Effects of roses extract (*Rosa damascena Mill.*) on healing of *Staphylococcus aureus* and *Candida albicans* induced-angular cheilitis on wistar male rats

Efek ekstrak bunga mawar terhadap penyembuhan angular cheilitis yang diinduksi *Staphylococcus aureus* dan *Candida albicans* pada tikus jantan wistar

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ABSTRACT
One type of plant used as herbal medicine is rose (*Rose damascena Mill*) which contains phenolic compounds and essential oils; has multi efficacy especially against *Staphylococcus aureus* and *Candida albicans*. One of the oral diseases caused by these microbes is angular chelitis which is a lesion and inflammation that is a combined infection between *Staphylococci*, *ß-hemolytic Streptococcus*, and *Candida* that affects the tissues in the corners of the mouth. Laboratory experimental research with a posttest only control group design using 24 male Wistar rats which were divided into group-1 induced by *S.aures* and given rose flower extract (RFE), group-2 induced by *S.aureus* and given gentamicin, group-3 induced by *C.albicans* and given RFE, and group-4 induced by *C.albicans* and given miconazole. All mice were treated and observed the wound length and erythema of each group for 7 days then the data were processed using the SPSS. On the third day, the wound length of group-1 dan -2 were 0.00±0.0 mm, group-3 was 0.08±0.20 mm, and group-4 was 0.16±0.39 mm. Friedman test showed significant differences in wound length in each treatment group. It is concluded that RFE has an effect on the healing of angular cheilitis in Wistar male white rats induced by S.aureus and C.albicans and RFE is more effective on the group induced by S.aureus.
Keywords: roses, angular cheilitis, wound infection healing, wistar male rat

ABSTRAK
Salah satu jenis tanaman yang digunakan sebagai pengobatan herbal adalah bunga mawar (*Rose damascena Mill*) yang mengandung senyawa fenolik dan minyak atsiri; memiliki khasiat multi terutama terhadap *Staphylococcus aureus* dan *Candida albicans*. Salah satu penyakit mulut yang disebabkan oleh mikroba tersebut adalah angular chelitis yang merupakan lesi dan peradangan yang merupakan infeksi gabungan antara *Staphylococci*, β-*hemolytic Streptococcus*, dan *Candida* yang memengaruhi jaringan di sudut mulut. Penelitian eksperimen laboratorium dengan desain *posttest only control group* menggunakan subjek 24 ekor tikus jantan galur Wistar yang dibedakan atas kelompok-1 diinduksi *S.aureus* dan diberi ekstrak bunga mawar (EBM), kelompok-2 diinduksi *S.aureus* dan diberi gentamisin, kelompok-3 diinduksi *C.albicans* dan diberi EBM, serta kelompok-4 diinduksi *C.albicans* dan diberi mikonazol. Semua tikus diberi perlakuan dan diamati panjang luka dan eritema setiap kelompok selama 7 hari kemudian data diolah menggunakan SPSS. Pada hari ketiga panjang luka kelompok-1 dan -2, 0,00±0,0 mm, kelompok-3, 0,08±0,20 mm, dan kelompok-4, 0,16±0,39 mm. Uji Friedman menunjukkan perbedaan yang signifikan panjang luka setiap kelompok perlakuan. Disimpulkan bahwa EBM berpengaruh terhadap penyembuhan angular cheilitis pada tikus putih jantan galur Wistar yang diinduksi *S.aureus* dan *C.albicans*; EBM lebih efektif pada kelompok yang diinduksi *S.aureus*.
Kata kunci: bunga mawar, angular cheilitis, penyembuhan infeksi luka, tikus jantan galur wistar
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INTRODUCTION

Rose is an ornamental flower plant with prickly stems, many are planted in the garden and most are sold in flower shops as cut flowers or blossoms. Roses contain *geraniol* and *citronellol* with concentrations of both reaching 75% of oil. In addition, there are also *linalool, citral and phenyl ethyl alcohol, geraniol, nerol, farnesol, eugenol*, and *nonylic aldehyde* in small amounts.[7] Geraniol and limonene compounds contained in rose extract can function as antiseptics. Emerson's research proves that rose extract contains *phenol, carvacrol, thymol*, and *terpene* high can kill almost all microbes.[8] In Windi's study, it was also proven that rose essential oil has the ability to inhibit energy metabolism and damage cell walls and bacterial cell membranes. In addition, essential oils also contain functional groups of hydroxyl (-OH) and carboxyl so that high levels of phenol will cause coagulation of proteins and bacterial cell membranes. As well as roses prove that it can also be an antifungal in the Diah study, because the active substances contained in red rose extract function as antiseptics and antifungi including tannins and *cytronellols*. Tannins are complex compounds that have a mixture of *polyphenols*. The compound *phenol* in tannins has antiseptic and antifungal action.[8]

Angular chelitis is a lesion, sometimes accompanied by the usual inflammation seen in the labial commissure which is a joint infection between *Staphylococcus*, *Streptococci ß-hemolytic*, and *Candida* which affects the tissue at the corners of the mouth.[9] *Angular cheilitis*

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can occur unilaterally or bilaterally, with pain or without symptoms.[10] This lesion is characterized by a rough triangular area, erythema, fissure, rupture, edema accompanied by burning, pain, and dryness in the corners of the mouth.[11] The etiology of *angular chelitis* is multifactorial, caused by infection with *S.aureus*, *C.albicans* and deficiencies of nutrients such as iron and vitamin B12, as well as the result of the use of not-adequate dentures which causes a low occlusal vertical dimension. Other causes are caused by bad habits such as wetting the lips with saliva, licking the corners of the lips, and dysfunction of the salivary gland.[12,13] Therefore, this article aims to examine the effects of rose extract that can be used as an alternative cure for angular cheilitis induced by *S.aureus* and *C.albicans*.

METHODS

This experimental laboratory with a posttest only control group design was conducted at the Phytochemical Laboratory of the Faculty of Pharmacy, Hasanuddin University, and the Biology Laboratory of the Faculty of MIPA Makassar State University, in September-October 2018. By using simple random sampling, 24 wistar (*Rattusnovergicus*) male rats induced by *Staphylococcus aureus* and *Candida albicans* as subjects of this study divided into four treatment groups; group-1 was *S.aureus*-induced and given rose flower extract (RFE), group-2 *S.aureus*-induced and given gentamicin, group-3 was *C.albicans*-induced and given RFE and group-4 was *C.albicans*-induced and given miconazole. The study was carried out under medical ethical approval (0080/PL.09/KEPK FKG-RSGM Unhas/2018) Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia.

The RFE is extracted by maceration method in ethanol solvent with a concentration of 70% and then evaporated using a rotary evaporator to get thick extract, that was then prepared in 100% concentration by mixing 1% NaCMC solvent with a ratio of 1:1. Inoculums of *S.aureus* and *C.albicans* were obtained from the Biology Laboratory of the Faculty of Mathematics and Natural Sciences, Makassar State University.

The study was carried out by injuring the corner of the mouth of the Wistar male rat by pulling together between the two corners of the upper and lower lips together to make a fissure wound, but because the angle of the mouth of the Wistar male white mouse produced an invisible wound that needed help in the form of tweezers to make a cut. Wounds are made from 4 mm so that bacteria and fungi can attack quickly, then the induction was performed with the first and second *S.aureus* inoculum and inoculum of *C.albicans* in the third and fourth groups using sterile spherical ose. Furthermore, the wound was left for 24 hours without being treated for bacterial and fungal growth so the infections occurred on both sides of the mouth of the Wistar. After 24 hours, the infected wounds were given RFE in the first and third groups, gentamicin in the second control group and miconazole in the fourth control group topically applied. The length of the wound and erythema were observed in each group for 7 days.

DISCUSSION

Based on the results of this study, RFE has an effect on wound healing *angular cheilitis* in white male rat

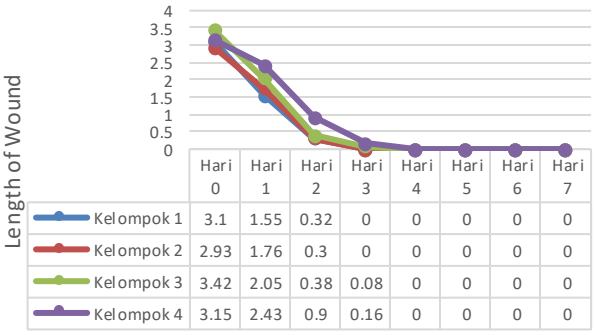

Figure 1 The average length of angular cheilitis wound

RESULTS

Table 1 The average length of angular cheilitis wound

KP	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD
1	3.10±0.32	1.55±0.51	0.32±0.72	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	2.93±0.52	1.76±0.32	0.30±0.38	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
3	3.42±0.46	2.05±0.58	0.38±0.44	0.08±0.20	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
4	3.15±0.86	2.43±0.81	0.90±1.06	0.16±0.39	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00

Tabel 2 The average length of angular cheilitis wound with Friedman test

KP	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	P-Value
	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	
1	3.10±0.32	1.55±0.51	0.32±0.72	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.002
2	2.93±0.52	1.76±0.32	0.30±0.38	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.000
3	3.42±0.46	2.05±0.58	0.38±0.44	0.08±0.20	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.001
4	3.15±0.86	2.43±0.81	0.90±1.06	0.16±0.39	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.001

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Table 3 The average length of angular cheilitis wound with Mann Whitney test

KP	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD
1	3.10±0.32	1.55±0.51	0.32±0.72	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	2.93±0.52	1.76±0.32	0.30±0.38	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
P-Value	0.626	0.291	0.629	-	-	-	-	-

Table 4 The average length of angular cheilitis wound with Mann Whitney test

KP	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD
1	3.10±0.32	1.55±0.51	0.32±0.72	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
3	3.42±0.46	2.05±0.58	0.38±0.44	0.08±0.20	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
P-Value	0.144	0.144	0.526	0.361	-	-	-	-

Table 5 The average length of angular cheilitis wound with Mann Whitney Test

KP	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD	mean±SD
3	3.42±0.46	2.05±0.58	0.38±0.44	0.08±0.20	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
4	3.15±0.86	2.43±0.81	0.90±1.06	0.16±0.39	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
P-Value	0.200	0.423	0.406	0.902	-	-	-	-

wistar induced by *S.aureus* and *C.albicans*. Roses have essential oils, and flavonoids are potentially antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, anticancer, anti-convulsant and antidiabetic.

Physical observation on day-0 for the four groups after treatment, bacterial infection occurred in the first group induced by *S.aureus* and given RFE and in the second group induced *S.aureus* and given gentamicin, which was characterized by tissue damage in the surrounding area lesion. Whereas in the third group that was induced by *C.albicans* and given rose extract and in the fourth group induced by *C.albicans* and given miconazole, fungal infections were characterized by severe damage around the lesion. Fungal infection wounds are more severe than bacterial infection wounds. On day 1 all groups experience an inflammatory phase which is a living tissue defense reaction to all forms of injury involving the function of blood and blood vessels, nerves, spleen, fluid and cells around the wound. In the stage of an inflammatory reaction an infection which is the entry process of a number of pathogenic microorganisms in this case are *S.aureus* and *C.albicans* to the injured area. A number of pathogenic microorganisms will enter the network through an open area due to injury.[34]

Based on Table 1 and Fig. 1, the group that was induced by *C.albicans* using RFE had a higher average reduction in wound length than to the other groups, followed by the first group induced by *S.aureus*, using RFE. With the decline, then descriptively RFE has an effect on healing *angular cheilitis*. Group of RFE induced by *S.aureus* and *C.albicans* have a better healing effect than the positive control group *S.aureus* and *C.albicans* given gentamicin and miconazole.

Based on Table 2, Friedman-test was conducted to determine the difference in wound length of each treatment group on each observation day. It shows the closure of wounds on days 0 to 7 days. The first group on the third day wound closure has occurred, from the results of statistical tests obtained p-value (0.002) <0.05 mm which means that there are significant changes in wound length. The second group on the third day has wound closure, from the results of statistical tests obtained p-value (0.000) <0.05 which means that there is a significant change in the length of the wound starting from Day 0 to Day 7. The third group, wound closure occurred on the fourth day, from the results of statistical tests obtained p-value (0.001) <0.05, which means that there is a significant change in wound length Day 0 to Day 7. Whereas the group-4, wound closure on the fourth day, from the statistical test results obtained p-value (0.001) <0.05 which means that there is a significant change in the length of the wound starting from Day 0-7.

The third group is induced with *C.albicans* and the first group is induced by *S.aureus* given RFE was a group that was faster in *angular cheilitis* wound closure compared to the control group. This is in accordance with the research conducted by Diah regarding RFE which has a inhibitory effect on *C.albicans* because the active substances contained in rose extract function as antiseptics and antifungi including tannins and citronellol, then research of Windi regarding RFE as an antibacterial effective against bacteria Gram-positive *S.aureus*. Based on research conducted by Windi, it was stated that rose extract contains compounds including *phenyl ethyl alcohol, geraniol, eugenol*, and several other compounds that have the ability to inhibit energy metabolism and damage cell walls and bacterial cell membranes. In addition, it also contains hydroxyl (-OH) and carboxyl groups so that high phenol levels will cause coagulation of proteins and bacterial cell membranes. In Windi's study, RFE demonstrate its effectiveness as an antibacterial to inhibit the growth of *S.aureus*.[8]

The results of research conducted by Retnani proved that compound *citronellol* α-and *pinene* is a compound which are antifungal and terpenoids compounds shown antimicrobial power which can inhibit the growth of *C. albicans*. Based on the results of this study it was concluded that roses have a significant inhibitory effect on the growth of *C.albicans*. Likewise in the study of Hossein et al and Ulusoy et al showed that essential oils from roses have strong antibacterial activity. This RFE contains *geraniol* and *citronellol* with concentrations of both reaching 75% of essential oils. In addition, there are also *linalool, citral* and *phenyl ethyl alcohol, nerol, farnesol, eugenol*, and *nonylic aldehyde*.[20]

Other studies include antibacterial and antifungal activity from *Rosa damascena Mill* by *Mohamed Shohayeb* et al. RFE for antimicrobial activity, from some of the fungi studied, *C.albicans* is one of the most sensitive fungi, and also research on 10 bacteria, namely 7 gram-positive bacteria and 3 gram-negative bacteria. Of the 7 gram-positive bacteria studied by *S.aureus* including the most sensitive bacteria and bacteria *B.Subtilis* whereas in the most sensitive gram-negative bacteria was *K.pneumoniae*, from the results of this study higher sensitivity was in Gram-positive bacteria than Gram-negative, this can be attributed to the fact that Gram-negative bacteria have an outer membrane that acts as a barrier that prevents or decreases the penetration of various antimicrobials, the lack of an outer membrane in Gram-positive bacteria makes it more susceptible to destructive molecules leading to leakage of Gram-cytopasma contents positive. The results of this study concluded that RFE has broad-spectrum antimicrobial activity against Gram-positive, Gram-negative, and fungal bacteria.[21,22]

Table 3 shows the different tests performed on one treatment group induced by *S.aureus* and given RFE and two control groups induced by *S.aureus* and given gentamicin using the Mann Whitney test. The first and second groups showed a comparison of the length of wounds. On day 1, the length of wounds in group-1 was 1.55 mm and in group-2 was 1.76 mm; from the statistical test, p-values (0.291) > 0.05, which means there is no difference in wound length between group-1 and -2 on day-1. On day-2, the length of the wound in group-1 is 0.32 mm and in group-2 is 0.30 mm. The p-values (0.629) > 0.05 which means there is no significant difference in wound length between group-1 and -2 on day-2. From these results it can be concluded that the effect of the RFE treatment group as an antibacterial agent is the same as the influence of gentamicin positive control group onwound closure *angular cheilitis* in white male rats of the Wistar strain. For data on the day-3, the average measurement data for group-1 and group-2 is the same, namely 0 on this day the wound is completely closed.

Table 4 shows the different tests were carried out on treatment group-1 induced by *S.aureus* and given RFE, and the treatment group-3 induced by *C.albicans* and given RFE using the Whitney man test. A comparison of the length of the wound between the groups-1 and -3; on day-1, the length of the wound in group-1 was 1.55 mm and in group-3 was 2.05 mm. The p-values were 0.144 > 0.05 which means there were no differences in wound length between groups-1 and -3 on day-1. On day-2, the length of the wound in group-1 is 0.32 mm and in group 3 is 0.38 mm, from the statistical test p-value is obtained 0.526 > 0.05, which means there is no difference in wound length between groups 1 and 3 on day-2. In group-1 the wound has closed and in group 3 is 0.08 mm. The statistical test obtained p-value 0.361> 0.05 which means there is no difference in wound length between group-1 and -3 on day-3. It means that the effect of the RFE as an antibacterial agent is similar to the effect of the treating group-3.

Table 5 shows the different tests performed on the treatment groups-3 induced by *C.albicans* and given RFE and the control group-4 induced by *C.albicans* and given miconazole using the Mann Whitney test. On day-0, the length of the wound in group-3 was 3.42 mm and in group 4 was 3.15 mm; the statistical test p-value was 0.200> 0.05 which means there was no difference in wound length between groups-3 and -4 on day-0. On day-1, the length of the wound in group-3 was 2.05 mm and in group-4 was 2.43 mm; the p-values were 0.423 > 0.05 which means there were no differences in the length of wounds between groups-3 and -4 on day-1. On day-2, the length of the wound in group-3 is 0.38 mm and in group-4 is 0.90 mm; the p-value 0.406 > 0.05 which means there is no difference in the length of injury between groups-3 and -4 on day-2. On day-3, in group-3 along 0.08 and in group-4 is 0.16 mm; the p-value (0.902)> 0.05 which means there is no difference in wound length between groups 3 and 4 on day-3. It means that the effect of the RFE treatment group as an antifungal material is the same as the effect of the positive antifungal control group using miconazole on healing by wound covering the *angular cheilitis* in the white male Wistar strain rat. For data on the day-4, the average measurement data for groups of three and four is the same, namely 0 on this day, the wound was completely closed.

The group-1 induced by *S.aureus* which was given RFE and the group-2 induced by *S.aureus* given gentamicin had a difference in wound length but was not significant or the same. The group-2 was induced by *C. albicans* given RFE and the group-4 induced by *C.albicans* given miconazole had differences in wound length but were not significant. Then, between the group-1 in-

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duced by *S.aureus* given RFE and the group-3 induced by *C.albicans* and given RFE, had different lengths of injury but were not significant. Then for each group-1, group-2, group-3 and group-4 had a significant difference in wound length where the group that had the most significant results was a group-3 induced by *C.albicans* and given RFE.

It is concluded that RFE has an effect on healing wounds of angular cheilitis infection in Wistar male rats induced by *S.aureus* and *C.albicans*. Rose flower extract was more effective in healing wounds of angular cheilitis infection in Wistar male rats induced by *C.albicans* compared to angular cheilitis infection of Wistar male rats induced by *S.aureus*.

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