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Eman Shawki

ORIGINAL ARTICLE

Anti-inflammatory Effect of Angelica Shikokiana Makino Leaves Extract Gel on Lichen Planus Induced Oral Mucositis (Clinical Study)

Eman Shawki

Department of Oral Medicine and Periodontology, Faculty of Dentistry, Mansoura University, Mansoura, Egypt

Abstract

Objective: **To develop eco-friendly nanoemulsions of Angelica shikokiana natural extract gel and evaluate its anti-inflammatory activity by assessing the reduction of the present oral mucositis induced by oral lichen planus (OLP).**

Patients and methods: **In all 34 patients with OLP participated in this randomized controlled trial, classified into two main groups. The first group (study group) was given the prepared gel of A. shikokiana Makino (AS) leaves extract in orabase. The second group (control group) was given 0.1 % triamcinolone acetonide (TA), known as kenacort in orabase. Clinical improvement was evaluated using the Thongprasom scale, and pain reduction was recorded using a numeric rating scale. Initial, midway, and final assessments were performed on the patients. Also, the serum level of interleukin six was evaluated at the baseline and the end of the study.**

Results: **Statistical analysis showed that both groups' pain scores, overall lesion sizes, and Thongprasom scores improved with time. There was a statistically significant difference between week 2 and week 4 reports of improvement in the TA group and AS group (*P* value was ≤ 0.05) indicating that the trend towards better health persisted through week 4. TA's analgesic impact was superior to AS's during the second week, but by the fourth week, AS had caught up to TA. At the end of the research period, both treatments significantly reduced lesion size (*P* value ≤ 0.005) in both groups There was a practical improvement in the oral mucositis associated with OLP in all patients after treatment with our gel. There was no significant difference between the serum level of interleukin six at the baseline and the end of the study (*P* value 0.71825).**

Conclusion: **AS can be used as a treatment for OLP. It can be utilized as a backup plan in OLP when corticosteroids are not working or when individuals decline therapy for fear of adverse effects.**

Keywords: Lichen planus, Angelica shikokiana makino, Interleukin 6, Triamcinolone acetonide

Introduction

Oral lichen planus (OLP) is a chronic illness that is produced by T cell-mediated inflammation. This disorder affects the skin and the mucosal tissues, incorporating the oral mucosa.[1] OLP is defined as alternating times of improvement and worsening of symptoms. There are two times as many cases of OLP diagnosed in females as in males. In addition, malignant transformation rates of OLP are between 0.4 and 5 %.[2] There are six possible types of OLP: reticulated, popular, plaque-like, erythematous (atrophic), erosive-ulcerative, and bullous-erosive. Reticulated OLP is the most common type. The most prevalent type of signs are reticulated. These forms may manifest themselves alone or in a diverse range of varied configurations.[3] White keratotic lesions of the reticular, popular, and plaque-like types might not produce any discomfort. On the other hand, pain might be experienced in white keratotic lesions of the atrophic, erosive, and bullous types, respectively.[4,5]

Patients often report a burning discomfort that interferes with their ability to eat, speak, and maintain good oral hygiene. Because of the lesion's possible malignancy, the patient may also be very worried about cancerphobia. Furthermore, OLP might worsen patients' quality of life by increasing

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E-mail address: emanmira3@gmail.com.

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their stress, anxiety, and sadness. Long-term patient symptom catastrophizing correlates with worsening health outcomes.[6]

Because of their anti-inflammatory and immunomodulatory effects, corticosteroids are the drugs of choice for treating OLP. They can be used topically, taken orally, or injected directly into the injury site. The standard treatment for mild to moderately symptomatic lesions is topical corticosteroids. A decrease in pain and inflammation is their primary effect.[7]

Several potential adverse effects of topical corticosteroids have been linked to long-term use. Adrenal insufficiency, thin mucous membranes, and secondary candidiasis are some of them.[8] Therefore, herbal therapy is increasingly being used to treat OLP.[9]

Commonly known as 'Yamaninjin,' the unique species and perennial herb *Angelica shikokiana* (AS) (Japanese: Inutouki) is produced in Japan's Oita Prefecture as a pharmaceutical alternative to ginseng roots.[10] To treat cardiovascular and digestive disorders, liver dysfunctions, and hyperlipidemia,[11] and to prevent anemia, high blood pressure, diabetes, neuralgia, dermatitis, and the signs of age,[12] the stems, and roots are used to make a healthy tea preparation. Whole plant extract has been shown to have anticancer effects[13] and to stimulate hair growth.[14] The prepared ethanol and water extracts of AS's roots, stems, leaves, and seeds and tested for a variety of biological activities like melanin synthesis inhibition, anti-inflammatory, anti-lipase, and anti-acetylcholine esterase, antibacterial, and antioxidant because a search of the cited literature turned up no evidence of a prior work comparing the biological activities of roots and stems.[15]

In Japan, AS has been used as a health food for its anticancer, anti-inflammatory, antibacterial, antiallergic, and blood vessel dilation effects. It can also be used to prevent and treat hepatitis, diabetes, hyperlipidemia, and arteriosclerosis.[16] This research aimed to determine if the gel used by AS topically helped treat OLP in healthy participants.

Patients and methods

Informed consent

This study was authorized by the Ethical Committee of the Faculty of Dentistry at Mansoura University (approval number M02060230M). Patients were given information about the research and its aims. All participants read, understood, and signed a written informed consent form.

Participants

From April 2023 to the end of June 2023, patients with OLP from Mansoura University's Faculty of Dentistry's Oral Medicine clinic gathered for the current study.

Patients who satisfied the following criteria were taken into consideration for inclusion in the study: Patients were considered eligible for participation in the study if they fulfilled all three of the following criteria:

(1) They had reached the age of 18 or older.
(2) Exhibited symptoms consistent with OLP according to the clinical and histological criteria established by the WHO in 1978.[17]
(3) They were not currently taking corticosteroids or had not done so within the previous 6 months.
(4) They were willing to participate in the research and had no systemic problems that prevented them from doing so. Patients with lesions other than OLP or lichenoid reaction and smokers and pregnant women were not allowed to participate in the trial. Smokers were also barred from participating in the trial.

Interventions

The sample size was determined using G*Power version 3.1.9.2 with an alpha level of significance of 0.05 and 80 % power, by the effect size published by Thomas et al.[18] A total of 34 patients were included in the study after the initial sample size of 14 in each group was expanded to 17 to account for attrition.

Triamcinolone acetonide (TA) or AS cream was applied topically to the individuals. The website www.randomizer.org was used to generate a random number. The treatment allocation was concealed in numbered, opaque, sealed envelopes.

Group A (the intervention group) comprised 17 individuals who were provided with a gel containing 2 % AS.

A. shikokiana gel preparation

The gel was prepared at the Department of Pharmacognosy Faculty of Pharmacy, Mansoura University. A 20 g portions of the roots, stems, leaves, and seeds of AS plants were extracted separately with ethanol (150 ml × 3) at room temperature (25 °C) to prepare root ethanol (RE), stem ethanol (STE), leave ethanol (LE). Another 20 g of each part was extracted with water (100 ml × 3) to prepare root water (RW), stem water (STW), and

leave water (LW). Ethanolic extracts were concentrated on a rotary evaporator, and water extracts were dried using a lyophilizer. The gel was prepared from the obtained extracts.

Group B (the control group) was prescribed 0.1 % TA (Kenalog orabase 10 g oral gel); each gram of Kenalog in Orabase provides 1 mg (0.1 %) triamcinolone acetonide in emollient dental paste containing gelatin, pectin, and carboxymethylcellulose sodium in Plastibase (Plasticized Hydrocarbon Gel), a polyethylene and mineral oil gel base. And they were instructed to utilize the medication as directed.

After breakfast and lunch and again before bed, patients were instructed to apply the medication. They were also instructed to wait 30 min following therapy application before consuming anything. Although this study did not involve blinding of patients, the outcome assessor was not informed of the patient's treatment status.

Pain measured on a numeric rating scale[18,19] was the primary outcome. The whole width of the affected area in centimeter^2 calculated with a calibrated probe was also the primary outcome and classified according to Thongprasom et al.[20] Thongprasom scale was used to score OLP. Score 1 referred to mild white striae only, and score 2 referred to white striae with an atrophic area less than 1 cm^2. Score 3 referred to white striae of more than 1 cm^2. Score 4 referred to white striae with an erosive area of less than 1 cm^2, and score 5 referred to white striae with an erosive area of more than 1 cm^2. The treatment-related adverse events serve as secondary outcomes. The results of the study were measured at the start of the trial (T0), after 2 weeks, and after 4 weeks.

Interleukin six serum level assessment

Serum samples from each patient will be withdrawn at the first visit and the final visit to determine the level of interleukin six to be correlated with the clinical grade of oral mucositis.

SPSS (version 20) was used for the statistical analysis. Mean and standard deviation (SD) were used to characterize quantitative data, whereas frequencies and percentages were used to describe qualitative categorical variables. All quantitative variables were tested for normality using the Shapiro–Wilk normality test so that appropriate parametric and nonparametric tests could be selected.

Since the normal distribution is assumed for pain analysis, the paired sample t-test was used to compare values within each group, while the independent sample t-test was utilized to evaluate differences across the groups. Nonparametric tests were used since the lesion size variables did not follow a normal distribution. Within-group comparisons of lesion size were performed using the Wilcoxon Signed Ranks test, whereas inter-group comparisons were performed using the Mann–Whitney U test. The χ^2 test was used for all contingency tables involving categorical variables. The relationship between the quantitative variables was calculated using the Pearson correlation coefficient. P 0.05 was used as the threshold for statistical significance. All statistical tests are considered to be two-tailed throughout the analysis.

Results

The progression of one of the patients through the study is shown in Fig. 1. As we can see in Fig. 1, there was a noticeable reduction in the reddish inflamed area and the size of the lesion after 4-week treatment.

Table 1 displays the patients' demographic information. While Table 2 records the mean values of numerical rating scale (NRS) and lesion size in the

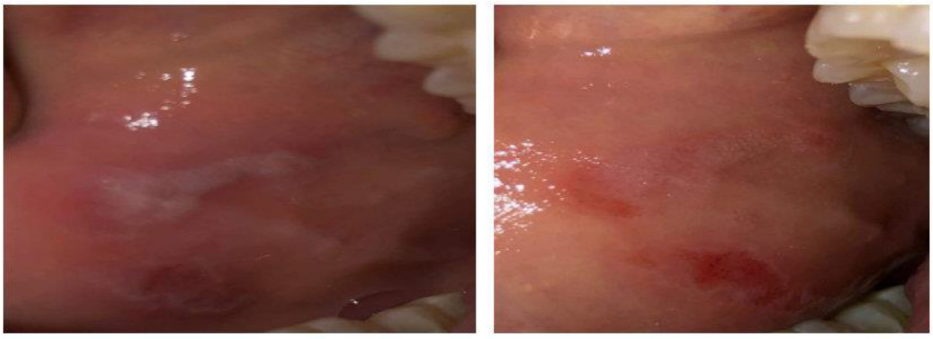

Fig. 1. Case of erosive lichen planus, before and after Angelica Shikokiana topical treatment application.

Table 1. The clinical features of the participants that were recruited.

	Angelica shikokiana ($n = 17$)	Triamcinolone acetonide ($n = 17$)
Age (Mean ± Standard Deviation)	55.13 ± 7.65	55.41 ± 7.75
Sex (female/male)	12/5	10/7
Different varieties of oral lichen planus		
Erosive OLP	53 %	47 %
Atrophic OLP	48 %	52 %
Site Distribution		
Skin lesion	0	0
Cheek mucosa	82.3 %	94.1 %
Labial mucosa	17.6 %	0
Tongue	35.3 %	29.4 %
Palate	11.8 %	11.8 %
Lip	0	0

Table 2. A comparison of the mean values of numerical rating scale and lesion size in the triamcinolone acetonide group with the Angelica shikokiana group in the first, second, and fourth weeks.

Numerical rating scale				
	Angelica shikokiana Mean ± standard deviation	Triamcinolone acetonide Mean ± standard deviation	*P* value	*t*-test
First Visit	7.21 ± 1.91	7.49 ± 1.97	0.792159	−0.4207
Second week	4.27 ± 2.19	4.79 ± 2.12	0.020993	−0.5955
Fourth week	3.00 ± 2.27	3.06 ± 2.25	0.050343	−0.0774
Size of the Lesion				
First Visit	71.91 ± 71.01	97.95 ± 97.14	0.701000	−0.8923
Second week	36.94 ± 66.05	55.09 ± 54.70	0.016000	−0.8726
Fourth week	30.58 ± 67.70	31.12 ± 36.54	0.023000	−0.0289

TA group and the AS group during the first, second, and fourth weeks.

In this investigation, the primary result was the NRS for recording pain. The patient rated the pain from 0 (no pain) to 10 (worst pain). The TA and AS groups showed immediate and substantial improvement between week 0 and week 2 (P value ≤ 0.005).

As we can notice, Table 2 shows a statistically significant difference between week 2 and week 4 reports of improvement (P value (TA) $= 0.020993$), indicating that the trend towards better health persisted through week 4. TA's analgesic impact was superior to AS's during the second week, but by the fourth week, AS had caught up to TA (P value $= 0.050343$). At the end of the second week, both treatments significantly reduced lesion size ($P = 0.016000$ in both groups). At the end of the trial period, both treatments showed a statistically significant effect in reducing lesion size ($P = 0.023000$ in both groups). In contrast to AS, the therapeutic agent (TA) showed a more rapid impact within 2 weeks.

Table 2 also displays the intergroup comparison by using the paired t-test that showed no significant difference between the degree of improvement in terms of NRS and the lesion size between the two studied groups (t-test ≤ 0.05).

In terms of adverse effects, it was noted that two patients in the TA group complained of an unpleasant taste. In contrast, four patients in the AS group reported a disagreeable odor, and five patients reported an unpleasant taste.

Table 3 shows interleukin six serum level; the blood sample was obtained from each patient at the first visit plus at the final visit of the study. There

Table 3. Compares the mean values of interleukin six serum level in the triamcinolone acetonide group with the Angelica shikokiana group in the first, second week, and fourth weeks.

Interleukin six serum level			
	Angelica shikokiana Mean ± standard deviation	Triamcinolone acetonide Mean ± standard deviation	*P* value
First Visit	42.33 ± 1.82	43.12 ± 1.23	0.467321
Second week	36.34 ± 1.15	31.66 ± 1.11	0.356210
Fourth week	20.00 ± 1.13	18.06 ± 1.25	0.258143

was no significant difference in the serum interleukin six serum level between the two groups (P value ≥ 0.05).

Discussion

Despite recent advances in medical technology, no cure for OLP has been developed. The care focuses on symptom control, minimizing the lesion's size, and preventing any possible progression to cancer.[9] We aimed to see if AS provides a natural therapeutic option similar to more standard topical corticosteroids.

This is the first randomized controlled clinical trial examining the efficacy of AS cream compared with TA in curing OLP.

According to the current research findings, applying a cream containing AS to a patient's skin can significantly reduce the patient's sense of pain and the clinical signs related to OLP. These discoveries were made around the end of the second week of treatment, which suggests that AS can produce quick changes in clinical status. In their study on treating OLP, Lopez Jornet et al.[21] evaluated the effectiveness of an AS oral gel containing 2 % compared with a placebo. These results are congruent with those obtained by those researchers. The study's authors found a difference that might be considered statistically significant between the two groups.

In some of the other studies, the participants were given medications that had elements of the treatment being researched. Amirchaghmaghi et al.[22] treated OLP by combining quercetin pills with dexamethasone mouthwash. This was done to achieve optimal results. In contrast to the first study, which utilized a medicine that was given topically 3 times daily, quercetin was administered intravenously twice daily. The study's findings showed no statistically significant difference between the placebo tablets and the quercetin tablets.

AS extract that is applied topically has been investigated for potential use in treating a wide range of conditions. Andishe Tadbir et al.[23] employed chamomile for the curing of aphthous ulcers, which is an immunologically produced oral condition that is comparable with OLP. The authors compared the effects of chamomile in orabase and TA in orabase or curing of aphthous ulcers. They concluded that chamomile was just as beneficial as TA in reducing inflammation and irritation, but it was significantly less successful in lowering the size of ulcers. This fits in reasonably well with the conclusions of the study, which are the subject of discussion at the moment.

According to Table 2, TA was significantly more effective at the end of the second week than AS. By the end of the fourth week, however, we found no statistically significant difference between the two groups, yet, there was a sizeable clinical difference in favor of TA. Similarly, we found no statistically significant difference between both groups in terms of the amount their Thongprasom score improved. Within the TA group, two patients showed an unpleasant taste, but three patients reported a disagreeable fragrance with the AS Chamomile group. In addition, five patients reported an unpleasant taste. While AS significantly improved pain, lesion size, and the Thongprasom score after 2 weeks, it still could not compete with TA. By week 4, there was no longer a significant difference between the TA and AS groups regarding lesion size, despite TA having a much more considerable lesion reduction impact at week 2. While these results suggest that AS was able to catch up to TA's effect, they also reveal that TA works more quickly to reduce the lesion. To our knowledge, this is the first study to evaluate the anti-inflammatory effect of AS leaves extract gel on lichen planus-induced oral mucositis, so more future studies are needed to be made on a large scale of patients to document our results.

Conclusions

This study provides conclusive evidence that AS can be used as a treatment for OLP. It can be utilized as a backup plan in OLP when corticosteroids are not working or when individuals decline therapy for fear of adverse effects. The authors suggest incorporating natural product therapy with corticosteroids to see if there is an additional or synergistic impact, as well as doing future investigations of varying concentrations of AS for the treatment of OLP.

Funding

This research received no external funding.

Data availability

The data used in this article was collected from patients who came to the oral medicine and diagnosis department, faculty of dentistry, Mansoura University while the material understudy has been prepared at faculty of pharmacy, Mansoura University. Data is available upon reasonable request from the author.

Conflicts of interest

There are no conflicts of interest.

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