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Analyzing Glycyrrhiza Glabra (Licorice) Extract Efficacy in Recurrent Aphthous Stomatitis Recovery

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ABSTRACT

Oral aphthous is of prevalent oral ulcers occurring as the recurrent ones. Various factors influence oral aphthous etiology such as mental disorders, immunity, blood disorders and stress. To treat these ulcers, different methods including steroids, antibiotics, anti-inflammatory and analgesics are recommended. In the present study, the effect of a sort of buccoadhesive licorice tablet has been analyzed for aphthous stomatitis recovery. The current research is of clinical trials. The study community has been selected out of those referring to Oral and Maxillofacial Diseases Department of The Faculty of Dentistry affiliated with the University of Medical Sciences of Mazandaran in 2016.In the first stage, according to the inclusion criteria, 42 subjects have been selected by convenient sampling and in the continuation, the samples have been randomly and alternately assigned to two groups. Twenty-one (21) patients have been placed in the mucoadhesive licorice tablets intervention group and twenty-one (21) ones in non-medicine base buccoadhesive control group. Finally, the results will enter SPSS20 for analysis. Based on Chi-square test, the time of reaching analgesia and full recovery from aphthous ulcer in the intervention group is meaningfully lower than that of the control group (P<0.001). Also all the intervention group subjects have fully recovered on day 7 (P<0.001). Regarding the anti-inflammatory effects of licorice and the current study derived results, mucoadhesive licorice extract tablets has the potential to alleviate pain, reduce ulcer's diameter and its surrounding inflammation and to accelerate the aphthous stomatitis recovery time.

Keywords: Recurrent Aphthous Stomatitis, Licorice Plant, Mucous Membrane

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is of the most common oral mucous diseases worldwide.

The ulcer prevalence varies from % 5 to 25 and occurs most in the age range 10-40 years old [1, 2]. The etiology of aphthous is unknown, yet there are factors intervolved in its outbreak including genetic factors, food allergies, surface trauma, endocrine glands' changes (menstrual cycle), stress and anxiety, smoking quit, some chemicals and microbial agents [3]. Various medical methods are employed for oral aphthous recovery such as 1) Local anesthetics like Lidocaine gel or spray relieving symptoms and reducing the treatment duration, 2) Anti-inflammatory and antiseptic drugs like mouthwashes containing chamomile extract or chlorhexidine,3) Topical corticosteroids like triamcinolone,4) Topical treatment with tetracycline, relieving pain and shortening treatment duration .Other therapeutic methods have been assessed ,too, including toothpaste containing certain enzymatic compounds, decreasing the aphthous attacks number and relieving pain [4]. Considering the chemical drugs induced side effects, the majority of the patients are willing to take herbal medicine. Some studies supported the effectiveness of Chamomile and Aloe Vera in recurrent aphthous treatment. Flavonoid compounds existing in Chamomile and Aloe Vera with their anti-inflammatory effects have been reported to be effective in alleviating ulcer's severity. In another research, the paste containing Myrtus communis has been effective in relieving pain, reducing ulcer's size and erythema in the patients with aphthous, which has contributed to the patient's life quality promotion [5].

Glycyrrhiza glabra, often known as Licorice is one of the most important medicinal plants in traditional medicine, growing in diverse regions around the world and it's approximately 400 years used for the purpose behind the medicinal treatment [6]. This plant is found in areas such as the Mediterranean regions, Central to South Russia, parts of Asia and Iran and recently it's extensively found in Europe [7]. The root of this plant contains Glycyrrihizin (%3.36-13.6), flavonoids (%1.5), coumarin, alkaloids and polysaccharides, sitosterol and amino acids [8]. Glycyrrihizin is a compound with sodium / potassium salts and Glycyrrihizic Acid, known as the main anti-inflammatory component in this plant [7]. In addition, this plant contains useful pharmacological properties such as anti-inflammatory, anti-viral, anti-bacterial, anti-allergic effects, anticancer activity, and immune system regulating and protective effects on heart and liver tissue [6]. In Japan, this plant is frequently used for the treatment of chronic hepatitis. In Europe, it is also widely used for stomach ulcer and results in preventing the growth of harmful intestinal bacteria such as Helicobacter pylori [9].

In plenty of studies, this plant induced medicinal effects on digestive tract and oral ulcers have been pointed out [6]. In a study on the Glycyrrhiza glabra induced anti-inflammatory effects, it has been mentioned that through inhibiting the enzyme β-hydroxysteroid dehydrogenase, this plant inhibits converting hydrocortisone into cortisone as an inactive anti-inflammatory steroid, proving its therapeutic effects on the target tissue [10].

Thus, given the Licorice induced anti-inflammatory and pharmacologic effects on the treatment of ulcer and lack of study on oral aphthous, we've decided to analyze and evaluate this plant exerted effects on aphthous stomatitis, as a lesion and inflammatory process in the patients referring to Faculty of Dentistry in Sari.

MATERIALS AND METHODS

The current study is a double blind clinical trial. The study community has been selected out of the patients referring to Oral and Maxillofacial Diseases Department of the Faculty of Dentistry affiliated with the University of Medical Sciences Of Mazandaran in 2016.

The sample size has been determined based on the study by Babaee *et al*., with mean and standard deviation of the ulcer's diameter as 1.29±0.66 on day 7 in the intervention group and as 0.60±0.69 in the control group with confidence level %95, test power %90 and for two-slope or double-sided test, it has been set as 42 subjects (21 in the intervention group and 21 in the control group).In the first stage, based on the inclusion criteria, 42 subjects have been chosen by convenient sampling method and in the continuation, the samples have been randomly divided into two groups [11].

The patients suffering from recurrent aphthous stomatitis have been at least 18 years old and all with a record of minor aphthous ulcers in areas such as lips and buccal mucous and according to

the inclusion criteria, they have been divided into the selection plan and alternately in two groups: 21subjects in the intervention group and 21 ones in the comparison group.

This research has been verified by the Research Department of Medical Ethics Committee and all the patients entered the study after being provided with the adequate explanations about the disease treatment, probable complications, treatment process and signing the consent form.
The study inclusion criteria cover the individuals with sufficient knowledge and education to understand the treatment related explanations and legally competent to sign the consent form.
The study exclusion criteria cover those with major recurrent stomatitis and herpet form, the patients with aphthous ulcers other than on the lip and buccal mucous, those with systematic disease, the ones taking immunosuppressive drugs during the previous month, dentures wearers, antibiotic recipients, pregnant patients, the people not able to use mucoadhesive tablet, the ones suffering from the syndromes aphthous ulcers is one of whose manifestations (Behcet's syndrome), smokers and the individuals not able to pursue the study due to personal or social reasons [11].

The patients were required to refer to the clinic within the early 24h after the aphthous emerging and this time has been considered as the baseline.
In the initial meeting, the patients were asked to get through the consent form and sign it in addition to filling in the questionnaire containing the patient's history.

The study patients have been randomly divided into two groups .In the 1st group, the patients were given mucoadhesive tablets to use morning, noon and night .The patients were instructed on how to use the mucoadhesive tablets, so that they had to abstain eating and drinking for 30 m .In the control group, the same procedure was done with a placebo .To clinically evaluate the pain and recovery level, the subjects' ulcers have been examined on D0 (before entering the study),D3,D5 and D7 using the metal caliber to determine the diameter of the ulcers and the surrounding inflammatory zone [12].

The patients were also instructed to set the pain severity based on VAS (Visual Analogue Scale) criterion .This scale is a 10cm line where 0 stands for lack of pain, and 10 means maximum pain. The patient sets the point signaling their pain in this scale and uses Number Scale (e.g., from 1 to 10) for estimating pain severity. The subjects have to record VAS in the questionnaire 3 times daily after each meal and the ulcer's diameter less than 1mm is taken as recovered [13].

The data have been entered into SPSS20 for analysis. After refining, the data have been analyzed with Kolmogorov test. The demographics description has been determined with mean, standard deviation and frequency %. In order to compare the pre-and post-intervention means in each group, paired t-test or its non-parametric equivalent, i.e., Kruskal Wallis and independent t-test or Mann-Whitney has been employed for the mean comparison between the two groups. Moreover, in order to compare the treatment process outcome (0, 1, 3, 5 and 7) in the two groups, Repeated Measure or its non-parametric equivalent, i.e., Friedman has been used. The significance level less than 0.05 is set as the criterion of judgment.

Preparing Licorice Extract and mucoadhesive tablets

In order to prepare the extract, licorice plant root was prepared from the hucksters and the following steps have been done in order:

Plant Sample Preparation

Extraction: to prepare the extract, licorice root is prepared and after pulverizing, it is extracted using maceration technique with hydroalcoholic carrier. The prepared extract is condensed by vacuum condenser and then dried by Liofilizator device.

Mucoadhesive tablet Formulation Preparation Method

In order to prepare the bio licorice extract mucoadhesive tablet product, various polymers are applied. For this, for each tablet, 10mg extract is mixed with biopatch polymers (Carbopol, Polycarbophil and HPMC) and the other required additives are added. The bioadhesive tablets are prepared from licorice extract. The mucoadhesive tablet disintegration rate and strength is determined externally.

The study formulations' mucoadhesive tablet strength has been set by sodium alginate gel. For this purpose, using a spool and string attached to

the tablets, after the tablets attaching the gel surface, by pouring water in the string end vessel, the required force for separating the tablets from the gel surface is measured. To compute after measuring the weight force applied to pull the tablets, the question weight is multiplied by acceleration of gravity and regarding the tablets surface area, the adhesion force is determined per unit area in N / m2.

RESULTS

Out of 47 patients referring to Dentistry Clinic of the University of Medical Sciences of Mazandaran, 2 lacked the required qualification to enter the study and 3 withdrew from continuing and cooperation .And at last, 42 (18 women and 44 men) went on the treatment course and managed the study successfully .

Since based on the Kolmogorov-Smirnov test, the variables lacked normal distribution, on-parametric tests have been applied to compare the question variables' significance level in the two groups.

Eleven (11) women (%52.4) and 10 men (%47.6) have been in the control group and the control or treatment group have been made of 13 women (%61.9) and 8 men (%38.1).And overall, %42.9 of the study participants have been men and %57.1 women, revealing no meaningful statistical difference (P=0.533).

Besides, the mean age of the control group has been 38.95±14.76 yrs. and of the intervention group as 35.47±14.80 yrs., showing no significant statistical difference (P=0.451).

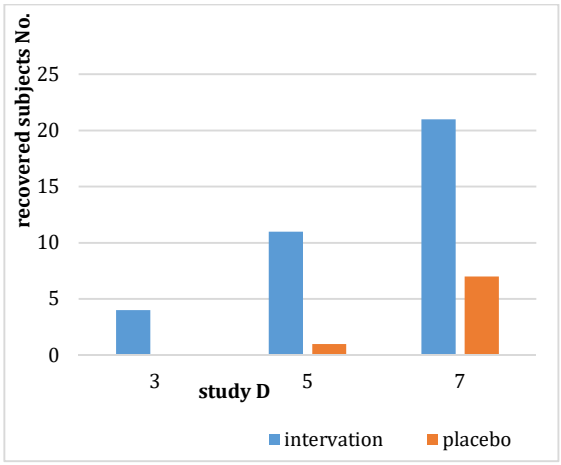
The exact Fisher test derived results indicated that the recovery rate didn't exhibit any meaningful statistical difference (P=0.107) on day 3 between the control and intervention group so that %19 of the study group subjects have recovered.

Chi-square test has shown significant recovery rate on day 5 between the control and intervention groups (P=0.001). %28.6 of those in the two groups have recovered in that day out of which %26.2 have belonged to the intervention group and %2.4 to the control group.

Pain relief time (VAS≤1) and ulcer recovery time (diameter less than 1mm) on study day 7 based on chi-square test in the intervention group has been meaningfully lower than that of the control group (P=0.001).So that for all participants in the intervention or treatment group, full recovery has occurred on day 7.In addition, %33.3 of the control group participants have recovered at the end of day 7 (Table 1, and Graph 1).

Table 1: Comparing recovery rate in the two groups during the study days

Study day	Group		P-Value
	Control	Treatment	
D3	0	4	0.107
D5	1	11	0.001 *
D7	7	21	0.001*

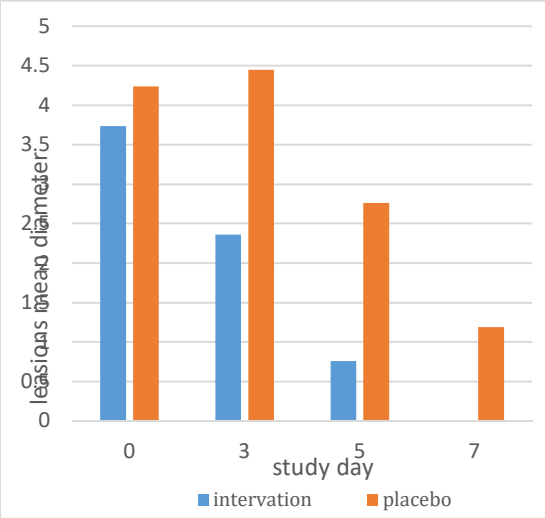


Graph1: comparing recovery rate in the two groups during the study days

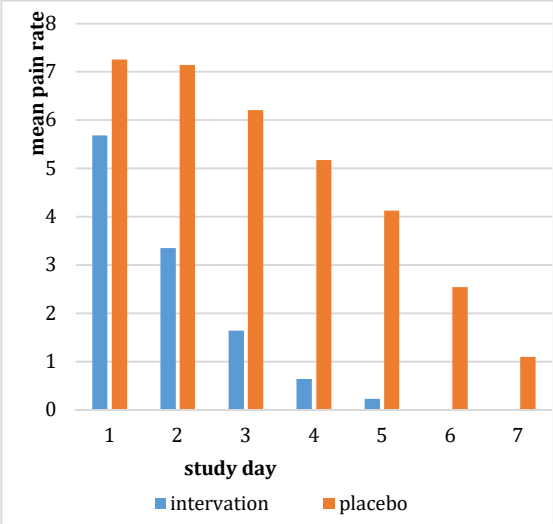
The mean diameter of the ulcer's lesions and inflammatory zone has presented no significant difference on day 0 between the two study groups, but on day 3, day 5 and day 7 , in the intervention group it has been meaningfully lower than that of the control group (P=0.001)(Table 2 and Graph 2).

Table 2: comparing mean diameter of the ulcers in the two groups during the study days

Study Day and Group	No.	Mean	S. D	P-Value
D 0				
Control	21	4.2381	1.41084	0.264
Treatment	21	3.7381	1.44585	
D3				
Control	21	4.4524	1.34075	0.001 *
Treatment	21	2.3571	1.51775	
D 5				
Control	21	2.7619	1.43718	0.001 *
Treatment	21	0.7619	0.94365	
D7				
Control	21	1.1905	1.13442	0.001 *
Treatment	21	0.0000	0.00000	



Graph 2: comparing ulcers' diameter in repeated measurements during the study days



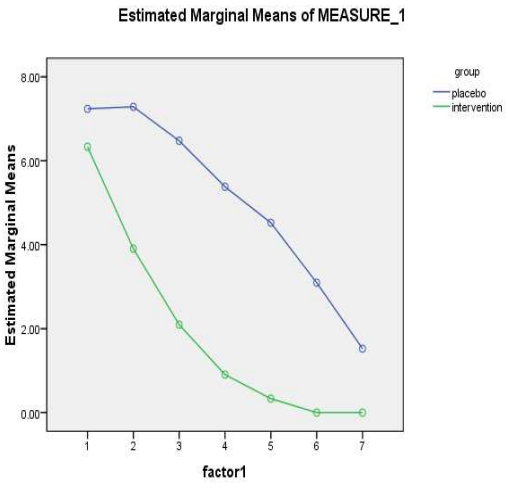
Graph 3: comparing mean pain rate in the two groups during the study days

Mann-Whitney test has exhibited significant statistical results comparing the mean score of VAS during 7 study days so that the mean pain difference in the two groups has been statistically significant on day 1(P=0.009) ,day 2(P=0.001),day 3(P=0.001),day 4(P=0.001) ,day 5(P<0.001),day 6(P<0.001) and day 7(P<0.001) (Table 3 and Graph 3).

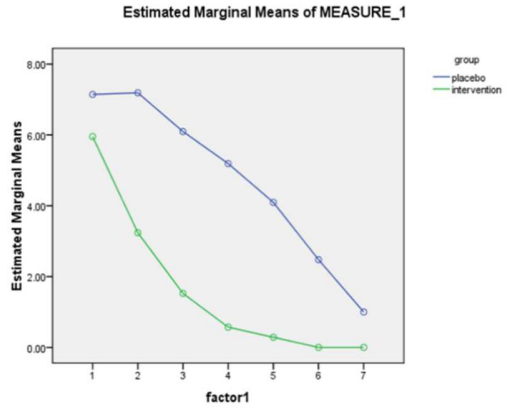
Table 3: comparing mean pain in the two groups during the study days

Study day & group	No.	Mean	S. D	P-Value
1st day				
Control	21	7.2540	1.19678	0.009 *
Intervention	21	5.6825	2.00410	
2nd day				
Control	21	7.1429	1.56550	0.000 *
Intervention	21	3.3492	2.00410	
3rd day				
Control	21	6.2063	1.56516	0.000 *
Intervention	21	1.6349	1.73175	
4th day				
Control	21	5.1746	1.87859	0.000 *
Intervention	21	0.6349	1.20603	
5th day				
Control	21	4.1270	1.74953	0.000 *
Intervention	21	0.2222	0.66944	
6th day				
Control	21	2.5397	1.49991	0.000 *
Intervention	21	0.0000	0.00000	
7th day				
Control	21	1.0952	1.07571	0.000 *
Intervention	21	0.0000	0.00000	

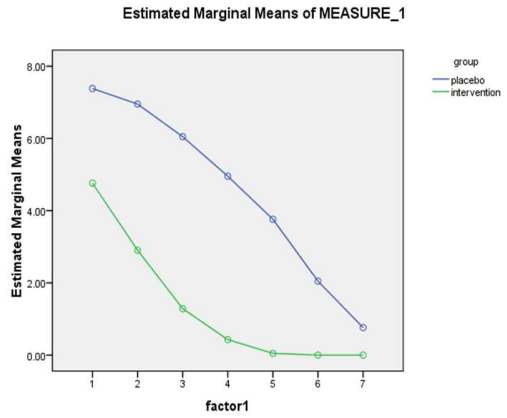
Based on Friedman test, VAS score has been separately analyzed in the repeated measurements 3 times in the two study groups. The mean VAS results for morning, noon and night have been depicted as a graph. Only on day 1, VAS in the morning and noon hasn't revealed any meaningful statistical difference in the two control and intervention groups. While during 6 other days, VAS has shown significant statistical difference at these times in the two groups (P<0.001) (Graph 4, 5 and 6).



Graph4: comparing mean morning times VAS score between the two groups



Graph 5: comparing mean noon times VAS score between the two groups



Graph 6: comparing mean night times VAS score between the two groups.

DISCUSSION

Recurrent aphthous stomatitis is a prevalent oral mucous disorder emerging with painful and recurring painful ulcer on non-keratinized oral mucus [14]. Considering the unknown and unpredictable course of the disease, there is no certain treatment for aphthous [15]. The first goal behind aphthous treatment is to relieve pain, to reduce ulcer's period and restore normal oral function and the second goal is to reduce the disease frequency and relapse severity and maintain its recovery [16].

Generally speaking, the applied treatments for aphthous recovery include topical anesthetics, anti-inflammatory and antiseptic drugs, topical corticosteroids and topical treatment with antibiotics (Tetracycline) [4].

Various factors such as herbal medicines have been discovered that are effective by being prescribed systemically or topically .Yet these medicines don't work out in all cases and no accurate cause has been found for aphthous so far. This study analyzes mucoadhesive licorice extract tablets as a medication system on pain rate and ulcer's diameter and recovery duration on day 3, day 5 and day 7 and comparing it with placebo mucoadhesive tablets. This plant includes some useful pharmacological properties such as anti-inflammatory, antiviral, anti-bacterial, anti-allergic, anti-cancer activity, immune regulator and protective effects on heart and liver tissue and also in multiple studies, the therapeutic effects of this plant have been mentioned on digestive tract and oral ulcers [6]. This plant's root contains Glycyrrihizin, flavonoids, coumarin, alkaloids and polysaccharides, cytosterols and amino acids, in which Glycyrrihizin is known as the main anti-inflammatory component in this plant [7, 8].

In the current research, the remarkable reduction of the ulcer's diameter and its surrounding inflammatory zone on day 3, day 5 and day 7 has been observed in the intervention group compared with the control group that can be attributed to its anti-inflammatory and protective traits. Moreover, the intervention group pain level has dropped meaningfully compared to that of the control group and their pain has got relieved. In the research on GLycyrrhiza glabra anti-inflammatory effects, it has been noted that via inhibiting β- hydroxysteroid dehydrogenase enzyme, this plant blocks the conversion of hydrocortisone to cortisone as an inactive anti-inflammatory steroid, revealing its therapeutic effects in the target tissue [10].

In an identical study done by Marin *et al.,* it has been suggested that the ulcer size has dramatically decreased on D8 using mucoadhesive licorice extract tablets, consistent with our study derived result [17].

Another research by Motallebnejad *et al*. on mucoadhesive containing tragacanth compared Triamcinolone acetonide mucoadhesive and stated that the mucoadhesive reduces the

aphthous ulcers' pain severity and Triamcinolone exerts no impact on the treatment duration [18].
Moghamnia *et al*. also reported that mucoadhesive with or without licorice can significantly mitigate pain level [19]. They've used mucoadhesive licorice extract %1 for RAS treatment and asserted that this treatment alleviates pain and ulcer's size, but this alleviation isn't significant compared to medicine-free mucoadhesive and ultimately, they've concluded that mucoadhesive based treatment is effective for pain control and licorice has no impact .While this conclusion is inconsistent with the present study derived results since compared with the control group using placebo mucoadhesive, in our study the intervention group patients have revealed meaningful difference in pain and ulcer's diameter and this can be due to the applied licorice dose difference in producing mucoadhesive tablets. Because in our research mucoadhesive tablets containing %17.25 licorice dose have been used with no side effects .The previous studies derived results indicate that the products covering mucous patch alleviate pain and shorten treatment course [20-22]. In the studies using Cyanoacrylate based bioadhesive, meaningful drop in pain severity, recovery duration and ulcer's size have been spotted, but the problem of Cyanoacrylate and Hydroxypropyl based bioadhesive production is related to its being costly. Consequently, we've applied another product with lower expense for producing mucoadhesive.

Some studies have supported the efficacy of Chamomile and Aloe Vera plants in treating recurrent aphthous [5]. This study reported that with their anti-inflammatory effects, flavonoid compounds found in Chamomile and Aloe Vera are effective in alleviating ulcer's severity. In addition, Licorice used as medicine in our study contains flavonoid and can have anti-inflammatory property on aphthous ulcer.

Xiao Weng- Jiang stated that allicin as a mucoadhesive tablets cannot reduce aphthous ulcer's size, while it has the potential to alleviate its pain during 6 days. Allicin is an active element derived from garlic, with anti-inflammatory and antimicrobial activity. Allicin inhibits inflammatory products [23]. As stated, licorice has the same effect on reducing inflammatory outcomes.

Sinem Yapark performed another method for recurrent oral aphthous with bioadhesive gel containing solid lipid nanoparticles of Cyclosporine an in vitro/in vivo, in which the exposure time with mucous tissue is highly critical for the medicine to reach mucus [24]. In our research, the mucoadhesive is put on the aphthous ulcer and through its appropriate adhesion property with mucus, licorice is directly exposed to the ulcer to exert its healing effects.

According to the result of present study derived results, licorice extract has the potential to alleviate pain, reduce ulcer's size and its surrounding inflammation and boost aphthous stomatitis recover time.

CONCLUSION

1-Mucoadhesive Licorice extracted tablets meaningfully alleviates recurrent aphthous stomatitis pain level.
2-Mucoadhesive Licorice extracted tablets reduces the aphthous ulcer necrotic part's diameter.
3- Mucoadhesive Licorice extract tablet reduces the aphthous ulcer's inflammation zone diameter.

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