Efficacy differences of Queen's crepe-myrtle (*Lagerstroemia speciosa*) and aloe vera extract on the interleukin-6 and osteoblast levels in the healing process of alveolar osteitis

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ABSTRACT

Introduction: Alveolar osteitis is the most common complication after tooth extraction, which occurs 2 to 4 days after and causes disruption of wound healing. Pucuk Bungur/Queen's crepe myrtle (Lagerstroemia speciosa) and aloe vera have biological and pharmacological benefits in experimental animals: antimicrobial, anti-inflammatory, and antioxidant. They also affect the wound healing process. These benefits are a good combination as an alternative remedy for alveolar osteitis treatment. This study was aimed to analyse the effect of Lagerstroemia speciosa compared to aloe vera extracts gel on the wound healing process after tooth extraction in Sprague-Dawley mice with alveolar osteitis. **Methods:** This research was an experimental laboratory. Twenty-seven Sprague-Dawley mice were randomly divided into three groups. The first group was the osteitis (control) group treated with 1:1000 adrenaline insertion for 1 minute on the left maxillary first molars socket; the second group was the osteitis group administered with the application of Lagerstroemia speciosa, and the third group was the osteitis group administered with the application of aloe vera gel. Normal mice in the control group were not given any treatment, only osteitis mice. The interleukin-6 level was examined after, and the number of osteoblasts was also calculated on the 3rd, 5th and 14th day after necropsy was performed. Data were analysed with one-way ANOVA to compare the effectiveness of wound healing of alveolar osteitis in each group. **Results:** From the data analysis, the osteitis group applied with Lagerstroemia speciosa gel had good activity in the inflammation phase of the healing process of alveolar osteitis compared to other groups. **Conclusion:** *Lagerstroemia speciosa* can be a potential alternative treatment to reduce inflammation and accelerate the healing of osteitis because it shortens the inflammatory phase and accelerate collagen production in wound healing.

Keywords: Aloe vera; alveolar osteitis; Queen's crepe myrtle; *Lagerstroemia speciosa*; Sprague-Dawley; interleukin-6; osteoblasts

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INTRODUCTION

Alveolar osteitis or dry socket is the most common complication occurring after tooth extraction and usually appears on days 3-5 after surgery. The incidence is around 1-4% after the usual dental extraction procedure[1]. The main complaint is severe pain[2], which does not subside with administration of analgesia.[3]

The clinical appearance shows an open alveolar, enveloped in necrotic tissue and accompanied by gingival inflammation and halitosis. Histologically alveolar osteitis consists of remnants of blood clots and inflammatory cells such as neutrophils and lymphocytes around the socket. Some factors that can increase the incidence of osteitis are excessive trauma during extraction, bacterial infection, reduced blood supply from surrounding bone tissue due to vasoconstriction in local anesthetic drugs, use of contraceptive drugs or due to systemic conditions.[4,5,6]

The treatment of alveolar osteitis varies and depends on clinical experience, including the irrigation of saline solutions with prescription analgesics. Another common method is to clean the socket and insert the dressing medication into the tooth socket that has alveolar osteitis.[7,8] Based on the active content, the alveolar osteitis dressing material that is inserted into the tooth socket is classified into four classes, namely: dressing material which has antibacterial properties, dressing ingredients that have anti-pain properties, topical anesthetic dressing ingredients, and a combination of all three.[9,10] However, effective and specific treatments for alveolar osteitis have never been published. Therapy for alveolar osteitis includes debridement of necrotic tissue, administration of topical analgesics and gels for tissue regeneration such as alloclair. And also can be given oral premedication. With this research, it is hoped that alternative materials will be found with sufficient availability and low prices.

Aloe vera is one of the medicinal plants that can cure various diseases. *Aloe vera barbadensis* Miller contains 72 substances needed by the body. Among the 72 substances, there are 18 kinds of amino acids, carbohydmicees, fats, water, vitamins, minerals, enzymes, hormones and substances class of drugs such as antibiotics, antiseptics, antibacterial, anti-cancer, anti-virus, anti-fungal, anti-infection, anti inflammation, anti-swelling, anti-parkinsonism, anti-atherosclerosis, and anti antibiotic-resistant drugs. Two hormones that are known to contain aloe vera, namely auxins and gibberllins. Both play a role in wound healing and anti-inflammatory effects.[11,12,13,14]

The plant that is also known as its benefits as an herbal treatment, namely pucuk bungur/ Queen's crepe-myrtle (*Lagerstroemia speciosa*) which is a tropical plant with a small and green leaf shape. *Lagerstroemia speciosa* has properties to cure various disorders because it has antioxidant activity, anti-diabetes, anti-inflammatory, anti bacterial and anti-viral.[15,16,17] This study was aimed to analyse the effect of *Lagerstroemia speciosa* compared to aloe vera extracts gel on the wound healing process after tooth extraction in Sprague Dawley mice with alveolar osteitis.

METHODS

Type of research was experiment laboratory. Samples were drawn randomly using consecutive random sampling using the lottery model. Experimental animals that met the inclusion criteria were taken as research subjects. The research object was post tooth extraction wounds in twenty-seven Sprague-Dawley mice induced to develop alveolar osteitis (using 1:1000 adrenaline vasoconstrictor and not given antibiotic therapy for 3 days after tooth extraction). Twenty-seven Sprague-Dawley mice were randomly divided into 3 groups with nine samples each group.

The first group was the osteitis (control) group treated with 1:1000 adrenaline insertion for 1 minute on the left maxillary first molars socket; the second group was the osteitis group administered with the application of Lagerstroemia speciosa, and the third group was the osteitis group administered with the application of aloe vera gel. This research use aloe vera as a comparison, which currently on the market there is the Alloclair trademark which is often used in dentistry.

The second group was the osteitis group given gel application *Lagerstroemia speciosa* and the third group was the osteitis group given the application of aloe vera gel. The teeth used in this research were left maxillary first molars,

extracted with small bein, excavator and artery clem. On the 3rd, 5th and 14th day necropsy was performed and the extraction of dental sockets in the form of soft tissue together with hard tissue and 2cc of blood collection. The tooth socket and tissue was soaked in buffer formalin solution for 24 hours, then decalcification was done using 20% HCl solution for 3-4 days. Then the paraffin block was made and cut with 4-5 µm size pieces. Preparations were made and stained with hematoxylin eosin for examination of osteoblasts.

Assessment of the number of osteoblasts was calculated using software version J version 1.49. For the assessment, a magnification of 4x, 10x, 20x, and 40x was performed. To look at osteoblasts we read on the three areas for each magnification. Criteria for osteoblast scoring used[18] were as follows: 0: There is absolutely no osteoblasts (0%); 1: Osteoblasts are noticed but in a small amount (1-5%) in wound tissue; 2: Moderate osteoblasts (> 5-20%) in wound tissue, especially at the edges of the wound; 3: Osteoblasts tend to be more (> 20-30%) on the peripheral of the wound tissue; 4: Dominant osteoblasts (> 30%) in wound tissue, especially in the peripheral area of the wound. Blood samples inserted into the tube were examined for interleukin levels in the ELISA Kit. Statistical analysis to compare the results of treatment using ANOVA statistical tests.

Extraction of *Lagerstroemia speciosa* and aloe vera was carried out in the Chemical Laboratory of IPB University, using the maceration method. The results of maceration are filtered using a Buchner funnel and vacuum. The extract obtained was then evaporated and concentrated with a low pressure evaporator at 65°C. To get optimal extract levels according to plant characteristics. This evaporation temperature can be done at temperatures of 55°C, 60°C and 65°C. The evaporation extract was dried in a vaporiser cup until thick extract was obtained.

The research gain ethical approval from IPB University Research Commitee with approval number of 111/KEH/SKE/VIII/2018. The research was conducted at the Chemistry Laboratory and Pharmacy Laboratory of IPB University; Educational Animal Hospital of IPB University; Pathology Department, Clinical Department, Reproduction and Pathology, Faculty of Veterinary Medicine, IPB University; during October 15-29, 2018.

RESULTS

The results of the research were carried out by observing clinical pathology and histopathology, calculating and statistical tests of the healing indicators measured by interleukin-6 levels and the number of osteoblasts. Histopathological examination using haematoxilin eosin and calculating osteoblasts using a binocular light microscope with 40x magnification with image J64 software. Figure 1A and 1B are histological picture of osteoblasts with staining HE observed through a microscope.

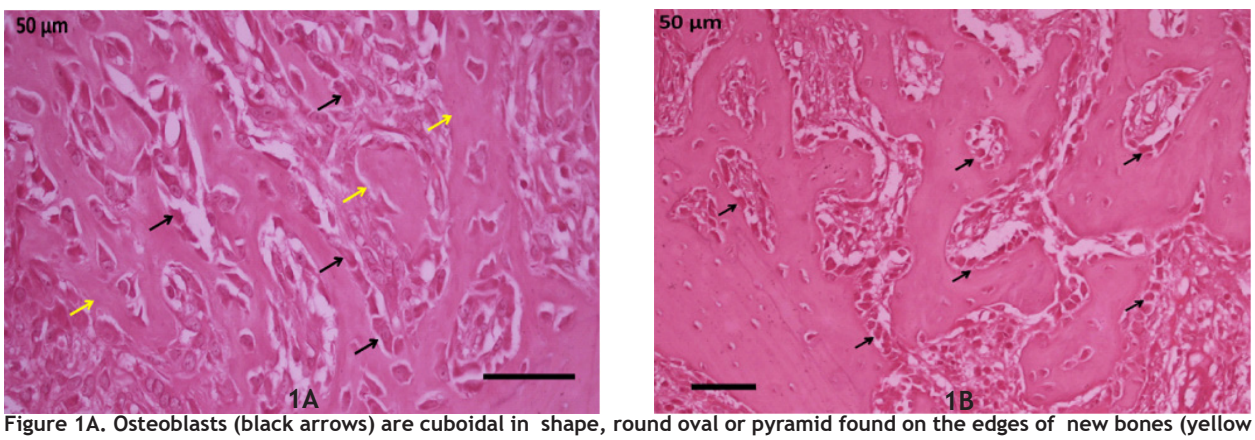

Figure 1A. Osteoblasts (black arrows) are cuboidal in shape, round oval or pyramid found on the edges of new bones (yellow arrows). HE coloring, 50µm bar; 1B. Osteoblasts (black arrows) are found at the edges of the spicula (new bone). HE coloring, 50µm bar

On the third day, the tooth socket still dominated by inflammatory cells. Especially in the control group who had osteitis without gels. Whereas in the other two composts even though there were still inflammatory cells but collagen and fibroblasts have begun and osteoblasts were

formed in small amounts. In the third day tooth socket in the osteitis group given the gel application *Lagerstroemia speciosa*, there were still inflammatory cells and a little blood clot and the socket wall is filled with fibroblast tissue (Figure 2). Histological examination was performed repeatedly for all three groups, on days 3, 5 and 14, which were then observed for the number of osteoblasts formed from each group based on the examination day.

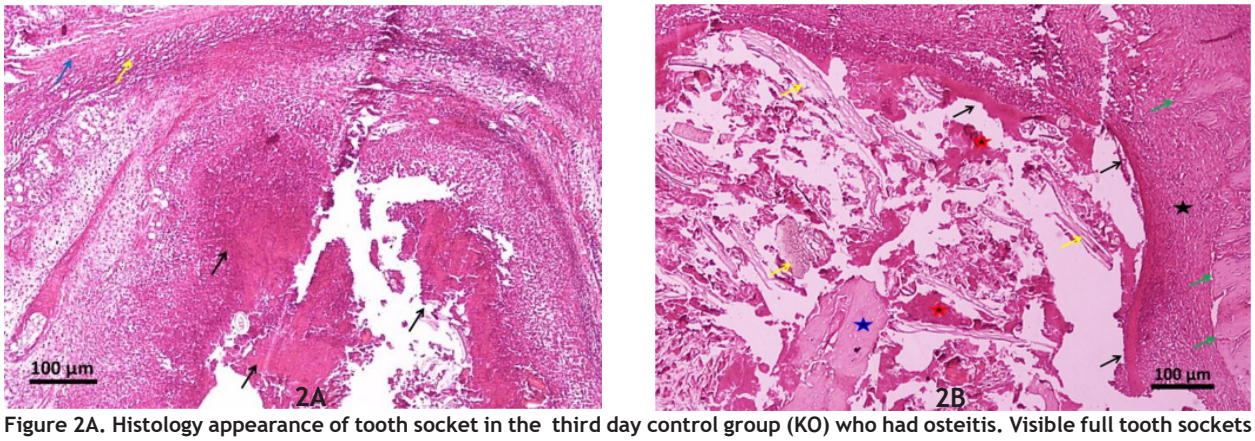

Figure 2A. Histology appearance of tooth socket in the third day control group (KO) who had osteitis. Visible full tooth sockets filled with blood clots, inflammatory cells and debris. But at the edges of the socket (blue arrow), a little fibroblast tissue has begun to form (yellow arrow); 2B. Histology appearance of 3rd day *Lagerstroemia speciosa* tooth socket that has osteitis. Visible tooth sockets are filled with *L. speciosa* extract fibers (yellow arrows), inflammatory cells, debris and a little blood clot (red star). The blue star shows the bones of the teeth that are left behind (the cut tooth tissue). On the edge of the wall of the socket (black arrow) filled with fibroblast tissue (black star) and also has begun to grow new reinforcement/spicula (green arrow). HE coloring, bar 100 µm; Magnifications 10x.

The results of the calculation of interleukin-6 levels and the number of osteoblasts after the extract gel *Lagerstroemia speciosa* compared to aloe vera gel were given to the wound healing process after extracting Sprague-Dawley mice teeth with alveolar osteitis on the 3rd day, 5th day and 14th day. The calculation results are presented in Table 1 and Table 2.

On the 14th day all groups were re-examined (Figure 3). As a result of the examination, the three groups were dominant in the presence of osteoblasts, but differed in numbers. In addition to examining osteoblasts, interleukin-6 was also examined. Examination of interleukin cytokines was carried out on IL-6 using the sandwich method for ±4 hours in units of pg/mL.

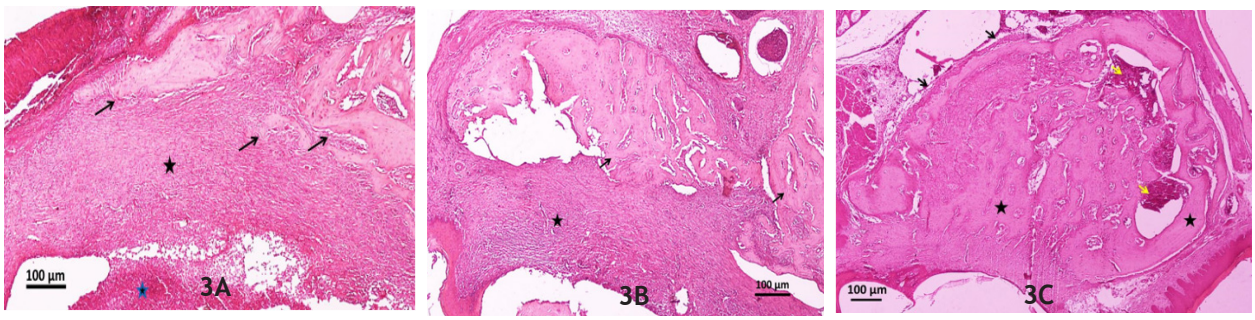

Figure 3. Day 14: 3A. Histology appearance of tooth sockets in negative control group, blood clots and inflammatory cell (lymphosit) (blue stars) are still found, with granulation tissue consisting of fibroblasts and collagen (black stars). New bones/spicules have begun to form at the edges of the socket (arrow); 3B. Histological appearance of the tooth socket of the Aloe vera group that has osteitis. The entire contents of the socket consist of fibroblasts and collagen (stars), and the new bone has filled half of the socket volume (arrow); 3C. Histological description with magnifications of 4x of tooth socket in *L. speciosa* group that have osteitis. Almost all tooth sockets are filled with new bones/spicules (star). At the edge of the socket there were still a few blood clots (yellow arrows). HE coloring, bar 100 µm

Table 1. Interleukin-6 (IL-6) (pg/L) levels on *L. speciosa* extract gel were compared with aloe vera gel on days 3, 5, and 14

Variable	Control	Aloe vera gel	L. speciosa gel	P-value
IL-6 day 3				
(SD)	4.80 ± 1.56	6.56 ± 0.76	6.92 ± 0.16	0.103
Median	5.3	6.74	7.01	
Range	3.05 ± 6.05	5.73 ± 7.22	6.74 ± 7.01	
IL-6 day 5				
(SD)	10.20 ± 4.79	6.28 ± 1.38	6.14 ± 3.80	0.548
Median	10.22	6.64	7.92	
Range	5.40 ± 14.98	4.76 ± 7.44	1.77 ± 8.72	
IL-6 day 14				
(SD)	117.43 ± 74.73	17.02 ± 9.82	6.56 ± 3.20	0.027[(a)]
Median	160.58	12.2	5.99	
Range	31.14 - 160.58	10.54 - 28.31	3.69 - 10.01	

Description: Different superscript letters on the same line show significant differences (p<0.05)

Table 2. The number of osteoblasts in the administration of *L. speciosa* extract gel compared to aloe vera gel on days 3, 5, and 14

Variable	Control	Aloe vera gel	L. speciosa gel	P-value
Osteoblast (day-3)				
No osteoblast	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.097
In a very small amount (1%-5%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	
Moderate (>5%-20%)	1 (33.3%)	2 (66.7%)	1 (33.3%)	
Tend to be more (>20%-30%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	
Dominant (>30%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	
Osteoblast (day-5)				
No osteoblast	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.461
In a very small amount (1%-5%)	3 (0.0%)	0 (0.0%)	0 (0.0%)	
Moderate (>5%-20%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	
Tend to be more (>20%-30%)	0 (0.0%)	2 (66.7%)	0 (0.0%)	
Dominant (>30%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	
Osteoblast (day-14)				
No osteoblast	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.030[(a)]
In a very small amount (1%-5%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	
Moderate (>5%-20%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Tend to be more (>20%-30%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	
Dominant (>30%)	0 (0.0%)	2 (66.7%)	3 (100.0%)	

Description: Different superscript letters on the same line show significant differences (p<0.05)

The results of the calculation of the Mann Whitney test showed that IL-6 in the control group was significantly different from aloe vera gel and also Queen's crepe myrtle.

Likewise Queen's crepe myrtle differs from aloe vera gel but not significant because they have the same value as alpha (α = 5%). The result show in Table 3.

Table 3. Mann-Whitney advanced test

Measurement time	Comparison		P-value
IL-6 day-14	Control	Aloe vera	0.046
		Lagerstroemia sp	0.046[(a)]
	Aloe vera	Control	0.046[(a)]
		Lagerstroemia sp	0.050[(a)]
Osteoblast day-14	Control	Aloe vera	0.034[(a)]
		Lagerstroemia sp	0.025[(a)]
	Aloe vera	Control	0.034[(a)]
		Lagerstroemia sp	0.317

Description: Different superscript letters on the same line show significant differences (p<0.05)

DISCUSSION

In this study, the values of IL-6 levels in the *Lagerstroemia speciosa* group tend to be lower than the other two groups, it means *Lagerstroemia speciosa* was effective in reducing inflammation. It is in accordance with studies found an increase of IL-6 in the acute inflammatory stage to the sub acute/chronic stage, when IL-6 levels peak, the next stage down regulated cytokine IL-6 as a form of ending the inflammatory phase.[20,21] After this inflammatory phase ends, it will continue with an anti-inflammatory phase which is much regulated by the presence of IL-1039 cytokines.[20,21] Gupta et al.[15] found similar results with this study that mice given *Lagerstroemia speciosa* with doses ranging from 100 mg/kg to 400 mg/kg had an anti-inflammatory function comparable to aspirin, morphine or naloxone. However, in this study it was not specific to examine cytokines that were affected by *Lagerstroemia speciosa*.[22]

Interleukin 6 (IL-6) is one of the proinflammatory cytokines and myocin which regulates many aspects of the immune and inflammatory responses.[23,24] These cytokines are secreted in the acute or chronic phase of infection,[24,25] and induce a transcriptional response through IL-6 RA, inducing B cell maturation. Interleukin is responsible for stimulating acute phase protein synthesis, as well as neutrophil production in the bone marrow that supports B cell growth.,[26]

Interleukin plays an important role in the inflammatory response and is produced when macrophages are active and secretion is carried out in the presence of endotoxin, complex immune, toxin, physical injury or various inflammatory mediators.[27,28] Interleukins are polypeptides released by lymphocytes and are numbered according to the amino acids that affect the process.

Interleukin-6 will be detected in the blood circulation several hours after trauma occurs and has several biological effects including activation of B lymphocytes and macrophages, induction of growth factors, stimulating chemotaxis from neutrophils and synthesis of collagen.[29]

This study found that the largest increase in the number of osteoblasts was influenced by aloe vera which had an effect on wound healing after osteitis with the incorporation of lysine and proline resulting in increased collage fibers and osteoblasts. Both of these gels increase the occurrence of microcirculation in the exposed area, then absorbed mitochondria and stimulation of tissue oxygenation formation, increased ATP and activation of nucleic acid synthesis which will stimulate immunological reactions, which will cause vasodilation in the area. This vasodilation will carry oxygen and immune cells into the tissues.[30,31] Oxygen is needed in collagen synthesis and epithelialization of wounds, so it can accelerate collagen production and accelerate wound healing.[32]

Previous research found that one of the active ingredients contained in the leaves of Lagerstroemia species can stimulate osteoblasts found in mice, the active ingredient being corosolic acid. At low concentrations from 0-5 micromol, corosolic acid can significantly stimulate differentiation of osteoblasts without causing poisoning. In the early stages of osteoblast differentiation, corosolic acid affects NF-kB and MAP kinase activity and the final stage of osteoblast differentiation will increase the transcription factor AP-1 factor.[33,34,35]

Lagerstroemia speciosa extract gel can be an alternative treatment option to accelerate the healing of osteitis because it shortens the inflammatory phase with low IL-6 values, increases the number of osteoblasts that accelerate collagen production in wound healing and the availability of this material is quite large and inexpensive. The consideration of this research is as a comparison material for aloe vera gel which is currently an Alloclair gel product which is often used in dentistry to help the healing process. The limitations in this study included the presence of swallowed gels and irritating animal behavior of Sprague Dawley mice.

CONCLUSION

In this study, it was found that the application of Queen's crepe-myrtle (*Lagerstroemia speciosa*) gel after tooth extraction species with osteitis was more effective in reducing the expression of IL-6 compared to the use of aloe vera gel. While the application of aloe vera gel after tooth extraction that has osteitis is effective in increasing the

number of osteoblasts compared to the use of gel *Lagerstroemia speciosa*. *Lagerstroemia speciosa* extract gel can be an alternative treatment option to accelerate the healing of osteitis because it shortens the inflammatory phase with low IL-6 values, increases the number of osteoblasts that accelerate collagen production in wound healing and the availability of this material is quite large and inexpensive.

The consideration of this research is as a comparison material for aloe vera gel which is currently an Alloclair gel product which is often used in dentistry to help the healing process.

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