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Research Article

EVALUATION OF THE EFFECT OF GAMBIER (*Uncaria gambier*) EXTRACT FOR TREATMENT OF RECURRENT APHTHOUS STOMATITIS

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is one of the most common ulcerative diseases of the oral cavity. RAS causes discomfort so that adequate care is needed to reduce the pain and accelerate the healing of RAS with minimal side effects. Gambier (*Uncaria gambir*) is used in Indonesian traditional medicine for some oral treatments without significant side effects. This study aimed to evaluate the effect of gambier (*Uncaria gambir*) extract on pain reduction and the healing of RAS. This pretest-posttest controlled group was conducted on 30 subjects. The subjects were divided into two groups; gambier extract and placebo. They were instructed to apply gambier extract or placebo ointment three times daily for seven days. The severity of pain was measured by using visual analog scale (VAS), the healing duration of recovered RAS was observed, and the changes in the size of the lesion were measured using probe UNC at baseline, day 1, day 3, and day 7. Data were analyzed using SPSS ver. 22 and using two-tailed Mann Whitney and Wilcoxon. This study showed that the pain, the healing, and the size of RAS in gambier extract group significantly reduced on the third and seventh day compared to placebo ($p<0.05$). It can be concluded that gambier extract has potential effect on the treatment of RAS.

Keywords: gambir extract, healing, pain, stomatitis aphthous recurrent, placebo

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common inflammatory ulcerative condition with the prevalence of worldwide is 1 %.[1] The etiology of RAS is unknown, but several predisposing factors are often associated. These factors are stress, trauma, hormonal changes, genetics, nutritional deficiencies, hypersensitivity, systemic disease, and infections.[2] RAS occurs to everyone, predominantly affected females in the age range 10-40 years old.[3]

The characteristics of RAS generally are painful recurrent, single or multiple, round or oval with yellow-gray base surrounded by halo erythematous.[4] According to its clinical presentation, RAS divided into three types including minor, major and herpetiform.[5] Minor RAS is characterized by round and superficial ulcer with diameter of <10 mm. It can be recovered without leaving scarring within 10 to14 days. Major RAS has a larger ulcer in size of >10mm and longer duration of healing (can be more than 14 days). Herpetiform RAS exhibits multiple small and deep ulcers and recovers within 7 to 14 days.[5,6]

The aim of RAS treatment is to relieve inflammation, pain, and reduce the duration and recurrence of ulcers. Since ancient times, people have known and used medicinal plants to treat various types of diseases. The use of extracts from plants has increased because they have minimal side effects.[7] One of them is gambier (*Uncaria gambir*).

Gambier (Uncaria gambir) is commonly found in Southeast Asia and has been used widely as medicinal plant to treat some diseases.[8] Previous study reported that gambier had analgesic, antibacterial and anti-inflammatory activities.[9] Dewi *et al* reported that gambier had antiseptic effect on gingival wounds in rats.[10] Pambayun *et al* informed that gambier contained in betel quid had antiseptic effect on mucosal wound.[11] Another study also reported that gambier had antibacterial activity and antioxidant.[12] Study about the effect of gambier in treating recurrent aphthous t been done. The aim of this study was to evaluate gambier (*Uncaria gambir*) extract on the treatment of RAS.

MATERIALS AND METHODS

This study was conducted in Chemistry Laboratory of Politeknik Sriwijaya, Indonesia, Dental Hospital of Province of Sumatera Selatan, Indonesia, and Dental Clinic of Universitas Sriwijaya, Indonesia. The protocol had been approved by Health Research Review Committee, Mohammad Hoesin General Hospital and Faculty of Medicine Universitas Sriwijaya, with the ethical certificate number of 132/kepkrsmhfkunsri/2019.

The study was designed as a pre-post-test, randomized, single-blind. Thirty patients with recurrent aphthous stomatitis participated in this study. The subjects were divided into two groups. Group A was gambier extract ointment, and group B was placebo ointment. They were diagnosed with minor recurrent

aphthous stomatitis over the past years, with duration of healing process of RAS more than 4 days. Smokers, patients with systemic disease, patients consuming systemic steroids, anti-inflammatory drugs, vitamins, and gargling mouthwash were excluded from this research.

Preparation of gambier extract

40-60 mesh of gambier pollen taken from traditional market of gambier garden, Sekayu, Indonesia, were pondered for 60 grams. The material was identified and authenticated by Faculty of Agriculture, Universitas Sriwijaya, Indonesia. Gambier was packed in filter paper (Whatman no.45) and put into soxhletation tube. The tubes were filled with ethyl acetate 98% for 300 mL. And then heated at a temperature of 50-60^{0}C for 12 hours until the solvent became clear. The solvent evaporated with rotary evaporator (IKA RV10, Staufen, Germany) for two days until it got pure extract in dry preparation. [11]

Preparation of ointment

The standard formula of ointment was 15% adaps lanae and 85% vaseline album. Gambier extract with concentration of 10% was taken by mixing 30 mg of gambier extract with 40.5 mg adaps lanae and 229.5 mg vaseline album. The mortar was heated in the oven (Cole-Palmer Ltd, UK) at 50^{0}C temperature for 10 minutes. The materials of ointment were stirred by using pestle until homogenous. The ointment was put in the labeled pots and was kept in the refrigerator.[13]

Preparation of patients

The patients were explained with the purpose of the study, the procedures and duration of the research, the potential risks and the advantages of joining the participation. The patients who agreed with all aspects of the trial and voluntarily confirmed their willingness to participate in this trial were asked to sign the informed consent.

The patients with recurrent aphthous stomatitis were examined intraorally with mouth mirrors (4Rho, Medesy, Italy) to evaluate the location and the number of RAS. The data were recorded. The patients were matched based on Visual Analogue Scale (VAS) to equalize their pain intensity. They divided into two groups, group A was treatment group, and group B was placebo. All patients were given sterile cotton swabs and ointments for 7 days. They were also instructed to apply the ointment on the stomatitis for 3 times daily for 3 minutes. Patients should not eat and drink for an hour following the procedure of treatment.

Evaluation of RAS

The condition of patients was followed up every day for 7 days. The data were recorded prior to treatment, at one, three and seven days post-treatment. The evaluation included severity of pain, size of RAS, and duration of recovery. Pain intensity was measured using VAS. The patients were given paper with 100 mm horizontal line to represent their pain. The left side indicated no pain, while the right side described the most painful feeling. The patients were requested to grade their pain perception. The size of RAS was measured using UNC periodontal probe (Medesy, Italy). The largest diameter of stomatitis was recorded. As the criteria for healing of RAS, we assessed the day in which the ulcer was completely healed.

The data were analyzed using SPSS ver. 22. Shapiro-Wilks test and Levene's test were used to know the normality and homogeneity data distribution (P>0.05). Mann-Whitney and Wilcoxon were used for non-parametric data distribution, while independent t-test was used for parametric distribution of collected data. The level of significance in this study was 0.05.

RESULTS

Thirty females participated in this study, with range of ages was 19-23 years old. The locations of lesions were in buccal mucosa (43.33%), labial mucosa (30%), lateral border of tongue (16.67%), floor of the mouth (6.67%) and gingiva (3.33%). Table 1 described the severity of pain on baseline, one, three and seven-day post-treatment. It showed that on the third and seventh day there was significant effect in the reduction of pain between treatment group and placebo.

Table 1. Mean of VAS score before and after treatment

Variables	Groups		P-value
	Gambier extract (n=15)	Placebo (n=15)	
	Mean±SD	Mean±SD	
Baseline	71.33±14.6	69.0±12.6	0.52[a]
Day 1	67.67±11.3	68.7±12.3	0.68[a]
Day 3	6.70±9.00	62.7±16.9	0.00*[a]
Day 7	0.31±1.30	33.3±8.40	0.00*[a]

[a] Mann Whitney, *P<0.05 (significant)

From table 2, it could be seen that the size of RAS significantly reduced on the third and seventh days after giving gambier extract treatment.

Table 2. Comparison of the ulcer size

Variables	Groups		P-value
	Gambier extract (n=15)	Placebo (n=15)	
	Mean±SD (mm)	Mean±SD (mm)	
Baseline	8.9±4.6	11.5±13.5	0.54[a]
Day 1	8.3±4.2	11.7±13.1	0.88[a]
Day 3	4.2±3.7	17.6±13.5	0.00*[a]
Day 7	1.2±2.2	9.7±8.2	0.00*[a]

[a]Mann Whitney, *P<0.05 (significant)

Table 3 showed that treatment with gambir extract accelerated the duration of stomatitis healing significantly.

Table 3. Comparison of duration of recovery

Variables	Groups		P-value
	Gambier extract (n=15)	Placebo (n=15)	
	Mean±SD (mm)	Mean±SD (mm)	
Duration	6.2±1.2	9.2±1.6	0,00*[b]

[b]Independent t- test, *P<0.05 (significant)

Table 4 showed that there was no significant effect of pain intensity between baseline and one day after treatment in both groups. On comparation of baseline and three days after treatment, it showed that gambier extract group had significant effect on the reduction of pain, while placebo had no significant effect. VAS score on baseline and seventh day, first day and third day, first day and seventh day, third day and seventh day had reduced significantly in both groups. The patients in placebo group experienced pain for a longer duration than patients in gambier extract group.

Table 4. Comparison of pain intensity within groups

Variable	Groups	
	Gambier extract (n=15)	Placebo (n=15)
	P-value	P-value
Baseline - Day one	0.06[c]	0.16[c]
Baseline - Day three	0.00*[c]	0.06[c]
Baseline - Day seven	0.00*[c]	0.00*[c]
Day one - Day three	0.04*[c]	0.02*[c]
Day one - Day seven	0.00*[c]	0.00*[c]
Day three - Day seven	0.01*[c]	0.00*[c]

[c] Wilcoxon, *P<0.05 (significant)

Statistically, gambier extract accelerated the closure of stomatitis. There was significant effect in healing the ulcer from day three after treatment on gambier extract group. (Table 5).

Table 5. Comparison of ulcer size of RAS within groups

Variable	Groups	
	Gambier extract (n=15)	Placebo (n=15)
	P value	P value
Baseline - Day one	0.18[c]	0.58[c]
Baseline - Day three	0.04*[c]	0.10[c]
Baseline - Day seven	0.00*[c]	0.06[c]
Day one - Day three	0.05*[c]	0.51[c]
Day one - Day seven	0.00*[c]	0.11[c]
Day three - Day seven	0.00*[c]	0.04*[c]

[c] Wilcoxon, *P<0.05 (significant)

DISCUSSION

Pain in RAS is caused by inflammation of the tissue. Tissue damage stimulates the release of inflammatory mediators, such as prostaglandin E2 (PGE2), histamine, leukotriene. They affect vasodilator and vascular permeability leading to redness, swelling, and pain caused by the activation of neurons.[14] The purposes of therapy of RAS are to reduce pain and stimulate healing of ulcers. Tropical treatment is mostly used due to fewer side effects.[15]

The available data indicated that gambier extract had good effect for treatment of RAS. Gambier extract decreased pain intensity in RAS. Septiani *et al* reported that the main content of gambier played important role in reducing inflammation and lessen the pain severity.[16] Gambier has some polyphenol constituents in the form of catechins. Catechins have immunomodulatory capabilities, reduce inflammation, and stimulate wound healing.[17] Fetchner and Ahmed stated that catechins interfered interleukin 1 signaling pathway to regulate interleukin-6 and interleukin-8 production, cyclooxygenase-2 and cyclooxygenase-1 enzymes.[18] Riswana *et al* reported that gambier leaf had anti-inflammatory effect because it inhibited XO enzyme activities.[19] Those anti-inflammatory mechanisms reduce pain caused by inflammation. Pambayun *et al* reported that gambier as one component of betel quid formulation had an anti-inflammatory effect on the mucosal wound of rats.[20]

The antibacterial and anti-inflammatory effects of gambier extract stimulate proliferation and remodeling process of wound healing. An opened ulcer on mucosa is a favorable place for bacterial colonization, especially Gram-positive. It influenced the delayed healing process.[21] Bacterial infection interfered regeneration of oral mucosa. Removing oral microbial supported normal wound healing process.[22] Catechins contained in gambier extract have ability in reducing some bacteria in oral ulcers. Catechins alleviate the membrane fluidity and cause loss of membrane structure then lead to bacterial cell death.[23] Previous studies reported that gambier extract has antiseptic effects in mucosal wounds.[10,11] Another study also reported that gambier extract was effective in reducing *Streptococcus mutans* on saliva.[24]

By keeping the wound sterile, gambier stimulates the wound healing process due to acceleration of angiogenic response. Sumosa *et al* found that gambier increased the percentage of wound recovery significantly.[25] Musdja *et al* revealed that gambir catechin crude decreased the number of inflammatory cells, increased neocapillary formation, and accelerated the healing process on the inflammatory phase and proliferation.[26] Handayani *et al* stated that ethanolic extract of *Uncaria gambir* shortened the

duration of wound healing in dose-dependent manner.[27] Lestari *et al* reported that gambier extract influenced gingival wound healing process by reducing PMN leucocytes, increasing fibroblast cells, thickness epithelial layer and collagen fiber.[28]

Recurrent aphthous stomatitis is self-limiting disease. Normally the duration of ulcer healing is 8 to 14 days after injury. The healing process includes inflammatory phase that involves homeostasis and inflammation (4 to 6 days), proliferation phase involves re-epithelialization which begins from the wound edge, angiogenesis, collagen deposition in the granular tissue (4 to 14 days), and maturation phase.[29,30] Topical gambier extract on RAS accelerates the inflammation phase, stimulates re-epithelialization of ulcer, precipitates wound closure and shortens the duration of stomatitis. Catechins in gambir regenerate epithelial cells and stimulate angiogenesis, granulation tissue and epithelial thickness in wound.[28,31,32]

CONCLUSION

This study showed that gambier extract had potential effect on the treatment of RAS. It was also effective in reducing pain severity and accelerating wound closure. Further study was also needed to find the stability of gambier in ointment to obtain the optimum period of storage. Another formulation by giving flavor and aroma could be tried to make the ointment more comfortable for patients.

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