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The Anti-inflammatory effect of Onion extract in rabbit with Corneal ulcer

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ABSTRACT:

Corneal ulcer is a pathological condition of the cornea characterized by corneal tissue discontinuity on stromal epithelium. The most common cause of corneal ulcers is due to Staphylococcus bacterial infection. Staphylococcus aureus infects the cornea by secreting alpha-toxin and protease, which degrade the corneal extracellular matrix. Neutrophils, as an innate immune system, will be involved in bacterial phagocytosis. If the corneal ulcer is not treated properly, it will become scar with neovascularization, which cause partial or total blindness. Onion (Allium cepa L.) contains quercetin, which has antibacterial properties and is thought to inhibit the angiogenic mediator, namely Vascular Endothelial Growth Factor (VEGF). This study aimed to determine the effect and minimum effective concentration of onion extract administration, which can decrease the neutrophils, scar area, and neovascularization number in corneal ulcer rabbit induced with Staphylococcus aureus. This study is true experimental research with a post-test only control group design. Corneal ulcers in rabbits are made by intra-stromal injection of the Staphylococcus aureus. After the corneal ulcer formed, each group received one of the following treatments: moxifloxacin HCl 0.5%, onion extract 1.5%; 3%; 6%; and 12% for 7 days. The results showed that onion extract (Allium cepa L.) could decrease neutrophil count at a concentration of 6.5% and inhibit the formation of neovascularization at a concentration of 3%.

KEYWORDS: Corneal ulcer, Staphylococcus aureus, onions, neutrophils, neovascularization, corneal scarring.

INTRODUCTION:

Corneal ulcer is one of the causes of visual impairment and blindness in the world. WHO estimates that approximately 1.5 million to 2 million new cases of unilateral blindness each year due to corneal ulcers and ocular trauma. At Cipto Mangunkusumo Hospital, Jakarta, from January 2008 to December 2011, 220 cases of corneal ulcer were found due to bacterial infection. From 656 new cases of corneal ulcer, the most frequent risk factors were ocular trauma (45,8%) and gram-positive coccus infections (65,7%)[1].

Staphylococcus aureus (*S. aureus*) is a Gram-positive microorganism that can easily enter the eye through lesions due to ocular trauma, contact lens use, viral infections or other diseases. *S. aureus* infects the cornea by secreting alpha-toxin and protease that will degrade the extracellular matrix of the stroma[2]. After the *S. aureus* bacteria invades the cornea, there was neutrophil infiltration, as an innate immune system. Neutrophils will phagocyte the bacteria. Therefore, in bacterial-inflammatory reactions, the number of neutrophils is increasing. Neutrophils also play a major role in the degradation of stromal extracellular matrix[3].

Appropriate treatment is needed to prevent the expansion of ulcers, which is by eradicating the pathogen of corneal ulcers and preventing tissue damage due to bacterial enzymes and toxins. Broad-spectrum antibiotics, such as a fluoroquinolone, can be administered to eradicate the bacteria. Giving a combination of antibiotics can be considered if monotherapy is not sufficient.[2,4,5] Recent studies show that *S. aureus* becomes resistant to antibiotics so that infections caused by these bacteria become difficult to treat.[2] If the infection was not appropriately handled, the corneal ulcer would develop into scar and neovascularization, which can cause partial or total blindness.[6]

The plants have been used as medicine for *S. aureus* infection for a long time.[7,8] One of which is onion (*Allium cepa* L.). It is an essential source of food and is also widely used for various treatments.[9,10] Onion is known as a natural source of flavonoids, quercetin. It has 300 mg/kg of quercetin level.[11] Meanwhile, garlic has 47 mg/kg of quercetin level.[12] Several studies have reported a link between flavonoid consumption and reduced risk of chronic diseases, including cancer, diabetes, and coronary heart disease.[13,14] Flavonoids have antibacterial and antifungal properties.[9,15] According to those studies, quercetin and flavonoids are effective in inhibiting Gram-positive bacteria. Flavonoid also has proven in many studies to enhance wound healing.[16,17,18] Besides, quercetin can also inhibit Vascular Endothelial Growth Factor (VEGF) in choroid invitro and retinal angiogenesis.[19] Lisi et al. (2011) mentioned that quercetin also has anti-proliferative fibroblast properties by blocking factor-β or Smad-signaling transformation pathways.[20]

This study aimed to determine the effect and minimum effective concentration of onion extract administration, which can decrease the neutrophils, scar area, and neovascularization number in corneal ulcer rabbit induced with Staphylococcus aureus.

MATERIAL AND METHOD:

Bacteria:

The *Staphylococcus aureus* was cultured by taking one ose of pure *S. aureus* culture then scratched on Tryptic Soy Agar (TSA) media. It was incubated at 37°C for 24 hours. The colony from TSA was taken using sterile ose wires and suspended in a test tube containing 10 ml of 0.9% NaCl solution until having the same turbidity with a 0.5Mc Farland standard solution. The turbidity indicates that the concentration of bacteria in suspension is 1.5 x 10^8 CFU/mL.

Animals and Treatments:

Male healthy rabbits, age 4-6 months, with body weight of 1-2 kg, were injected with 0.05ml of *Staphylococcus aureus* (CFU/mL) intrastromal using a 30G tuberculin syringe. Then four scratches were made using a 27G sterile needle. The corneal ulcers were evaluated two days post-injection using the fluorescein test (Aldebasi et al., 2012; Tang et al., 2012).[21,22] The corneal ulcers rabbits were divided into 5 groups: K (+): receiving Moxifloxacin HCl 0.5%; P1: receiving 1.5% onion extract; P2: receiving 3% onion extract; P3: receiving 6% onion extract; and P4: receiving 12% onion extract. The treatments were given as eye drop, 1 drop every 6 times/day for seven days. It was given two days after corneal ulcer was made. The onion extract was made using the ultrasonic bath method at Biology Laboratory of Faculty of Pharmacy, University of Jember.

Animal Anesthesia:

Before making ulcers, rabbits were anesthetized by subcutaneous injection with a combination of ketamine 44mg/kg BW and xylazine 5mg/kg BW. The subcutaneous injection area is between the os. Scapula. Furthermore, it was given topical anesthesia using one drop of pantocaine 0.5%.[23] The procedures were approved by Health Research Ethics Committee of University of Jember.

Measurement of Scarring Area:

Measurement of scar tissue area by taking pictures of the scar tissue and then measuring its area using the ImageJ application (mm^2).

Measurement of Neovascularization Area:

The area with neovascularization in the Rabbit's corneas was measured by taking pictures of the Rabbit's eyes using a camera. Areas with blood vessels in the cornea were marked with a line as a boundary and then calculated using the ImageJ application.[24] The data obtained were expressed in mm^2.

Termination and Enucleation:

The rabbit termination was carried out by administering intravenous sodium pentobarbital at a dose of 100mg/kg BW 25 hours after the last treatment. The Rabbit's eye was enucleated. Then the corneal tissue was removed by making a circle around the palpebra starting from the edge of the lateral canthus. The circular incision was formed and followed by slicing m. orbicularis oculi, which has fibers encircling the superior and inferior palpebra. Next, the limbus was pierced and cut in a circle, after which it is cleaned to obtain corneal tissue in the form of a transparent membrane, which is fixed in 10% formaldehyde for histopathological examination. Histological preparations were made by cutting into three parts, then stained with hematoxylin-eosin and analyzed using a microscope.

Neutrophils Count:

The number of neutrophils was calculated in the wound area using a binocular light microscope with a magnification of 400x (cell/hpf). The image was taken with an optilab that had been connected with a computer. This procedure was carried out at the Anatomical Pathology Laboratory of the Faculty of Medicine, University of Jember, with a single-blind method.

RESULTS:

Corneal Scar Size:

Table 1 showed that the smallest corneal scar size could be found in K (+) group, while the largest was P4 group. The order of the treatment group with the smallest to the largest scar size is K (+), P3, P2, P1, and P4.

The corneal scar size in rabbits can be seen in the table below.

Table 1. Corneal Scar Size

Group	Corneal Scar Size (mm^2) ± SD
K(+)	2,39 ± 0,37
P1	8,87 ± 2,56
P2	5,48 ± 1,27
P3	4,86 ± 0,72
P4	16,53 ± 2,34

Corneal Neovascularization:

The area of corneal neovascularization can be seen in Table 2 below. Table 2 showed that the group with the smallest neovascularization area was K(+), which was given Moxifloxacin HCl 0,5%. Meanwhile, the largest area of corneal neovascularization was found in the treatment group that was given 6% onion extract (P3). The group that was treated with 3% onion extract (P2) had the smallest area of neovascularization among the other groups who were treated with onion extract.

Table 2. Area of Corneal Neovascularization

Group	Corneal Area with Neovascularization (mm^2) ± SD
K (+)	0,231 ± 0,265
P1	21,629 ± 22,139
P2	2,961 ± 4,209
P3	47,263 ± 16,200
P4	30,040 ± 29,270

Neutrophil Count:

According to Table 3, the highest number of neutrophils was found in P4 group, and the lowest was found in the positive control group. The maximum effective concentration of onion extract obtained from the quadratic curve of the regression test is 6.5% (P3). Microscopic images of neutrophils in rabbit eye corneas with 400x magnification from each group after treatment can be seen in Figure 1.

Table 3. Neutrophil Count

Group	Neutrophil count
K(+)	7,00 ± 0,89
P1	24,08 ± 2,96
P2	21,83 ± 2,54
P3	19,58 ± 9,52
P4	36,56 ± 7,16

DISCUSSION:

Corneal ulcer is a pathological condition of the cornea characterized by suppurative infiltration and corneal tissue discontinuity from the stromal epithelium.[25] Corneal ulcers can be caused by various causes, both infection, and non-infection. Infection is the most common cause of corneal ulcers, either due to bacteria, fungi, viruses, or Acanthamoeba. The bacteria which is often found is *Staphylococcus aureus*.[26]

Figure 1. Hematoxylin-eosin staining of Rabbit's cornea showed neutrophil (yellow arrow) in the negative control group
(A), positive control group (B), P1 group with onion extract concentration of 1.5% (C), P2 group with onion extract concentration of 3% (D), P3 group with onion extract concentration of 6% (E), P4 group with onion extract concentration of 12% (F).

Staphylococcus aureus is a gram-positive bacterium that can easily enter the eye if lesions are found in the eye due to ocular trauma, contact lens wear, viral infections or other diseases. *S. aureus* infects the cornea by secreting alpha-toxin and protease that will degrade the stromal extracellular matrix.[2]

When there is a bacterial infection, the body has a natural immune response against the bacteria mainly through the mechanism of phagocytosis by neutrophils, monocytes, and tissue macrophages. The invasion of *S. aureus* through the cornea will induce neutrophil infiltration. Therefore, the number of tissue neutrophils is increasing.[3] Moreover, the macrophages will clear the debris and carry out cell apoptosis. If the inflammation lasts longer, macrophages also express angiogenesis mediators, namely VEGF-A, VEGF-C, and VEGF-D, so that corneal neovascularization appears.[6] Corneal ulcers can cause scarring that disrupts visual function.[27] Scar tissue formation is the result of abnormal wound healing due to an imbalance between proliferation and apoptosis of fibroblasts.[28]

In this study, the positive control group, which is treated with moxifloxacin HCl 0.5%, showed the best results in dealing with corneal ulcers. Moxifloxacin HCl 0.5% is the first-line therapy in bacterial corneal ulcers at present. It has a sensitivity to *Staphylococcus aureus* infections so that the infections are appropriately treated.[29,30,31]

The group treated with 6% onion extract (P3) gave the smallest scar tissue, and neutrophils count among the other extract concentrations and the negative control group. This related to the content of quercetin in onion extract, which can damage cell walls and bacterial cell membranes. Therefore, the bacterial infection and recruitment of neutrophil cells will also reduce. A study mentioned that quercetin inhibits bacteria by damaging bacterial cell walls and membranes so that the bacterial cytoplasmic leaked. It prevents bacteria from infecting host cells.[32] Moreover, onion extract can also inhibit the proliferation and differentiation of the fibroblasts into myofibroblasts, which play a role in the formation of scar tissue.[33]

However, the P3 group produced the largest area of neovascularization among all groups and even had a larger area than the negative control group. It is likely because the infection in the P3 group was more massive than the other groups. It was

influenced by the volume of bacteria that had been successfully injected into the rabbit corneal stroma, which could not be ascertained the same. Intrastromal injection method has a disadvantage, which is the ability to perceive the right depth perception (around 2-3 mm).[34] Also, the degree of infections affects the inflammatory response. The presence of pathogenic bacteria and their products triggers corneal epithelial cells to secrete proinflammatory cytokines, such as TNF-α and IL-6, to recruit inflammatory cells to the site of infection as a defense response. The more pathogenic bacteria or products, the more proinflammatory cytokines are formed so that the inflammatory response is more significant.[35,36] During inflammation, corneal epithelial and endothelial cells, macrophages, and inflammatory cells produce VEGF and fibroblast growth factors. Inflammation also induces the migration of Langerhans cells into the cornea. This results in additional formation of angiogenic cytokines and corneal immune cells. Therefore, the angiogenesis occurs, and corneal neovascularization is formed.[37,38,39]

The groups given 3% (P2) and 1.5% (P1) onion extract produced smaller corneal scar, smallerneovascularization area, and smaller number of neutrophils than the negative control group. This might relate to the quercetin content which also act as an antibacterial. However, quercetin antibacterial activity is not as good as 0.5% Moxifloxacin HCl of the positive control group. Moxifloxacin works by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV which are bacterial enzymes needed for the process of replication, translation, repair, and DNA recombination. Inhibition of both enzymes results in bacterial death.[21] On the other hand, quercetin damages cell walls and bacterial cell membranes so that the infection process does not occur. Therefore, moxifloxacin is considered more effective in inhibiting the process of bacterial growth since DNA replication inhibition.

The decrease of onion extract effect at a concentration of 12% (P4) was thought to be due to the toxic effect of the onion extract itself. There was a lack of improvement in inflammatory markers, and a decrease in neutrophil counts. Quercetin, as one of the onion extract active compound, is flavonoids with catechol moiety. Flavonoids are antioxidants that in phase 1 metabolism undergoes oxidation, which activates the flavonoid. In phase 2 metabolism, flavonoids undergo detoxification reactions. The catechol of natural food products encourages cancer chemopreventive activity. Catechol moiety is the target of phase 2 metabolism that is mutagenic to pro-oxidant. In this case, quercetin is toxic and antigenic. The antigenic stimulation will induce neutrophils to release β-glucoronidase to the plasma. Therefore, the more quercetin is obtained, the more toxic it becomes, and the more neutrophils were produced not only in intracellular but also in plasma and interstitial fluid.[40] From this study, we conclude that the administration of onion extract (*Allium cepa* L.) decreased the neutrophil count, area of neovascularization, and corneal scar size in rabbits with corneal ulcer. In this study, the effective concentration of onion extract in reducing neutrophil counts was 6.5% and 3% in inhibiting the formation of neovascularization.

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CONFLICT OF INTEREST:
The authors declare that there is no conflict of interests regarding the publication of this paper.

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