2;273(40):25903–14.
54. Bagus Komang Satriyasa, I Gusti Ayu Widianti, I.B.G. Fajar Manuaba. Depot Medroxyprogesterone acetate reduces spermatogonia cells and spermatid cells in the seminiferous tubules of male mice. Bali Med J. [Internet]. 2022 Apr. 30 [cited 2023 Jun. 4];11(1):508-12. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/3459.
55. Fariz M, Indriaswati L, Sutjipto. Effect of medroxyprogesterone and doxycycline on vascular endothelial growth factor (VEGF) expression and corneal neovascularization in corneal alkali trauma. Bali Med J. [Internet]. 2023 Apr. 28 [cited 2023 Jun. 4];12(2):1377-80. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/4366.
56. Urolita TY, Fathimah FSN, Karima A, Nurwasis, Zuhria I. Epigallocatechin gallate effect on Interleukin-1b and MMP-9 expression as Pseudomonas aeruginosa keratitis adjuvant therapy. Bali Med J. [Internet]. 2023 May 27 [cited 2023 Jun. 4];12(2):1691-5. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/4382.