

Effective licorice gargle juice for aphthous ulcer pain relief: A randomized double-blind placebo-controlled trial

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Abstract: The aim of this study was to determine the effects of licorice gargle juice on aphthous ulcers, which is a common and painful disease that causes loss of normal mucous tissues and results in inflammatory ulcers in the oral mucosa. A randomized double-blind placebo-controlled trial involving primary care patients suffering from aphthous ulcer was performed. The intervention group received licorice gargle juice for 1 and 2 days. Of the 54 patients that participated in the study, 30 were included in the intervention group and 24 in the placebo group. A 10-point visual analog scale (VAS) was used to assess the patients' self-assessed pain levels before and after treatment. Statistical analyses were performed by using the nonparametric Mann-Whitney test. The licorice gargle juice group had a significantly reduced pain level rate compared with the placebo group at day 1 (mean VAS, 2.47 [95% CI, 1.95-2.98] vs. 4.75 [3.96-5.54]; $P < 0.001$) and day 2 (mean VAS, 1.07 [95% CI, 0.81-1.32] vs. 4.08 [3.23-4.94]; $P < 0.001$). The current study indicates that licorice gargle juice rapidly reduce pain and healing time and thus can improve the quality of life of a patient with aphthous ulcer.

Keywords: Licorice, glycyrriza, aphthous ulcers, canker sores, randomized controlled trial, mouthwashes.

INTRODUCTION

Aphthous ulcer, also known as canker sore, is a common and painful disease of the oral mucosa; it causes loss of normal mucous tissues and often results in inflammatory ulcers (Sánchez-Bernal *et al.*, 2020). Aphthous ulcer is characterized by open and round-shaped painful wounds. The prevalence rate of oral ulcers in children and elderly varies among different studies according to the investigated populations and up to one-half of people with oral ulcers experience a repeat occurrence within three months (Akintoye and Greenberg, 2014; Scully and Porter, 2008). Tabolli *et al.* (2009) found that oral mucosal disorders are often painful and always interfere with the patients' health-related quality of life and are associated with different psychological problems; thus, quickly relieving pain due to an oral ulcer is necessary.

Aphthous ulcers usually have three recognized distinct clinical forms based on their typical features, namely, minor, major, or herpetic forms (Akintoye and Greenberg, 2014). Minor aphthous ulcers are some of the most common oral mucosa ulceratives, showing clear and round lesions that are usually less than 5 mm in diameter and takes 10-14 days to heal without scarring (Scully and Porter, 2008). Major aphthous ulcer wounds are larger than 1 cm. Curing this ulcer will take 20-30 days or more and often leads to scarring (Scully and Porter, 2008). The third and least common recurrent aphthous ulcer is the widespread herpetic ulcer, which involves 1-100 large irregular pain ulcers, each of which is 2-3 mm in diameter (Porter *et al.*, 1998; Scully and Porter, 1989).

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The exact cause of aphthous ulcers is still unknown. In recent years, the identified factors include certain nutrient deficiencies, such as iron, folic acid and vitamin B12; hypersensitivity reactions to certain foods; various systemic immunogenic disorders; gastrointestinal disorders and infection with the human immunodeficiency virus and the environment (Grattan *et al.*, 1986; Muñoz-Corcuera *et al.*, 2009; Nolan *et al.*, 1991; Olson, 1982; Porter *et al.*, 1989; Porter *et al.*, 1998; Porter *et al.*, 2000).

Licorice (*Glycyrriza glabra*) has been used since ancient times in the East and West. Its root is sweet and often added to mixed botanicals to balance the bitterness of other herbs (Morinaga *et al.*, 2005; Abascal and Yarnell, 2010). Licorice herbal medicines have anti-inflammatory effects (Shibata, 2000; Bell *et al.*, 2021) and licorice can strengthen muscles and bones and promote muscle growth and wound healing (Marshall *et al.*, 1987). *Glycyrrhiza* extract promotes the healing of stomach and mouth ulcers (Baker, 1994). The first scientific article on "Glycyrrhiza juice" for gastric ulcers was published by Revers (1946), who also researched the effects of licorice juice treatment on duodenal ulcer (Revers, 1948). Licorice is an excellent Chinese medicinal drug for peptic ulcer and gastric ulcers and may thus be used to treat aphthous ulcers (Brogden *et al.*, 1974; Revers, 1946; Revers, 1948). In addition, research indicates that Licorice Gargle can reduce Sore Throat (Agarwal *et al.*, 2009; Ruetzler *et al.*, 2013). Messier *et al.* (2012) reviewed that licorice might be an effective therapy for aphthous ulcers and had potential effects against oral diseases.

Our purpose was to make a gargle juice with simple and natural licorice root and determine its effectiveness in

treating aphthous ulcer, reducing pain and promoting healing. Our study was a randomized, double-blind and placebo-controlled trial.

MATERIALS AND METHODS

Participants

The research design was a randomized, double-blind and placebo-controlled trial. The study was conducted between December 2017 and May 2018 in central Taiwan (the Taichung City region) at a dental clinic. At the baseline appointment, candidates received full written and verbal information about the study and the possible side effects of the treatment. This study excluded patients with known systemic diseases (Behçet disease, rheumatoid arthritis, lupus and acquired immunodeficiency syndrome), who had received other treatments, were suffering from aphthous ulcer for over five days, had Leber's optic atrophy, had a known group vitamin B deficiency, suffered from psychosis, or were pregnant or nursing.

The subjects were recruited through posted announcements and word of mouth from four health centers in Taichung city. All the subjects were adult patients who were older than 20 years and had been suffering from aphthous ulcers. They were selected by dental physicians licensed in Taiwan for 11 years. Participants were recruited daily from the clinical dental clinic during the study period. After obtaining the consent of the subjects, the baseline data and the study measurements were recorded.

Preparation of mouthwashes

The intervention group received mouthwash juice with a decoction of licorice mouthwash juice and gargled four times daily. We purchased licorices from a traditional Chinese herbal store shop in Taichung city. The licorices were obtained from China. The plant was identified and approved by an herbalist (Miss. Sedigheh Khademian) in the Herbarium center of the school of pharmacy, SUMS (Voucher no. PM407). Also, standard Sesame oil was purchased from Golkaran Co. The decoction contained 40g licorice root boiled for 30min in 1L of water. After cooling the licorice mouthwash juice, a drop of natural coloring with caramel was added. The licorice mouthwash juice was poured inside a 200cc bottle. The control group received mouthwash with xylitol mouthwash juice. The placebo oral gargle juice contained 2mg of xylitol in a 200cc bottle with a drop of natural coloring with caramel.

Study design and experimental protocol

The study protocol was approved by the Institutional Review Board of Changhua Christian Hospital (IRB#170815). Data were collected and assessed primarily by oral health educators. A research assistant in the clinical dental department recruited participants daily

during the study period. Once consent was obtained and baseline data and study measurements were recorded. The participants were randomized placebo-controlled clinical trial had a two-arm parallel design with allocation by using computer-generated (<https://www.random.org/integers/>) batch numbers into the intervention group and the control group. The participants were randomly divided between the intervention group and the placebo group. The two types of mouthwash juice with identical sweet flavor, size, shape and color were in the mouthwash bottles. The physicians and the participants were blind to the group assignment until the end of the study. Fig. 1 shows the CONSORT diagram of the subject flow through the study. A personal informational questionnaire was given to each subject and an ulcer type diagnosis assessment was performed by the dental physicians. This questionnaire includes questions regarding the site, size, surface status and type of ulcer; ulcer history (number of ulcers experienced in the previous year); previous treatment and medications received from a dental nurse. Each patient received a package that contains one 200cc mouthwash bottle at the start of the study and after 2 days. The patients rinsed with the mouthwash for 10-20 s and four times daily. The research assistant was blind to the group assignments.

Outcome measurements

The subjects were told by oral health educators to mark a vertical line at the point that best represented the present pain level caused by the ulcer. The research assistant recorded their baseline pain score, which was measured with a 10cm point visual analogue scale (VAS) before randomization and after 1 and 2 days of treatment. The VAS is a self-reporting device that is widely used for pain measurement. The VAS in this study was measured by a 10 cm horizontal line. VAS represents the oral ulcer pain intensity, which is continuous from one end to "no pain=0," and the other end is "unbearable pain=10." Patients only saw a horizontal line on one side with a "painless" label on one end and an "unbearable pain" label on the other end. In this study, the participants were asked about their pain levels and the oral health educator marked the vertical line at the point that best represented a subject's current level of pain due to oral ulcer. The research assistant used VAS to record the patients' baseline pain scores before randomization and after each day of treatment.

STATISTICAL ANALYSIS

We used MATLAB to run the statistical analysis. Descriptive data were conducted as medians or means with standard deviations for continuous variables and percentages for categorical data (table 1). The results of the chi-square test and the Fisher's exact test showed that testing a correlation coefficient requires a pair of variables to be either binary or continuous with a normal

distribution. The nonparametric Mann-Whitney test was used to compare the measurements of the VAS scores of days 0, 1 and 2 and compare the pain experience before and after pain scores. Then, 95% confidence intervals (CIs) were calculated for the analysis. A P-value of ≤ 0.05 was considered statistically significant.

RESULTS

Participant baseline characteristics

The physicians selected 79 patients, but only 58 agreed to participate in the study; 15 of the patients who did not participate were worried about the possibility of being assigned to the placebo group and 6 patients stopped participating in the study because their pain and ulcer symptoms were not reduced in the placebo group.

Through randomization, 30 and 24 subjects were assigned to the licorice and placebo groups, respectively. Table 1 shows the socio-demographic characteristics of the licorice and placebo groups. No statistically significant differences were found between the licorice and the placebo groups with respect to sex, age, marital status, education, number of ulcers in the past one year and ulcer cause, size, surface and type. No abnormal laboratory values at the beginning of the study were found in either group.

The patients in both groups (30 females and 24 males; mean \pm SD age 37.72 ± 17.21) recorded a pain degree of 5.52 ± 1.95 , which table 2 showed the baseline pain level. No significant difference was observed between the pain scores of the licorice gargle juice and the control groups before randomization (mean VAS, 5.53 [95% CI, 4.90-6.17] vs. 5.50 [4.54-6.46]; $P = 0.96$) (table 2).

Comparison of pain between the licorice and placebo groups

Overall, the patients in the licorice gargle juice group showed improvement in pain degree from the baseline levels over the course of the study and experienced 25% complete ulcer healing after the second day. The table 2 showed significant VAS reduction of oral ulcers by using licorice gargle juice compared with the control group during day 1 (mean VAS, 2.47 [95% CI, 1.95-2.98] vs. 4.75 [3.96-5.54]; $P < 0.001$) and day 2 after treatment (mean VAS, 1.07 [95% CI, 0.81-1.32] vs. 4.08 [3.23-4.94]; $P < 0.001$).

The results are shown in fig. 2. The x-axis shows the three time points: Baseline, day 1 and day 2. The y-axis shows the levels of pain. Fig. 2 plots the mean values of the placebo and the licorice groups. Both pain levels in the licorice and placebo groups dropped at days 1 and 2, but the pain level of the licorice group shows a sharper decrease than that of the placebo group.

Participants were asked in licorice and placebo group at each follow-up for any observed adverse effects. There was no report on serious adverse effects by researchers on the follow-up visit. Moreover, no abnormal examination was detected by dental physicians on the follow-up visit.

DISCUSSION

To our knowledge, this study is the first to report that licorice gargle juice can reduce pain and promote healing rapidly in a population of patients suffering from aphthous ulcers. Our aim was to investigate whether the use of licorice gargle juice four times a day considerably reduces pain associated with aphthous ulcers and promote healing. The licorice gargle juice adjunctive care in this study consistently provided significant symptomatic pain relief experienced by patients ($P < 0.001$). Licorice gargle juice significantly reduced the peak of pain during healing in the first and second days. Ten subjects from the intervention group described that licorice gargle juice has a natural and sweet taste, good moisturizing capabilities and provided relief from aphthous ulcer.

Tewari and Trembalowicz (1968) first explained that licorice root can be used for the treatment of gastric and duodenal ulcers in 1968. Das *et al.* (1989) utilized elements of licorice root to treat aphthous ulcers in 20 patients by using a deglycyrrhizinated form of licorice as a regular mouthwash; results show that 15 patients reported 50%-75% pain relief in 24 h and had completely healed ulcers by the third day. Unfortunately, Das *et al.* (1989) no measurement was conducted in this study and the mouthwash concentration was not indicated. Moghadamnia *et al.* (2009) directly applied 1% of a licorice bioadhesive patch to aphthous ulcers. The patients treated through this approach showed enhanced pain relief and healing time compared with untreated patients; the diameter of the ulcer inflammation zone treated with licorice patch was significantly reduced on day 5. Martin *et al.* (2008) investigated the efficacy of licorice dissolving patches to improve ulcer pain compared to the use of a placebo group. However, most patients have difficulty in applying bioadhesive patch containing 1% licorice. Compared to previous studies, current study introduced a simple and efficient application to reduce ulcer pain with gargle licorice juice. Additionally, the current study pointed out that the licorice extract isoliquiritigenin mainly exerts an analgesic effect by inhibiting the Na^+ channel on the sensory noxious fibers. This pharmacological mechanism suggests that isoliquiritigenin can be used for pain relief and provides scientific evidence for licorice at the ingredient level (Miyamura *et al.*, 2021).

Our findings are consistent with the reduced pain levels reported in previous studies (Das *et al.*, 1989; Martin *et*

Table 1: Demographic and basic clinical characteristics of population

	Intervention Group (n=30)	Control Group (n=24)	p-value
	n(%)	n(%)	
Gender			
male	14 (46.7%)	10 (41.7%)	0.46*
female	16 (53.3%)	14 (58.3%)	
Age(years)			0.51**
Mean (SD)	36.53 (18.97)	39.50 (14.45)	
Range	20 ~ 80	21 ~ 65	
Marital status			0.23 [§]
Single	18 (60.0%)	10 (41.7%)	
Married	10 (33.0%)	12 (50.0%)	
Widow	2 (6.7%)	0 (0%)	
Education			0.50 [§]
Primary School	2 (6.7%)	2 (8.3%)	
High School	6 (20.0%)	8 (33.4%)	
Academic	22 (73.3%)	14 (58.3%)	
Number of Aphthous ulcer history in 1 year (frequency)			0.31**
Mean [95% CI]	4.60 [2.55~6.65]	4.18 [1.85-6.52]	
Cause Aphthous ulcer			0.10*
unknow	22 (73.3%)	12 (50.0%)	
accident	8 (26.7%)	12 (50.0%)	
Ulcer's surface			0.23*
smooth	26 (86.7%)	18 (75.0%)	
rough	4 (13.3%)	6 (25.0%)	
Type of Aphthous ulcer			0.07 [§]
minor	20 (66.7%)	22 (91.7%)	
major	8 (26.7%)	2 (8.3%)	
minor clusters (herpetiform)	2 (6.7%)	0 (0%)	

*Fisher's exact test. **Analysis of variance. [§]Chi-square test. 95% CI: 95% confidence interval

Table 2: Patient pain levels and ulcer size (mm) before randomization and after treatment.

	Licorice (n=30) Mean (SD)	Placebo (n=24) Mean (SD)	Mean difference [95% CI]	P-value
Level of pain Baseline	5.53 (1.70)	5.50 (2.27)	0.03 [-1.13~2.29]	0.96
Day 1	2.47 (1.38)	4.75 (1.87)	2.28 [1.49~3.07]	< 0.001
Day 2	1.07 (0.69)	4.08 (2.02)	3.01 [2.16~3.86]	< 0.001
Ulcer size(mm) Baseline	5.00 (3.06)	4.17 (1.95)	0.83 [-0.51~2.17]	0.23
Day 1	2.73 (2.86)	4.08 (1.79)	1.35 [2.60~0.10]	0.03
Day 2	1.33 (1.92)	3.83 (1.43)	2.50 [3.39~1.01]	< 0.001

Level of pain indicated on a visual analog scale. Pain intensity ranged from 0 to 10. No differences were observed at baseline between groups. 95% CI: 95% confidence interval. SD: Standard deviation. [* denotes p < 0.05].

al., 2008). A rapid, beneficial and effective treatment for pain and wounds of patients suffering from any types of aphthous ulcer using licorice gargle juice was evident during the early days of the ulcer. Based on previous studies, this effect could be exerted by the anti-inflammatory effect of licorice (Kobayashi *et al.*, 1993; Messier *et al.*, 2012; Roehr, 1998; Shibata, 2000).

The licorice compound called glycyrrhizic acid, which is a sweet-tasting glycoside that is 50 times sweeter than sugar, made people easily accept licorice gargle juice (Hanrahan, 2001). Therefore, the results suggest that clinical physicians and nurses can use licorice gargle juice

as an immediate relief to help patients with aphthous ulcers eat, swallow and talk.

Although the number of patients in this study is small, the participants of the licorice and placebo groups were randomly selected. We followed each step strictly. Both groups participated voluntarily and were allowed to stop any time. Some participants from the placebo group dropped out of the study because they did not feel improvement in their conditions. However, no subject from the licorice group dropped out because the participants immediately felt relief. Our findings may contribute to the effective management of pain due to aphthous ulcers.

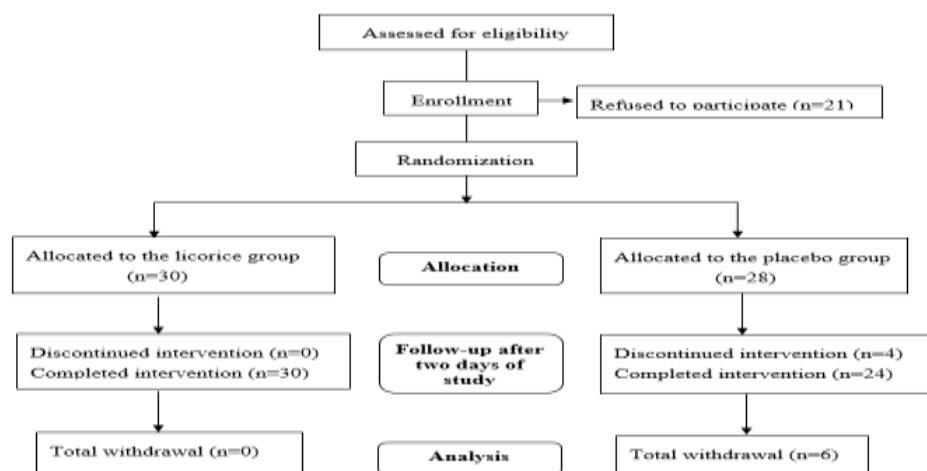


Fig. 1: CONSORT diagram of the study flow.

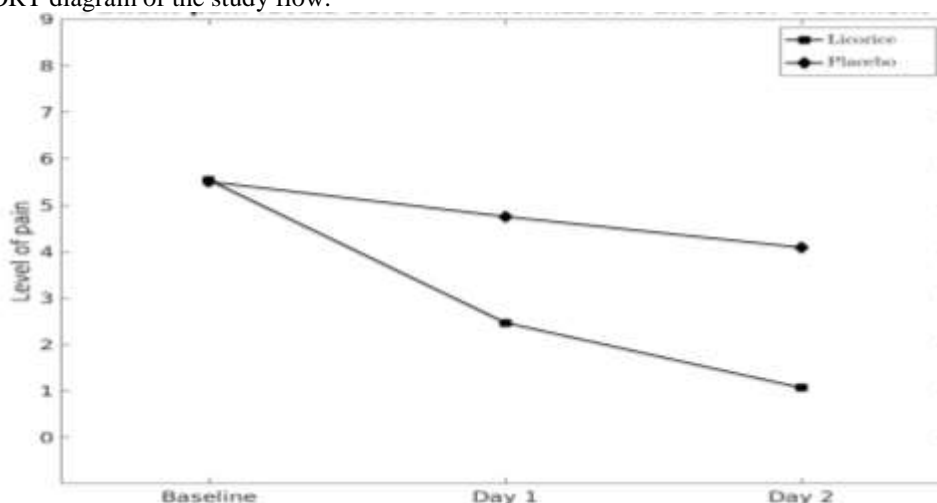


Fig. 2: Patient pain levels before randomization and after treatment. Level of pain is indicated on a visual analog scale. Pain intensity ranged from 0 to 10. The X-axis shows the three time points: baseline, day 1 and day 2. The Y-axis displays the levels of pain. No differences were observed at baseline between the two groups, but the licorice group shows larger drop in levels of pain compared to the placebo group at Day 1 and Day 2.

CONCLUSIONS

This study demonstrated that licorice gargle juice can provide fast-acting pain relief and is capable of healing aphthous ulcer wounds upon topical application. Moreover, licorice root juice is useful as a pain reliever for aphthous ulcers and is inexpensive, natural, accessible and effective. Although the sample in the study was small, the recommendations can serve as general principles for researchers who plan to study oral wounds in the same context.

ACKNOWLEDGMENTS

The authors thank Siao-Fan Zhou, DMD for her attending and many contributions. The authors gratefully acknowledge the financial support of Central Taiwan University of Science and Technology through its grant CTU106-P-01.

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