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Effectiveness of honey therapy combined with photobiomodulation in the treatment of oral lichen planus: a randomized placebo-controlled trial

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Abstract

Introduction. Oral lichen planus (OLP) is a chronic inflammatory disorder that commonly occurs in the skin and mucosa of the oral cavity. This study aimed to evaluate the effectiveness of honey therapy (HT) combined with photobiomodulation (PBM) in the treatment of OLP.

Methods. The study involved 46 patients aged 40–55 (48.15 ± 6.28) years with erosive or atrophic OLP in the buccal mucosa. They were randomly allocated to 2 groups: study group (HT/PBM) (n = 23) and placebo group (golden syrup/PBM) (n = 23). Both groups received PBM (980-nm gallium-aluminium arsenide) with a power output of 0.3 W, 3 sessions per week for 4 weeks. At the same time, each patient in the study group was instructed to apply pure commercial honey, while patients in the placebo group were instructed to apply golden syrup, during the whole treatment period. All patients were assessed at baseline and after the treatment via visual analogue scale (VAS), oral function scores, and evaluation of OLP clinical manifestation.

Results. Patients in both groups were homogeneous in terms of age and gender, as well as the 3 clinical assessment values ($p > 0.05$) before the treatment. In the study group, post-treatment results regarding VAS ($p < 0.0001$), oral function scores ($p < 0.0001$), and OLP clinical manifestation ($p < 0.05$) were statistically significantly better than those in the placebo group.

Conclusions. HT combined with PBM reduced pain and improved OLP clinical manifestation and oral function scores in patients with OLP.

Key words: oral lichen planus, honey therapy, photobiomodulation, golden syrup, oral function scores

Introduction

Oral lichen planus (OLP) is a long-lasting inflammatory defect which commonly occurs in the skin and mucosa of the oral cavity. Furthermore, oesophageal mucosa, conjunctiva, and genital organs can be involved. OLP is diagnosed in around 2% of the population, mostly in individuals over the fourth decade of life, with a higher prevalence in females than in males. Usually, the buccal mucosa or other oral cavity sites such as labial mucosa, tongue, and gingiva can be affected [1].

The clinical presentations of OLP are characterized by reticular, plaque-like, atrophic, papular, erosive, and bullous lesions [2]. The commonest type is reticular OLP, which looks like white lacy streaks surrounded by a red margin and appears without symptoms [3]. Otherwise, the atrophic, erosive, and bullous lesions are associated with many symptoms such as erythema accompanied by an inflammatory process and/or decreased thickness of the epithelial layer in addition to the ulcer of the mucosa and keratotic striae around the lesion borders [4]. The majority of OLP cases present with chronic lesions, unusually recovering spontaneously and difficult to cure [5]. Atrophic and erosive OLP is usually associated with clinical manifestations starting from episodic pain to exacerbating discomfort that affect normal functions as mastication, swallowing, liquid intake, and taste sensation [6].

The aetiology and pathology of OLP are unclear; the onset of the disease may be due to infiltration and an autoimmune response of T-cells as a reaction to certain antigens in the oral mucosa. This autoimmune response starts the apoptosis of epithelial cells within the oral mucosa, which finally results in the development of OLP lesions [7]. Other causes of OLP are bacterial and viral infections, genetic factors, dental tools, medications, and allergic reactions [8, 9].

Although it is hard to achieve full recovery from OLP, there are various treatment options that have been attempted [10]. The first choice of treatment is local corticosteroid application. If local treatment fails, systemic corticosteroids can be used [11]. Corticosteroid administration may be accompanied by numerous complications and side effects, like the development of candidiasis, atrophy of oral mucosa, dehydration, tastelessness, and delayed recovery [12].

Honey therapy (HT) is considered as a potential alternative treatment, utilized as a nutrient and as a drug in different systemic (respiratory, urinary, and gastrointestinal) disorders [13] or local disorders of the skin and mucosa like ulcers, wounds, eczema, and OLP [14]. Honey exerts antioxidant and anti-inflammatory effects through elevation of the cell osmotic pressure that can absorb water from bacteria and viruses, leading to their death [15]. Inflammatory elements, such as nuclear factor kappa B (NF-κB), play a vital role in OLP pathogenesis. Honey contains strong anti-inflammatory constituents polyphenols, as well as an effective antibacterial substance which supports the process of healing wounds associated with ulcers in OLP [16, 17].

Photobiomodulation (PBM) is considered as a non-invasive physical therapy intervention and is used in the treatment of patients suffering from OLP, with the advantage of no adverse or side effects [18]. PBM is applied in various inflammatory conditions to reduce pain, achieve immunomodulation and bio-stimulation, or accelerate the wound healing

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process [19]. PBM exerts high phagocytic effects through increasing the number and size of lymphatic vessels, reducing the permeability of blood capillaries, and promoting neovascularization of microscopic blood vessels, besides reducing cell swelling [20].

Various studies described the usage of different types of PBM, and some reported HT application in the treatment of OLP, separately. The necessity for using safe and effective anti-inflammatory medications for OLP lesions has led to honey application in conjunction with PBM. Even so, there are no previous studies assessing HT combined with PBM in the treatment of OLP. Hence, a trial has been presented in this paper to evaluate the effectiveness of HT combined with PBM in the treatment of patients with OLP.

Subjects and methods

Study design and participants

A randomized, placebo-controlled, parallel-group, double-blinded study was performed. Overall, 46 patients (27 women, 19 men) were referred to the Physical Therapy Department, New Kasr El Aini Teaching Hospital, Faculty of Medicine, Cairo University, from the Dermatology Department and Dental Clinic during the period from January to October 2019. The participants were aged 40–55 years, with both clinical and histopathological identification of erosive or atrophic OLP (≤ 3 cm) in the buccal mucosa and symptomatic lesions unresponsive to local corticosteroids. Individuals with current malignancy, corticosteroid application within 1 month before the study procedures, pregnancy or lactation, diabetes mellitus, hypertension, or circulatory or vascular diseases were excluded.

The sample size was estimated by utilizing the PASS software, version 15.0.5 (NCSS, Kaysville, UT, USA). Estimates of means and standard deviations of visual analogue scale (VAS) scores were collected from a pilot study that included 10 patients with OLP lesions who received treatment similar to that applied in this study (mean 1 = 3.55 with *SD* = 1.14, and mean 2 = 2.50 with *SD* = 0.58). An independent *t*-test and a significance level of 0.05 implied that a total sample size of 30 subjects (15 in each group) was needed to achieve a power of approximately 87%. A total of 52 patients were recruited to compensate for the dropout rates.

Randomization was carried out by a blinded investigator utilizing www.randomization.com before starting the study procedures. The 46 patients were randomly allocated into 2 equal groups (*n* = 23): the study group (HT/PBM) and the placebo group (golden syrup [GS]/PBM). The randomization was sealed (1:1). After that, dark envelopes including the data of both groups in accordance with the random arrangement were labelled with successive numbers of 1–46.

Outcome measures

All patients were assessed at baseline and after the treatment accomplishment via VAS as a primary outcome measure, while oral function scores and the evaluation of OLP clinical manifestation constituted the secondary outcome measures.

Pain assessment

VAS is a self-reporting numerical pain scale consisting of a straight bar, frequently 10 cm in length, with 2 indications on both sides. One end is nominated '0' and the other end is '10,' standing for no pain and exacerbating pain, respectively. All patients were asked to mark a point that represented their pain intensity. By using a ruler, the result was identified by measuring the length in cm between the 'no pain' point and the patient's mark [21].

Oral function scores

Oral function scores were used to assess mastication, swallowing, liquid intake, and changed taste sensation. Each function was evaluated within the following scale: score 0 (effortlessness), score 1 (mild difficulty), score 2 (moderate difficulty), score 3 (severe difficulty), and score 4 (cannot perform the function) [22].

Evaluation of OLP clinical manifestation

Clinical information was assessed for OLP severity in accordance with Thongprasom et al. [23] with the following scores of OLP manifestation: score 0 (no lesions), score 1 (mild white striae only), score 2 (white striae with an atrophic area ≤ 1 cm^2), score 3 (white striae with an atrophic area > 1 cm^2), score 4 (white striae with an erosive area ≤ 1 cm^2), and score 5 (white striae with an erosive area > 1 cm^2). A Mitutoyo digital calliper (Mitutoyo, Kawasaki, Japan) was used to determine the size of the lesions (accuracy: 0.01 mm). For patients with multiple lesions, the total score was calculated by gathering the areas on the right and left buccal mucosa.

Interventions

Patients in both groups received active PBM combined with a topical substance: pure commercial honey as HT in the study group (HT/PBM) or GS as sham treatment in the placebo group (GS/PBM). The patients were blinded to the topical substance as it is difficult to differentiate between commercial honey and GS.

Any side effects or adverse reactions that occurred in any patient of either group during the treatment procedures were reported.

All patients in both groups were advised to use a soft toothbrush and non-irritant toothpaste, such as cinnamon or mint, prevent accidental damage of oral soft tissues, apply alcohol-free chlorhexidine mouthwash to decrease infection and mycosis, and avoid spicy, acidic, tough, hot drinks and foods during the whole period of the study [24].

Photobiomodulation

Patients in both groups were treated with PBM. PBM was produced with a 980-nm gallium-aluminium arsenide (GaAlAs) diode laser; it radiates infrared light in a non-contact continuous mode (DM980; DMT, Lissone, Italy). The diameter of the probe was 0.6 cm, with a spot area of 0.28 cm^2. The power output was 0.3 W, and the power density equalled 1 W/cm^2. A 'spot' mode was implemented directly to the centre of an OLP lesion and the perimeter of oral mucosa up to 0.5 cm around the lesion; the controlling light set up by the manufacturer was seen as red light. The dose for each spot area was 4 J/cm^2, and the probe was applied vertically at a length of 2 mm away from the area of the OLP lesion. The delivery time for each area was estimated with the following formula:

$$t\ (\text{time}) = D\ (\text{dose}) \times A\ (\text{area}) / P\ (\text{power output})$$

Consequently, the calculation was: t = 4 × 0.28/0.3 = 3.73 s in the continuous mode. So, the time of radiation equalled 13.3 s/cm^2. Each patient received PBM treatment time depending on the size of OLP lesions, 3 sessions per week for 4 successive weeks, in a rule of session every other day, with a total of 12 sessions. All the protecting PBM procedures were respected; the patient and the physical therapist were instructed to wear protective mesh goggles during the application [20].

Topical substance

Each patient was instructed to apply a fine layer of 10 ml of the topical substance (pure commercial Mawasem® cedar honey as HT in the study group or sweet sugar syrup used as a substitute for honey as GS in the placebo group) during the whole treatment period, via a piece of sterilized cotton, 4 times per day (after meals and before sleep). Eating, drinking, smoking, chewing gum, and using a mouthwash were forbidden for half an hour after applying the topical substance [16]. PBM was applied directly to the affected area of the OLP lesion that was not covered with any topical substance.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, version 25, IBM Inc., Armonk, NY, USA) was used for data analysis. The Kolmogorov-Smirnov test for normality was performed to assess the data distribution. To evaluate the differences between the HT/PBM and GS/PBM groups, an unpaired *t*-test was utilized for normally distributed data and the Mann-Whitney and chi-square tests were applied for non-normally distributed data. Data were shown as a mean ± standard deviation. The significance level was set at $p < 0.05$.

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved by the Institutional Scientific Review Ethical Committee (No. PT-019-004).

Informed consent

Informed consent has been obtained from all individuals included in this study.

Results

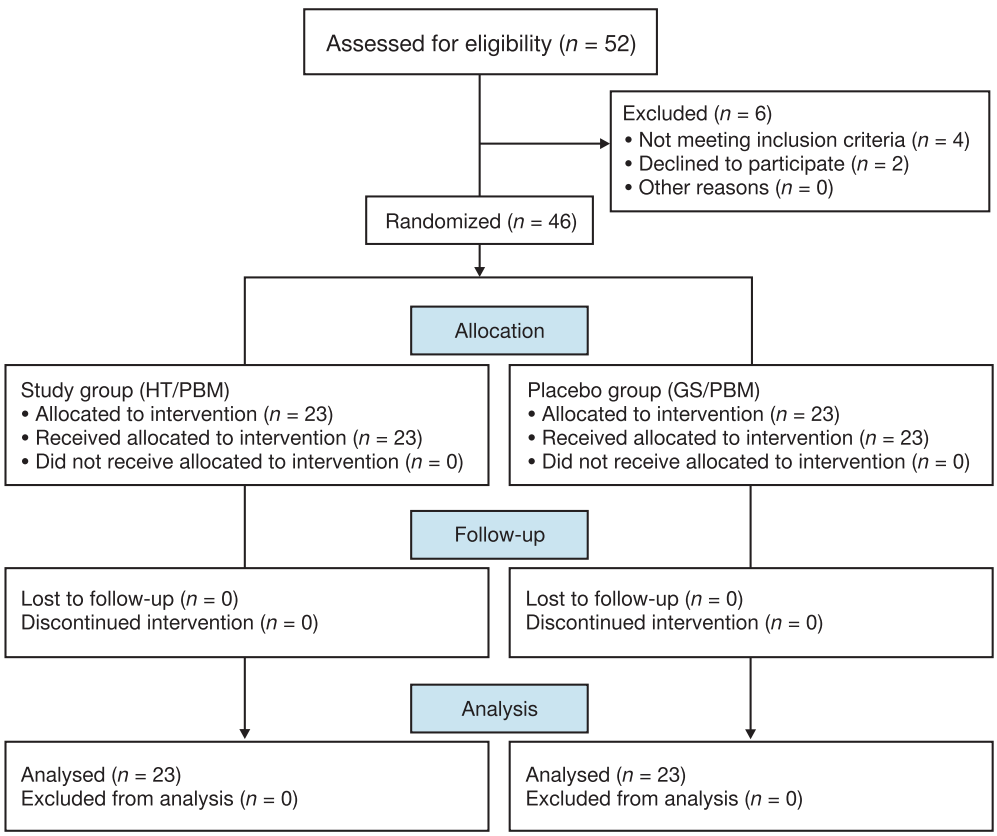
Overall, 46 patients aged 40–55 (48.15 ± 6.28) years with erosive or atrophic OLP in the buccal mucosa were enrolled in this study. There were 13 women and 10 men in the study group and 14 women and 9 men in the placebo group. A flowchart of the study is presented in Figure 1. Patients in both groups were homogeneous in terms of age and gender, as well as the values of VAS, oral function scores, and clinical manifestation of OLP before the treatment procedures ($p > 0.05$) (Table 1).

Pain assessment

The mean values of VAS with OLP lesions significantly decreased in both groups after finishing the study procedures ($p < 0.05$) (Table 2). Also, there were statistically significant differences in VAS mean scores between the groups at the end of treatment in favour of the study group ($p < 0.05$) (Table 3).

Oral function scores

All mean values of oral function scores (mastication, swallowing, liquid intake, and changed taste sensation) signifi-



HT – honey therapy
PBM – photobiomodulation
GS – golden syrup

Figure 1. CONSORT flowchart of the study

Table 1. Baseline characteristics of patients in both groups

Variables	Study group (*n* = 23)	Placebo group (*n* = 23)	*p*
Age (years)	47.6 ± 6.37	48.7 ± 6.21	0.556
Gender (W/M)	13/10	14/9	0.922
VAS score	7.26 ± 1.58	6.87 ± 1.47	0.391
Oral function scores			
Mastication	3.41 ± 0.51	3.38 ± 0.57	0.852
Swallowing	3.23 ± 0.72	3.26 ± 0.69	0.886
Liquid intake	3.12 ± 0.77	3.15 ± 0.81	0.898
Changed taste sensation	3.06 ± 0.84	3.11 ± 0.82	0.839
OLP clinical manifestation	4.13 ± 0.73	4.28 ± 0.61	0.454
Score 0, *n* (%)	0 (0)	0 (0)	0.889
Score 1, *n* (%)	0 (0)	0 (0)	
Score 2, *n* (%)	2 (8.7)	1 (4.3)	
Score 3, *n* (%)	2 (8.7)	2 (8.7)	
Score 4, *n* (%)	10 (43.5)	9 (39.1)	
Score 5, *n* (%)	9 (39.1)	11 (47.9)	

Data expressed as mean ± *SD* or as frequency (percentage).
W – women, M – men, VAS – visual analogue scale, OLP – oral lichen planus

Table 2. Variable mean values before and after treatment in both groups

Variables	Study group (*n* = 23)			Placebo group (*n* = 23)		
	Before	After	*p*	Before	After	*p*
VAS score	7.26 ± 1.58	2.17 ± 1.31	< 0.0001	6.87 ± 1.47	4.73 ± 1.38	< 0.0001
Oral function scores						
Mastication	3.41 ± 0.51	1.22 ± 0.32	< 0.0001	3.38 ± 0.57	2.19 ± 0.41	< 0.0001
Swallowing	3.23 ± 0.72	1.34 ± 0.46	< 0.0001	3.26 ± 0.69	2.11 ± 0.53	< 0.0001
Liquid intake	3.12 ± 0.77	1.27 ± 0.51	< 0.0001	3.15 ± 0.81	2.44 ± 0.67	0.0023
Changed taste sensation	3.06 ± 0.84	1.47 ± 0.49	< 0.0001	3.11 ± 0.82	1.97 ± 0.56	< 0.0001
OLP clinical manifestation	4.13 ± 0.73	1.15 ± 0.38	< 0.0001	4.28 ± 0.61	2.78 ± 0.45	< 0.0001
Score 0, *n* (%)	0 (0)	12 (52.2)	0.0017	0 (0)	3 (13)	0.0234
Score 1, *n* (%)	0 (0)	5 (21.8)		0 (0)	2 (8.7)	
Score 2, *n* (%)	2 (8.7)	1 (4.3)		1 (4.3)	4 (17.3)	
Score 3, *n* (%)	2 (8.7)	2 (8.7)		2 (8.7)	5 (21.8)	
Score 4, *n* (%)	10 (43.5)	1 (4.3)		9 (39.1)	4 (17.3)	
Score 5, *n* (%)	9 (39.1)	2 (8.7)		11 (47.9)	5 (21.8)	

Data expressed as mean ± *SD* or as frequency (percentage).
VAS – visual analogue scale, OLP – oral lichen planus

cantly improved in both groups, with minimum scores after finishing the study procedures ($p < 0.05$) (Table 2). Additionally, there were statistically significant differences in all mean oral function scores between the groups at the end of treatment in favour of the study group ($p < 0.05$) (Table 3).

Evaluation of OLP clinical manifestation

The mean values of OLP clinical manifestation were significantly improved in both groups, with minimum scores after finishing the study procedures ($p < 0.05$) (Table 2). Furthermore, there were statistically significant differences in all mean values of OLP clinical manifestation between the groups at the end of treatment in favour of the study group ($p < 0.05$) (Table 3).

After finishing treatment, the numbers and percentages of patients were 12 (52.2%) for no lesions, normal mucosa (score 0); 5 (21.8%) for score 1; 1 (4.3%) for score 2; 2 (8.7%) for score 3; 1 (4.3%) for score 4; and 2 (8.7%) for score 5 in the study group, while the respective values in the placebo group equalled 3 (13%), 2 (8.7%), 4 (17.35%), 5 (21.8%), 4 (17.35%), and 5 (21.8%) (Table 3).

Table 3. Variable mean values after treatment in both groups

Variables	Study group (*n* = 23)	Placebo group (*n* = 23)	*p*
VAS	2.17 ± 1.31	4.73 ± 1.38	< 0.0001
Oral function scores			
Mastication	1.22 ± 0.32	2.19 ± 0.41	< 0.0001
Swallowing	1.34 ± 0.46	2.11 ± 0.53	< 0.0001
Liquid intake	1.27 ± 0.51	2.44 ± 0.67	< 0.0001
Changed taste sensation	1.47 ± 0.49	1.97 ± 0.56	0.0024
OLP clinical manifestation	1.15 ± 0.38	2.78 ± 0.45	< 0.0001
Score 0, *n* (%)	12 (52.2)	3 (13)	0.0125
Score 1, *n* (%)	5 (21.8)	2 (8.7)	
Score 2, *n* (%)	1 (4.3)	4 (17.35)	
Score 3, *n* (%)	2 (8.7)	5 (21.8)	
Score 4, *n* (%)	1 (4.3)	4 (17.35)	
Score 5, *n* (%)	2 (8.7)	5 (21.8)	

Data expressed as mean ± *SD* or as frequency (percentage).
VAS – visual analogue scale, OLP – oral lichen planus

Discussion

OLP is a chronic immunologic inflammatory disorder of oral mucosal membrane, characterized by remissions and exacerbations. It is hard to achieve full recovery in patients with OLP, and they often necessitate a multidisciplinary treatment team, including dermatologists, dentists, gastroenterologists, and, recently, physical therapists. The management is primarily focused on the improvement of oral functions such as talking, eating, drinking, and using dental prostheses. As earlier stated, PBM is an effective modality progressively utilized in health care, which has possible bio-stimulation influences on the oral mucosa. This study was conducted to evaluate the effectiveness of HT combined with PBM in the treatment of patients with OLP.

The applied intervention turned out effective in treating OLP patients. The study revealed a reduction in pain severity with an improvement of oral function scores and clinical manifestation of OLP lesions in the study group, treated with HT combined with PBM. In turn, patients treated with GS as placebo honey combined with PBM also improved in the performed clinical assessments, but to a lesser extent than the HT/PBM group.

Currently, PBM is used in many medical conditions such as musculoskeletal, neurological, dermatological, and dental disorders, especially lesions of oral mucosa in the course of OLP [25]. The main advantage of PBM is that it constitutes a non-surgical treatment option which accelerates the healing of wounds and decreases tissue swelling, pain, and inflammation. Laser PBM provides direct bio-stimulation light energy to cells, exerting anti-inflammatory and analgesic effects by elevating the morphine level. It induces vasodilatation, improves microcirculation that carries oxygen, and increases immune response in the tissue [26].

Excimer and CO_2 lasers are characterized by minimal penetration of beams with a superficial effect [27]. On the contrary, a diode PBM (980 nm) laser radiates infrared light, which has the attributes of deep penetration into tissues (3–15 mm). So, a diode PBM (980 nm) laser plays a vital role in the destruction of inflammatory constituents of the epithelial layer and underlying connective tissue within the OLP lesion. Soliman et al. [28] reported that the advantageous influence and non-invasive character of diode PBM (980 nm) brought about acceptable results in the treatment of OLP manifestations.

Using diode PBM (980 nm) at the power of less than 1 W has bio-stimulation, anti-inflammatory, and analgesic effects. The inflammation of oral mucosa can be controlled by PBM through the modulation of mast cell functions, as well as decreasing tumour necrosis factor alpha (TNF-α), prostaglandin-endoperoxide synthase 2 (PTGS2), prostaglandin E_2 (PGE2), interleukin 1 beta (IL-1β), tissue swelling and haemorrhage, in addition to an inflow of white blood cells into the cell and producing an antioxidant effect [29]. Other influences that may be relevant to mitochondrial stimulation are increasing adenosine triphosphate (ATP) output, leading to an enhancement of reactive oxygen species, which impacts on redox signalling, and affecting intracellular homeostasis of cell production [30].

Nowadays, honey is a potential alternative treatment; it has certain constituents with antioxidant and anti-inflammatory characteristics, which build up a valuable material in the treatment of OLP lesions [31]. Particularly, the antioxidant constituents include polyphenols, especially flavonoids (plant chemicals), as well as catalase enzyme, glucose oxidase enzyme, organic acids (organic compounds with acidic properties), vitamin C, proteins, carotenoid-like substances, and amino acids (organic compounds that combine to form proteins) [32]. Honey has an anti-proliferative activity owing to the ability to prohibit the growth of the affected cells. Anti-inflammatory properties of honey consist in stimulating white blood cells to release cytokines, TNF-α, IL-1, and IL-6, which participate in overcoming infection by the immune system [33].

In a study by El-Haddad and Al-Shawaf [14], HT was used to decrease inflammation, hasten wound healing, and relieve pain in OLP lesions, with the elimination of erythema and/or ulceration without utilizing corticosteroids. Also, HT application in an early stage of signs and symptoms in one patient with OLP resulted in complete recovery. In other patients, HT was implemented after the outbreak of lesions and

a rapid recovery of the lesions was observed without any crust formation.

The concept of combination therapy is always an attractive idea, potentially allowing to gain the benefits of more than one treatment modality to attain full recovery in a short time. In this study, a combination of HT with PBM had apparent effects because of the multiple influence of anti-inflammatory, antioxidant, and analgesic properties of both HT and PBM. A combination of laser PBM [28] and honey [15] was chosen because they are both mentioned separately in the treatment of patients with OLP with good results, but to the best of our knowledge, there are no studies reporting these therapies combined in the treatment of OLP lesions. Although it has not been clarified how the combination of HT with PBM operates, the effects may be due to the synergistic impact of these 2 therapeutic modalities: the disappearance of erythema accompanied by inflammation in addition to the acceleration of mucosal ulcer healing and pain relief. This combination can help achieve substantial improvements in the healing of mucosal tissue and beneficial effects in the treatment of OLP symptoms, without any adverse and/or side effects.

The investigated treatment combination proved to decrease pain, reduce inflammation, accelerate the healing of oral ulcers, and restore oral functions. One more advantage of the study was the absence of any side and/or adverse impacts. Thus, further studies using standardized outcome measures such as histopathological evaluation, assessment at intervals throughout the treatment procedure, and follow-up assessment are required. Moreover, quality of life research could be beneficial in the overall management of patients with OLP.

Conclusions

The application of PBM has an effective and positive impact in the treatment of patients with OLP, while the combination of HT with PBM showed more effective results, without the side effects that are related to other treatment options. On the basis of this study findings, HT combined with PBM reduced pain in addition to improving clinical manifestation and oral function scores in patients with OLP.

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Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

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